A study of pain management practices during the prolonged hospitalisation of infants.

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A research thesis submitted in total fulfilment of the requirements of Doctor of Philosophy

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DEDICATION

This work is dedicated to Mum who was proud of all our achievements, no matter how big or how small.
ABSTRACT

Purpose: The purpose of this study was three-fold; to investigate the use of pain assessment tools and pain reduction strategies during minor painful procedures in neonatal units in Australia; to map the history of an infant's prolonged hospitalisation in a tertiary neonatal intensive care unit with respect to painful procedures and pain management practices, and to describe the effectiveness of oral sucrose in reducing procedural pain during the course of an infant's prolonged hospitalisation (≥ 28 days).

Design and methods: A cross-sectional postal survey was conducted to ascertain nationwide pain assessment and pain management practices in Australian neonatal intensive care units. A prospective, observational, longitudinal study of a cohort of infants nursed in a tertiary referral Level Three neonatal intensive care unit, with a predicted prolonged length of stay was conducted to map painful procedures, documentation of pain assessment scores and the use of analgesic and sedative medications over the course of the infants’ hospitalisation. To ascertain analgesic effects of repeated and multiple doses of oral sucrose over a prolonged hospitalisation, successive pain responses during heel lancing, at weekly, or more or less frequent intervals depending on the requirement for pathology testing, were also studied in the same cohort of infants. Prior to, and during observed heel lance procedures, oral sucrose was administered as per routine clinical practice. The pain assessment method used was a combination of behavioural and physiological parameters. Crying duration and a four-point facial expression score comprised the behavioural measures, whilst the physiological parameters measured were heart rate and oxygen saturation.

Findings: The nationwide pain assessment and pain management survey was posted to 181 nurse unit managers of Level Two and Three neonatal units and returned by 105 respondents, a response rate of 58%. Six units (6%) used pain assessment scores on a routine basis, and 16 units (15%) had an articulated policy directing pain management during minor procedures. Twenty-four (23%) units reported using oral sucrose or other sweet tasting solutions for management of procedural pain, however the actual use of sucrose during commonly performed minor painful procedures was infrequent. This was despite 63% of respondents being aware of the analgesic efficacy of sweet
tasting solutions. Non-nutritive sucking and other comfort measures were the pain management strategies used most frequently during minor painful procedures.

Results of the longitudinal cohort study, which included 55 infants with a length of stay of 28 days or more, showed that 3806 painful procedures were recorded over the course of the infants’ hospitalisation. There were 201 major procedures, of which 98 were surgical procedures, and 3605 minor procedures. The large majority (71%) of minor procedures documented were heel lances. Either oral sucrose was specifically given for reduction of pain, or morphine was being administered as part of medical management, for 85% of all minor procedures. There was ubiquitous use of analgesic and sedative medications administered over the course of the infants’ hospitalisation, yet infrequent documentation of the effectiveness of the pharmacological agents using pain assessment scores.

For the 55 infants in the cohort, 446 pain assessments during routine heel lancing were conducted. Results showed that during the majority of heel lance procedures assessed, the lowest facial expression score of zero, indicating no facial expression of pain, was assigned at all observation points. At the time-point of the initial heel lance, considered to be the most painful part of the procedure, a score of zero was assigned in 64% of assessments. Crying occurred in only 50% of the assessments where infants had a capacity to audibly cry. Over the course of the hospitalisation, despite some variability in pain responses, there was no increase or decrease in either behavioural or physiological responses. This lack of an increase in pain responses, in the context of the predominantly low behavioural responses to the painful procedure of heel lance, is suggestive of a sustained analgesic effect of oral sucrose throughout the infants’ hospitalisation. This study is the first to describe the apparent effectiveness of oral sucrose in sick infants over the full course of a hospitalisation, and is also the only study to describe concomitant use of sucrose in conjunction with opioid analgesics.

Conclusion: The reported nationwide practices of infrequent use of oral sucrose and pain assessment tools in Australian neonatal units do not comply with recommendations from international bodies concerning recognition, and management of, pain in infants. There was substantial use of a variety of both analgesics and
sedatives in the cohort of infants with a prolonged length of stay; most of which currently have an inadequate evidence base to support prolonged use in clinical practice. Yet, the paucity of evidence relating to safety and efficacy of long-term use of both analgesic and sedative agents makes it difficult for health professionals caring for sick infants, to manage pain and distress occurring as a result of invasive procedures, assisted ventilation and associated care, within an evidential base. However, the lack of any significant change in successive responses to a routine painful procedure adds evidence to consistent analgesic effectiveness of oral sucrose after multiple doses. This evidence contributes significantly to the knowledge-research gap concerning analgesic effectiveness of repeated use of oral sucrose. Results of these three inter-related phases of the study have highlighted important issues relating to pain assessment and pain management in sick neonates and infants. This evidence can be used to inform future clinical practice changes and future neonatal pain research with the aim of continuing to improve pain management in sick infants.
PUBLICATIONS ARISING FROM THIS WORK


POSTERS AND PRESENTATIONS ARISING FROM THIS WORK

2007: Invited Speaker

Mythbusting the oral sucrose myths. *Pain in Child Health, Online Lab Meeting, Canadian Institute of Health Research*, Canada

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Harrison D, Loughnan P, Manias E, Johnston L. The effectiveness of oral sucrose in the reduction of procedural pain during the course of an infant's prolonged hospitalisation. *Perinatal Society of Australia and New Zealand 11th Annual Congress*, Melbourne, Australia. (Oral presentation)

Harrison D. Myths and Mythconceptions: Busting the oral sucrose myths. *Australian College of Neonatal Nurses 2nd Annual Seminar*, Melbourne, Australia (Oral presentation)

2006: Invited Speaker

Pain management practices during the prolonged hospitalisation of infants; the findings. *Neonatal Grand Rounds. Royal Women’s and Children’s Hospital*, Melbourne, Australia
Neonatal pain assessment. Neonatal Grand Rounds. Royal Women’s and Children’s Hospital, Melbourne, Australia

The visible difference: Real changes to women’s and babies lives through innovative nursing and midwifery practice. 2006 Eileen Patricia Goulding and Betty Lawson Seminar. Royal Women’s Hospital, Melbourne, Australia.

A study of pain management practices during the prolonged hospitalisation of infants. Clinical research seminar. Montreal Children’s Hospital, Montreal, Canada

A study of pain management practices during the prolonged hospitalisation of infants. Clinical research seminar. Vancouver Children’s Hospital, Vancouver, Canada

What should midwives do about neonatal pain management. Freemasons Maternity Hospital, Melbourne, Australia.

Pain management practices in a cohort of complex infants. Pain Workshop. Neonatal Unit, Royal Children’s Hospital, Melbourne, Australia.

Assessment and recognition of neonatal pain. Neonatal surgical seminar, Royal Children’s Hospital, Melbourne, Australia.

2006: Abstracts Accepted


Harrison D, Loughnan P, Manias E, Johnston L. Analgesic and sedative administration in a cohort of infants with a prolonged length of stay. 6th Pain in Child Health Institute, Rockwater Resort, British Columbia, Canada (Poster presentation)


**2005: Invited Speaker**


Sucrose and pain – All we know, don't know & what we're not too sure about. *Pain in Childhood week. Royal Children’s Hospital*, Melbourne, Australia.


Pain assessment and procedural pain management practices in Australian neonatal units. *Neonatal Professional Links, Department of Human Services*, Melbourne, Australia

Sucrose and pain, what we know, what we don’t know and what we’re not so sure about. *Pain in Child Health, Online Lab Meeting, Canadian Institute of Health Research*, Canada

Pain reduction for procedure-related pain in sick infants. *Night Shift Staff update, Royal Children’s Hospital*, Melbourne, Australia.

Developmental Care, How is it practiced in Australian NICUs? *Australian College of Neonatal Nurses Annual Seminar*, Adelaide, South Australia
2005: Abstracts Accepted

DECLARATION OF AUTHORSHIP

I, Denise Margaret Harrison, declare this thesis contains only my original work undertaken towards the Doctor of Philosophy Degree.

Due acknowledgment has been made in the text to all other material used.

The thesis is less than 80,000 words in length, exclusive of tables, maps, bibliographies and appendices.

Denise Margaret Harrison

April 2007
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First of all, I would like to thank all the sick babies and their families who stimulate my passion to search for ways in which to improve care, and make life in the NICU that bit more positive than it may have been before.

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“If a new skin in old people be tender, what is it you think in a newborn Babe? Doth a small thing pain you so much on a finger, how painful is it then to a Child, which is tormented all the body over, which hath but a tender new grown flesh? If such a perfect Child is tormented so soon, what shall we think of a Child, which stayed not in the wombe its full time? Surely it is twice worse with him.”

Felix Wurtz, 1612, The Children's Book.
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“The anaesthesiologist who presided said, it has never been shown that premature babies have pain” (Lawson, 1986a)

Anaesthesia is unnecessary for infants because “it has neither the anticipation nor remembrance of suffering, however severe…” (Bigelow, 1848)

“Jeffrey, had holes cut in both sides of his neck, another hole in his right chest, an incision from his breastbone around to his backbone, his ribs pried apart, and an extra artery near his heart tied off. This was topped off with another hole cut in his left side for a chest tube. The operation lasted 1½ hours. Jeffery was awake through it all. The anesthesiologist paralysed him with Pavulon, a curare drug that left him unable to move, but totally conscious.” (Lawson, 1986b)

These three quotes highlight the prevalent beliefs and practices of an era spanning almost 140 years that newborn infants neither felt pain, anticipated pain, nor remembered pain, therefore infants did not require any analgesics for either repeatedly occurring minor procedures or major surgical procedures. In addition, anaesthetists and surgeons were faced with a combination of inadequate intra-operative monitoring and limited knowledge of the safety of analgesic and anaesthetic use in premature infants (Berry & Gregory, 1987). These beliefs and practical concerns accounted for the pervading practices of performing operative procedures on premature and sick infants with no anaesthesia or analgesia until the mid 1980s (Lippmann, Nelson, Emmanouilides, Diskin, & Thibeault, 1976; Berry & Gregory, 1987; Lawson, 1988b). As the evolution of the neonatal intensive care unit (NICU) resulted in increased survival rates for premature and sick infants (Donoghue & Australian and New Zealand Neonatal Network, 2003), this change also brought about increased numbers of infants exposed to surgical and medical procedures and to other noxious stimuli during the course of their hospitalisation. However, many studies continued to be published which reported that invasive procedures were regularly performed on sick infants with no analgesia (Bauchner, May, & Coates, 1992; Barker & Rutter, 1995;
Johnston, Collinge, Henderson, & Anand, 1997; Porter & Anand, 1998; Simons, van Dijk et al., 2003; Stevens et al., 2003). One report showed that 54 infants, over a three-month period, underwent 3283 procedures, most of these being capillary blood sampling (Barker & Rutter, 1995). Although in their report, Barker and Rutter discussed available pain reduction methods, no actual pharmacological or non-pharmacological pain reduction strategies were used during any procedures. Porter and Anand (1998) conducted a longitudinal study of premature infants’ exposure to painful procedures in a neonatal unit in the USA and reported that 144 premature infants underwent 7000 procedures, of which 6000 were heel lances. There were no analgesic agents administered specifically prior to, or during, any heel lance procedures. Simons et al. in 2003 reported a mean of 14 painful procedures per infant per day; no analgesic agent was given for alleviation of pain during the majority of these procedures. In another study, Stevens et al. (2003) reported that infants in a NICU underwent a mean of 10 painful procedures per day during the first two days of life. Contrary to previously commonly held beliefs that infants neither felt nor remembered pain (Bigelow, 1848), adverse consequences of pain in premature and sick infants had started to become increasingly evident (Anand & Hickey, 1987).

Effects of pain in the infant

Anecdotal evidence of adverse effects of pain experienced in the neonatal period was primarily brought to the public attention midway through the 1980s by a parent of a critically ill premature infant. Jill Lawson played a pivotal role as a consumer of health services, in highlighting to both the medical community and to the public, seriously inadequate pain management practices in sick infants. She publicly lobbied for changes in intra-operative pain management practices following her son’s surgery for ligation of a patent ductus. During the surgery, muscle relaxants only were administered, with no supplementary analgesic or anaesthetic agents (Lawson, 1986a, 1986b, 1988a, 1988b).

Within the medical profession, it was primarily through a series of studies undertaken by Anand and colleagues, demonstrating adverse effects of surgery performed on neonates and infants with no or minimal analgesic or anaesthetic agents, which was instrumental in revolutionising neonatal anaesthetic practices (Anand & Aynsley-
Green, 1985; Anand et al., 1985; Anand, Sippell, & Aynsley-Green, 1987; Anand & Aynsley-Green, 1988; Anand, Sippell, Schofield, & Aynsley-Green, 1988; Anand, 1990; Anand & Hickey, 1992). One of the earliest of these published studies described metabolic and hormonal responses occurring in response to surgery in 26 term and seven premature infants. Anand et al. (1985) reported that anaesthetic agents only, with no opioid analgesics were given intra-operatively during all surgical procedures, and post-operative pain management comprised administration of intermittent intramuscular injections of opioid analgesics; either morphine or Omnopon®. The key findings were that, in both the preterm and term infants, surgery resulted in hyperglycaemia, hyperlactaemia, exaggerated secretion of catecholamines and inhibition of insulin secretion, all of which have the potential to severely compromise sick infants (Anand et al., 1985).

Following this descriptive study, a randomised, controlled trial was conducted, in which metabolic and hormonal responses to surgery, as well as post-operative complications, were compared in premature infants randomised to receive either standard intra-operative administration of nitrous oxide alone, or with the addition of the opioid analgesic agent, fentanyl (Anand et al., 1987). Sixteen infants undergoing surgery for ligation of a patent duct arteriosus were enrolled into the study. The results showed that the eight infants in the treatment group had a significant reduction in stress hormone levels, as well as reduced circulatory and metabolic complications post-operatively, compared to the group of infants who underwent surgery with standard anaesthesia (Anand et al., 1987). Although the numbers of infants enrolled in this study were small, the positive findings of an improved post-operative outcome associated with the administration of an opioid intra-operatively were convincing.

Another randomised, controlled trial compared stress hormone levels in two groups of infants undergoing surgery, and randomised to receive either the potent anaesthetic agent; halothane, in addition to standard anaesthesia of inhaled nitrous oxide and muscle relaxants, or standard anaesthesia alone (Anand et al., 1988). Numerous metabolic and stress responses were measured intra-operatively and for 24 hours post-operatively. Participants were 36 term and pre-term infants, aged between two and four weeks. The main findings were that the 18 infants in the treatment group
demonstrated diminished metabolic and stress responses compared to the control group, as illustrated by a reduction in serum concentrations of adrenaline, noradrenaline, cortisol, glucose and ketones. The authors’ key recommendation was that effective analgesia (used to block the conscious perception of pain, or to relieve pain) and anaesthesia (used to block the sensation of pain and other sensations) should be administered to newborn infants undergoing surgery and other invasive medical procedures (Anand et al., 1988).

Morbidity and mortality rates as well as hormonal and metabolic responses in newborn infants undergoing cardiac surgery, were evaluated in a further randomised, controlled trial (Anand & Hickey, 1992). Infants were randomised to either the experimental group, to receive deep anaesthesia (intra-operative sufentanil), and post-operative continuous morphine infusion, or the control group to receive light anaesthesia (intra-operative inhaled halothane, low dose ketamine, low dose morphine) and intermittent doses of morphine and diazepam for analgesia and sedation post-operatively. Results showed significantly improved outcomes for the infants who received deep anaesthesia and continuous morphine infusion post-operatively compared with the control group. Improved outcomes included diminished hormonal and metabolic responses, reduced infection rates and reduced incidence of metabolic acidosis and disseminated intravascular coagulation occurring within 24 hours post-operatively. Four of the 15 infants in the control group died following surgery, whereas no deaths occurred in the 30 infants receiving the deep anaesthetic and continuous morphine infusion. Specific reasons for the four deaths were not reported, however, the poorer outcomes were attributed to persistent metabolic acidosis, partly as a result of the metabolic stress response, and increased incidence of sepsis associated with exaggerated hormonal stress responses.

In this series of studies, Anand and colleagues clearly demonstrated evidence of serious physiological and metabolic compromise occurring in infants during surgery and in the post-operative period, which was significantly minimised with effective anaesthesia and analgesia. Dissemination of this evidence resulted in recommendations for routine administration of effective doses of anaesthetic and analgesic agents to infants in the peri-operative period (American Academy of Pediatrics & Canadian Paediatric Society, 2000). As evidenced by a significant
difference in findings of two consecutive surveys of analgesic prescribing practices for infants undergoing surgery, intra-operative analgesia prescribing practices did indeed change to conform to recommendations (De Lima, Lloyd-Thomas, Howard, Sumner, & Quinn, 1996). The two surveys were conducted in Great Britain and Ireland in 1988 and 1995. In the first survey conducted in 1988 and returned by 60 of 66 anaesthetists (91% response rate), intra-operative opioid analgesics were routinely administered to neonates by only two percent of anaesthetists, and no regional analgesics were administered to any infant. In contrast, results of the second survey conducted in 1995, which was sent to 151 anaesthetists and returned by 107 (71% response rate), showed that all infants received either systemic opioids or regional anaesthesia intra-operatively (De Lima et al., 1996).

In addition to the considerable body of evidence demonstrating physiological, hormonal and metabolic compromise occurring as a result of major surgery, adverse effects of pain and stress as a result of minor invasive procedures and monitoring occurring during the course of infants’ hospitalisation have also been demonstrated. Descriptions of responses to painful and noxious stimuli have included adverse short and long-term physiological, behavioural, and possible neurological outcomes (Perlman, 2001).

Infants’ responses to noxious stimuli

Responses exhibited during or immediately following noxious procedures in the neonatal period have been systematically and extensively documented since the mid 1980s. Immediate effects of pain and stress on sick and preterm infants as early as 24 weeks gestational age include a multitude of behavioural, physiological and biochemical changes (Golub & Corwin, 1982; Craig, Whitfield, Grunau, Linton, & Hadjistavropoulos, 1993; Johnston, Stevens, Yang, & Horton, 1995; Johnston, Sherrard et al., 1999; Johnston, Stevens et al., 1999; Grunau, 2002; Holsti, Grunau, Oberlander, & Whitfield, 2004). Procedures in which these responses have been studied include endotracheal tube suctioning, handling for nursing care, during elevated noise levels, and the most frequently studied noxious stimuli; heel lancing, to obtain capillary blood for sampling. Frequently documented physiological responses to noxious stimuli have included elevated heart rate, decreased oxygen levels and
altered respiratory rate changes (Owens & Todt, 1984; Johnston & Strada, 1986; Bozzette, 1993; Craig et al., 1993; McIntosh, van Veen, & Brameyer, 1993; Stevens & Johnston, 1994; Grunau, Oberlander, Holst, & Whitfield, 1998; Porter, Wolf, & Miller, 1999; Grunau, Oberlander, Whitfield, Fitzgerald, & Lee, 2001; Harrison, Johnston, Loughnan, & Evans, 2002). Results of these numerous studies have demonstrated that infants respond physiologically in a relatively consistent manner to procedure-related pain despite variability in the extent of responses. These results illustrate the capacity of newborn infants, including premature infants, to mount an observable response to painful procedures.

Heart rate changes in response to heel lancing have been shown to increase from baseline levels and remain elevated both throughout the duration, and following completion of the procedure (Owens & Todt, 1984; Craig et al., 1993; Stevens & Johnston, 1994; Harrison et al., 2002; Harrison, Johnston, & Loughnan, 2003a). Changes in infants’ oxygen saturation levels or transcutaneous oxygen tension, in response to heel lancing, generally show a consistent pattern of a reduction from baseline levels during the lance and squeeze phases of the procedure, and a return to baseline following completion of the procedure (Bozzette, 1993; Craig et al., 1993; McIntosh et al., 1993; Stevens & Johnston, 1994; Porter et al., 1999; Harrison et al., 2002). Respiratory rate changes occurring in response to a heel lance have been reported as less evident and less consistent than heart rate responses (Craig et al., 1993; McIntosh et al., 1993).

Infants’ behavioural responses to procedural pain, including facial expressions, body movements and crying characteristics have also been studied extensively. Facial expressions occurring in response to pain and distress have been cited as the most specific indicator of pain in response to noxious stimuli (Stevens, Johnston, Petryshen, & Taddio, 1996). Charles Darwin first systematically described infants’ facial expressions during periods of crying in his works titled, The Expression of the Emotions in Man and Animals (Darwin, 1872). In the section titled ‘Special Expressions of Man: Suffering and Weeping’, a series of photographs accompanies written explanations of the facial muscles involved in the formation of expressions of distress. In more recent times, facial expressions occurring in response to the painful procedure of heel lancing have been systematically described and categorised by
Grunau and Craig (1987). Four facial expressions of brow bulge, eye squeeze, nasolabial furrow and open lips have been demonstrated to be the most specific behavioural indicators of acute procedural pain in infants regardless of gestational age (Johnston & Strada, 1986; Craig et al., 1993; Stevens et al., 1996; Grunau, Oberlander et al., 1998). Due to the specificity of facial expressions in response to an acute painful procedure in all groups of infants including premature and sick infants, facial expressions form the basis of the majority of composite and multidimensional pain assessment tools used to quantify pain in infants (Stevens et al., 1996; Peters, Koot, Grunau et al., 2003).

A range of body movements has also been demonstrated to occur in response to procedural pain. In a systematic observational study of body movements occurring in response to heel lancing in 56 premature and term newborn infants, hand and foot movements, including flexion, extension, finger splay, fist clench, twitching, rotation of the ankle, spreading, twitching, or flaring of the toes, plus movements of the arm, leg, head and torso were described (Craig et al., 1993). Similar responses to heel lancing were observed in a study which used the Newborn Individualized Developmental Care and Assessment Program (NIDCAP) (Als, Lester, Tronick, & Brazelton, 1982), to code body movements (Holsti et al., 2004). Findings were that, of the 85 listed NIDCAP behaviours; eight were associated with procedural pain in premature infants. Aside from the facial expression of frown, the remaining seven identified NIDCAP behaviours were body movements comprising flexion and extension movements of all limbs, finger splay, and specific hand movements.

Infants’ crying characteristics in response to either noxious stimuli or medically related procedural pain have been extensively documented over the previous 30 years (Michelsson, 1971; Michelsson, Sirvio, & Wasz-Hockert, 1977a; Owens & Todt, 1984; Johnston & Strada, 1986; Grunau & Craig, 1987; Grunau, Johnston, & Craig, 1990; Fuller, 1991; Hadjistavropoulos, Craig, Grunau, & Johnston, 1994; Johnston, Sherrard et al., 1999). Crying characteristics evaluated in response to procedure-related pain have included acoustic and temporal features. Acoustic analyses of crying have shown that cries in response to pain are generally of a higher pitch than cries in response to either hunger or tactile stimulation (Fuller, 1991; Runefors, Arnbjornsson, Elander, & Michelsson, 2000). Temporal crying characteristics in
infants in response to painful procedures have also been reported. Short cry latencies, with cry latency being defined as time between the painful stimulus and the first cry, have been reported in healthy infants (Grunau et al., 1990; Runefors et al., 2000). In addition, a prolonged first cry, defined as the duration of audible distressed vocalisations with a continuous pattern before a quiet interval of five seconds has also been shown to occur in response to pain (Ramenghi, Griffith, Wood, & Levene, 1996; Runefors et al., 2000). Other crying characteristics studied have included number of cry cycles (Grunau & Craig, 1987; Runefors et al., 2000), plus total duration of crying time during and following painful procedures (Johnston & Strada, 1986; Grunau & Craig, 1987; Grunau et al., 1990; Runefors et al., 2000; Harrison et al., 2002).

Various permutations of physiological parameters and behavioural characteristics occurring in response to procedural pain have been incorporated into composite and multidimensional pain assessment scoring tools. In addition, various combinations of the parameters and behaviours have been used as outcome measures in studies of interventions aimed at reducing pain. Further discussion on the validity, reliability and clinical utility of physiological and behavioural responses utilised in studies of pain in infants is addressed in the ‘measurement of pain and stress’ section of this literature review.

Cumulative outcomes and effects of pain

Although immediate and short-term effects of surgical and procedural pain have been extensively documented since the mid 1980s, there is less known about the longer term implications of early pain experiences. There is uncertainty as to whether consequences of painful events experienced in the neonatal period persist beyond the time of the original injury, and even further into later infancy and into childhood. Much of the work done in systematically evaluating consequences of repeated painful stimuli has been in the province of animal research with results being extrapolated to that of the human newborn; predominantly to infants born prematurely and undergoing repeated painful procedures. Animal studies are important in the investigation of long-term consequences of pain as the animals’ environment, exposure to the chosen stimuli and interventions can be carefully controlled, unlike that of the changing environment and random exposure to noxious stimuli and
interventions experienced by sick infants in a neonatal intensive care unit (Johnston, Walker, & Boyer, 2002). The animal model used almost exclusively in studies relating to pain in the neonatal period has been the newborn rat. Rats have a short lifespan, ranging from one to three years, allowing observation of long-term effects of early pain exposure in a short time. The rat pup is also born more immature than other animals and humans. The neurological development occurring in the postnatal period is considered to developmentally correspond to the central nervous system development in the third trimester of human gestation (Marsh, Hatch, & Fitzgerald, 1997; Johnston, Walker et al., 2002), and the first three weeks of a rat’s life is considered to equate with human development from infancy and childhood through to adolescence (Fitzgerald & de Lima, 2001).

One of the key findings of animal model studies of long-term effects of pain has been of an increased sensitivity to pain following injury inflicted in the neonatal period (Woolf, 1983; Fitzgerald, 2004). Sensitisation in the context of pain refers to the process whereby an increased responsiveness upon repeated exposure to a stimulus occurs with subsequent painful procedures (United States National Library of Medicine & National institutes of Health, 2003). Pain responses may also occur during non-painful stimuli. In one study, designed to model the inflammatory process associated with repeated heel lances in human premature infants, inflammation arising as a consequence of initial inflammatory injury in the neonatal rat’s paw persisted into adulthood (Ruda, Ling, Hohmann, Peng, & Tachibana, 2000).

Another study showed that rat pups exposed to repetitive needle stick injury to the paws during their first week of life, exhibited increased pain sensitivity compared with the control group of rats without such early pain exposure (Anand, Coskun, Thrivikraman, Nemeroff, & Plotsky, 1999). This increased pain sensitivity was seen to persist into adulthood. Also demonstrated in the same study, was that a subgroup of 12 animals exposed to repeated painful stimuli in the neonatal period had a significantly increased alcohol consumption compared to the 11 animals exposed to repeated tactile stimulation only. These differences in pain sensitivity and increased preference for alcohol between the two groups of rats persisted into adulthood, demonstrating long-term consequences of repetitive pain in the neonatal period.
A series of studies examining consequences of early localised injury on the process of skin innervation, illustrates clearly the process by which injury inflicted during the neonatal and early infancy period result in both physical and behavioural alterations in normal development (Reynolds & Fitzgerald, 1995; De Lima, Alvares, Hatch, & Fitzgerald, 1999). Reynolds and Fitzgerald (1995) and De Lima et al. (1999) showed that when skin wounds were inflicted on neonatal and young rats, marked hyperinnervation around the injured area of the paw developed, resulting in increased sensitivity of the surrounding area. Further results of studies of 74 rats in total, showed that both the hyperinnervation and increased sensitivity persisted for more than three weeks following the initial wound, long after the wound itself had healed (Reynolds & Fitzgerald, 1995). Abnormal growth of nerve fibres and increased sensitivity for a prolonged period following the initial injury was not however observed when the injuries were inflicted on the adult rats. Findings of other studies also showed that local tissue injury inflicted during the neonatal period, but not during adulthood, resulted in prolonged increased responses to subsequent noxious stimuli (Torsney & Fitzgerald, 2002; Torsney & Fitzgerald, 2003; Ren et al., 2004). Similarly, long-term or permanent effects have not been demonstrated when the initial injury or series of injuries has been made in adult rats, demonstrating further the plasticity of the immature nervous system and the vulnerability of the developing animal during the neonatal period (Reynolds & Fitzgerald, 1995; Anand, Coskun et al., 1999).

Fitzgerald and Beggs (2001), in summarising the results of the large body of animal studies, highlighted that, in addition to causing distress and delayed recovery, pain in infancy is a developmental issue. Repetitive pain occurring in the newborn period potentially results in alterations in the developing nervous system which can lead to prolonged structural and functional alterations in pain pathways that can last into adult life (Fitzgerald & Beggs, 2001).

Although such carefully controlled studies cannot be undertaken in human infants, findings of observational studies examining outcomes of tissue injury occurring in the neonatal period have also showed increased responses to subsequent mechanical and painful stimuli (Fitzgerald, Millard, & MacIntosh, 1988; Fitzgerald, Millard, & McIntosh, 1989; Andrews & Fitzgerald, 1994; Taddio, Goldbach, Ipp, Stevens, &
Koren, 1995; Taddio, Katz, Ilersich, & Koren, 1997; Anand, 2000a; Taddio, Shah, Gilbert-MacLeod, & Katz, 2002). One of the earliest of these studies involved serial measurements of pain sensitivity in 11 premature infants following repeated heel lancing on one side of the heel (Fitzgerald et al., 1988). Pain sensitivity was measured using calibrated von Frey hairs, a commonly used reliable and easily observable test of flexion withdrawal reflex (Woolf, 1985; Fitzgerald et al., 1989). Findings showed a significantly lower pressure threshold on the injured side of the foot compared to the uninjured side of the foot, demonstrating local tissue hypersensitivity (Fitzgerald et al., 1988). Another study, which included 50 infants with gestational ages at birth ranging from 23 weeks to term, showed that hypersensitivity could be produced in premature infants by repeated mechanical stimulation of the infants’ heel using the fine von Frey hairs (Andrews & Fitzgerald, 1994). Hypersensitivity could not however, be produced in the same manner in the more mature infants over 35 weeks corrected gestational age.

In a series of studies of healthy term infants, Taddio and colleagues also demonstrated abnormally heightened responses to pain subsequent to early pain exposure (Taddio et al., 1995; Taddio et al., 1997; Taddio et al., 2002). In two of these studies, male infants’ responses to routine immunisation, subsequent to circumcision performed in the first week of life, were examined (Taddio et al., 1995; Taddio et al., 1997). The earliest of these two studies was a retrospective analysis of pain responses during immunisation in 42 full-term newborn male infants, of whom 30 (71%) had been circumcised (Taddio et al., 1995). Subsequently, a prospective study of 87 male infants was undertaken of whom 55 (63%) had been circumcised. Of these 55 infants, 29 (53%) were circumcised following application of the topical anaesthetic cream; EMLA®, and 26 (47%) were circumcised with no analgesic agent (Taddio et al., 1997). Results of both studies showed that the infants who had been circumcised in the first few days of life exhibited greater distress during routine immunisation when aged four or six months, than uncircumcised infants (Taddio et al., 1995; Taddio et al., 1997). In the prospective study conducted in 1997, the third group of infants who had been treated with EMLA® prior to circumcision, demonstrated a reduced response to pain during immunisation compared to the infants circumcised with no topical anaesthetic cream, however, an increased response compared to that of the
uncircumcised infants was still observed. The authors concluded that neonatal circumcision with either no or minimal pain relief affected pain responses for several months after the event (Taddio et al., 1995; Taddio et al., 1997).

In a further study including two groups of term newborn infants at three days of age, pain scores during routine venepuncture performed for newborn screening were compared (Taddio et al., 2002). Twenty-one infants of diabetic mothers, who had required frequent blood sampling by heel lancing in the first two days of life, comprised one group. Twenty-one healthy term infants with no such history of repeated heel lances comprised the control group. Findings were that the infants of diabetic mothers, with the history of prior exposure to frequent heel lancing had significantly higher pain scores and increased duration of crying during the venepuncture procedure compared to the control infants with no such early pain exposure. These differences were apparent upon cleansing of the skin with alcohol, and continued throughout the duration of the procedure. This result, attributed by the authors as a central sensitisation to pain (Taddio et al., 2002), clearly illustrates potential consequences of repeated exposure to pain in newborn infants occurring over a relatively short time frame.

In summary, both localised and central hypersensitivity following tissue injury occurring as a result of painful procedures in both premature and term infants has been well demonstrated in the studies presented. However, the evidence of whether such effects or other consequences of cumulative pain persist beyond the neonatal period and the first few months of infancy is less clear. An elegant series of studies, the majority of which were conducted by Grunau and colleagues, have begun to address these questions (Grunau, Whitfield, & Petrie, 1994; Grunau, Whitfield, Petrie, & Fryer, 1994; Johnston & Stevens, 1996; Grunau, Whitfield, & Petrie, 1998; Whitfield & Grunau, 2000; Grunau et al., 2001; Morison, Grunau, Oberlander, & Whitfield, 2001; Grunau, 2002; Grunau, Weinberg, & Whitfield, 2004).

Grunau and colleagues undertook a series of studies comparing pain responses in children born prematurely, with those children born healthy and at term (Grunau, Whitfield, & Petrie, 1994; Grunau, Whitfield, Petrie et al., 1994; Grunau, Whitfield et al., 1998). The first of this series of studies compared parental reports of pain
sensitivity in children at 18 months corrected gestational age (Grunau, Whitfield, & Petrie, 1994). Sensitivity to pain was based on parental report, on a five-point likert scale, of the statement, "Child is very sensitive to burns or cuts or other common hurts" (Page 342). A score of one signified 'not characteristic of their child', whilst the parental score of five, signified 'very characteristic of their child'. Results showed that parents of 124 children who had weighed less than 1000 grams at birth were more likely to have reported low sensitivity to pain in their children, than were parents of both 42 heavier preterm infants and 29 infants born at term. However, the authors acknowledged that the results of decreased sensitivity may have been a reflection of maternal perception rather than actual infant responses (Grunau, Whitfield, & Petrie, 1994).

In another study, parents of two groups of children who had been prospectively enrolled at birth, were interviewed about their child’s pain related complaints when the children were between four and five years of age (Grunau, Whitfield, Petrie et al., 1994). The groups comprised 36 children born prematurely weighing less than 1000 grams, and 36 full-term controls, who had been matched at three years of age on corrected age, gender and mother’s level of education. To score pain-related complaints, parents completed a 30-point somatisation scale which included questions relating to occurrence of pain such as headaches, stomach aches, leg pain and other somatic complaints of unknown origin. There was no reference to the development, or validity or reliability testing of this somatisation scale presented in the report. Grunau, Whitfield, Petrie et al. (1994) reported that the mothers of the prematurely born children rated their child’s somatisation scores significantly higher than did parents of children born at term. However, within the premature cohort, there were large variations in somatisation scores despite there being no differences in actual medical problems, highlighting that, based on the somatisation scale used, there was not necessarily a direct association between prematurity and somatisation scores.

A further comparative study included the same cohort of prematurely born children four years later, when the children were eight to ten years of age (Grunau, Whitfield et al., 1998). The children self-reported their affect and intensity of pain, as well as fear of potential painful events resulting from 24 different painful scenarios, as depicted in drawings from the Pediatric Pain Inventory (Lollar, Smits, & Patterson, 1982). The
scenarios encompassed four settings; Medical, including procedures such as injections; Recreational, including scenarios such as falling off a skate-board; Activities of Daily Living, including pulling off a band-aid, or getting a finger jammed in a door; and Psychosocial, including scenarios such as being laughed at by school friends, or reprimanded by a teacher. Results generally showed little differences between the cohort in the children’s ratings of the drawings, although children born prematurely rated medical pain intensity significantly higher than psychosocial pain, unlike their term counter-parts. Duration of hospitalisation in the neonatal intensive care unit was also related to increased pain ratings occurring as part of recreation and daily living, although there were no differences in self-complaints of actual physical pain between the two groups of children.

A study by another group of researchers compared pain sensitivity in 60 adolescents who were born prematurely, with pain sensitivity in 60 children who were born at term (Buskila et al., 2003). Results showed both a statistically significant increased sensitivity to pain and increased number of painful areas upon palpation in the prematurely born adolescents compared to the adolescents born at term. However, self-reports of prevalence of daily pain, severity of pain and pain-related symptoms such as stiffness and sleep problems did not differ between the two groups. The authors of this study commented that physicians taking care of children born prematurely need to be aware of potentially altered pain sensitivity, so as to recognise exaggerated pain responses to various stimuli and potential future development of pain syndromes.

This collection of studies of long-term outcomes subsequent to exposure to painful and noxious procedures in the neonatal period is important, in that it highlights that early exposure to painful events has the capacity to alter pain experience and perceptions throughout early and late childhood, although there remain uncertainties about exactly how this impacts on the growing child. Despite these uncertainties the available evidence lends credence to the need to both ensure appropriate pain management in infants, as well to continue to measure and evaluate pain-related outcomes in infants exposed to painful invasive procedures.
Research has also been conducted which has focussed on consequences of pain occurring as a result of major surgery in the neonatal period. In one such study, 50 infants who had undergone major surgery within the first three months of life were studied during immunisation at either 14 months or 45 months of age (Peters, Koot, de Boer et al., 2003). In contrast to the findings of Taddio and colleagues (1995, 1997), which were of increased responses during immunisation subsequent to circumcision, Peters, Koot, de Boer et al. (2003) showed that pain responses during immunisation did not differ between children who had undergone surgery in the neonatal period, to the pain responses observed in 50 matched control infants (matched by type of immunisation and the paediatrician administering the injection) who had not undergone previous surgery. However, the authors reported that morphine had been administered according to a standardised protocol to all the infants following major surgery, whereas the infants undergoing circumcision had been administered either no analgesic, or only the topical anaesthetic cream, EMLA® (Taddio et al., 1997). In their discussion, Peters and colleagues acknowledged that the conflicting results may have been due to appropriate analgesics provided to the infants during, and following, major surgery compared with the lack of appropriate analgesics administered during circumcision. The provision of adequate analgesia post-operatively may have been sufficient to prevent altered responses and hyperalgesia to subsequent painful procedures.

It is unclear whether routine systematic provision of appropriate analgesia and comfort measures during early exposure to painful procedures can minimise or prevent adverse short and long-term consequences of pain. Based on available findings suggesting the potential for long-term adverse consequences of cumulative pain in infancy, as well as the lack of studies evaluating outcomes following routine systematic provision of appropriate analgesia, recommendations for further systematic long-term follow up of infants exposed to multiple painful procedures and infants born prematurely have been made (Grunau, Whitfield et al., 1998; Buskila et al., 2003).

As potential adverse effects of pain and its consequences in the newborn have become more evident, health professionals caring for newborn infants have searched for
means of accurately assessing responses to pain so that effective pain and stress reduction strategies can be systematically evaluated. Despite ongoing methodological challenges in the area of accurate measurement of pain in infants (Franck & Miaskowski, 1997; van Dijk, Peters, Bouwmeester, & Tibboel, 2002), a large number of studies have examined various behavioural, physiological and biochemical parameters in attempts to accurately assess pain and to evaluate effectiveness of pain reduction strategies.

Measurement of pain and stress

**Behavioural responses to procedural pain**

Behavioural responses of infants of all gestational ages to procedural pain have been extensively described since the latter part of the 1980s. Specific facial expressions in response to acute noxious stimuli have been most frequently described in the literature (Duhn & Medves, 2004) and are acknowledged as the most specific indicator of pain in infants in response to noxious stimuli (Stevens et al., 1996). The Neonatal Facial Coding System (NFCS) (Grunau & Craig, 1987) is a list of ten specific facial expressions which were described following observation of 140 healthy newborn infants undergoing heel lancing. The NFCS was originally based on a 46-point facial expression score developed for the study of emotional states in adults (Ekman & Friesen, 1978). The specific facial expressions as categorised in the NFCS were subsequently detected in infants of all gestational ages in response to a heel lance procedure (Craig et al., 1993; Grunau, Oberlander et al., 1998), although with less frequency and vigour in the most premature infants compared to the more mature infants (Craig et al., 1993). A number of studies evaluating aspects of validity, reliability and clinical utility of the NFCS have been conducted in various settings, including a comparative study with the original 46-point Facial Action Coding System (Craig, Hadjistavropoulos, Grunau, & Whitfield, 1994), an investigation of the validity of the scale in the post-operative setting (Peters, Koot, Grunau et al., 2003), and investigating the feasibility for clinical use at the bedside (Rushforth & Levene, 1994; Grunau, Oberlander et al., 1998; Harrison et al., 2002). A limited subset of four of the original ten NFCS facial expressions has been reported to occur most frequently as a result of a heel lance procedure. ‘Brow bulge’, ‘eye squeeze’, ‘naso-labial furrow’ and ‘open lips’ were observed in 99% of infants studied within six seconds of
instigation of the heel lance (Grunau & Craig, 1987). This subset of the four most frequently occurring facial expressions forms the basis for many composite pain assessment tools developed for pain assessment in infants.

Body movements in response to procedural pain have also been systematically evaluated in both preterm and full term infants (Craig et al., 1993; Holsti et al., 2004). The Infant Body Coding System (IBCS), categorised by Craig et al. (1983), comprises a number of hand and foot movements, limb movements, finger splay, hand clenching and head and torso movements. A number of limitations to the use of body movements as a measure of procedure-related pain and stress in infants have been identified. In contrast with facial expressions, body movements have been shown to be less specific in response to acute procedural pain, and also reduced in preterm infants relative to full term newborns (Craig et al., 1993). In addition, when a subset of the IBCS was tested at the bedside to assess procedure-related pain, poor inter-rater agreement was demonstrated (Harrison et al., 2002). Furthermore, there is sufficient evidence to support developmental care practices of swaddling or holding infants when feasible during procedures (Corff, Seideman, Venkataraman, Lutes, & Yates, 1995; Fearon, Kisilevsky, Hains, Muir, & Tranmer, 1997; Ward-Larson, Horn, & Gosnell, 2004), thus preventing unobstructed observation of body movements. Thus, body movements are less reliable and less specific to acute pain, and less clinically feasible as a measurement of responses to procedural pain in infants, than facial expressions.

Sick infants’ crying characteristics have also been studied in response to noxious stimuli and procedural pain. In the 1970s, Michelsson and colleagues first described crying characteristics of healthy infants and premature infants, and in addition, compared crying characteristics of well infants to that of sick infants and infants with neurological abnormalities (Michelsson, 1971; Michelsson et al., 1977a; Michelsson, Sirvio, & Wasz-Hockert, 1977b). Results of these studies demonstrated that sick infants, and those with neurological abnormalities, generally had a higher pitch of cry and shorter duration of cry in response to painful procedures when compared with well infants. Further descriptive studies of crying characteristics, evaluating both acoustic and temporal characteristics of infants’ cries have been conducted more recently (Johnston & Strada, 1986; Grunau & Craig, 1987; Grunau et al., 1990; Fuller,
Fuller (1999), Goberman and Robb (1999), Lenti Boero (1998) and Clarici et al. (2002) all reported that the cries of healthy infants during heel lancing had a higher pitch than that observed during periods of hunger or fussiness. Grunau et al. (1990) observed a similar finding; of a higher pitch cry in association with a painful procedure (intra-muscular injection) compared to pitch of cry during non-invasive procedures (alcohol swab or umbilical cord care). Runefors et al. (2000), in their analysis of acoustic characteristics of infants’ cries in response to heel lancing, reported that crying was high pitched immediately upon heel lance, and reduced in pitch over the course of the procedure.

Much has been learnt through analyses of acoustic crying properties in healthy and sick infants in response to pain and other noxious stimuli. However, the requirement for specialised equipment and computer software, which is not readily available in most clinical settings, precludes routine use of acoustic analyses of infants’ cries in studies of pain responses in the clinical setting. Temporal crying characteristics may also elicit important information in regards to infants’ responses to procedure-related pain, and are easily observable and measurable in the clinical setting. Temporal crying characteristics include cry latency, defined as time between the painful stimulus and the first cry (Grunau et al., 1990; Runefors et al., 2000), duration of first cry, defined as the duration of audible distressed vocalisations with a continuous pattern before a quiet interval of five seconds (Ramenghi, Griffith et al., 1996), number of cry cycles (Grunau & Craig, 1987), as well as total duration of crying time during and following painful procedures (Johnston & Strada, 1986; Grunau & Craig, 1987; Grunau et al., 1990; Runefors et al., 2000).

Infants’ cry characteristics elicit important information, and can be an objective and useful measure in studies evaluating pain reduction strategies. However, many factors other than acute pain may cause infants to cry. Crying is not an “accurate” pain measurement in isolation, is not unique to pain, and also needs to be evaluated in light of the infant’s condition (Fuller, 1991; Carbajal, Chauvet, Couderc, & Olivier-Martin,
1999) and sleep/wake states (Grunau & Craig, 1987). In addition, some infants do not always cry in response to known painful procedures, crying characteristics may be altered in a sick infant, may be unable to be assessed in an intubated infant, and may vary widely from infant to infant at any given time. One study showed a low incidence of crying in a group of premature infants in response to heel lancing (Stevens et al., 1996), whilst another showed that incidence of crying was higher in the smaller and sicker premature infants compared to their more mature and less sick counterparts (Johnston, Sherrard et al., 1999). In summary, crying characteristics have been shown to be extremely variable between infants, yet, if infants have a capacity to audibly cry, temporal crying characteristics in response to a known acute painful procedure, remain useful, objective and clinically feasible measures of distress when used in conjunction with facial expressions (Grunau et al., 1990; Runefors et al., 2000).

As aptly summarised by Franck and Miaskowski (1997, p.371), “The accurate interpretation of behavioural responses to painful stimuli remains problematic.” Health professionals have not developed sufficiently reliable and clinically feasible ways to take into account factors such as severity of illness and previous exposure to painful stimuli or previous administration of analgesics or sedatives, all of which may affect the way in which sick and premature infants respond to pain (Franck & Miaskowski, 1997). Yet, due to the limited means of assessing pain in infants, the inclusion of behavioural responses remains necessary in the ongoing investigation of pain measurement in infants.

**Physiological responses to procedural pain**

Various physiological responses to procedural pain have also been systematically evaluated. Systematic evaluation of heart rate, respiratory rate and oxygen saturation levels have provided much objective information about infants’ responses to painful and noxious stimuli, however, these parameters have limited meaning when interpreted as an isolated measure of pain. Their applicability is limited by lack of specificity as changes in these physiological parameters may also occur in response to illness and cardiorespiratory compromise, as well as in response to pain and stress (Stevens & Franck, 1995). Many alternative approaches have therefore been trialed in the search for objective, specific, physiological measures of responses to pain in
infants. Included in this list are; heart rate variability (Porges, 1992; McIntosh et al., 1993; Lindh, Wiklund, Sandman, & Hakansson, 1997; Oberlander et al., 2000; Grunau et al., 2001; Morison et al., 2001; Oberlander & Saul, 2002); skin blood flow or skin conductance changes (McCulloch, Ji, & Raju, 1995; Storm, 2000; Storm, 2001b; Storm & Fremming, 2002); cerebral blood oxygenation changes or intracranial pressure changes (Stevens, Johnston, & Horton, 1993; Stevens & Johnston, 1994; Gagnon, Leung, & Macnab, 1999) and electroencephalographic changes (Fernandez et al., 2003).

Heart rate variability (HRV), or vagal tone, has been promoted as a more specific measure of pain and stress in infants and children than the measure of heart rate alone (Porges, 1992; McIntosh et al., 1993; Johnston et al., 1995; Lindh et al., 1997; Oberlander et al., 2000; Grunau et al., 2001; Morison et al., 2001; Oberlander & Saul, 2002). HRV is defined as the length of time between each heart beat, or the interbeat interval (Smith, 2003). Although heart rate itself is under both sympathetic and parasympathetic nervous system control, HRV is believed to reflect more specifically the parasympathetic effect on the heart rate (Porges, 1992; Franck & Miaskowski, 1997), thereby considered to be more closely associated with stress. Using various parameters of HRV as a means to examine infants’ responses to painful or stressful procedures, HRV has been shown to decrease in response to heel lanceting (Lindh et al., 1997) and endotracheal intubation (Bhutada, Sahni, Rastogi, & Wung, 2000). HRV has been used as one of the physiological outcome measures in studies of interventions aimed at reducing pain or stress in both premature infants (Smith, 2003; Boyer, Johnston, Walker, Filion, & Sherrard, 2004) and three-month old infants during immunisation (Lindh, Wiklund, Blomquist, & Hakansson, 2003). Although HRV is reported to be promising as a more specific and more sensitive measure of stress than gross heart rate changes (Smith, 2003), it is a complex measure with multiple methods of quantification and interpretation (Berntson et al., 1997). Further studies examining feasibility and clinical utility are warranted before HRV is conceivably able to be routinely and widely used in the clinical research setting.

Skin blood flow has also been evaluated as an objective method of measuring pain and stress in response to noxious and painful procedures (McCulloch et al., 1995; Moustogiannis, Raju, Roohey, & McCulloch, 1996). Skin blood flow is measured
using laser Doppler flowmetry to continuously measure abdominal skin perfusion. McCulloch et al. (1995), measured skin blood flow changes in 15 premature infants during 145 NICU procedures including heel lance, nursing care, endotracheal tube suctioning and chest physiotherapy. Results of their study showed a substantial sudden increase in blood flow upon commencement of all procedures with the exception of endotracheal tube suctioning, when a closed suction system was in use. McCulloch et al. (1995) also reported that, following administration of a single dose of 0.1mg/Kg of morphine, skin blood flow was significantly attenuated. In a subsequent observational study, Moustogiannis et al., (1996) utilised skin blood flow as a method of pain assessment during insertion of percutaneous central venous catheters. Recordings of 19 procedures in 18 infants took place, in which morphine was administered prior to the procedure in ten instances. Although the results need to be interpreted with caution due to the small numbers of infants participating in the study, the findings were of a sudden elevation in skin blood flow with large variability in the response during the procedure in six of the eight infants who had not received morphine. In contrast, there was minimal variability in skin blood flow and minimal increase from baseline during the catheter insertion observed in the infants administered morphine. This method of measuring stress in infants seems promising as a useful non-invasive physiological indicator which could potentially be used in sick infants, and indeed, the authors of both studies claimed that skin blood flow has potential as a useful physiological indicator of pain and stress (McCulloch et al., 1995; Moustogiannis et al., 1996). However, the lack of publication of further studies of skin blood flow in response to NICU procedures precludes further appraisal of the validity, reliability and feasibility of this potentially useful method of measuring pain in infants.

In recent years, various parameters of skin conductance has been reported to be a useful, valid, non-invasive physiological measure of pain and stress in both premature and term infants, which is unaffected by cardiorespiratory status (Storm, 2000; Storm, Fremming, Odegaard, Martinsen, & Morkrid, 2000; Storm, 2001b; Hellerud & Storm, 2002). Skin conductance is the measure of the psychogalvanic reflex response due to activation of the sympathetic nervous system in response to stress, resulting in filling of the palmar and plantar sweat glands (Grimnes, 1982; Gladman & Chiswick, 1990). Each time the sympathetic nervous system is activated, the palmar and plantar sweat
glands are filled and the ionic properties of perspiration increase the electrodermal activity of the skin, causing a spontaneous wave of increased skin conductance (Gladman & Chiswick, 1990).

Although early reports suggested that the psychogalvanic response did not occur in response to stress until infants were around eight weeks of age (Kuno, 1956), more recent reports demonstrated palmar and plantar water loss in newborn term infants in response to heel lancing (Harpin & Rutter, 1982; Gladman & Chiswick, 1990). Since 2000, technical advances in skin conductance activity measurement and methods of analysis has resulted in skin conductance changes, in response to pain and stress, being reported in infants as immature as 29 weeks gestational age (Storm, 2000; Storm, 2001a, 2001b; Hellerud & Storm, 2002). Storm (2000) reported a sudden rise in skin conductance activity occurring in infants in response to heel lancing, which decreased slowly back to pre-baseline levels and Hellerud and Storm (2002) showed an increase in skin conductance activity occurring both in response to heel lancing and to sensory stimulation in premature and newborn term infants.

Despite the potential for skin conductance to be a useful measure of pain and stress in premature and term infants, the measurement of skin conductance has continued to remain in the province of a small number of research studies. Further studies systematically evaluating this potentially objective, reliable and specific measure of pain and stress need to be conducted before skin conductance is incorporated into routine clinical research and bedside monitoring in newborn infants.

Cerebral blood oxygenation changes; measured non-invasively by near infrared spectrophotometry; in response to painful procedures and noxious environmental stimuli, were also evaluated in a pilot study of ten ventilator-dependent infants (Gagnon et al., 1999). Frequent and considerable variation in cerebral blood oxygenation was observed in response to noise occurring during conversations, opening incubator doors and electronic paging sounds, as well as in response to nursing care and heel lance procedures. The authors commented that the frequent variations in response to high noise levels and nursing care was of concern, especially as most of the incidents which resulted in cerebral oxygenation changes, were not detected clinically. However, the small numbers of infants in the study severely limit
the generalisability of the results. In addition, the feasibility of using such a method of physiological monitoring in routine practice in the NICU is questionable. Regardless of these limitations, the authors suggested that routine non-invasive monitoring of cerebral oxygenation changes could be a valuable way in which to monitor the high-risk environment of a NICU (Gagnon et al., 1999).

Intracranial pressure, as measured non-invasively via the fontanel, has also been evaluated as a measure of pain and stress in premature infants in a NICU. Results of two such studies conducted in infants between 32 and 34 weeks gestational age showed a consistent pattern of increase in intracranial pressure following heel lancing, which was sustained throughout the duration of the blood collection (Stevens et al., 1993; Stevens & Johnston, 1994). The authors however, reported a large variation in this response at all time points during the heel lance procedure. In commenting about the utility of intracranial pressure monitoring, Stevens et al. (1993) stated that the measurement may lack both sensitivity and specificity to pain. As no further studies evaluating either cerebral blood oxygenation or intracranial pressure as indicators of pain or stress in infants have been identified, it would seem that these physiological methods of pain and stress evaluation, similar to that of skin blood flow, are destined to remain in the province of pilot study research without any further rigorous evaluation.

Numerous biochemical markers have also been evaluated in the search for objective, specific methods by which pain and stress can be monitored in neonates and infants. Such biochemical markers of stress have included release of hormones such as cortisol, adrenalin, noradrenalin, growth hormones, and endorphins. Of these, cortisol has been one of the most frequently assayed stress hormones in infants (Franck & Miaskowski, 1997). Serum cortisol levels have been shown to increase following surgery (Anand et al., 1985; Anand et al., 1987; Anand & Hickey, 1987; Anand & Aynsley-Green, 1988; Anand & Carr, 1989; Anand, 1990), in response to endotracheal tube suctioning and in response to routine nursing care (Pokela, 1994; Pokela & Koivisto, 1994). Serial measurements of serum cortisol levels were also reported to be higher in sick and premature infants compared to healthy term and premature infants over the first month of life (Economou, Andronikou, Challa, Cholevas, & Lapatsanis, 1993). However, the requirement for a blood collection for
measurement of serum cortisol levels, which is in itself a painful procedure, limits the utility of this marker of stress. Salivary cortisol, which is sufficiently correlated with serum cortisol levels, has been proposed as a less invasive method of monitoring cortisol levels (Umeda et al., 1981).

Umeda and colleagues reported a high positive correlation between cortisol levels in saliva and in serum of healthy adults, subsequently recommending salivary cortisol as a valid proxy of serum cortisol (Umeda et al., 1981). Subsequent studies comparing salivary and serum cortisol levels in preterm and term infants have demonstrated moderate to high correlation (Francis et al., 1987; Gunnar, Connors, & Isensee, 1989; Kurihara et al., 1996; Peters, 2001; Calixto, Martinez, Jorge, Moreira, & Martinelli, 2002). Salivary cortisol has also been used in studies examining infants’ responses to painful procedures. However, an increase in salivary cortisol levels in response to painful or stressful procedures has been demonstrated in some studies (Lewis & Thomas, 1990; Kurihara et al., 1996; Felt et al., 2000), although not in others (Gunnar et al., 1989; Joyce, Keck, & Gerkensmeyer, 2001; Greenberg, 2002). Conflicting results have been attributed to the type of stimulus, the mode of delivery of the infant (Gunnar et al., 1989) and the number of previous exposures to the same stimulus (Gunnar, 1989; Gunnar et al., 1989; Gunnar, Hertsgaard, Larson, & Rigatuso, 1991).

There are conflicting published reports relating to the ease of collection of sufficient amounts of saliva from infants for cortisol assay. In one study, the procedure was reported as being simple to undertake (Chang, Anderson, & Wood, 1995), whilst in others, difficulties have been reported in obtaining adequate amounts of uncontaminated saliva for analysis (Ben-Aryeh, Lapid, Szargel, Benderly, & Gutman, 1984; Joyce et al., 2001; Herrington, Olomu, & Geller, 2004). Improved techniques for analysing salivary cortisol, requiring collection of smaller volumes of saliva compared to the volumes required using older methods of assay, have been reported (Nelson, Arbring, & Theodorsson, 2001; Morelius, Nelson, & Theodorsson, 2004). Although elevated cortisol levels can be one of the many ways in which pain and stress is infants is demonstrated, the conflicting and wide variability of responses, and the various difficulties in obtaining adequate volumes of saliva for analysis, limit this biochemical marker as a clinically feasible and reliable measure of pain and stress.
Despite promising findings of objectivity of many of the physiological and biochemical measures of pain and stress evaluated in infants, most measures have remained in the realm of relatively small research studies, rather than routine clinical practice. This is in all probability due to insufficient establishment of clinical utility, reliability and validity in a sufficient number of sick infants.

In addition to the individual behavioural, physiological and biochemical indicators used in both the research and clinical setting to assess pain and stress in infants, a considerable number of combinations of these indicators have been grouped into composite pain scoring systems. In a review of pain assessment methods, 35 pain assessment tools were identified which were deemed appropriate for the assessment of pain in neonates and infants (Duhn & Medves, 2004). The basis of most of these pain assessment tools is similar; a combination of behavioural indicators, including crying characteristics, facial expressions, various body movements, and various physiological parameters. Additional indicators included less frequently in composite pain assessment tools include sleep characteristics such as sleep pattern or quality (Barrier, Attia, Mayer, Amiel-Tison, & Shneider, 1989; Hodgkinson, Bear, Thorn, & van Blaricum, 1994; Joyce et al., 1994; Krechel & Bildner, 1995; Buchholz, Karl, Pomietto, & Lynn, 1998; Debillon, Zupan, Ravault, Magny, & Dehan, 2001), consolability (Barrier et al., 1989; Joyce et al., 1994; Pokela, 1994; Buchholz et al., 1998; Debillon et al., 2001; Breau, Finley, McGrath, & Camfield, 2002), contextual factors, such as gestational age and behavioural state (Stevens et al., 1996; Hummel, Puchalski, Creech.S, & Weiss.M, 2003) and nurses’ perception of the presence or absence of pain (Hodgkinson et al., 1994). Reliability, validity, clinical utility and feasibility have been established to varying degrees for many of the 35 or more assessment tools used in the context of neonatal pain measurement. However, no single tool has been widely accepted as the gold standard and sufficiently sensitive and specific to be accepted into routine clinical practice for measurement of pain in all situations (van Dijk et al., 2002; Duhn & Medves, 2004).

The compilation of behavioural, physiological and biochemical parameters trialled, as well as the large number of composite pain assessment scores developed for use in infants to measure responses to painful and stressful procedures, highlights the ongoing search by health professionals for reliable, specific, sensitive parameters.
which can be used to quantify pain and/or stress in newborn infants. The inclusion of heart rate, oxygen saturation, blood pressure and respiratory pattern remain the physiological parameters used most frequently and consistently to assess pain, with most composite pain assessment scores for infants including one or more of these parameters within their scoring systems. These physiological parameters are likely to be available for use at the bedside in most clinical situations, especially in neonatal intensive care settings. In terms of behavioural responses to procedure-related pain, facial expressions remain the most specific indicator used for the measurement of pain in infants, and are incorporated into most composite and multidimensional pain assessment tools. Crying characteristics, although unable to be measured in infants who are intubated, remain a useful and objective measure, which are also incorporated into many pain assessment tools. Combinations of these parameters have been commonly utilised as outcome measures in studies of the efficacy of various pain reduction strategies in infants.

Procedural pain reduction strategies

Many strategies aimed at reducing pain and stress during procedures and over the course of an infant’s hospitalisation have been explored over the years. This exploration has become increasingly important as potentially harmful effects of untreated pain in sick newborn and young infants have been identified. Pharmacological strategies such as exogenous opioids, topical anaesthetic agents, paracetamol (acetaminophen), as well as oral sucrose have been studied to various degrees, as have non-pharmacological strategies such as feeding during procedures, kangaroo care (KC), non-nutritive sucking (NNS), music therapy and developmentally supportive strategies such as swaddling.

Pharmacological agents for the reduction of procedure-related pain

Opioid administration

The analgesic and sedative effects of both naturally occurring and synthetic opioids in infants undergoing surgery have been well demonstrated (Anand et al., 1987; Anand, 1990; Anand & Hickey, 1992) and consequently, opioid analgesics are routinely administered to neonates and infants during and following surgical procedures (De
Lima et al., 1996). Although the administration of opioid analgesics have been considered an important aspect of therapy for premature and term infants requiring assisted ventilation (Menon, Anand, & McIntosh, 1998; Anand, Barton et al., 1999; Larsson, 1999; Anand & International Evidence-Based Group for Neonatal Pain, 2001), there are uncertainties regarding both the efficacy and safety of opioid analgesics in premature and sick infants in the reduction of pain and stress during such periods of assisted ventilation as well as during invasive procedures occurring during the course of a critical illness.

Although reduced pain responses in association with morphine administration during minor procedures have been demonstrated in some studies (Pokela, 1993, 1994; Moustogiannis et al., 1996; Anand, Barton et al., 1999; Scott et al., 1999), other findings obtained predominantly from more recent evidence suggests that morphine has either minor, or no analgesic effects during minor painful procedures (Franck et al., 2000; Simons, van Dijk et al., 2003; Anand et al., 2004). In addition, there are conflicting findings regarding the role of continuous intravenous morphine in premature infants, in reducing dangerous cerebral blood flow changes, and therefore reducing the risk of subsequent neurological abnormalities, occurring as a result of painful and distressing procedures (Anand, Barton et al., 1999; Anand et al., 2004).

Results of a pilot study, in which 67 premature infants requiring assisted ventilation were randomised to one of three groups to receive continuous infusions of morphine, or the sedative agent, midazolam or placebo, demonstrated both short and long-term benefits of morphine (Anand, Barton et al., 1999). Premature infants randomised to receive morphine demonstrated lower pain scores during and following endotracheal tube suction, as well as a reduction in the incidence of poor neurological outcomes compared with the infants receiving either midazolam or placebo solutions. However, contrasting results were obtained from a subsequent large multi-centre, randomised, controlled trial; the Neurologic Outcomes and Pre-emptive Analgesia in Neonates (NEOPAIN) trial, in which almost 900 infants between 23 and 32 weeks gestational age were randomised to receive a continuous infusion of either morphine or placebo (Anand et al., 2004). Overall results showed no differences in neurological outcomes, as defined by severe intraventricular haemorrhage, or periventricular leucomalacia, or death rates between the two groups. Contrasting results between the original pilot
study and the large multi-centre randomised, controlled trial may be attributed to differences in the design and sample size of the two studies, with the larger multi-centre trial having adequate power to detect statistically significant differences in neurological outcomes between the two groups of infants (Anand et al., 2004). Despite the lack of overall differences in the composite outcomes (death, severe intraventricular haemorrhage, or periventricular leucomalacia) between the morphine treated infants and the placebo treated infants in reported in the NEOPAIN) trial (Anand et al., 2004), there was a concerning finding of a higher risk of severe intraventricular haemorrhage in the middle aged group of infants, those between 27 and 29 weeks gestational age. There were twice as many infants in the morphine treated group with severe intraventricular haemorrhage (12% versus 6%). The authors acknowledged the higher risk of hypotension in this age group, as a result of the higher dose of morphine used (20µg/kg/hr) compared to the 10µg/kg/hr morphine dose used for the more premature infants. Hypotension did in fact occur more frequently in the morphine group, both at the end of the 100µg/kg bolus infusion given over one hour, and at 24 hours after the morphine infusion had been running. The authors in their conclusion, recommended judicious and cautious of continuous morphine infusions in premature infants, as indicated by severe pain.

Findings of a study of neuro-developmental outcomes in a cohort of children aged five to six years, who as premature infants had been participants in a randomised, controlled trial of morphine or placebo, found no statistically significant differences in outcomes between the two groups of children (MacGregor, Evans, Sugden, Gaussen, & Levene, 1998). The authors however, commented that a trend towards improved outcomes in the cohort who had received morphine was evident. In another study, in which a retrospective review of over 1100 records of premature infants in six different NICUs in the United States of America was undertaken, no differences in incidence of intraventricular haemorrhage between infants who had been randomised to receive morphine or placebo were demonstrated (Kahn et al., 1998). Despite recommendations to administer continuous opioid analgesics to premature infants on the basis of potential benefits and ethical and humane grounds (Taddio, 2002), there is a paucity of data concerning both safety and efficacy of opioid administration in sick hospitalised newborns, and for long-term management of procedural and disease-related pain in infants with complex medical conditions.
Paracetamol

There is also a paucity of data relating to the efficacy of paracetamol in sick hospitalised infants. The analgesic efficacy of enterally administered paracetamol (acetaminophen), in newborn and young infants has received little research attention despite being widely used in this population (Penna, Dawson, & Penna, 1993; Anderson, Anderson, & Hastie, 1996; Dawson, McIlvenny, Quinn, & Harron, 1996; Arana, Morton, & Hansen, 2001; Lamb & Henry, 2004). Findings from the few studies which have included newborn and young infants have generally shown little analgesic benefit of paracetamol [Macke, 2001 #853; van Lingen, 2001 #632; Shah, 1998 #73; Howard, 1994 #633; Bremerich, 2001 #697; van Lingen, 1999 #852]. Situations in which analgesic effects of enteral paracetamol in neonates have been evaluated in randomised, controlled, trials are; following delivery by vacuum extraction [van Lingen, 2001 #632], prior to capillary blood sampling (Shah et al., 1998) and prior to circumcision (Howard et al., 1994). In these three paracetamol trials, allocation of the treatment condition was well blinded and power calculations to determine sample size had been performed. Despite the different clinical situations and the different methods of pain assessment used, results of the three trials were similar; showing nil or minimal analgesic benefits of enterally administered paracetamol.

A study which compared analgesic efficacy of four different doses of rectally administered paracetamol when dispensed to infants and young children immediately prior to surgery for repair of cleft palate, also failed to show significant differences in the early post-operative period (Bremerich et al., 2001). In addition, Bremerich et al. (2001) reported that both single and multiple doses of paracetamol also failed to reduce opioid analgesic requirements. The failure of any significant analgesic effects of paracetamol may have been due to the route of administration, as rectally administered paracetamol in neonates and infants is known to be poorly or erratically absorbed and higher doses are required to achieve therapeutic plasma levels and consequently, adequate analgesia [Bremerich, 2001 #697; Hansen, 1999 #698; Lin, 1997 #700; Anderson, 1998 #699; van Lingen, 1999 #136]. In fact, rectally administered paracetamol doses of 30 mg/Kg followed by doses of 20 mg/Kg at six to
eight hour intervals have been recommended in order to reach therapeutic concentrations (van Lingen et al., 1999).

Despite the dearth of high quality evidence to support the use of paracetamol in newborn and young infants, paracetamol is commonly prescribed and administered in hospital settings to infants and young children (Anderson et al., 1996; Dawson et al., 1996; Arana et al., 2001; Lamb & Henry, 2004). No studies have been identified to date which address the use of paracetamol in infants with complex health needs, requiring long-term hospitalisation.

*Topical anaesthetics*

Analgesic effects of topical anaesthetic agents in neonates and infants have been evaluated during minor invasive procedures in a number of studies in the last decade. Results of a systematic review (Taddio, Ohlsson, Einarson, Stevens, & Koren, 1998), and randomised, controlled trials published since the systematic review, showed that topical anaesthetic agents had no analgesic effects during heel lancing (Rushforth, Griffiths, Thorpe, & Levene, 1995; Stevens, Johnston, Taddio et al., 1999), variable analgesic effects during lumbar puncture (Enad, Salvador, Brodsky, & Hurt, 1995; Taddio et al., 1998; Kaur, Gupta, & Kumar, 2003), and no or minimal analgesic effects during insertion of percutaneous catheters (Ballantyne, McNair, Ung, Gibbins, & Stevens, 2003). In regards to analgesic benefits of topical anaesthetic agents during the procedure of venepuncture, findings are inconclusive. Results of a blinded, randomised controlled trial which included 120 healthy full term infants, showed that the topical anaesthetic cream EMLA® resulted in reduced facial expression scores immediately following the needle insertion, but did not result in reduced duration of crying throughout the procedure (Larsson, Tannfeldt, Lagercrantz, & Olsson, 1998).

The result of another blinded, randomised, controlled trial showed that amethocaine gel was more effective than placebo in reducing pain during venepuncture in newborn infants over 32 weeks gestational age (Moore, 2001). Considerable limitations to this study by Moore were however evident, including a failure to report or display any actual pain responses, other than to report a statistically significant P value of <0.01. In addition, no power analysis was reported and the sample size was small,
comprising 20 infants in each of the two groups. In contrast to the findings reported by Moore, findings of another blinded randomised, controlled trial which included 60 healthy newborn infants, demonstrated that EMLA® was ineffective in reducing behavioural responses during venepuncture (Lindh, Wiklund, & Hakansson, 2000). However, as discussed by the authors, all infants had been fed within the previous hour, and all infants were held in their parents’ arms during the procedure. These non-pharmacological strategies may have had a greater effect than EMLA® in reducing behavioural responses during the procedure. A statistically significant attenuation in heart rate response in the infants in the EMLA® group was however reported in that study (Lindh et al., 2000). In contrast, a small placebo controlled, cross-over trial which included 19 medically stable premature infants undergoing venepuncture failed to show any analgesic benefits of EMLA® (Acharya, Bustani, Phillips, Taub, & Beattie, 1998), although the small numbers of participating infants may have been insufficient to detect any statistically significant differences in any outcome measurements between the two conditions. The analgesic efficacy of EMLA® has also been compared to both oral sucrose (Abad et al., 2001) and oral glucose (Gradin, Eriksson, Holmqvist, Holstein, & Schollin, 2002). Both of these studies were blinded, randomised, controlled trials, and in both trials, sample size calculations were performed, blinding of allocation was complete and combinations of physiological and behavioural outcome measures were used. Results of both studies showed that the sweet tasting solutions were more effective in reducing pain during venepuncture than EMLA®. In addition, Abad et al. (2001) showed that concomitant use of EMLA® with oral sucrose was no more effective than oral sucrose alone.

Analgesic efficacy of topical anaesthetic agents during immunisation, in infants up to two years of age have however, been clearly shown in four blinded, randomised, controlled trials (Uhari, 1993; Taddio, Nulman, Goldbach, Ipp, & Koren, 1994; Halperin, McGrath, Smith, & Houston, 2000; Halperin, Halperin, McGrath, Smith, & Houston, 2002). All four trials included sufficient numbers of infants based on sample size calculations, ranging from 96 up to 160 infants. In a further randomised controlled trial, a combination of EMLA® and oral glucose, compared to placebo cream and oral water, was evaluated during immunisation in 90 infants, at three months of age (Lindh et al., 2003). Results clearly showed that both behavioural and
physiological responses to the immunisation were significantly reduced in the infants who had received the combination of EMLA® and oral glucose compared to the control group who received placebo cream and water.

Aside from the conflicting findings of the analgesic effectiveness of topical anaesthetic agents in newborn premature and term infants undergoing various painful procedures, there are safety concerns regarding the use of such products in young infants. Safety concerns arose following a small number of case reports describing dangerous levels of serum methaemoglobin levels in young infants following application of topical anaesthetic agents (Kumar, Dunn, & Naqvi, 1997; Sinisterra, Miravet, Alfonso, Soliz, & Papazian, 2002). Yet, in other studies, safe levels of methaemoglobin following both single and repeated doses of topical anaesthetic agents in both preterm and term infants were reported (Taddio et al., 1998; Essink-Tebbes, Wuis, Liem, van Dongen, & Hekster, 1999; Stevens, Johnston, Taddio et al., 1999), and importantly, methemoglobinemia has not been reported when EMLA has been used as recommended (Stevens, Johnston, Taddio et al., 1999). However, due to the risk of methemoglobinemia, especially when co-administered with paracetamol (American Academy of Pediatrics Committee on Drugs, 1997), EMLA® is not recommended for use for infants less than six months of age (Donohoo, 2004). Despite such recommendations, and despite inconsistent reports regarding the analgesic efficacy of topical anaesthetic agents during most minor procedures in infants, national and international guidelines concerning pain management in infants have included topical anaesthetic creams as one of the recommended strategies for the reduction of procedure-related pain in newborns (American Academy of Pediatrics & Canadian Paediatric Society, 2000; Anand & International Evidence-Based Group for Neonatal Pain, 2001).

In summary, there is conflicting research evidence in relation to both the efficacy and safety of topical anaesthetic agents in young infants, yet the agents are promoted in the clinical setting as one of the available strategies to use in the reduction of procedural pain. There are no published reports of actual rates of utilisation of topical anaesthetic agents during painful procedures in neonates and infants, therefore the degree to which topical anaesthetic agents are used in clinical practice is not known.
Alternative methods to heel lancing

As heel lancing is known to be a painful procedure, venepuncture, as an alternative method of blood collection, has been investigated. Evidence from four trials included in a systematic review of venepuncture compared to heel lance did indeed show that in a term infant population, venepuncture, when performed by a skilled phlebotomist, resulted in less pain responses compared to heel lancing (Shah & Ohlsson, 2004). However, due to difficulties in obtaining intravenous access in sick hospitalised infants who require many blood tests and intravenous catheters over the course of their hospitalisation, heel lancing currently remains the principal method of blood collection for premature and sick infants.

Non-pharmacological strategies for the reduction of procedure-related pain

In addition to the studies evaluating the analgesic efficacy of pharmacological agents during minor painful procedures, there are a number of non-pharmacological strategies which have been evaluated for their stress and pain-reducing benefits in newborn infants. Skin to skin contact, or kangaroo care (KC), is one such non-pharmacological strategy which has been studied in the context of procedural pain reduction in healthy term newborn infants (Gray, Watt, & Blass, 2000) and medically stable preterm infants (Johnston et al., 2003). The mechanism involved is thought to be due to the combination of maternal heart-beat, maternal voice, rocking, containment (Ludington-Hoe & Swinth, 1996) or increased release of the hormone, oxytocin as a result of chest wall stimulation during skin-to-skin contact (Sofroniew, 1983; Lund et al., 2002). Lund et al. (2002) reported that the hormone oxytocin is involved in analgesia by means of specific areas of pain modulation in the brain and its close association with the endogenous opioid system. The analgesic mechanism involved is considered to be similar to that involved in massage; one of the oldest methods used to promote a feeling of well-being and alleviation of pain (Haldeman, 1999).

Statistically significant reductions in behavioural and physiological responses during heel lancing when KC has been employed, compared to control conditions, have been demonstrated in two studies (Gray et al., 2000; Johnston et al., 2003). Gray et al. (2000) conducted a randomised, controlled trial in which 30 healthy term newborn
infants were enrolled. The authors reported that 30 participants were required, based on a power calculation, on the basis of a “clinically significant reduction in grimacing and crying” (p. 2). However, what was actually considered a clinically significant reduction was not reported, making it difficult to reliably interpret the results of the trial. The crossover study by Johnston et al. (2003) included 74 medically stable infants between 32 and 36 weeks gestational age in the first ten days of life. Despite the possible methodological limitations of the small sample size in the trial conducted by Gray et al. (2000), which potentially mitigates the reliability of the findings, in both the studies, kangaroo care was recommended as a potential effective and safe strategy which could be easily implemented (Gray et al., 2000; Johnston et al., 2003).

As all infants included in the two KC studies were medically stable, the research findings cannot necessarily be generalised to a population of sick infants undergoing invasive procedures in a NICU. Further research examining both efficacy and feasibility of KC is warranted in sick infants before this intervention can be widely recommended in the clinical setting as an effective strategy to reduce procedure-related pain in the NICU.

A number of other non-pharmacological developmentally supportive strategies aimed at the reduction of procedural pain have been evaluated in infants. The strategy of containment, by means of tucking or swaddling has been evaluated during the procedures of heel lancing (Campos, 1989; Corff et al., 1995; Faron et al., 1997), endotracheal suction (Ward-Larson et al., 2004) and immunisation (Campos, 1989). The analgesic efficacy of swaddling in these studies was variable. Although shown to be effective in many groups of infants, neither behavioural nor physiological parameters were modulated during the swaddling condition during heel lancing in premature infants less than 31 weeks corrected gestational age (Faron et al., 1997). Swaddling was also demonstrated to be less effective than non-nutritive sucking in reducing pain during heel lancing in term infants (Campos, 1989). Other non-pharmacological strategies, including prone positioning (Stevens, Johnston, Franck et al., 1999; Grunau, Linhares, Holsti, Oberlander, & Whitfield, 2004), rocking (Campos, 1994; Johnston, Stremler, Stevens, & Horton, 1997), and music therapy (Burke, Walsh, Oehler, & Gingras, 1995; Bo & Callaghan, 2000; Butt & Kisilevsky, 2000; Chou, Wang, Chen, & Pai, 2003) have been evaluated during either heel
lancing or endotracheal suction. Both prone positioning and simulated rocking have been shown to be ineffective in reducing pain during heel lancing (Campos, 1994; Johnston, Stremler et al., 1997; Grunau, Linhares et al., 2004).

The efficacy of music therapy in the reduction of pain during heel lancing has been evaluated in two studies, both of which included a small number of infants only, and both of which used a cross-over design (Bo & Callaghan, 2000; Butt & Kisilevsky, 2000). Bo and Callaghan (2000), in their cross-over study of 27 infants reported that the combination of music therapy with non-nutritive sucking was more effective in reducing behavioural responses during heel lancing, than when either music therapy was used alone, or when music therapy was not used. Butt and Kisilevsky (2000), who included 14 infants, suggested that music delivered during the recovery period following heel lancing, effectively reduced the time taken for physiological responses, facial expression scores and behavioural state to return to baseline levels, but only in the infants older than 31 weeks corrected gestational age. Music therapy was shown to be ineffective for the less mature infants.

Many of the studies which have evaluated the efficacy of non-pharmacological strategies as KC, swaddling, music therapy, positioning or rocking, in reducing procedure-related pain in diverse groups of infants provide useful information, and many of the strategies can be easily incorporated into the developmentally supportive care of hospitalised infants. However the studies are small in number, have generally included a small number of participants, and in most cases, are non-randomised research designs. This limits the extent to which the findings can be reliably interpreted. Nevertheless, international bodies concerned with pain management in infants recommend that appropriate developmentally supportive strategies be used whenever possible during minor procedures, and also further evaluated in conjunction with pharmacological analgesic agents (American Academy of Pediatrics & Canadian Paediatric Society, 2000; Anand & International Evidence-Based Group for Neonatal Pain, 2001).

**Non-nutritive sucking**

Non-nutritive sucking (NNS) has long been an intervention commonly used by neonatal nurses to calm infants, promote physiological stability and as a pain
management strategy (Franck, 1987). Positive effects of NNS, both in promoting calm, as well as providing analgesia during minor invasive painful procedures, have been demonstrated in many studies, as reported in a meta-analysis (Shiao, Chang, Lannon, & Yarandi, 1997). NNS, compared to either no intervention, or compared to developmentally supportive interventions such as prone positioning, rocking or swaddling, has been shown to reduce various behavioural or physiological responses to procedural pain in both term and premature infants (Field & Goldson, 1984; Campos, 1989; Miller & Anderson, 1993; Campos, 1994; Shiao et al., 1997; Stevens, Johnston, Franck et al., 1999; Corbo et al., 2000). Although the exact mechanism underlying the calming and analgesic effects of NNS remains unclear (Franck & Lawhon, 1998), the effects are thought to be mediated via a non-opioid mechanism, as evident by the analgesic effects being unaffected by the administration of an opioid antagonist such as naloxone (Blass & Ciaramitaro, 1994; Blass & Shah, 1995; Anseloni et al., 2002). The analgesic effects of NNS are reported to be present only when sucking is occurring (Smith, Fillion, & Blass, 1990; Blass & Watt, 1999), with “rebound” crying occurring when NNS ceases (Campos, 1989, 1994; Bo & Callaghan, 2000). The combination of NNS and sweet tasting solutions, or small amounts of milk, has however, been shown to be more effective in reducing procedural pain in infants than NNS alone (Blass, Shide, & Weller, 1989; Smith et al., 1990; Blass & Hoffmeyer, 1991; Blass & Watt, 1999; Carbajal et al., 1999; Stevens, Johnston, Franck et al., 1999; Bucher, Baumgartner, Bucher, Seiler, & Fauchère, 2000; Gibbins & Stevens, 2001; Gibbins et al., 2002).

Oral feeding
Analgesic effects of oral feeding during noxious and painful procedures have been evaluated in both the animal model and human infants. Using the animal model, studies conducted in the late 1980s showed that infant rats, when receiving food either by suckling or direct infusions of milk into the mouth, demonstrated increased pain thresholds during testing on a hotplate, compared to that observed when no milk was administered (Blass & Fitzgerald, 1988; Blass, Shide et al., 1989). In human infants, breastfeeding has also been shown to be analgesic when occurring either prior, to or during, venepuncture or heel lancing (Bilgen, Ozek, Cebeci, & Ors, 2001; Gray, Miller, Philipp, & Blass, 2002; Carbajal, Veerapen, Coudere, Jugie, & Ville, 2003; Gradin, Finnstrom, & Schollin, 2004). The mechanisms behind the analgesic effects
of breastfeeding are probably multifactorial, and involve a combination of skin to skin contact, suckling, pleasant taste (Gray et al., 2002) and in addition, intake of naturally occurring endorphins present in the breast milk (Blass & Blom, 1996; Ren, Blass, Zhou, & Dubner, 1997; Zanardo et al., 2001). It must be noted that these studies included only healthy infants born at term, therefore the feasibility of breastfeeding infants during procedures unquestionably remains in the realm of medically stable infants. The feasibility of implementing such a strategy in premature infants remains to be investigated, and the strategy is obviously not suitable for sick infants.

Sucrose and other sweet tasting solutions

Three of the trials evaluating the analgesic effects of breastfeeding during procedures also included extra arms to the trial, to compare the analgesic effects of small volumes of oral sucrose or glucose with that of feeding (Bilgen et al., 2001; Carbajal et al., 2003; Gradin et al., 2004). Sample size calculations were performed for all three trials, and numbers of infants randomised to each group ranged from 30 to 45. Results were that oral glucose or sucrose were either equally or more effective in reducing pain during heel lancing or venepuncture, than breastfeeding alone.

The administration of oral sweet tasting solutions to infants prior to minor painful procedures has been the most studied procedure-related pain reduction strategy in neonatal care (Stevens, Yamada, & Ohlsson, 2004). Although randomised controlled trials examining analgesic effects of sweet tasting solutions in infants were not being published until the late 1980s, there are numerous historical references pertaining to the analgesic benefits of sweet substances dating back to 632 AD, when Prophet Mohammed recommended giving infants a well chewed date (Voice, 2002). The first book of paediatrics written by an Englishman in 1545, included the following recommendation for crying at night: “...and if ye can gette any syrue of popye, geue it the chylde to licke…” (Phaire, 1955, p.12). Sugar solutions, often mixed with a combination of alcohol and cocaine or opium were used to calm infants in the late 1840s and early 1900s (Holbrook, 1959; Norberry, 1996), whilst Perry Davis pain killer, an over-the-counter concoction of sugar, alcohol and opium, was promoted as a cure for infantile colic (Holbrook, 1959). Sugar mixed with wine or whisky was also given to infant boys undergoing circumcision (Blanton, 1917), and in 1938, recommendations were made that anaesthesia for infants during surgery was often not
required, and that “a sucker consisting of a sponge dipped in some sugar water will often suffice to calm a baby” (Thorek, 1938, p. 2021).

The underlying mechanism of the analgesic effects of sweet tasting solutions is considered to be due to an orally mediated release of endogenous opioids (Blass & Ciaramitaro, 1994). A large body of research demonstrates the opioid-based sweet taste relationship, that primarily emerged from animal studies conducted from the late 1970s, showing analgesic and stress reducing effects of sweet tasting foods or fluids (Rowland & Antelman, 1976; Lowy, Maickel, & Yim, 1980; Dum, Gramsch, & Herz, 1983; Bertiere, Sy, Baigts, Mandenoff, & Apfelbaum, 1984; Czirr & Reid, 1986; Blass, Fitzgerald, & Kehoe, 1987; Blass, Shide et al., 1989; Shide & Blass, 1989; Ren et al., 1997). The earliest of these studies conducted by Rowland and Antelman (1976), clearly demonstrated that rats which had been mildly stressed by exposure to frequent tail pinches, preferentially increased their sweet food intake compared to control rats, which had not been exposed to the noxious stimuli. Using a similar methodology, the same stress induced over-eating was demonstrated in four other studies (Lowy et al., 1980; Morley & Levine, 1980; Vaswani, Tejwani, & Mousa, 1983; Bertiere et al., 1984). In addition, the rats in these latter studies were administered the opioid antagonist, naloxone, which effectively reversed the stress induced over-eating, thus demonstrating a close relationship between stress, sweet food ingestion and the endogenous opiate system.

The same sweet food ingestion and endogenous opiate system association was evident in a study which showed that rats consuming sweet tasting chocolate or chocolate milk had an increased occupation of opioid receptors in their brain compared to control animals (Dum et al., 1983). The increased opioid receptor occupation was theorised to be the result of increased levels of the endogenous opioid, beta-endorphin, resulting from intake of the palatable sweet chocolate substances. The association between sweet food intake, stress reduction and the opioid system has been further confirmed in studies where exogenous opioids have been administered, resulting in a preferential increase in sweet food intake (Calcagnetti & Reid, 1983; Czirr & Reid, 1986).
Another study which shed further light on these findings, also demonstrated that exposing rats to the stress of repeated tail pinches immediately resulted in preferential drinking of sweet solutions, which was suppressed following administration of an opioid antagonist (Bertiére et al., 1984). Bertiére et al. also showed that if the rats were injected with a beta-endorphin concentrate, the preferential high intake of sweet fluids was suppressed. The authors explained that both the opioid antagonist and the opioid itself, have the same suppressant effect on sweet taste intake; the antagonist because it suppresses the reward provoked by the sucrose, and the opioid itself, because it makes the reward unnecessary (Bertiére et al., 1984).

A series of studies conducted by Blass, Fitzgerald and Kehoe (1987) confirmed that the sweet tasting solution of sucrose, when given prior to or during painful and stressful situations, resulted in a reduction of pain and distress in newborn rat pups. The authors established that the analgesic effect was dependent on the sweet taste, with the most concentrated, therefore sweetest taste, being more effective than less sweet-tasting solutions. Blass and colleagues also demonstrated that analgesic effects of sweet taste were blocked by the administration of an opioid antagonist, thereby further confirming an opioid-based sweet taste relationship (Blass et al., 1987).

In 1989, Blass and colleagues first published a study which evaluated the calming effects of sweet tasting solutions in human infants (Blass, Fillion et al., 1989). In a study of 31 healthy newborn infants, Blass and colleagues demonstrated that crying infants given two 0.2 mL volume doses of a 12% weight per volume (wt/vol) sucrose solution, rapidly became calm, and the calming effects persisted up to five minutes following completion of the sucrose doses. Following on from this pioneering study, numerous subsequent studies also demonstrated that small volumes of sucrose given orally effectively calmed healthy crying infants (Blass & Smith, 1992; Smith, Stevens, Torgerson, & Kim, 1992; Barr et al., 1994; Smith & Blass, 1996; Graillon, Barr, Young, Wright, & Hendricks, 1997; Barr, Pantel et al., 1999; Barr, Young, Wright, Gravel, & Alkawaf, 1999). Blass and Smith (1992) also ascertained that the calming effects were sweet taste mediated, by demonstrating that the sweeter tasting sugars of sucrose and fructose, were more effective than the less sweet tasting sugars of glucose and lactose. Lactose was in fact, reported to be no more effective than water in reducing crying. Also made evident was that calming effects were not
dependent on volume, as small volumes of 0.2 mL of sucrose were equally as effective as larger volumes of 0.6 mL and 1.0 mL.

The efficacy of oral sucrose in calming infants born to mothers who were taking methadone was also evaluated (Blass & Ciaramitaro, 1994). As infants born to mothers on methadone have a poorly functioning endogenous opioid system, the sweet taste-mediated analgesia should, in theory, be ineffective in this group of infants (Blass & Ciaramitaro, 1994). Findings did indeed confirm that oral sucrose was ineffective in calming infants born to mothers on methadone, further establishing the close association between sweet taste, an intact endogenous opioid system and analgesia.

Not only were Blass and colleagues the first to demonstrate and publish calming effects of sucrose on crying infants, they were also the first to undertake blinded, randomised, controlled trials demonstrating the efficacy of small volumes of sucrose in the reduction of procedure-related pain in infants (Blass & Hoffmeyer, 1991). In a trial including 24 healthy newborn infants, Blass and Hoffmeyer demonstrated that infants randomised to receive 2.0 mL of 12% (wt/vol) sucrose, cried for a significantly shorter time during a heel lance procedure than the infants in the control group who received water. Analgesic effects of oral sucrose in infants undergoing circumcision were also demonstrated. Thirty male infants in total were randomised to receive a pacifier moistened by either a 24% (wt/vol) sucrose solution or water, prior to and throughout the duration of the circumcision procedure (Blass & Hoffmeyer, 1991). No additional analgesics were given during the procedure. Results showed that the infants randomised to receive sucrose cried for a significantly reduced duration of the procedure than the infants administered water.

Although no sample size calculations were performed prior to these early evaluative studies of sucrose analgesia, the compelling evidence demonstrating both the profound effects of oral sucrose in inducing and maintaining a calm state, and the analgesic effects of sucrose during a painful procedure in human infants set the stage for an abundance of further research. Following these two trials, a large number of randomised, controlled trials evaluating analgesic effects of sucrose or other sweet tasting solutions in the reduction of procedure-related pain have been conducted. A
systematic review of the efficacy of sucrose in the reduction of pain during either heel lance or venepuncture in term and preterm neonates was first undertaken in 1997, and 13 randomised, controlled trials were identified for inclusion (Stevens, Taddio, Ohlsson, & Einarson, 1997). Five trials met the inclusion criteria and results showed that, with the exception of a 5.8% and a 7.5% (wt/vol) sucrose solution, sucrose or other sweet tasting solutions were effective in reducing crying during, and following, a painful stimulus. The 5.8% and 7.5% (wt/vol) sucrose solutions used in the studies which failed to demonstrate analgesic effects were not considered sweet enough to stimulate the orally mediated endogenous opioid system (Rushforth & Levene, 1993; Blass & Shah, 1995).

In the most recent systematic review of sucrose for analgesia in newborn infants undergoing painful procedures, a total of 44 studies were identified, of which 21 studies were included in the final review (Stevens et al., 2004). Findings were that small volumes of sucrose or other sweet tasting solutions, compared with either placebo solutions or no treatment, were effective in reducing behavioural signs of pain and multi-dimensional behavioural and composite pain scores, during and following completion of either heel lance or venepuncture. In three trials, the multidimensional composite pain score, the Premature Infant Pain Profile (PIPP), was used as the outcome measure to evaluate pain (Johnston, Stremler, Horton, & Friedman, 1999; Stevens, Johnston, Franck et al., 1999; Gibbins et al., 2002). The results of these trials were consequently pooled for meta-analysis. Results showed that PIPP scores were significantly reduced in the infants administered sucrose compared to the infants in the control groups who received either water, a combination of NNS and water, or were positioned in a prone or side-lying, contained manner (Stevens et al., 2004).

Although sweet tasting solutions universally resulted in a reduction in behavioural responses during or following painful procedures, the effectiveness of oral sucrose or other sweet solutions, in reducing physiological responses to acute pain is less clear. As reported in the systematic review of sucrose for analgesia in newborn infants undergoing painful procedures (Stevens et al., 2004), the degree of oxygen desaturation occurring during heel lance or venepuncture was not influenced by oral sucrose, and in only half of the randomised, controlled trials, oral sucrose was reported to be more effective than placebo in reducing heart rate changes from
baseline (Stevens et al., 2004). Oral glucose has in fact, been found to cause an increase in heart rate in healthy term newborn infants, possibly due to the sweet taste invoking a strong sucking response, resulting in an increased heart rate (Eriksson, Gradin, & Schollin, 1999).

Comparison of sucrose and oral feeds

Many of the sucrose efficacy trials demonstrated that the combination of NNS and oral sucrose was shown to be more effective in reducing pain than when either sucrose or NNS were used alone (Blass, Shide et al., 1989; Blass & Hoffmeyer, 1991; Blass & Watt, 1999; Stevens, Johnston, Franck et al., 1999; Gibbins et al., 2002). Six studies were also identified in which analgesic effects of small volumes of either breast milk, artificial formula milk or milk fats were compared with sucrose or other sweet tasting solutions (Blass, 1997; Skogsdal, Eriksson, & Schollin, 1997; Örs et al., 1999; Bucher et al., 2000; Bilgen et al., 2001; Blass & Miller, 2001). Although sample size calculations based on power analyses were only reported in three of these six studies (Örs et al., 1999; Bilgen et al., 2001; Blass & Miller, 2001), five studies included substantial numbers of infants in each allocated group. The exception was the trial by Blass (1997) in which 72 infants were randomised to one of nine treatment groups, resulting in only eight infants in each group. Nevertheless, findings of all studies were consistent; demonstrating superior sucrose-induced analgesia compared to small volumes of milk or fat solutions. In fact, three of the trials demonstrated that milk was no more effective than water in reducing pain (Skogsdal et al., 1997; Örs et al., 1999; Bilgen et al., 2001).

Although small volumes of milk given prior to procedures may not be effective in reducing pain, either breastfeeding or the administration of substantial volumes of expressed breast milk have been shown to be effective compared to placebo, and at least as effective as small volumes of either sucrose or glucose (Carbajal et al., 2003; Gradin et al., 2004; Upadhyay et al., 2004). The discrepancy relates to the contribution of multiple factors other than taste alone, including the combination of skin to skin contact, sucking, taste and significant intake of naturally occurring endorphins present in breast milk (Blass & Blom, 1996; Ren et al., 1997; Zanardo et al., 2001; Gray et al., 2002).
Although sucrose in its various concentrations has been used in the majority of studies examining analgesic effects of sweet tasting solutions in infants, other sweet tasting solutions have also been shown to be effective in reducing procedural pain. Alternative sweet tasting solutions evaluated have included hydrogenated glucose syrup; the artificial sweetener used in paracetamol (Ramenghi, Griffith et al., 1996), and glucose solutions at concentrations higher than ten percent (Skogsdal et al., 1997; Guala et al., 2001; Bauer, Ketteler, Hellwig, Laurenz, & Versmold, 2004; Eriksson & Finnstrom, 2004). The evidence obtained from such studies demonstrating the analgesic effects of any sweet tasting solutions in the reduction of procedural pain, highlight the fact that the analgesic effect is sweet-taste mediated; and as long as the solutions given to the infants are sufficiently sweet, the effects will be similar, regardless of whether the solutions used are sucrose, glucose, or artificial sweeteners.

A limitation of the large majority of trials examining the analgesic effects of oral sucrose in the reduction of procedure-related pain is that several groups of infants, have been consistently excluded. Infants with congenital abnormalities, infants who have undergone surgery, have received opioid analgesics, have chronic medical problems, or suspected or proven necrotising enterocolitis or other bowel disorders, have not been eligible for entry into most trials examining the efficacy of sucrose or other sweet solutions. Only one randomised, controlled trial included such infants. Results of that trial, similar to results of many studies of sucrose efficacy during painful procedures, showed that sucrose was effective in reducing behavioural responses, but not physiological responses, to heel lance pain (Harrison et al., 2003a). Infants with such complex medical conditions comprise a large proportion of infants admitted to tertiary neonatal and paediatric referral centres, and often require prolonged hospitalisation and multiple investigations and procedures (Harrison et al., 2003a). The paucity of knowledge concerning efficacy and safety of oral sucrose in this unique population of infants with complex medical conditions is therefore concerning, and further research is warranted.

Knowledge gaps relating to sucrose efficacy

Despite the large body of research relating to the analgesic effects of sucrose in premature infants as well as healthy, term, newborn infants, there remain a number of
knowledge gaps. In addition to the fundamental knowledge gap concerning the efficacy of sucrose in both critically ill and chronically ill infants, and those infants previously exposed to surgery, there are uncertainties regarding the safety of sucrose for infants. Although no adverse effects associated with oral sucrose in infants have been reported per se (Gibbins et al., 2002), concerns raised in the literature have related to the risk of hyperglycaemia, necrotising enterocolitis, bacterial contamination of the solutions and potential dental caries.

Although there is a theoretical risk of hyperglycaemia resulting from repeated doses of oral sucrose, the few studies that have reported blood glucose levels following administration of sucrose to infants have found that neither single nor multiple doses of oral sucrose, at concentrations of 24% or 50%, were associated with hyperglycaemia (Bucher et al., 1995; Gormally et al., 2001; Johnston, Filion et al., 2002). Further illustrating this point, a study in which systemic absorption of oral glucose in adult participants was measured, poor absorption of glucose through the oral mucosa was evident, demonstrating that substantial volumes of the solution needed to be swallowed in order for an increase in blood sugar level to occur (Gunning & Garber, 1978). As only small volumes of sucrose are required for sucrose-induced analgesia (Blass and Smith, 1992; Stevens et al., 2004), it is unlikely that infants would be administered large enough volumes to effect blood glucose levels.

Although concerns have been raised relating to an increased risk of necrotising enterocolitis in premature infants, associated with the use of oral sucrose solutions (Ramenghi, Wood, Griffith, & Levene, 1996; Acharya, Annamali, Taub, & Field, 2004), there is no evidence to suggest that the small volumes of oral sucrose used for reduction of procedural pain increases the risk of necrotising enterocolitis. This concern stems from a report in 1977 in which there was an increased incidence of necrotising enterocolitis in premature infants administered multiple doses of calcium suspended in a 20% sucrose solution (Willis, Chabot, Radde, & Chance, 1977). The high incidence of necrotising enterocolitis was attributed to the hyperosmolar effects of the suspension. As many medications currently used in routine care of sick infants have a higher osmolality than the 25-50% sucrose and 30-50% glucose solutions used in the majority of trials to date (Mutz & Obladen, 1985; Bucher et al., 2000; Women's
& Children's Hospital Pathology  Royal Children's Hospital, 2004), it is unlikely that the small volumes of oral sucrose or glucose required for procedural-pain reduction would be associated with an increased risk of necrotising enterocolitis.

The risk of promoting dental caries as a result of administering oral sucrose solutions to infants has been raised (Bucher et al., 1995; Ramenghi, Griffith et al., 1996). There have been no studies examining dental health in infants and children who had received sucrose for pain management in the neonatal or early infancy period. However, it is unlikely that the small volumes of sweet solutions given to infants prior to painful procedures is associated with the development of dental caries (Lewindon, Harkness, & Lewindon, 1998). In addition, as pointed out by Lewindon et al. (1998), the small volumes of sucrose given prior to procedures is comparable in volume and sugar content to commonly administered proprietary syrups, including antibiotics and antipyretics.

Another potential risk identified has concerned bacterial overgrowth of sucrose solutions within a short time period (Abu-Arafeh, Callaghan, Hill, & Hislop, 1998). Significant bacterial contamination of a 10% sucrose solution, occurring 24 hours after preparation, was recounted in a letter to an editor (Abu-Arafeh et al., 1998). The authors stated that the unacceptable level of bacterial growth made it necessary for the sucrose solution to be prepared on the same day of use. Sucrose, is however, well known for its preservative properties (Chirife, Herszage, Joseph, & Kohn, 1983), and such concentrations of sucrose are used commonly in preservatives for their antibacterial properties. However, following the findings by Abu-Arafeh et al. (1998) bacteriology testing of sucrose solutions used in clinical areas should be conducted as a quality measure to safeguard against the risk of administering contaminated solutions to newborn and young infants.

Sucrose efficacy following prolonged use
In summary, there is no evidence to show that oral sucrose increases the risk of dental caries, hyperglycaemia, bacterial infection or necrotising enterocolitis in infants. There is however, a paucity of evidence relating to both the efficacy and safety of repeated doses of sucrose or other sweet solutions in premature and sick infants. This is a vital gap in the knowledge pertaining to the use of sucrose in this population as
premature and sick infants are potentially exposed to numerous painful procedures over the course of their hospitalisation (Barker & Rutter, 1995; Johnston, Collinge et al., 1997; Simons, van Dijk et al., 2003; Stevens et al., 2003). There are only a small number of studies which have examined the analgesic effects of more than a single dose of sucrose, and these, with the exception of one study (Mucignat et al., 2004), have been of a relatively short duration (Johnston, Filion et al., 2002; Eriksson & Finnstrom, 2004).

Eriksson and Finnstrom (2004) conducted a study to determine if repeated doses of oral glucose given to newborn infants during the first few days of life was associated with subsequent development of sweet-taste tolerance to procedural pain. Following an a priori sample size calculation, with a sample size of 20 infants in each group deemed sufficient to detect an anticipated 50% reduction in crying duration during heel lancing, 43 infants subsequently completed the study. On the day of birth the infants were randomised to receive three daily 1.0 mL doses of either 30% glucose or water over a period of three to five days. Following this period, heel lancing was performed to obtain capillary blood for newborn screening. Prior to blood sampling, all 43 infants were given 1.0 mL of a 30% glucose solution. The authors hypothesised that if a tolerance to sweet-taste induced analgesia had developed in those infants who had received glucose, there would be a reduction in the analgesic effect of glucose during heel lancing, compared to that seen in the control group. Results however, showed similar pain scores in both groups of infants during and following completion of the heel lance procedure, demonstrating the lack of an observed sweet taste tolerance (Eriksson & Finnstrom, 2004). The study design was severely limited however, by the short-term period of glucose administration, over a three to five day period. In addition, the total volumes of glucose administered each day for the three to five days were small, with only three daily doses, each of 1.0 mL volume, being given over the time period. Based on the knowledge of opioid tolerance and withdrawal in infants (Katz, Kelly, & Hsi, 1994; Suresh & Anand, 1998), these small doses of glucose given intermittently over such a short time span would be insufficient to produce opioid tolerance.

In another study, repeated doses of sucrose were also administered to infants during the first few days of life (Johnston, Filion et al., 2002), although the number of doses
given were far in excess of that reported by Eriksson and Finntrom (2004). Johnston and Filion et al. (2002) examined the safety of repeated doses of sucrose in premature infants less than 32 weeks gestational age during the first week of life. A total of 103 infants were randomised to receive either 0.1 mL volumes of 24% sucrose, or water, prior to all invasive and noxious procedures, including insertion of gastric tubes, adhesive tape removal and endotracheal suction. A mean number of 63 doses of sucrose per infant in the treatment group and 58 doses of water per infant in the control group were administered over the first week of life. As results showed that sucrose remained more effective than water in reducing procedural pain over the course of the seven-day study period, the conclusion was drawn that there was no reduction of sucrose-induced analgesia following repeated doses. There were however, safety concerns which arose from secondary analyses of the data, showing an increased incidence of lower neurodevelopmental scores, based on a subset of the Neuro-Behavioural Assessment of the Preterm Infant (NAPI) (Kornere et al., 1987), in infants in the sucrose group, who had received a high number of sucrose doses. This finding however requires further discussion. First and foremost, results showed no differences in neurobehavioural outcomes between infants in the control group compared to the infants in the sucrose group, at any of the three assessment points (32, 36 and 40 weeks gestational age). However, a secondary analysis of the data, of scores in the sucrose group only, indicated that higher doses of sucrose, compared to lower doses of sucrose, predicted poorer neurobehavioural outcomes at 36 and 40 weeks gestational age.

One explanation given by the authors for this finding, was, as a possible consequence of withdrawing the sucrose after multiple doses given during the first week of life, an increased sensitivity to pain developed, affecting the infants’ neuro-behavioural scores of alertness, orientation, movement and vigour (Johnston, Filion et al., 2002). Another possibility postulated by the authors was that the multiple doses of sucrose given to these premature infants resulted in repeated stimulation of an immature endogenous opiate system. Consequently, this may have interfered with the normal developmental functioning and maturation of the infants’ immature endogenous opiate system. Alternatively, a methodological explanation was given, relating to the inadequate sample size included in the secondary analyses. The actual number of infants included in the secondary analyses is unable to be determined from the
reported results, making further critical appraisal of the findings difficult. To date, this has been the only published study which has examined associations between repeated sucrose doses and neurodevelopmental outcomes. As the findings are difficult to interpret, uncertainty remains regarding whether or not sucrose should be routinely administered to premature infants prior to all painful or noxious procedures. However, despite Johnston, Filion et al. (2002) acknowledging the limitations of their study, cautionary use of repeated doses of sucrose in premature infants was nevertheless subsequently recommended.

Analgesic effects of multiple doses of oral sucrose were also evaluated in another study (Mucignat et al., 2004). Mucignat and colleagues studied 33 premature infants over a six-week period during subcutaneous injections of erythropoietin factor. The injections were given to minimise anaemia of prematurity, and were administered three times a week, totalling 265 injections given over the six weeks. Two investigators simultaneously scored pain, using two validated pain assessment tools, based on behavioural parameters (Craig et al., 1993; Carbajal, Paupe, Hoenn, Lenclen, & Olivier-Martin, 1997). Despite the long period of observation, and the progressive assessments over the six-week period, results were not analysed in terms of comparison of successive pain scores, therefore changes in pain responses over time were not examined. Statistical analysis of this crossover study was confined to comparison of pain scores between four different conditions; comprising 30% oral sucrose, topical EMLA®, NNS, or a combination of all three interventions. Each infant acted as their own control during the four interventions. Results showed a significant reduction in pain scores during the oral sucrose intervention compared to both NNS and EMLA® alone, with the combination of interventions resulting in a further reduction in pain scores. Although this information adds to the considerable body of literature concerning analgesic effects of oral sucrose in infants, and its superior analgesic properties over NNS and EMLA® alone, it does not contribute to the knowledge gap around efficacy or safety of prolonged use of sucrose.

A significant knowledge gap therefore remains concerning the analgesic effects of sucrose when administered repeatedly to infants over an extended period, which has implications for infants requiring prolonged hospitalisation and exposure to repeated
painful procedures during the course of the hospital stay. A small number of animal studies have been conducted which provide insight into the potential effects of multiple doses of oral sucrose given over a prolonged period (Lieblich, Cohen, Ganchrow, Blass, & Bergmann, 1983; Holder & Bolger, 1988; Fidler, Kalman, Ziemer, & Green, 1993), although the volumes of sweet solutions administered to the animals in these studies were far higher than would conceivably be administered to human infants. In the study by Lieblich et al. (1983), 20 genetically selected rats of two different strains were given unlimited access to a solution of the sweet tasting artificial sweetener, saccharine, daily for 28 consecutive days, whilst 13 rats allocated to the control group were allowed to drink only water for the 28-day period. The first strain of rats is known for its self-stimulation and consequent excessive intake of sugar, whilst the second strain, in comparison, has low rates of self-stimulation and sugar intake. Results showed that the first strain of rats given unlimited access to saccharine solution drank about 50 mL each day, compared to the second strain, which drank a mean of 24 mL daily. Otherwise, water intake, food intake and body weight did not differ between the different treatment groups. The animals that had consumed 50 mL of the saccharine solution daily subsequently demonstrated an increased response to pain during contact with a hot plate, and, when administered morphine or naloxone, showed neither morphine analgesia nor normal response to naloxone. This response was in contrast to the rats in both the control group and the second strain of rats that drank reduced volumes of the saccharine solution. This finding supports the suggestion that chronic intake of sweet solutions may result in opioid tolerance due to increased release and utilisation of endogenous opiates. Two other related studies reported similar findings; that a constantly high intake of sucrose was associated with reduced pain threshold and morphine tolerance (Holder & Bolger, 1988; Fidler et al., 1993). The value of these studies lies in their theoretical understanding of the opioid system’s response to excess sweet taste-mediated analgesia rather than its capacity to be used to guide clinical practice or to be replicated in the clinical setting in human infants.

Sucrose efficacy beyond the neonatal period

As has been made clear, the role of sucrose in reducing pain and distress in human infants has been studied primarily over short time periods during the first 28 days of
life. There is limited research relating to both sucrose efficacy when administered over prolonged periods and sucrose efficacy in infants beyond the neonatal period.

The analgesic effects of sucrose in human infants beyond the neonatal period have primarily been studied in well infants during immunisation (Barr et al., 1995; Allen, White, & Walburn, 1996; Lewindon et al., 1998; Lindh et al., 2003; Reis, Roth, Syphan, Tarbell, & Holubkov, 2003). With the exception of one trial (Barr et al., 1995), these studies have been randomised, controlled trials evaluating the efficacy of oral sucrose administered prior to either a single injection, or two or more injections given during one episode of routine immunisation. Barr et al. (1995) conducted a longitudinal randomised, controlled trial, in which the same infants were observed twice, during immunisation at two and four months of age. Although results of all the studies showed analgesic benefits of oral sucrose or glucose in the infants ranging in ages from two months corrected post-natal age up to 18 months, the effects were demonstrated to be more moderate compared with the profound analgesia exerted by sweet tasting solutions in the neonatal period (Stevens et al., 2004).

Although these studies conducted during routine immunisation in infants provide valuable insight into the analgesic effects of sucrose in infants beyond the neonatal period, up to 18 months of age, various aspects of the design of these studies limit the value of the findings. The trial conducted by Lindh et al. (2003), which included 90 infants in total was the only study in which the sample size was based on a sample size calculation. In two studies, either the volume or concentration of sucrose used was higher than recommended neonatal doses (Stevens et al., 2004). Lewindon et al. (1998) used 2.0 mL of a 75% sucrose solution and Reis et al. (2003) used 10 mL of a 25% sucrose solution. In addition, the method of pain assessment used in one study had not been validated in infants (Lewindon et al., 1998) and as a combination of strategies rather than sucrose alone was used in three studies, any analgesic effects demonstrated could not be attributed to sucrose alone (Lewindon et al., 1998; Lindh et al., 2003; Reis et al., 2003). Consequently, although the results of these studies do contribute to the understanding of analgesic effects of oral sucrose beyond the newborn period, insufficient evidence remains to confidently recommend routine use of oral sucrose during immunisation as an effective method of pain reduction in infancy.
Guidelines for practice/standards

A number of important knowledge and research gaps in relation to the analgesic effects of sucrose remain. Sick infants with complex medical conditions who may require lengthy hospitalisations, surgery and opioid analgesics, and who potentially undergo multiple invasive procedures, have been consistently excluded from the large majority of studies of procedural pain reduction. In addition, there remains little knowledge concerning efficacy of repeated doses of sucrose over a period beyond one week of use and efficacy of sucrose analgesia in infants beyond the neonatal period. In addition, there is scarce evidence, regarding the capacity of consistently administered evidence-based pain reduction strategies, both pharmacological and non-pharmacological, to preterm and sick term newborn infants to decrease the risk of adverse sequelae associated with frequent and repeated painful procedures. Despite these knowledge gaps, the need to systematically provide universal pain reduction strategies to reduce potential acute and long-term impact of early procedural pain has been recommended (Porter et al., 1999). In 2002, Franck advised that health professionals caring for sick infants have an ethical and professional responsibility to provide a safe environment, to minimise pain and to utilise current evidence-based pharmacological and non-pharmacological pain reduction strategies (Franck, 2002).

In light of available evidence to support use of evidence-based pain management strategies as well as current knowledge regarding potential harmful consequences of untreated pain in infants, experts representing several different countries, professional disciplines, and practice settings developed a Consensus Statement for the prevention and management of pain in the newborn (Anand & International Evidence-Based Group for Neonatal Pain, 2001). Recommendations from this group included the need to utilise strategies to reduce pain during procedures, and the need to regularly undertake and document assessment of pain. The use of small volumes of oral sucrose or other sweet tasting solutions is included as one of the key strategies for pain reduction during minor procedures.

In addition, a number of other groups have issued similar guidelines for assessment, prevention and management of pain in infants. The American Academy of Pediatrics
and the Canadian Paediatric Society (2000) issued a joint Statement on the prevention and management of pain and stress in the neonate which includes the recommendation to use appropriate environmental, non-pharmacological, and pharmacological interventions to prevent, reduce, or eliminate pain and stress in neonates. In addition, the Australian College of Neonatal Nurses developed Position Statements concerning both the assessment and management of pain in sick infants (Australian College of Neonatal Nurses, 2003, 2004). The Australian College of Neonatal Nurses Pain Management Statement recommends that evidenced-based pain management strategies aimed at preventing or reducing pain and stress in sick infants, should be implemented, and that recurrent painful stimuli should be avoided or reduced when possible.

Utilisation of evidence-based pain management strategies

Both prior to, and since, the dissemination of such Consensus statements, Position Statements and Evidence-based Guidelines, there have been numerous reports of low or variable rates of utilisation of evidence-based pain reduction strategies during painful procedures, inconsistent analgesia and sedation practices for mechanically ventilated infants and low utilisation of pain assessment tools in neonatal intensive care units (Anand, Selanikio, & SOPAIN Study Group, 1996; Johnston, Collinge et al., 1997; Porter, Wolf, Gold, Lotsoff, & Miller, 1997; Kahn et al., 1998; Porter & Anand, 1998; Heaton & Herd, 2000; Sabrine & Sinha, 2000; Debillon et al., 2002; Rohrmeister et al., 2003; Simons, van Dijk et al., 2003; Rennix, Manjunatha, & Ibhanesebhor, 2004). Findings of one such report of pain management practices in 14 Canadian neonatal intensive care units were that neonates were exposed to an average of two painful procedures per day, with some infants having up to eight procedures in one day (Johnston, Collinge et al., 1997). Blood sampling by heel lancing was the most commonly performed painful procedure, and of the 1298 heel lance procedures audited, no analgesics specific to the procedure were administered.

Two consecutive surveys of procedural pain management practices in neonatal units in New Zealand, conducted in 1999 and in 2001, showed an increase in routine analgesic administration during procedures in the second survey compared to the first (Heaton & Herd, 2000; Fernando, Heaton, & Herd, 2001). The first survey, returned
by 15 out of 18 medical directors of neonatal units, showed that despite all respondents agreeing that the listed procedures of venepuncture, heel lance and arterial puncture caused pain, ten of the 15 neonatal units did not routinely use any analgesics during procedures (Heaton & Herd, 2000). Despite the remaining five units reporting routine use of analgesics, analgesic agents were actually administered during less than ten percent of procedures. Sucrose was routinely used in only one unit despite 13 of the 15 respondents regarding oral sucrose as a safe and effective analgesic. When the same survey was administered two years later, and returned by 14 of the 18 medical directors of neonatal units in New Zealand, results showed increased routine use of analgesics although frequency of use of analgesics specifically for procedure-related pain was extremely variable. Four of the 14 units in the second survey reported routine use of oral sucrose for procedure-related pain compared to one unit in 1999 (Fernando et al., 2001).

In Austria, a survey of pain management practices by consultant neonatologists in 28 neonatal units, showed that pain assessment scores were routinely used in only three units (11%) and sucrose was administered during procedures in only four units (14%), despite 13 (42%) neonatologists being aware of the analgesic benefits of oral sucrose (Rohrmeister et al., 2003). In the majority of units, no pharmacological or non-pharmacological pain reduction strategies were routinely used during minor painful procedures such as heel lancing, eye examinations or intramuscular or subcutaneous injections.

A survey was also undertaken in neonatal units in France regarding pain assessment and pain management practices during five given clinical situations; endotracheal intubation, prolonged mechanical ventilation, management of acute necrotising enterocolitis, central venous catheter insertion and management of cephalhaematoma (Debillon et al., 2002). Completed surveys were returned from 116 of 143 units, a response rate of 81%. Results showed that pain assessments were routinely conducted for assessment of acute pain in 60% of units and in 53% of units for assessment of chronic pain. Analgesics were used either ‘often’ or ‘most of the time’ by the majority of neonatal units for pain management during four of the five clinical situations, with the exception being prolonged mechanical ventilation for chronic lung disease, where analgesics were routinely used in only 30% of neonatal units. The improved routine
use of pain assessment scores and pain management strategies reported in this survey compared with results of similar surveys may be due to the clinical situations presented; with no data collected on procedural-pain assessment or pain management during the more commonly performed minor painful procedures of heel lancing and venepuncture.

A prospective audit of analgesic use and number of procedures performed on neonates in a NICU in the Netherlands was also conducted (Simons, van Dijk et al., 2003). Results showed that for the 151 neonates enrolled, a mean of more than 14 noxious or painful procedures per day were performed, with airway suctioning being performed most frequently, followed by heel lancing. Pharmacological and non-pharmacological pain reduction strategies were rarely used during the multiple minor invasive procedures performed. Of note, the audit included documentation of failed attempts at procedures, with results showing that more than 30% of first attempts at intravenous catheter insertion, arterial catheter insertion and umbilical catheter insertion were unsuccessful. The authors highlighted that failed attempts at procedures account for significant, yet under-reported exposure to pain in sick infants (Simons, van Dijk et al., 2003).

In another audit of pain management practices in two tertiary referral NICUs in Canada, a mean of more than ten painful procedures per infant per day in the first few days of life was reported (Stevens et al., 2003). The most frequently performed tissue-damaging procedures were heel lancing for blood sampling, and intravenous catheter insertion, both of which were predominantly performed with no analgesic cover. In another study, nurses and physicians working in 15 neonatal units in a metropolitan area in the USA were surveyed to ascertain the degree of pain they perceived infants would experience during 12 different commonly performed NICU procedures, as well as the frequency of pharmacological or non-pharmacological pain reduction strategies they believed were used during procedures (Porter et al., 1997). From the 467 questionnaires distributed, 374 (80%) were returned. Results showed that although both nurses and physicians rated nine of the 12 listed procedures as being painful, neither pharmacological nor comfort measures were believed to be used frequently during most procedures. Both physicians and nurses believed that analgesics and non-pharmacological strategies should be used more frequently to reduce pain in infants.
during painful procedures. Results of yet another survey, conducted in 86 NICUs in the United Kingdom, showed that analgesics were never used in the large majority of cases during procedures of venepuncture or peripheral arterial or venous line insertion (Sabrine & Sinha, 2000).

In conclusion, there are a substantial number of infants nursed in tertiary referral NICUs and in paediatric settings who require prolonged hospitalisation. Health professionals working in these areas have an ethical responsibility to provide high-quality evidence-based care in all domains, including pain assessment and pain management. However significant knowledge gaps around best evidence, such as the paucity of research into the prolonged use of oral sucrose, may be contributing factors to the low frequency of analgesic use and variable pain management practices in neonatal units around the world. As a result of these knowledge gaps it is clear from the surveys of pain management practices in NICUs around the world, that sick infants may not be receiving appropriate pain management during minor painful procedures.

Similar surveys of pain management practices in neonatal units have not been conducted to date in Australia, with the result that the extent to which pain reduction strategies are being utilised in Australian neonatal units remains unknown. Health professionals caring for sick infants in Australia therefore have no knowledge of current local practices on which to base pain reduction implementation strategies, nor is there baseline information to guide further research.

In order to reduce these significant knowledge gaps, the aims of this thesis were threefold:

1. To ascertain pain assessment methods and procedural pain management strategies used in Australian neonatal units
2. To record a detailed history of both painful procedures and pain reduction strategies used throughout the period of hospitalisation in a cohort of infants hospitalised for a prolonged period
3. To describe the effectiveness of oral sucrose in reducing procedural pain during the course of the same infants’ prolonged hospitalisation, by mapping responses to pain during successive heel lance procedures.
It is expected that the knowledge obtained by the exploration of these issues will address questions relating to the translation of evidence into practice within the national context and contribute valuable information regarding pain management strategies and, in particular, the use of oral sucrose over a prolonged hospitalisation in the cohort of sick infants with chronic illness.
CHAPTER 2. RESEARCH DESIGN AND METHODS

Nationwide pain assessment and pain management survey

Significance
There is no published research on current pain assessment and pain management practices in Australian neonatal settings. Determining baseline data on current practices regarding implementation of pain assessment tools and utilisation of evidence-based strategies for reduction of procedure-related pain will inform future education approaches and research questions relating to best pain assessment and pain management practices for infants in Australia.

Method
The method used to ascertain pain assessment practices and pain management strategies used during minor painful procedures in Australian neonatal units was a cross-sectional postal survey. This method was deemed the most effective way to collect the required information from relatively large numbers of neonatal units throughout Australia. The survey was based on one previously developed for use in New Zealand (Heaton & Herd, 2000), and modified with the authors’ permission. The original survey sent to Medical Directors of neonatal intensive care units in New Zealand, comprised nine questions relating to pain management practices during commonly performed minor painful procedures in neonatal intensive care units (Heaton & Herd, 2000). In addition, questions relating to staff attitudes towards pain in neonates were included. Issues relating to pain assessment practices and pain reduction strategies other than oral sucrose and topical anaesthetic creams were not addressed. Modifications were therefore made to the content and design of survey in order to address the issues targeted in this part of the thesis.

The modified survey was tested and refined during a pilot study conducted at the Royal Children’s Hospital (RCH), Melbourne. The pilot study participants were ten health care professionals comprising seven nursing staff from the Neonatal Unit (NNU) and three members of the Children’s Pain Management Service, RCH, Melbourne. It was not expected that members of this group would be respondents of the final survey. This group of ten participants completed the survey and provided
feedback on the content of the questions, clarity, formatting, ease of completion and time taken to complete the survey. Minor modifications to the survey were made based on the feedback.

The final survey (Appendix 1) comprised four sections with a total of 14 questions. The first section included five questions relating to pain assessment practices, with the first question asking if any pain assessment scores were used on a regular basis. If the answer to this question was “no”, respondents were asked to proceed to Question Six, which related to related to utilisation of pain management strategies during minor painful procedures. If the answer was “yes”, respondents were asked to complete Questions Two through Question Five, relating to details of situations in which pain assessments were conducted, if and where pain assessment scores were documented, and methods of pain assessment used.

Question Two asked respondents to specify the situations in which pain scores were routinely performed. Situations specified were; during regular documentation of vital observations; post-operatively; during procedures; for research purposes, and when on analgesic medications. Questions Three and Four related to the documentation of pain assessment scores, and Question Five sought to determine the methods of pain assessments or pain scores used. Ten options of different methods of pain assessment, including an “Other” option, were presented with corresponding tick boxes. Respondents were asked to tick all that were applicable.

The second section of the survey, comprising Questions Six through to Eleven related to the utilisation of pain management strategies during minor painful procedures. Question Six asked respondents if their unit had a policy or guideline directing pain management during minor procedures. Question Seven then asked for information relating to the frequency of use of pain management strategies during the following six commonly performed minor painful procedures.

- Heel lance
- Venepuncture or intravenous cannula insertion
- Lumbar puncture
- Eye examination
- Arterial line placement or arterial stab
Intramuscular or subcutaneous injection

The following strategies for pain reduction were listed:
- Oral sucrose alone (or other sweet tasting solutions)
- Non-nutritive sucking with oral sucrose
- Non-nutritive sucking alone
- Topical anaesthetic agents (EMLA®/AnGEL)
- Other, which included examples of cuddling, nesting and injected local anaesthetic.
- No analgesia/comfort measures used

Participants were asked to specify “Other” pain reduction strategies. With the exception of two procedures; lumbar puncture and eye examination, the option of breastfeeding was also included. For the procedure of eye examination, the option of local anaesthetic eye drops replaced the option of topical anaesthetic agents.

Respondents were asked to rate the frequency of use of each pain reduction strategy for each of the six procedures as either; Never, Occasionally, Often or Always.

Questions Eight to Eleven related to details of sucrose or other sweet tasting solutions used, and were relevant only to those respondents who reported using sweet solutions in their units. Question Eight sought details of the solutions; whether sucrose, glucose or other sweet tasting solutions were used. Details of the volume and the concentration of the relevant solutions used were also requested. Questions Nine and Ten related to contraindications to the administration of sucrose, and Question 11 sought to establish which health professionals were responsible for ordering sucrose for pain management.

Questions 12 and 13 in the third section of the survey sought information relating to knowledge of the safety, efficacy and availability of oral sucrose and topical anaesthetic agents. The final section of the survey related to demographics of the neonatal setting. Respondents were asked to specify whether their neonatal setting
was a Level Three neonatal intensive care unit (NICU), Level Two special care nursery (SCN), or newborn emergency transport service.

Setting and participants
All Level Three NICUs, Level Two SCNs and newborn emergency transport teams in Australia were included. Level One SCNs were not included, as these units do not provide ongoing care for sick infants. A list of all NICUs in Australia, and the publicly funded Level Two SCNs in the States of Victoria, New South Wales, Tasmania and South Australia, was provided by the Australian and New Zealand Neonatal Network (Donoghue & Australian and New Zealand Neonatal Network, 2003). This network does not include Level Two SCNs in the remaining Australian States and Territories or any privately funded Level Two SCNs, therefore representatives of the Australian College of Neonatal Nurses or the states’ newborn emergency transport teams were requested to assist in identifying remaining eligible neonatal care units. The total number of eligible organisations identified was 181, comprising six newborn emergency transport teams, 23 publicly funded Level Three NICUs, 90 publicly funded Level Two neonatal units and 62 privately funded Level Two SCNs. Surveys were addressed to the Nurse Unit Managers of each institution and mailed out between December 2003 and January 2004. Included with the survey was a letter of introduction explaining the purpose of the study, and an invitation for respondents to receive a summary of the results (Appendix 2). Included also were two reply-paid envelopes, one for anonymous return of the completed survey, and a second envelope for the request for a summary of the results. An email contact of the PhD candidate was also given for those respondents who chose to request a summary of the results electronically.

Ethics
The study was approved by the Ethics in Human Research Committee at the Royal Children’s Hospital, Melbourne on 23rd September 2003 (EHRC Reference Number: 23123 A) (Appendix 3). Anonymity of all participants and institutions was guaranteed. Consent was implied by return of survey.
Data analysis

Data were entered into Microsoft Excel version 2000 and imported into Stata 9.1 statistical software (StataCorp, 2001) for analysis of descriptive statistics. Data were primarily categorical, and were described using frequencies (percentages).

To map the history of an infant's prolonged hospitalisation with respect to painful procedures and pain management practices in a neonatal intensive care unit

Significance

The purpose of this phase of the study was to move beyond the procedural pain management strategies used in neonatal units throughout Australia, and to generate detailed knowledge relating to assessment and management of pain in infants throughout a whole hospitalization episode, in a single neonatal unit. The purpose was to record a detailed history of painful procedures and both analgesic and sedative medications used to reduce pain and distress throughout the duration of sick infants’ hospitalisation. Such an extensive study of pain and sedation management practices in a neonatal intensive care unit has not been conducted to date. Although sedatives do not provide analgesia as such, they are increasingly used in conjunction with analgesics in the management of distress associated with neonatal care (Ng, Klinger, Shah, & Taddio, 2002). The inclusion of sedative use was therefore considered an important component of this study of pain management practices in sick infants. The extent to which oral sucrose was utilised for infants undergoing painful procedures over the full course of a hospitalisation was also determined.

This detailed information was not systematically recorded as part of routine patient care documentation. Although the administration of analgesics and sedatives were ordered on medication charts, information relating to minor procedures was not recorded in detail in the individual infant’s medical and nursing notes. To obtain the required information in sufficient detail to enable a comprehensive report of painful procedures and associated pain management strategies used throughout an infant’s hospitalisation, a prospective study using a newly developed data collection record was required.
Method

Setting and participants

The method used for this part of the thesis was a prospective, longitudinal, observational study, following a cohort of infants admitted to the Neonatal Unit (NNU), Royal Children’s Hospital (RCH), Melbourne, with a predicted prolonged length of stay defined as 28 days or more. Although there is no national or international standard definition of prolonged length of stay, by defining at the outset a prolonged length of stay as ≥28 days, pain assessment and pain management practices were able to be investigated beyond the neonatal period in those infants with complex health needs requiring a long period of hospitalisation.

The RCH is a 250-bed paediatric referral centre, caring for 32,000 inpatients each year. The (NNU) within the RCH, is a 24-bed Level 3 neonatal intensive care and special care nursery, providing a state-wide service for infants with complex medical and surgical, genetic and metabolic conditions. Infants may also be referred from interstate, from Southern New South Wales and from Tasmania. Around 700 to 800 infants are admitted annually, most during the first two days of life. The mean length of stay is 9.7 days, although length of stay may range from one day through to many months for infants with ongoing specialist nursing, medical, surgical or nutritional needs. Based on admission data from the previous three-year period from 2001 to 2004, there were on average, 62 infants per year who were hospitalised in the NNU for longer than 28 days.

Participants considered for entry into the study included infants admitted to the NNU, RCH whose length of stay was predicted to be 28 days or more. Eligibility to enter the study was determined as soon as possible following admission of the infant, after considering exclusion criteria with the on duty medical and nursing staff. Exclusion criteria included:

- Infants born to mothers on methadone
- Spinal cord malformation (myelomeningocele, sacral teratoma)
- Suspected or known fructose intolerance
Data from the previous three years admissions to NNU, RCH informed the eligibility criteria for the current study. Table 1 presents a summary of diagnoses of infants from the year 2001 to 2004 whose stay in the NNU extended beyond 28 days. The list of diagnoses and signs presented in Table 1 served to assist in the identification of infants expected to have a prolonged hospitalisation.

Based on admission data from the previous three years, it was anticipated that 60 infants would be enrolled into the study and have complete data for the minimum 28-day period of hospitalisation.

Table 1. Summary of admission diagnoses associated with length of stay ≥28 days

<table>
<thead>
<tr>
<th>Diagnoses</th>
</tr>
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<tbody>
<tr>
<td>Abdominal: distension/surgery/bowel obstruction</td>
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<tr>
<td>Chronic lung disease</td>
</tr>
<tr>
<td>Congenital abnormalities:</td>
</tr>
<tr>
<td>Abdominal wall defects</td>
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<tr>
<td>Congenital Diaphragmatic Hernia</td>
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<tr>
<td>Renal abnormalities</td>
</tr>
<tr>
<td>Pierre Robin Sequence</td>
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<tr>
<td>Oesophageal Atresia</td>
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<tr>
<td>Meningitis</td>
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<tr>
<td>Necrotising Enterocolitis</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
</tr>
<tr>
<td>Prematurity with co-morbidities</td>
</tr>
<tr>
<td>Airway: Vocal cord palsy/airway obstruction</td>
</tr>
<tr>
<td>Meconium aspiration/Persistent pulmonary hypertension of the newborn</td>
</tr>
<tr>
<td>Seizures</td>
</tr>
</tbody>
</table>

**Instruments and procedure for data collection**

From the day of admission, a daily record of all analgesic and sedative medications administered, pain assessment scores documented and painful procedures performed was maintained. The use of sucrose and non-nutritive sucking (NNS) during minor painful procedures was also recorded. Painful procedures were defined for the purpose of this study, as skin breaking invasive procedures (Grunau, Weinberg et al., 2004) with the addition of eye examinations. This is consistent with the examples of painful procedures listed in the nationwide survey of pain assessment and procedural pain management practices in Australian neonatal units.
The daily record maintained for all infants enrolled in the study was continued throughout the hospitalisation until discharge or transfer from the NNU. Two separate data collection tools were utilised: a bedside nurses’ daily pain record (Appendix 4) and an investigator’s daily pain diary (Appendix 5).

**Bedside nurses’ daily pain record**

Nursing staff at the bedside caring for the infants in the study were requested to document all episodes, including numbers of attempts, of skin breaking minor painful procedures, as well as eye examinations, and the associated use of sucrose and NNS. This information is not systematically documented and would have been poorly captured without involving clinicians in the data collection. Commonly performed skin-breaking minor painful procedures were listed at the top of the pain record. Included in the list were heel lance, venepuncture, intravenous catheter insertion, arterial line insertion, arterial blood sampling, eye examination, suprapubic aspirate, lumbar puncture and peripherally inserted central catheter (PICC). Nursing staff were asked to fill in details relating to:

- Date and time of the procedure
- Name of the procedure
- Number of attempts until procedure completed
- Use of oral sucrose and NNS

To endeavour to achieve accurate information regarding all minor painful procedures, all records of painful procedures documented for each infant by the bedside nurses were checked by the PhD candidate (DH) against nursing and medical notes as well as pathology results. Procedures identified on these nursing, medical or pathology records, which had not been included on the infants’ specified pain diary, were added to the diary. If unrecorded procedures were identified, the infants’ medication charts were then checked for records relating to administration of oral sucrose at the time of the procedures. As these sources of patient information do not include the number of attempts at each procedure or the use of NNS during procedures, this information was noted as missing.
Investigator’s daily pain diary

In addition to the information collected by clinicians, the PhD candidate obtained a further set of data from the medical records on a daily basis (Appendix 5). This information was in relation to major procedures, documentation of pain assessment scores and administration of pharmacological agents known to affect pain. Each data collection day was for the 24-hour period from 0800 to 0800 hours. Included in this data collection were the following:

- Description of major procedures including surgery, endotracheal intubation, chest drain insertion and insertion of umbilical catheters and other central lines, with the exception of PICC lines, which were included in the minor procedure category.

- Number of Pain Assessment Tool (Hodgkinson et al., 1994) scores documented. Two medical records were checked daily for Pain Assessment Tool (PAT) score documentation; the designated post-operative NNU PAT scoring sheet, used in the NNU for documenting PAT scores for infants in the first 48 hours post-operatively, and the daily observation charts of each infant in the study.

- Analgesic and sedative agents. Details included the name of the agent, route of administration, the dose/Kg administered and the mode of administration (intermittent or continuous). If the medications were intermittently administered, the number of doses given in the previous 24-hour period was documented. Other information collected was the number of bolus doses administered if the agents were being administered by a continuous infusion. Data relating to the dose/Kg of analgesic and sedative agents administered were taken as from 0800 hours, reflecting the infant’s condition at the beginning of the day.

- Other medications known to influence pain responses, such as muscle relaxants and regional anaesthesia. Details relating to regional anaesthesia administration included the site and name of the anaesthetic used.

Other information collected on a daily basis included each infant’s feed status and volume of enteral feeds prescribed and ventilation status. Ventilation status was recorded and categorised as follows:
Chapter 2

- High Frequency Ventilation
- Conventional Mechanical Ventilation
- Continuous Positive Airway Pressure
- Airway with supplementary oxygen
- Airway without supplementary oxygen
- Supplementary oxygen
- Nil support

**Ethics**

The study was considered to be low risk with no alterations in medical or nursing care. The majority of criteria for an Expedited Review through The School of Nursing, The University of Melbourne, Departmental Human Ethics Advisory Group, were therefore fulfilled and ethics approval as an Expedited Review for Low Risk Research Projects was granted on the 5th August 2004 (HREC Project Number, 040641). (Appendix 6) All criteria for a Clinical Audit, through the Royal Children’s Hospital Ethics in Human Research Committee were fulfilled and the study was subsequently approved as a Clinical Audit on the 28th June 2004 (Reference number AUD/2001-). (Appendix 7) An introductory letter, explaining the purpose of the study, was given to parents of recruited infants (Appendix 8).

**Data analysis**

All data were entered into an Access database then imported into Stata 9.0 statistical software for statistical analysis (StataCorp, College Station, Texas, USA). Frequency and descriptive statistics were used to summarise the data. Continuous data are presented as means and standard deviations if normally distributed and as medians and interquartile (IQR) ranges if non-normally distributed. Categorical data is described using frequencies and percentages.

The effectiveness of oral sucrose in reducing procedural pain during the course of an infant's prolonged hospitalisation

**Significance**

The efficacy of oral sucrose in reducing pain during procedures has been well demonstrated in a number of well-conducted randomised, controlled trials. Studies to
date have primarily examined the analgesic efficacy of sucrose in reducing pain during a single painful procedure. Unanswered questions concern the ongoing effectiveness of oral sucrose in infants who are hospitalised and require repeated painful procedures. Both the age at which oral sucrose ceases to exert an analgesic effect, and the role of tolerance in reducing the efficacy of sucrose after multiple doses given over weeks to months to hospitalised infants prior to, and during, painful procedures, has yet to be elucidated. The aim of this part of the thesis therefore was to describe the effectiveness of oral sucrose in procedural pain reduction during heel lancing throughout the course of an infant’s prolonged hospitalisation.

**Method**

The methodology used was a prospective longitudinal observational cohort study. This observational design was considered to be appropriate in order to generate new knowledge relating to the analgesic effectiveness of administering oral sucrose during repeated episodes of painful procedures over the course of an infants’ hospitalisation. Pain assessments were conducted over the course of the hospitalisation during heel lances performed for the purposes of routine pathology testing. The choice of capillary blood sampling by heel lancing as the model of pain was considered the most suitable method to study responses to procedure-related pain. Heel lancing is a standardised procedure, and is one of the most frequently performed painful procedures in neonatal care (Barker & Rutter, 1995; Johnston, Collinge et al., 1997).

**Setting and participants**

The same cohort of infants as specified in Aim 2 were enrolled from the first capillary blood collection possible depending on the infants’ eligibility and the availability of the PhD candidate who was the sole investigator responsible for data collection. Infants who were unconscious or heavily sedated were not studied until they were responsive to handling, and considered eligible to receive oral sucrose for pain management as per the NNU, RCH Oral sucrose for procedural pain management in infants guideline (Harrison, 2001). In addition, pain assessments were not conducted in infants receiving muscle relaxants, until a period of 24 hours had passed since the previous dose. Infants at moderate or high risk of neurologic impairment were included as it has been shown that that these infants respond to the pain of heel
lancing in a manner similar to those of infants identified as having a low risk of neurologic impairment (Stevens et al., 2003).

Pain assessments were conducted during the routine monitoring of pathology. As per routine medical care, sick infants usually have weekly, or more frequent, pathology monitoring. Observations were conducted on a weekly basis if possible, or more frequently as time permitted. Pain assessments were conducted during only those heel lance procedures performed by the hospital-employed phlebotomists. Capillary blood collection by heel lance, when performed by the small group of experienced phlebotomists in the NNU, RCH is a standardised procedure and is performed at the same time each morning, thereby minimising the number of uncontrolled variables which could influence infants’ pain responses.

All infants received 33% weight per volume (wt/vol) sucrose solution orally prior to heel lance as per the NNU, RCH Oral sucrose for procedural pain guidelines (Harrison, 2001). A 33% (wt/vol) sucrose solution was implemented in 2001 (Harrison et al., 2003a; Harrison, Johnston, Loughnan, & Manias, 2005), and has since been routinely used for procedural pain management in infants in the setting where this study took place. This sucrose concentration was shown to be effective in a randomised, controlled trial conducted in the same setting as where this current study took place (Harrison et al., 2003a; Harrison, Johnston, Loughnan, & Manias, 2005) and is within the range of sucrose concentrations reported in other randomised, controlled trials of sucrose analgesia in newborn infants (Stevens et al., 2004). The sucrose solution was prepared as per routine practice in the Pharmacy Department, RCH, Melbourne, by diluting 150mL of Syrup British Pharmacopeia (BP) (David Craig Galenicals, Carole Park, Queensland, Australia), containing 66.7 g sucrose/100 g, with 250 mL sterile Water for Irrigation BP (Baxter Healthcare Pty Ltd, Sydney, NSW, Australia). As per the Oral sucrose for procedural pain guidelines, which were based both on evidence from the randomised, controlled trial conducted in the same NICU setting as where this study took place, and the Cochrane Systematic Review of sucrose analgesia in newborn infants (Harrison et al., 2003a; Harrison, Johnston, Loughnan, & Manias, 2005; Stevens et al., 2004), the total dose per procedure was 0.5 to 1.0 mL for infants on enteral feeds weighing >1500 grams. For those infants weighing less than 1500 grams, the maximum volume of sucrose given was 0.5 mL. If
the infant was nil orally at time of study, 0.2 mL maximum per procedure was administered. Where possible, if the infant was able to suck, all infants were offered a pacifier to encourage NNS.

Following documentation of baseline observations two minutes prior to lancing of the heel, a small amount (around 0.25 mL or 0.05 mL if infant was nil orally) of sucrose was syringed onto the infant’s tongue. A pacifier was offered if the infant was able to suck. Sucrose was given in small increments, upon commencement of the procedure, and every two minutes if the procedure continued beyond this time. Sucrose doses within this range have previously been shown to be effective in reducing infants’ responses to procedural pain, and have been administered to term and premature infants with no report of adverse events in relation to sucrose per se (Gibbins et al., 2002; Stevens et al., 2004).

*Instruments*

Data were recorded as per the procedural pain data collection sheet (Appendix 9). Baseline observations were documented prior to handling the infant for administration of the sucrose solution. Baseline observations comprised behavioural state (Prechtl, 1974), PAT score (Hodgkinson et al., 1994), proxy severity of illness score using the Neonatal Therapeutic Intervention Scoring System (NTISS) (Gray, Richardson, McCormick, Workman-Daniels, & Goldmann, 1992) and behavioural and physiological observations. Behavioural observations at baseline comprised a four-point subset of the Neonatal Facial Coding System (Grunau & Craig, 1987), and physiological observations comprised baseline heart rate and oxygen saturation levels. Also recorded was any handling which occurred in the previous hour prior to the heel lance procedure, as studies have shown that recent handling prior to a heel lance procedure may either increase behavioural and physiological responses to pain compared to infants not handled prior to the procedure (Porter, Wolf, & Miller, 1998), or conversely, result in a dampened response (Johnston, Stevens et al., 1999).

*Behavioural state*

Behavioural states of infants at the commencement of a heel lance procedure has been shown to impact on the responses elicited, with infants in a quiet sleep state
responding less than infants in an alert wake state (Grunau & Craig, 1987; Stevens et al., 1996). Behavioural state at baseline was therefore recorded, and categorised according to one of the five following distinct states (Prechtl, 1974):

State 1: Eyes closed, regular respiration, no movements.
State 2: Eyes closed, irregular respiration, small movements.
State 3: Eyes open, no movements.
State 4: Eyes open, gross movements.
State 5: Crying (vocalisation).

Severity of illness score

The Neonatal Therapeutic Intervention Scoring System (NTISS) (Gray et al., 1992), was used as a proxy severity of illness score, and was scored each day the PhD candidate conducted a pain assessment during heel lancing. This therapy-based score, which is a proxy severity of illness score, was chosen as the most suitable scoring system to best represent the illness status of infants on the day of study. The NTISS is a validated therapy scoring system consisting of a total of 63 items. Scores from one to four are assigned to items based on their therapeutic intensity and complexity, with individual items further grouped into eight categories. The eight categories comprise respiratory, cardiovascular, drug therapy, monitoring, metabolic/nutrition, transfusions, procedural and vascular access. The higher the NTISS score, the more interventions required, signifying a sicker infant (Appendix 10).

All NTISS scoring was done by the PhD candidate. NTISS scores were collected by review of the infants’ charts each day a pain assessment during heel lancing was conducted. Minor adaptations of the NTISS scores were required to facilitate use of the scoring system for the population of infants included in this study, especially as therapies listed did not include surgical therapies. Also, as scoring was done throughout the period of hospitalisation, time limits were imposed on some of the subgroups. Although some procedures would still impact on the behaviour of the infant weeks after the event, to score all therapies that the infant had been exposed to during the course of their hospitalisation would have resulted in misleadingly high scores for all the infants. Therefore, the following interpretations of the NTISS scoring system, including the specified time limitations, were made:
- Respiratory: Surfactant administration within the last two weeks.
- Cardiovascular: Infants on cardiovascular medications not otherwise listed, such as captopril, enalapril, digoxin, were allocated a score of one.
- Drug Therapy: Other unscheduled medications: All other medications that were not specifically listed but were prescribed on the infants’ medication chart were allocated a score of one. This included “routine” medications such as oral nystatin and sucrose as well as intravenous saline flushes.
- Monitoring: Phlebotomy: Included all venous and capillary samples taken in the last two weeks during admission at The Royal Children’s Hospital.
- Urinary Catheter: Included all catheters currently in situ. For example, suprapubic catheters nephrostomy tubes, ureteric catheters.
- Procedural:
  - Single chest tube in place: Included all ostomies, gastrostomy tubes, drainage tubes (other than urinary catheters), wound dressings, and nasogastric tubes on free drainage.
  - Minor Operation: Score of two was allocated for each minor operation within the previous seven days. Included surgically placed central lines.
  - Major Operation: Score of four allocated for each major operation within the previous seven days.
- Vascular Access: Score of one allocated for each venous catheter present

Pain assessment procedure

The PhD candidate ensured that all infants were being monitored continuously by a cardiorespiratory and pulse oximetry monitor. If, on the day of a study, an infant was not monitored continuously, electrocardiogram leads and a pulse oximetry probe were applied to enable continuous measurement of heart rate and pulse oximetry. One of two monitors was used: either a Philips IntelliVue patient monitor, model MP70 (Philips Medical Systems, Andover, MA, USA) or, if the infant required a monitor to be connected for the purpose of the study, a Hewlett Packard Transport Monitor, model M1276A (Hewlett Packard, Andover, MA, USA) was used. Application of appropriate leads for monitoring was completed at least thirty minutes prior to the infant’s participation in the study, to safeguard against the behavioural state at
baseline being influenced by the required handling. Where possible, all infants were swaddled during the procedure.

Following documentation of baseline observations, sucrose solution was administered onto the infant’s anterior tongue two minutes prior to the heel lance. A pacifier was offered if NNS was a normal part of care, conditional on the infant’s ability to suck. A further increment of sucrose solution was administered onto the infant’s anterior tongue immediately prior to the heel lance. The heel lance procedure was performed in a standardised manner by one of five experienced hospital employed phlebotomists using tenderfoot® preemie lancets (International Technidyne Corporation, Edison, New Jersey, USA). Following completion of the study, the infant’s comfort was assured, and continuous cardiorespiratory monitoring was ceased if it was no longer required.

**Pain Assessment Method**

A combination of behavioural and physiological measures was used to assess pain in infants in response to heel lancing. The behavioural and physiological responses were measured and recorded independently. As infants may not exhibit concordant behavioural and physiological responses to painful procedures, the independent measures of responses allowed separate analyses of each of the domains (Morison et al., 2001).

Behavioural measures comprised a four-point facial expression score plus measurement of the duration of crying. Facial expression scores were assigned at set observation points prior to, during, and in the three minutes following completion of the heel lance procedure.

The facial expression score used comprised a subset of four of the original ten-point Neonatal Facial Coding System (NFCS) (Grunau & Craig, 1987). The four facial expressions were brow bulge, eye squeeze, nasolabial furrow and open mouth. As reported by Grunau and Craig (1987), these four facial expressions were displayed by 99% of infants studied within six seconds of instigation of a heel lance. One point was scored for each facial expression if present, at each of the observation points.
Scoring was accomplished at the bedside whilst the procedure was in progress. The use of both the full NFCS and the four-point subset, has been shown to be valid and reliable as well as feasible for clinical use at the bedside (Rushforth & Levene, 1994; Grunau, Oberlander et al., 1998; Harrison et al., 2002). To ensure consistency of pain scoring, all pain assessments were conducted by the PhD candidate, who is experienced in the use of the four-point NFCS as a measure of procedure-related pain in hospitalised infants (Harrison et al., 2002; Harrison et al., 2003a).

As a quality check during the data collection period, to ensure reliability of the bedside scoring of the four-point NFCS, and to minimise the risk of bias occurring as a result of all assessments being conducted by the PhD candidate, inter-rater agreement was examined throughout the data collection period. Scoring was performed simultaneously at the bedside by the PhD candidate and a nursing research student during a total of 43 pain assessments over two separate four-week periods, six months apart. The students received approximately one hour of education on bedside assessment of procedural pain using the four-point NFCS. Using the Kappa statistic, agreement was shown to be high at both time periods. In the first time period, comprising pain assessments during 22 heel lance procedures, there was 97% agreement, giving a Kappa of 0.87 (p<0.05). In the second period, inter-rater agreement was calculated at 93.3%, giving a Kappa Statistic of 0.71 (p< 0.05).

If infants had a capacity to cry, audible crying, both during the heel lance procedure, and in the three-minute period following completion of the blood collection, was measured by recording infants’ cries with a digital audio recorder, using a Sony® IC Recorder (ICD-MS1). Cry data were recorded onto a memory stick, and downloaded onto a personal computer for later analysis. All recordings were analysed by the PhD candidate. Crying characteristics measured from the recordings were:

- Duration of the first cry until a five second pause
- Duration of crying time during the heel lance procedure, calculated as a percentage of crying during the blood collection
- Duration of crying time during the three-minute period following completion of the capillary blood collection procedure, expressed as the percentage of time crying during the three-minute observation period
As a quality check mid-way during the data collection period, to ensure satisfactory agreement on the measurements of crying duration, 31 cry recordings were randomly selected to be scored independently by a nursing research student. Agreement of proportion of crying time during the procedure, compared to the crying time originally recorded, was shown to be high, as evidenced by Lin’s concordance correlation coefficient of 0.98, with a mean difference between scorers of 0.4% (SD 5%). Figure 1 shows a Bland-Altman plot depicting agreement of crying times between the PhD candidate and the nursing research student.
Figure 1. Agreement of crying duration (%) between two assessors

Mean versus differences between percentages of crying during 31 heel lance procedures.
Physiological parameters monitored and recorded at pre-determined observation points during and following completion of the heel lance procedure comprised heart rate and oxygen saturation (SpO$_2$). Completion of the procedure was defined as cessation of handling on completion of blood collection.

Observation points at which pain assessments were documented were first at baseline, then at the following discrete time points:

- Upon heel lance
- 30 seconds following the heel lance
- One minute
- Minutely until either completion of the procedure, or for a maximum of three minutes if the procedure was prolonged beyond this time period
- Upon immediate completion of the heel lance procedure
- Minutely for three minutes following the completion of the procedure

A digital clock timer was used to time the procedure, and to ensure documentation of pain assessment scores at each of the pre-set observation points during and following completion of the procedure.

*Ethics*

The same ethics application as presented in the previous methods section was used. The study was considered to be low risk with no alterations in medical or nursing care. The majority of criteria for an Expedited Review through The School of Nursing, The University of Melbourne, Departmental Human Ethics Advisory Group, were therefore fulfilled and ethics approval as an Expedited Review for Low Risk Research Projects was granted on the 5$^{th}$ August 2004 (HREC Project Number, 040641). (Appendix 6) All criteria for a Clinical Audit, through the Royal Children’s Hospital Ethics in Human Research Committee were fulfilled and the study was approved as a Clinical Audit on the 28$^{th}$ June 2004 (Reference number AUD/2001). (Appendix 7)

An introductory letter, explaining the purpose of the study, was given to parents of recruited infants (Appendix 8). Included in this letter of introduction was the
explanation that the heel lance procedures observed in the study, and the accompanying administration of sucrose, were part of routine clinical care. The statement, “No blood test or drug administration will be done for the purpose of the study” was included.

Due to the low risk nature of the study, and there being no alteration in the care of infants as a result of them being included in the study, a request was made to the Departmental Human Ethics Advisory Group, The School of Nursing, The University of Melbourne, to waive the requirement to obtain informed parental consent. Parents of sick infants are vulnerable, and are exposed to a large amount of information, particularly in the first 48 hours of a sick infant’s admission to hospital (Harrison, Johnston, & Loughnan, 2003b). If the infants are newborn, the mothers are still recovering from the stresses of labour and birth, and are often not able to be present when their infant is admitted to the Royal Children’s Hospital, Melbourne. The fathers of the infants are therefore often required to take responsibility for understanding the explanations of health professionals concerning their sick infant’s illness, and communicating this back to the mother. Obtaining full informed consent for research studies at this time is extremely stressful (Mason, 1997; Morley, 1997). Due to the low risk nature of this study with no alteration in care, and no personal or new information collected from the medical records, it was determined by the investigators, that obtaining informed parental consent was not warranted and not in the best interest of parents. The request to waive the requirement for obtaining written informed parental consent was consequently granted. The plain language statement however advised parents to contact either the investigators of the study, or the Nurse Unit Manager of the NNU, or the Consumer Liaison spokesperson in the Clinical Support Services Team, Executive Office, Royal Children’s Hospital, if they had any concerns about the study, thereby giving parents the opportunity to withdraw their infant from the study at any time.

Data analysis

Data were entered into an Access database (version 2003) and imported into both Microsoft Excel version 2003 and Stata 9.0 Statistical Software (StataCorp, 2001) for analysis. Categorical data are described as frequencies and proportions, and continuous data are reported as means and standard deviations if normally distributed,
and medians and interquartile ranges if non-normally distributed. The method of summary measures was used to analyse changes in successive pain scores over time (Matthews, Altman, Campbell, & Royston, 1990). This method considered each individual infant’s pain response at each successive assessment. A linear regression slope was fitted to the individual infant’s scores, with the pain response as the dependent variable and the sequential number of the pain assessment performed as the explanatory variable. The regression coefficient of the slope of the line fitted to the individual infant’s scores was obtained. Each regression coefficient for all parameters measured, gave a slope estimate, which reflected whether the response for that infant was generally decreasing, remaining steady, or increasing. As this method summarises each individual’s own pattern of response, it is an appropriate, clinically relevant method of data analysis as the main point of interest is the way each individual responds over a period of time as expressed by successive pain assessments (Matthews et al., 1990). Inferences about the sample of individual infant’s regression slopes were then carried out to estimate the population average slope and to test whether the population average was zero. Results are expressed as an estimate of the 95% confidence interval. P-values of less than .05 were considered statistically significant.

All other data, including possible confounding influences on pain responses, are presented descriptively with no inferential statistical tests performed. Although further hypothesis testing was considered, it was expected that the data would not meet underlying statistical assumptions of independent measures.
CHAPTER 3. RESULTS: NATIONWIDE PAIN ASSESSMENT AND PAIN MANAGEMENT SURVEY

This chapter presents findings of the nationwide neonatal pain assessment and pain management survey which was conducted to ascertain procedural pain management strategies and pain assessment methods used in Australian neonatal units.

During December 2003 and January 2004 the survey was mailed to Nurse Unit Managers of Level Three neonatal intensive care units (NICUs), Level Two special care units (SCNs), and newborn emergency transport services (NETS) in Australia. A total of 181 institutions met the above criteria. One hundred and five surveys were returned (58% response rate). Three surveys were returned from six newborn emergency transport teams, a response rate of 50%, 13 from the 23 NICUs (56% response rate), and 89 from the 152 Level Two SCNs (58% response rate). There were 58 requests for a summary of the results from the 105 respondents.

Some respondents failed to answer all the questions, or components within the questions. These surveys were still included in the analysis. Discrepancies in numbers of responses for many of the survey questions therefore occurred. Discrepancies are explained in the relevant sections throughout this chapter.

Pain assessment practices

Question One on the survey asked, “Does your unit use any pain assessment scores on a regular basis?” Respondents were asked to proceed to Question Six if they answered “no”.

Respondents from six units (six percent) reported using pain assessment scores on a regular basis. Three of these units were Level Three NICUs, and three were SCNs. Question numbers from One to Five were therefore only relevant to these six respondents. Question Two sought to identify the situations in which pain scores were routinely performed.
In one Level Three NICU, pain assessment scores were used for all the five given situations; during regular documentation of routine observations, during procedures, for research purposes and when on analgesic medications. In the other five units, the situations in which pain assessment scores were used on a regular basis were: post-operatively (one unit), during procedures (three units), for research purposes (one unit) and when on analgesia (three units). Two respondents also ticked the “other” situation category, and specified; “on an ad hoc basis”, and “if infant unsettled, chest drains in situ, or clinically justified”.

Question Three asked, “If pain assessments are routinely performed, are they documented on a permanent record?”

Respondents from all six units that routinely used pain assessment scores reported that pain assessments were documented on a permanent record. In four units, pain assessments were documented on more than one record. In one unit, pain assessments were documented on four records; nursing notes, a separate pain assessment chart, observation charts and medical notes. Two respondents reported that pain assessments were documented on both a designated pain chart and an observation chart, and in one unit, pain assessments were documented in nursing notes and observation charts. In the remaining two units, pain assessments were documented in nursing notes only.

Of the six units in which there was regular use of a pain assessment method reported, a single pain assessment tool was used in four units, and two different pain assessment tools were used in two SCNs. Pain assessment tools used were, the Pain Assessment Tool (PAT), the Premature Infant Pain Profile (PIPP), the Neonatal Infant Pain Scale (NIPS) and the Comfort scale. In addition, one respondent reported that a new scale developed in their own unit was in use, and one respondent reported that pain assessment was based on both parents’ opinion of their own baby’s pain as well as “individual assessments based on behaviour, facial expressions and crying”.

*Procedural pain management practices*

Question Six of the survey asked, “Does your unit have a policy or guideline directing pain management practices during minor procedures?” One respondent failed to answer this question. Only 16 of the 104 respondents (15%) ticked the “Yes” box.
Four of these units were NICUs (30% of responding NICUs), and 12 were SCNs (13% of responding SCNs).

Question Seven of the survey asked respondents to rate the frequency of pain management strategies used during the six listed commonly performed painful procedures. Combining the results of all six procedures illustrated that in the majority of units, the pain management strategies used were primarily of a non-pharmacological nature, with NNS being used most frequently, followed by comfort measures such as cuddling, wrapping and nesting. For all minor painful procedures combined, there was infrequent use of oral sucrose or other sweet tasting solutions for the reduction of pain. NNS alone was the most frequently used strategy, with 77% of units using NNS either “occasionally”, “often” or “always” during the six painful procedures. Only ten percent of respondents reported that mothers breastfed their infants during heel lance, venepuncture or intravenous cannulation and intramuscular or subcutaneous injections. “Other” comfort measures such as cuddling, swaddling, nesting were used in 64% of units during procedures when possible.

The option of “No analgesia/comfort measures used” was either not ticked correctly or left blank by the majority of respondents. Most respondents continued to tick the option of “never used” as they worked their way down the list of pain management strategies, if the options of pain reduction strategies previously listed were also ticked as “never used”. Nine respondents also wrote critical comments on the survey in relation to this option. Such comments included that the option of “No analgesia/comfort measures used” was confusing, was a double negative statement, and should not be included on the survey. For these reasons of inaccurate or incomplete responses, results relating to the option of “No analgesia/comfort measures used” were omitted from analysis and will not be reported on further.

Pain management strategies used during heel lance

The number of respondents who completed all components of each of the questions relating to the six possible pain management strategies used during heel lancing ranged from 99 respondents through to 104. As shown in Figure 2, the pain management strategy reportedly used most frequently during a heel lance procedure was NNS alone. Out of the 102 respondents who entered an option of frequency of
use for NNS, seven respondents (seven percent) ticked the option of NNS “always” being used, 48% of respondents replied that NNS was used “often”, and 29% replied that NNS was used “occasionally”.

Results showed infrequent use of oral sucrose alone during a heel lance procedure. There were 93 respondents (90%) who reported that oral sucrose alone was never used, six respondents (five percent) reported that oral sucrose alone was sometimes used, and five (five percent) respondents reported that oral sucrose alone was often used. There were no respondents who reported that oral sucrose alone was always used. There was also infrequent use of oral sucrose combined with NNS. Six respondents (six percent) reported that this option was used often and 12 (12%) reported sucrose combined with NNS was used occasionally. The majority of respondents; 85 (82%), reported that sucrose combined with NNS was never used during heel lancings (Figure 2). “Other” pain reduction strategies, primarily cuddling, nesting and swaddling, were “always” used in 11% of units, “often” in 44% and “occasionally”, in 74% of the units. Two respondents also specified parental assistance as an “other” pain reduction strategy.

**Venepuncture and arterial line insertion**

The frequency of pain reduction strategies utilised during intravenous cannula insertion or venepuncture, and arterial line insertion were similar, with little use of oral sucrose, and frequent use of NNS (Figures 3 and 4). Breastfeeding was used in 24% of units during venepuncture, although for most units; both in Level Three NICUs and Level Two SCNs, breastfeeding was used only occasionally. During arterial line placement or arterial blood sampling, breastfeeding was used “occasionally” in seven units and “often” in two units. Listed in the “other” category, in addition to cuddling, nesting and swaddling, was “occasional” use of injected local anaesthetic, intravenous morphine or sedation. One unit indicated parental involvement was “always” used.
Data presented as percentage frequency of use reported for each pain reduction strategy, with numbers of respondents reporting each pain reduction strategy presented above each bar. Numbers of respondents vary between strategies as not all respondents placed a tick in each pain reduction strategy presented.
Figure 3. Frequency of use of pain reduction strategies during venepuncture

Data presented as percentage frequency of use reported for each pain reduction strategy, with actual numbers of respondents reporting each pain reduction strategy presented above each bar. Numbers of respondents vary between strategies as not all respondents placed a tick in each pain reduction strategy presented.

“Other” strategies specified were primarily cuddling/nesting/stroking or talking to the infant during the procedure (36), injected local anaesthetic (6), intravenous morphine or sedation (1) and involving parents in soothing infant (1).
Figure 4. Frequency of use of pain reduction strategies during peripheral arterial stab or peripheral arterial catheter placement

Data presented as percentage frequency of use reported for each pain reduction strategy, with numbers of respondents reporting each pain reduction strategy presented above each bar. Numbers of respondents vary between strategies as not all respondents placed a tick in each pain reduction strategy presented.

Use of “other” strategies specified were primarily a combination of cuddling and nesting. Two respondents reported using injected local anaesthetic “occasionally” and one respondent reported that injected local anaesthetic was always used.
**Lumbar Puncture**

As shown in Figure 5, of the 95 respondents who reported performing lumbar puncture, there was infrequent use of sucrose, whilst NNS alone was used at least “occasionally” in the majority of units. There was infrequent use of topical anaesthetic agents reported, although 12% of respondents reported use of injected local anaesthetic during lumbar puncture.

**Eye examination**

Ninety-four respondents completed the question relating to pain reduction strategies used during routine neonatal eye examinations. As illustrated in Figure 6, oral sucrose was infrequently used to reduce pain and distress during eye examination. NNS was used at least “occasionally” by 71% of units. Topical anaesthetic amethocaine eye drops were used in 50% of the units in total; 32% of respondents answered that amethocaine eye drops were “always” used, seven percent answered they were “often” used, and 12% answered amethocaine eye drops were “sometimes” used during eye examination (Figure 6).

**Intramuscular or subcutaneous injections**

This section was answered by 98 to 103 respondents, depending on the pain reduction strategies presented. The pain reduction strategy used most frequently during intramuscular or subcutaneous injections was NNS, with infrequent use of both oral sucrose and topical anaesthetic agents (Figure 7). Breastfeeding was offered more frequently during this procedure than other procedures, and was reportedly used in 32% of units “occasionally”, “often” in 12% of units, and “always” used in one SCN. “Other” pain reduction strategies included cuddling, wrapping, nesting or verbal soothing.
Figure 5. Pain reduction strategies used during lumbar puncture

Data presented as percentage frequency of use for each pain reduction strategy, with actual numbers of respondents reporting each pain reduction strategy presented above each bar. Actual numbers vary between strategies as not all respondents placed a tick in each pain reduction strategy offered. NB, in “other” category, 12 respondents specified the use of injected local anaesthetic. Five units used injected local anaesthetic occasionally, two units, often, and five units reported always using injected local anaesthetic during lumbar puncture. There was one respondent who reported that intravenous morphine or sedation was given if there was an intravenous catheter in situ.
Figure 6. Pain reduction strategies used during eye examinations

Eye examination was performed in 94 of the responding units. Data presented as percentage frequency of use for each pain reduction strategy, with actual numbers of respondents reporting frequency of use for each pain reduction strategy presented above each bar. Total numbers for each strategy do not always add up to 94, as some respondents failed to place a tick in all pain reduction strategies listed.
Figure 7. Frequency of pain reduction strategies reported during intramuscular or subcutaneous injection

Data presented as percentage frequency of use for each pain reduction strategy, with actual numbers of respondents reporting frequency of use for each pain reduction strategy presented above each bar. Total numbers for all strategies are not always identical, as some respondents failed to place a tick in all pain reduction strategies listed.
Question Eight sought details from respondents of units in which sweet solutions were used, on the type of solution used, as well as the volume and concentration. Respondents of 24 units (23%) reported that sweet tasting solutions were used, although, the actual frequency of use of sweet tasting solutions during minor painful procedures was low. Five of these units were NICUs (38% of responding NICUs), 17 SCNs (19% of responding SCNs) and two of the six newborn emergency transport teams. Eleven respondents reported use of oral sucrose, with concentrations ranging from 20% through to the undiluted Syrup British Pharmacopeia, an 88% (wt/vol) concentrate. Nine respondents ticked the “other” category of sweet solutions. All nine respondents wrote that the commercially available Glycerine BP ten percent was used. Eight of these respondents were from SCNs and one worked in a newborn emergency transport team. Glucose was used in four units, with concentrations ranging from a ten percent solution up to 50%. Volumes for all solutions ranged from a few drops on a pacifier, or a measured volume of 0.1 mL up to 2.0 mLs.

Question Nine asked those respondents who used sweet solutions, whether there were contraindications for the use of sucrose. Question Ten then sought further information about these contraindications. A list of ten contraindications was presented, and respondents were asked to tick all those which were relevant. Sixteen respondents ticked one or more contraindications for using sweet tasting solutions (Table 2).
Table 2. Contraindications for the administration of oral sucrorse

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental Refusal</td>
<td>12</td>
</tr>
<tr>
<td>Confirmed necrotising enterocolitis</td>
<td>11</td>
</tr>
<tr>
<td>Suspected necrotising enterocolitis</td>
<td>11</td>
</tr>
<tr>
<td>Other:</td>
<td>10</td>
</tr>
<tr>
<td>Known fructose intolerance</td>
<td>4</td>
</tr>
<tr>
<td>Un-repaired tracheoesophageal fistula</td>
<td>2</td>
</tr>
<tr>
<td>&gt; 3 months corrected gestational age</td>
<td>2</td>
</tr>
<tr>
<td>&lt;1000 grams</td>
<td>1</td>
</tr>
<tr>
<td>Infant of diabetic mother</td>
<td>1</td>
</tr>
<tr>
<td>Altered conscious state</td>
<td>8</td>
</tr>
<tr>
<td>Infants of mothers taking methadone</td>
<td>7</td>
</tr>
<tr>
<td>Nil by mouth for any reason</td>
<td>6</td>
</tr>
<tr>
<td>Infants on opioid infusion</td>
<td>5</td>
</tr>
<tr>
<td>Below a specified gestational age</td>
<td>4</td>
</tr>
<tr>
<td>&gt; 2 months corrected post-natal age</td>
<td>2</td>
</tr>
<tr>
<td>(Specified by respondents as 32 and 34 weeks)</td>
<td></td>
</tr>
<tr>
<td>&gt; 4 months corrected post-natal age</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 6 months corrected post-natal age</td>
<td>0</td>
</tr>
</tbody>
</table>

Question 11 was also directed at those respondents who reported use of sucrrose or other sweet tasting solutions in their units. This question elicited the health professional responsible for ordering the solutions. Twenty-three of the 24 respondents, who had reported using sweet tasting solutions, answered this question. Nine respondents answered that medical officers were responsible, four answered that nursing staff were responsible, and 11 ticked the option of “No written order required”.

Knowledge: Sucrose

Question Number 12 on the survey, concerning safety, efficacy and utility of oral sucrose, was left unanswered by 22% of respondents. Results showed that 52 of the 82 respondents (63%) were aware that oral sucrose or other sweet tasting solutions had been shown in clinical trials to be effective in reducing pain. However, only 40 respondents (49%) answered that sucrose was safe, 42 (51%) answered that sucrose works almost immediately and less than half of the respondents answered that sucrose was readily available for use in the ward setting (Table 3).
Table 3. Knowledge regarding safety, efficacy and utility of oral sucrose

<table>
<thead>
<tr>
<th>Oral sucrose:</th>
<th>True n (%)</th>
<th>False n (%)</th>
<th>Unsure n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective in reducing pain</td>
<td>52 (63)</td>
<td>4 (5)</td>
<td>26 (32)</td>
</tr>
<tr>
<td>Safe</td>
<td>40 (49)</td>
<td>6 (7)</td>
<td>36 (44)</td>
</tr>
<tr>
<td>Readily available</td>
<td>33 (40)</td>
<td>27 (33)</td>
<td>22 (27)</td>
</tr>
<tr>
<td>Works almost immediately</td>
<td>42 (51)</td>
<td>8 (10)</td>
<td>32 (39)</td>
</tr>
</tbody>
</table>

N = 82 respondents (78%)

Knowledge: Topical Anaesthetic Agents

Question Number 13, concerning knowledge related to safety, efficacy, availability and mechanism of action of topical anaesthetic agents was answered by 85 (81%) of respondents. Fifty-four of the 85 respondents (64%) answered that topical anaesthetic agents had been shown in clinical trials to be effective in reducing pain, although only 39% answered that these agents were safe. Fifty-one (61%) respondents answered that topical anaesthetic agents were readily available for use in the ward setting (Table 4).

Table 4. Knowledge regarding safety, efficacy and utility of topical anaesthetic agents

<table>
<thead>
<tr>
<th>EMLA®, AnGEL, other amethocaine creams</th>
<th>True n (%)</th>
<th>False n (%)</th>
<th>Unsure n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective in reducing pain</td>
<td>54 (64)</td>
<td>0 (0)</td>
<td>31 (36)</td>
</tr>
<tr>
<td>Safe</td>
<td>33 (39)</td>
<td>13 (15)</td>
<td>39 (46)</td>
</tr>
<tr>
<td>Readily available</td>
<td>51 (61)</td>
<td>16 (18)</td>
<td>18 (21)</td>
</tr>
<tr>
<td>Works almost immediately</td>
<td>14 (16)</td>
<td>49 (58)</td>
<td>22 (26)</td>
</tr>
</tbody>
</table>

N = 85 respondents (81%).

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Summary of survey results

In conclusion, this nationwide pain assessment and pain management survey, which was posted to Nurse Unit Managers or their nominees of 181 neonatal unit settings in Australia, was completed and returned by 105 (58%) respondents. Results showed that only 16 (15%) units had a policy or guideline directing pain management during painful procedures, and that pain assessment scores were routinely documented in only six (six percent) units. Oral sucrose or other sweet tasting solutions were reported as being used in 24 units (23%), although the actual frequency of use during the six nominated commonly performed minor painful procedures was low. Respondents also reported low frequency of use of breastfeeding during procedures when feasible, and almost no use of topical anaesthetic creams in all relevant nominated procedures. Non-nutritive sucking and other non-pharmacological comfort measures were the pain management strategies used most frequently during all six nominated minor procedures.

Although there was infrequent use of oral sucrose, either alone or in combination with NNS during all procedures, almost two thirds of respondents were aware of the analgesic effects of oral sucrose. However 36 (44%) respondents ticked that they were uncertain of the safety of oral sucrose.

This chapter presented findings of the first question of the study; the ascertainment of pain assessment methods and procedural pain management strategies used in Australian neonatal units. The following chapter presents results of the second question, which extended beyond pain management practices in multiple neonatal units, and focussed on mapping painful procedures, pain management practices and documentation of pain assessment scores in a single neonatal unit, in a cohort of infants throughout an entire hospitalisation episode.
CHAPTER 4. RESULTS: THE HISTORY OF AN INFANT'S PROLONGED HOSPITALISATION WITH RESPECT TO PAINFUL PROCEDURES AND PAIN MANAGEMENT PRACTICES

This chapter presents results of the second aim of the study, that of mapping painful procedures, analgesic and sedative administration and documentation of pain assessment scores throughout the duration of hospitalisation of a cohort of infants with a predicted length of stay in the Neonatal Unit (NNU), Royal Children’s Hospital (RCH) of 28 days or more. The design of this phase of the study was a prospective longitudinal observational study. Infants were enrolled within the first two days following admission to the NNU, RCH, if their length of stay was predicted to be 28 days or more.

Information was collated from two records; both the investigator’s daily pain diary and the bedside nurses’ pain record of minor painful procedures occurring in the cohort of infants. The information collected in the investigator’s daily pain diary was in relation to administration of pharmacological agents known to affect pain, major procedures, such as surgery, endotracheal intubation and insertion of chest drains, as well as documentation of pain assessment scores by clinicians. The pain record completed by the bedside nurses for each infant in the cohort included the number and type of minor invasive painful procedures, the use of NNS and sucrose during each procedure, and the number of attempts required for completion of each procedure.

Infant demographics

Data collection commenced on August 11th 2004. Infants were enrolled over an 11-month period until July 11th, 2005. Data collection for infants enrolled in the study continued until their discharge from the NNU, RCH. Data collection was completed on the 10th November 2005 when the last infant was discharged. During this period, there were 524 admissions to the NNU. There were 33 readmissions, giving a total of 491 infants admitted over the data collection period. As seen in Figure 8, of the 524 admissions to the NNU, 101 admissions had a predicted length of stay of 28 days or more. Two infants were ineligible due to suspected hereditary fructose intolerance in
one infant, and maternal antenatal methadone use in another infant. The length of stay in the NNU for the remaining 423 infants was predicted to be less than 28 days, however seven of these infants did have a length of stay over 28 days. The median length of stay for these seven infants was 38 days, ranging from 29 days up to 149 days. Listed are the diagnoses of these seven infants:

- Chylous ascites of unknown cause
- Chronic lung disease
- Meconium aspiration
- Gastrointestinal perforation in a term infant
- Lipid storage disease
- Necrotising enterocolitis
- Non-chromosomal congenital abnormality of unknown cause

Six of these infants survived to discharge. The infant with the lipid storage disease died 34 days following admission to the NNU.

Of the 101 infants enrolled into the study, 43 did not fulfil the criteria of a length of stay of 28 days or more. Thirty-seven infants were discharged or transferred to other neonatal care settings prior to 28 days, and six infants died prior to 28 days of stay. Fifty-six infants in total who were enrolled did have a length of stay for the pre-specified time period of 28 days or more. One infant was removed from the study after enrolment following the father’s request. Fifty-five infants enrolled in the study fulfilled the study criteria of a length of stay in the NNU of 28 days or more. Figure 8 illustrates the participant flow from admission to the NNU, throughout the study.
Figure 8. Participant flow from admission, throughout the study
All 55 infants in the cohort were admitted from another hospital. Thirty-seven (67%) infants were admitted either on the day of birth, or the following day, whilst the remaining infants’ age on admission was evenly distributed over the first month of life (Figure 9). Two infants in the cohort were older than one month of life when admitted to the NNU. Figure 10 shows the distribution of gestational age (weeks) at birth and on admission to the NNU. As shown, gestational age (weeks) ranged from 24 to 40 weeks with a median gestational age of 36 weeks and an interquartile range (IQR) of 33 to 38 weeks. Six infants were born younger than 28 weeks gestation and most infants were born at or near term. At the time of admission to the NNU, only two infants (4%) were less than 28 weeks corrected gestational age and the majority of infants (53%) were admitted at 37 weeks corrected gestational age or older (Figure 10). The median birth-weight was 2607 grams and ranged from 602 to 4120 grams.

There were 34 (62%) males and 21 females (38%) enrolled in the study. These proportions were consistent with the entire population of 524 admissions within the data collection period, with 328 (63%) being male and 196 (37%) of admissions being female. Forty-five of the 55 infants in the cohort were admitted with diagnoses of congenital abnormalities. Ten infants were admitted with a diagnosis of tracheo-oesophageal atresia, of whom five had other associated congenital abnormalities. Eight infants had congenital heart disease and associated abnormalities, eight infants were admitted with necrotising enterocolitis, and six infants were admitted with congenital diaphragmatic hernia. Diagnoses of all 55 infants are presented in Table 5.

The median length of stay for the 55 infants in the cohort was 50 days with an IQR of 38 to 77 days. The shortest length of stay was 28 days, and the longest was 181 days. In terms of discharge status, nine infants (16%) died as inpatients in the NNU. Twenty-seven (49%) infants were discharged direct to home. The remaining 19 (35%) infants were transferred to another paediatric or neonatal setting. Nine infants were transferred to a special care nursery, five infants were transferred to other neonatal intensive care units and five infants were transferred to paediatric wards within the RCH, Melbourne. The accumulated data collection days for this cohort of 55 infants were 3384 days.
Figure 9. Age (in days) on admission to the NNU

(N=55)
Figure 10. Gestational age (weeks) at birth and corrected gestational age on day of admission to the NNU

(N=55)
Some of the following data are presented by weeks of hospitalisation. Table 6 therefore lists the number of infants in the study during each week of hospitalisation. Data for the weeks of 20 through to 26 weeks of hospitalisation are aggregated as only two infants remained as inpatients in the NNU, RCH up to week 22, and from week 23 to 26, only one infant remained as an inpatient.
Table 6. Total number of infants enrolled by end of each week of hospitalisation

<table>
<thead>
<tr>
<th>Week of hospitalisation</th>
<th>Number of infants in study</th>
<th>Total number of data collection days for all infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>Days 1 - 2: 55 Days 3 - 7: 55</td>
<td>106</td>
</tr>
<tr>
<td>Week 2 – 4</td>
<td>55</td>
<td>385</td>
</tr>
<tr>
<td>Week 5</td>
<td>49</td>
<td>349</td>
</tr>
<tr>
<td>Week 6</td>
<td>42</td>
<td>287</td>
</tr>
<tr>
<td>Week 7</td>
<td>32</td>
<td>219</td>
</tr>
<tr>
<td>Week 8</td>
<td>26</td>
<td>184</td>
</tr>
<tr>
<td>Week 9</td>
<td>24</td>
<td>166</td>
</tr>
<tr>
<td>Week 10</td>
<td>17</td>
<td>117</td>
</tr>
<tr>
<td>Week 11</td>
<td>14</td>
<td>98</td>
</tr>
<tr>
<td>Week 12</td>
<td>12</td>
<td>86</td>
</tr>
<tr>
<td>Week 13</td>
<td>9</td>
<td>62</td>
</tr>
<tr>
<td>Week 14</td>
<td>8</td>
<td>54</td>
</tr>
<tr>
<td>Week 15</td>
<td>6</td>
<td>43</td>
</tr>
<tr>
<td>Week 16</td>
<td>4</td>
<td>28</td>
</tr>
<tr>
<td>Week 17</td>
<td>4</td>
<td>28</td>
</tr>
<tr>
<td>Week 18</td>
<td>4</td>
<td>27</td>
</tr>
<tr>
<td>Week 19</td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>Week 20</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Weeks 21 &amp; 22</td>
<td>2</td>
<td>14 per week</td>
</tr>
<tr>
<td>Weeks 23 – 26</td>
<td>1</td>
<td>7 per week</td>
</tr>
</tbody>
</table>

Analgesic and sedative administration

The following section reports results of data from the investigator’s daily pain diary (Appendix 5) relating to analgesic and sedative medications administered to the cohort of 55 infants throughout the infants’ hospitalisation. These data included administration, dosage, and route, of all analgesic and sedative agents including opioid analgesics, non-opioid strong analgesic medications, sedatives, oral sucrose, paracetamol, and regional anaesthesia following surgery. For the purposes of reporting, the term “strong analgesics” will refer to both opioid and non-opioid analgesics other than paracetamol and sucrose. For the purposes of reporting, this also includes the anaesthetic agent, ketamine.

The diary was completed for all enrolled infants on a daily basis for the hours from 0800 to 0800 (Appendix 5). Total numbers of analgesics or sedatives administered on an intermittent basis in the previous 24-hour period, as well as the total number of any
bolus doses of medications given in addition to continuous infusions, were recorded. If infants were on continuous infusions of medications, the dose/Kg being infused at 0800 hours was recorded. Table 7 lists the number and percentage of infants administered each medication as well as the median and interquartile days that each analgesic and sedative agent was administered.

Table 7. Administration of analgesics and sedatives to infants in the cohort

<table>
<thead>
<tr>
<th>Medication</th>
<th>n of infants receiving medication (%)</th>
<th>Median days on medication (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine (all morphine administered by all routes)</td>
<td>50 (91%)</td>
<td>11 (5-27)</td>
</tr>
<tr>
<td>Codeine</td>
<td>23 (42%)</td>
<td>3 (2-6)</td>
</tr>
<tr>
<td>Ketamine</td>
<td>5 (9%)</td>
<td>1 (1-5)</td>
</tr>
<tr>
<td>Clonidine</td>
<td>2 (4%)</td>
<td>9 (8-11)</td>
</tr>
<tr>
<td>Paracetamol (Intravenous)</td>
<td>3 (5%)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Paracetamol (Enteral)</td>
<td>51 (93%)</td>
<td>16 (11-28)</td>
</tr>
<tr>
<td>Fentanyl (intra-operative only)</td>
<td>32 (58%)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Sucrose</td>
<td>55 (100%)</td>
<td>21 (16-33)</td>
</tr>
<tr>
<td>Tramadol</td>
<td>1 infant on one day</td>
<td></td>
</tr>
<tr>
<td>Sedatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloral hydrate</td>
<td>36 (65%)</td>
<td>7 (2-20)</td>
</tr>
<tr>
<td>Midazolam</td>
<td>32 (58%)</td>
<td>6 (3-17)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>1 infant for 14 consecutive days</td>
<td></td>
</tr>
</tbody>
</table>

Calculation of median days on medication performed for those infants administered at least one dose of each analgesic or sedative.

**Opioid administration**

Only two infants did not receive any opioid analgesics throughout their hospitalisation. These two infants did not undergo any surgical or other major procedures such as endotracheal intubation or insertion of a chest drain during the course of their hospitalisation. The lengths of stay for these two infants were 28 days and 36 days respectively, substantially less than the median length of stay of 50 days for the infants in the cohort.

Morphine was the most frequently used opioid analgesic. Morphine was administered to 50 of the 55 infants on a total of 914 days equating to 27% of all data collection
days. This use of morphine included both continuous intravenous morphine infusions and morphine administered intermittently, via the intravenous or oral route. As shown in Table 7, the median number of days morphine was administered to the 50 infants was 11 days (IQR, 5-27). Forty-eight infants received continuous morphine infusions during the course of their hospitalisation. The median continuous morphine infusion dose was 20µg/Kg/hour (IQR, 16-32) and the median number of days on continuous morphine infusions for the 48 infants was 11 days (IQR, 5-22). A total of 223 bolus intravenous morphine doses in addition to continuous morphine infusions were administered to 42 of the 48 infants on 151 days.

Oral morphine was administered to eight infants on a total of 140 days. The median number of days on oral morphine for the eight infants was 12 days (IQR, 8-15). Two infants received oral morphine for three days, whilst one infant received oral morphine for a total of 67 days. On the days when oral morphine was administered, a mean of 4.7 ± 1.5 (SD) doses of oral morphine were given. The mean dose was 0.22 ± 0.26 mg/Kg (SD). On one day, one infant was administered both oral morphine and continuous intravenous morphine concurrently.

Opioid analgesics other than morphine, as well as non-opioid strong analgesics were used less frequently. Thirty-two (58%) infants received one or more intermittent doses of intravenous fentanyl. Fentanyl was only administered on an intermittent basis to infants whilst undergoing surgery, as per routine clinical practice in the RCH, Melbourne.

Enteral codeine was administered to 23 (42%) infants for a median of three days (IQR, 2-6). A total of 91 doses of codeine were administered to the 23 infants within three days following major surgery. Forty (44%) of the 91 doses of codeine were administered via the rectal route. Ketamine was administered to five infants and clonidine was administered to two infants only. One infant received clonidine for 12 consecutive days, and the other infant, for six consecutive days. Tramadol was administered to one infant on a single day only (Table 7).
Paracetamol administration

Paracetamol (acetaminophen) was administered to 51 of the 55 infants in the cohort. Of the four infants in the entire cohort who did not receive any paracetamol during their hospitalisation, one was a premature infant who underwent four surgical procedures during her stay, and was administered morphine for 24 of her 33 days of hospitalisation. Another infant was a medically stable, term infant who underwent one surgical procedure in which a single dose of morphine was administered at the time of surgery. With the exception of oral sucrose, no other analgesic was administered throughout her 29-day hospitalisation. The remaining two infants who received no paracetamol during their hospitalisation did not undergo any surgical or other major procedures. These two infants were the same infants who received no opioids or strong analgesics during hospitalisation, and whose lengths of stay were 28 and 36 days respectively.

At least one dose of paracetamol was administered on 1031 (30%) total data collection days. The total number of days in which paracetamol was administered to the 51 infants ranged from one day to eighty days, with a median of 16 days (IQR, 11-28). The total number of paracetamol doses administered to the 51 infants over the course of their NNU hospitalisation ranged from one dose to 179 doses, with a mean number of 44 ± 33 (SD) doses in total. The mean dosage of enterally administered paracetamol was 16 ± 3 mg/Kg (SD). Despite the institutional requirement to specify the route of administration of medications, the route of administration of paracetamol was not specified on the medication chart on 403 (39%) occasions. In 349 (34%) of cases, the route of administration of paracetamol was documented as orally and in 279 (27%) instances, the route was documented as rectally. The mean dose of paracetamol administered per Kg did not differ whether the route was un-recorded, or was either recorded as rectal or oral.

Intravenous paracetamol (Perfalgin®) became available at the NNU, RCH, midway through the data collection period and was administered to three infants in the cohort within 24 hours following a major surgical procedure. One infant received three doses at two days of age, one infant received two doses at 48 days of age, and the third infant received a single dose of intravenous paracetamol, when aged 53 days. Two of
these infants were also receiving continuous intravenous morphine infusions at 30µg/Kg/hour and 16 µg/Kg/hour respectively. The third infant was concurrently administered three doses of enteral paracetamol, at 15mg/Kg.

Sucrose administration
Sucrose was the most frequently used analgesic and was administered to the entire cohort of 55 infants over the course of the hospitalisation. A total of 2334 sucrose doses were recorded for the 55 infants. The median number of days when any sucrose was administered was 21 days (IQR, 16-33). The total doses of sucrose administered per day ranged from zero to a maximum of 11 doses documented for one infant, whilst the total doses of sucrose administered to each infant in the cohort over the course of the hospitalisation ranged from four to 174 doses. Figure 11 illustrates the pattern of administration of sucrose over successive weeks of hospitalisation. With the exception of the first two days following admission to the NNU, oral sucrose was administered between 38% and 60% of all data collection days, up until week 18 of hospitalisation. Administration of sucrose decreased substantially during week 18 although peaked again at 19 weeks, and reduced again from 20 weeks onward.
Figure 11. Percentage of data collection days when oral sucrose administered, as calculated over successive weeks of hospitalisation

Week 1 is separated into days one to two and day three through to seven. Data for weeks 20 to 26 are aggregated.
Due to reported safety concerns regarding the possible association of multiple doses of enteral sucrose with the development of necrotising enterocolitis, the incidence of confirmed necrotising enterocolitis diagnosed, following admission to the NNU, in the cohort of 55 infants was recorded. Only one infant in the cohort developed necrotising enterocolitis following admission to the NNU, RCH. This particular infant had been admitted with a large gastroschisis, which required a staged repair until primary surgical repair for closure of the abdominal sac was carried out at seven days of age. The infant developed necrotising enterocolitis at seven weeks of age, and was successfully treated conservatively with antibiotics without the need for further surgery. Forty-four doses of sucrose had been recorded for this infant prior to the diagnosis of necrotising enterocolitis. This was the only infant in the cohort with a new diagnosis of necrotising enterocolitis following admission to the NNU.

*Regional analgesics*

Six infants were treated with regional analgesics post-operatively. The median days of administration of regional analgesics was three days, with a range of two to four days. Two infants had epidurals and four infants had extra-pleural catheters in situ for infusion of continuous anaesthetic agents. The anaesthetic agent, bupivacaine was administered via an extra-pleural catheter for one infant and the remaining five infants received the anaesthetic agent levobupivacaine. Four of the six infants received regional analgesics following repair of tracheo-oesophageal fistula, one infant, following surgery to correct jejunal atresia and one infant following primary repair of a bladder extrophy. Additional opiate analgesics were administered to all six infants. Three infants had a continuous intravenous morphine infusion and three infants received codeine via the rectal route. One infant was administered both codeine and morphine post-operatively whilst the extrapleural regional analgesic was being infused.

*Sedative administration*

Sedatives were administered on 812 (24%) total data collection days. Forty-two (76%) infants in the cohort received sedatives during their hospitalisation. Fourteen infants (25%) received sedatives for over half of their hospitalisation days, whilst eight infants were administered sedatives for over two-thirds of their hospitalisation. As shown in Table 7, chloral hydrate was administered to 36 (65%) infants on a
median of seven days. The mean dose of chloral hydrate administered was $22 \pm 9$ mg/Kg (SD). The mean number of doses given to the 36 infants on the days when chloral hydrate was administered, was $2 \pm 1.2$ (SD) doses.

Intravenous midazolam was administered to 32 (58%) of the 55 infants in the cohort. Twenty-four infants were administered midazolam by means of a continuous intravenous infusion, whilst midazolam was administered on an intermittent basis to eight infants on 11 separate occasions. The mean infused dose of continuous intravenous midazolam was $1.0 \pm 0.6$ mg/Kg/hr (SD). Eleven infants received bolus doses of midazolam intravenously in addition to the continuous infusion. The number of bolus doses of midazolam varied widely between the eleven infants. One infant was administered 13 bolus doses on 12 different days over a period of eight weeks, another infant was administered nine bolus doses of midazolam over a 12-day period, and another infant received four bolus doses on two consecutive days. Two infants received three bolus doses of midazolam, two infants received two bolus doses and four infants received a single bolus dose of midazolam. Twenty-six infants received both chloral hydrate and midazolam during their hospitalisation, and for 17 of these infants, the two sedatives were administered concurrently.

Three doses of diazepam were administered for sedation to one infant on 14 consecutive days and a single dose of phenergan was administered for sedation to one infant on one day only.

_Painful procedures performed throughout the infants’ hospitalisation_

Data from the record of minor painful procedures kept by the bedside nurses, as well as the investigator's daily pain diary, relating to major procedures performed, were examined to ascertain the number and type of invasive procedures performed on the 55 infants in the cohort throughout their hospitalisation. Major procedures included episodes of surgery, as well as episodes of chest drain insertion, endotracheal intubation and insertion of umbilical catheters or other central venous catheters, with the exception of peripherally inserted central catheters (PICC). Any additional procedures occurring within an episode of surgery, whether they were major or minor
procedures, such as endotracheal intubation, intravenous or arterial catheter insertion were not recorded separately.

Nursing staff at the bedside caring for the infants in the study recorded episodes of invasive, skin breaking, minor painful procedures, as well as the number of attempts required during each episode. Commonly performed skin breaking minor painful procedures were listed at the top of the bedside nurses’ daily pain record, to serve as a guide for documentation. Included in the list were heel lance, venepuncture, intravenous catheter insertion, arterial line insertion, arterial blood sampling, suprapubic aspirate, lumbar puncture and insertion of PICCs as well as ophthalmology examination. Nursing staff also documented the associated use of sucrose and NNS during all minor procedures.

Data from both the investigator’s pain diary and the pain record kept by the bedside nurses showed that a total of 3806 procedures were recorded for the 55 infants in the study. As shown in Figure 12, although the majority of invasive procedures were performed during the first two weeks of hospitalisation, a substantial number of procedures continued to be performed throughout the duration of the infants’ hospitalisation.
Figure 12. Total number of procedures performed per infant

Data presented as total number of both major and minor procedures per infant during each week of hospitalisation. Data for weeks 20 through to 26 are combined as only two infants remained in the study by week 20, and only one infant from the weeks 22 through to 26.
Major procedures

Major procedures including surgery, endotracheal intubation, insertion of central venous catheters and insertion of chest drains, comprised 201 (5%) of the total 3806 procedures performed on the cohort of 55 infants. Ninety-eight of the major procedures were surgery, performed on 45 infants. The most frequently performed surgical procedure was laparotomy, with 16 laparotomies performed on 15 infants. There were 11 surgical procedures to repair tracheo-oesophageal atresia or fistula on ten infants (one infant needed a second repair of a fistula) and there were eight primary or staged gastroschisis repairs for the five infants with gastroschisis. Six infants had surgery to repair congenital diaphragmatic hernia, six infants had ligation of patent ductus arteriosus and six infants required surgical closure of bowel stomas.

Table 8 summaries the 98 episodes of surgical procedures performed on 45 infants.

Major procedures other than surgery, comprised 42 intubations occurring in the NNU, 27 central line insertions, (not including peripherally inserted central catheters) and 19 chest drain insertions. Other major procedures included eight episodes of silo reduction during conservative management of abdominal wall defects, four upper airway/upper gastro-intestinal flexible endoscopes, as well as one insertion of a peritoneal drain, one intra-osseous needle insertion, and one removal of a dislodged cuff from a Broviac catheter, which was performed under local anaesthetic.
Table 8. Description of surgical procedures

<table>
<thead>
<tr>
<th>Surgical Procedure</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparotomy</td>
<td>16</td>
</tr>
<tr>
<td>Tracheo-oesophageal atresia / fistula repair</td>
<td>11</td>
</tr>
<tr>
<td>Gastrochisis repair</td>
<td>8</td>
</tr>
<tr>
<td>Congenital diaphragmatic hernia repair</td>
<td>6</td>
</tr>
<tr>
<td>Closure of stomas</td>
<td>6</td>
</tr>
<tr>
<td>Patent ductus arteriosus ligation</td>
<td>6</td>
</tr>
<tr>
<td>Bronchoscopy</td>
<td>5</td>
</tr>
<tr>
<td>Broviac® catheter insertion</td>
<td>5</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>4</td>
</tr>
<tr>
<td>Insertion nasal stents</td>
<td>4</td>
</tr>
<tr>
<td>Fundoplication and gastrostomy</td>
<td>3</td>
</tr>
<tr>
<td>Mandibular distraction</td>
<td>3</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>2</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>3</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>2</td>
</tr>
<tr>
<td>Insertion of Rickhams reservoir</td>
<td>2</td>
</tr>
<tr>
<td>Open bowel biopsy</td>
<td>2</td>
</tr>
<tr>
<td>Removal nasal stents</td>
<td>1</td>
</tr>
<tr>
<td>Wound repair</td>
<td>1</td>
</tr>
<tr>
<td>Skin biopsy</td>
<td>1</td>
</tr>
<tr>
<td>Pyloric stenosis repair</td>
<td>1</td>
</tr>
<tr>
<td>Oesophageal dilation</td>
<td>1</td>
</tr>
<tr>
<td>Laser eye surgery</td>
<td>1</td>
</tr>
<tr>
<td>Cystoscopy &amp; inguinal hernia repair</td>
<td>1</td>
</tr>
<tr>
<td>Drainage of abscess</td>
<td>1</td>
</tr>
<tr>
<td>Bladder extrophy closure</td>
<td>1</td>
</tr>
<tr>
<td>Brachial artery graft</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>98</td>
</tr>
</tbody>
</table>
**Pain management following surgery**

Administration of continuous morphine infusion for management of post-operative pain occurred following 85 of the 98 episodes of surgery (87%). Of the 13 procedures where no morphine was administered post-operatively, regional anaesthesia was being administered on three occasions, and on the ten other occasions, the procedures performed were more minor in nature, such as removal of nasal stents, cystoscopy, surgically placed central venous catheters, or bronchoscopy. Inhalation anaesthesia was administered intra-operatively without additional opioid analgesics during these more minor procedures. On day two following surgery, morphine continued to be administered on 74 (75%) occasions. For the 24 surgical procedures in which morphine was not being administered on day two following surgery, on all except five occasions, paracetamol was administered and on 12 occasions, codeine was given. In addition, regional anaesthesia with a combination of paracetamol and codeine continued to be delivered on two occasions and regional anaesthesia in combination with paracetamol alone was given on one occasion. The five surgical procedures in which no analgesia was administered on day two following surgery comprised two bronchoscopy procedures, one skin biopsy, one Broviac® catheter insertion and one episode of surgery which comprised an inguinal hernia repair and cystoscopy.

**Minor procedures**

There were 3605 minor painful procedures recorded for the 55 infants in the cohort. This equated to an average of 65 minor procedures per infant during the course of their hospitalisation. As shown in Figure 13, the majority of minor painful procedures were performed during the first two weeks of hospitalisation, yet a substantial number of procedures continued to be performed throughout the duration of the infants’ hospitalisation. There were 1.1 minor procedures in total performed per each hospital day.
Figure 13. Total number of minor procedures performed per infant

Data presented as total number of both minor procedures per infant during each week of hospitalisation. Data for weeks 20 through to 26 are combined as only two infants remained in the study by week 20, and only one infant from the weeks 22 through to 26.
The large majority of minor painful procedures recorded were heel lances. Figure 14 shows the distribution of the types of minor procedures recorded for the cohort of infants. The procedure type, “Other” included all less commonly performed minor procedures, such as supra-pubic aspirate or peripherally inserted central catheter (PICC).
Figure 14. Number and type of minor painful procedures

Data presented as percentage of minor painful procedures performed, with actual numbers of each procedure type presented above each bar (N = 3605).

NB: IV = Intravenous catheter insertion or venepuncture
IM/SC = Intra-muscular or subcutaneous injection
IA = Arterial line insertion or arterial stab
Other = Less commonly performed minor procedures
In total, 282 minor procedures were recorded as “other”. On further analysis of the descriptions of these procedures, 149 procedures did not meet the criteria defined at the outset, as skin breaking invasive procedures. Such procedures recorded by the clinical nursing staff included placement of naso-pharyngeal tubes, removal of adhesive tapes, insertion of gavage tubes, turning of mandibular distraction pins following mandibular distraction surgery, colostomy bag changes and wound dressings as well as radiological procedures. In total, 133 procedures met the criteria of skin breaking invasive procedures. Table 9 lists the number and type of the 133 procedures, which met the criteria of skin breaking invasive procedures.

Table 9. Summary of “other” minor procedures meeting the criteria of skin breaking invasive procedures

<table>
<thead>
<tr>
<th>Other minor procedures (N = 133)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripherally inserted central catheter (PICC)</td>
<td>79</td>
</tr>
<tr>
<td>Supra-pubic aspiration (SPA)</td>
<td>31</td>
</tr>
<tr>
<td>Needling of Rickham's reservoir</td>
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<tr>
<td>Insuflon® insertion</td>
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<td>Rectal biopsies</td>
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<tr>
<td>Suturing</td>
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<tr>
<td>Infiltration of intravenous extravasation</td>
<td>1</td>
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<tr>
<td>Lance of pustule</td>
<td>1</td>
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</tbody>
</table>

Opioid analgesics and sucrose administration during minor painful procedures

The use of both oral sucrose and opioid or other strong analgesics in conjunction with each type of minor procedure performed on the cohort of 55 infants was ascertained. As per the NNU, RCH protocol, administration of oral sucrose is recommended for invasive, skin breaking, minor procedures as well as ophthalmology examinations. The recorded use of oral sucrose in association with each minor procedure documented was therefore determined. Although opioid or other strong analgesics were not administered specifically prior to minor procedures, many infants were being administered these analgesics as part of their medical management. Administration of continuous intravenous morphine, or of intermittent doses of opioids or other strong analgesics, within the corresponding 24-hour time-frame (0800 to 0800 hours), for each type of minor procedure, was also recorded. Enterally administered paracetamol has not been shown to be an effective analgesic for newborn and young infants.
undergoing heel lancing (Ramenghi, Griffith et al., 1996) or minor surgery (Howard et al., 1994; Bremerich et al., 2001) therefore its use in conjunction with minor painful procedures was not analysed.

The use of analgesics in association with the two most commonly performed minor painful procedures; heel lancing and intravenous line insertions or venepuncture, is depicted in Figures 15 and 16. All 55 infants had heel lance procedures recorded. A mean number of 47 heel lances were performed per infant, with a range from two to 175 heel lances. Oral sucrose alone, with no additional opioid or other strong analgesic was recorded for 1031 (40%) heel lance procedures and oral sucrose in conjunction with opioid analgesics were used on 496 (19%) occasions. Opioid analgesics were being administered without the additional use of sucrose during 685 (27%) heel lances, and 361 (14%) heel lances were performed with no recorded opioid analgesic or oral sucrose.

There were 492 intravenous line insertions or venepuncture procedures recorded for 54 of the 55 infants. With the exception of the one infant who had no intravenous line insertion or venepuncture recorded, infants were exposed to a mean number of nine venepuncture procedures, with a range of one to 31. As shown in Figure 16, sucrose was administered alone on 191 (39%) of intravenous line insertions or venepuncture procedures and during 65 (13%) procedures, sucrose was administered concomitantly with opioid analgesics. Opioid analgesics were being administered without the additional use of sucrose on 152 (31%) of occasions and there was no recorded use of analgesic during 86 (17%) of intravenous line insertions or venepuncture procedures.
Figure 15. Pain management strategies reported during heel lance procedures

Results presented as percentage of times sucrose or opioid analgesics administered, in conjunction with heel lancing (n = 2573). Actual numbers are presented above each bar. Opioid analgesics included both continuous infusion occurring at the time of the procedure and intermittent opioid analgesics administered in the corresponding 24 hour time-period.
Figure 16. Pain management strategies reported during intravenous catheter insertion or venepuncture

Results presented as percentage of times sucrose or opioid analgesics administered, in conjunction with the procedure (n = 492). Actual numbers are presented above each bar. Opioid analgesics included both continuous infusion occurring at the time of the procedure and intermittent opioids or ketamine administered in the corresponding 24-hour time-period.
A total of 115 intramuscular or subcutaneous injections were administered to 38 infants, with a maximum number of 17 injections for one infant over the course of the hospitalisation. The administration of oral sucrose was recorded for 70 (61%) injections. An opioid or other strong analgesic, without the recorded use of additional oral sucrose, was being administered for 27 (23%) injections. There were 18 (16%) injections performed with no documented analgesic.

There were 80 arterial catheter insertions or arterial stabs recorded for 34 of the 55 infants. Although two infants experienced ten or more arterial catheter insertions or arterial stabs, the majority of infants experienced one or two arterial stabs during the course of their hospitalisation. On 61 (76%) occasions opioid analgesics were being administered as part of the infants’ care. Sucrose was administered in addition to opioid analgesics on four occasions, and sucrose was administered alone, with no concomitant opioid analgesic on five occasions. No sucrose or opioid analgesics were recorded for 14 (18%) of arterial catheter insertions or arterial stab procedures.

Seventeen lumbar punctures were recorded for eleven infants. Pain management during the 17 lumbar puncture procedures included administration of oral sucrose alone on seven (42%) occasions and in addition to opioid or other strong analgesics on three (18%) occasions. On three other occasions, opioid analgesics were being administered without additional use of oral sucrose, and there were four (24%) lumbar puncture procedures in which opioid analgesics were not being administered, and no sucrose was recorded for pain management.

There were 46 neonatal ophthalmology examinations recorded for 28 infants in the cohort. Ophthalmology examinations involved insertion of an eyelid speculum to hold the eyelids open and manual movement of the eye into different positions using a scleral depressor in order to allow visualisation of the retina and retinal vessels with an ophthalmoscope. As per routine practice in the hospital where the study took place, local anaesthetic eye drops were instilled immediately prior to the examination. In the majority of cases (63%), neither oral sucrose nor opioid analgesics were administered during the ophthalmology examinations. In eight (17%) cases, sucrose was administered, and in ten (22%) cases, opioid analgesics were being administered as part of medical management.
When pain management strategies for the 133 procedures listed under the “other” category, which met the criteria of skin breaking invasive procedures were examined, results showed that either opioid analgesics were being administered as part of the infants’ management, or oral sucrose was used during the majority of procedures. During 17 (13%) procedures, neither oral sucrose nor opioid analgesic was recorded as being used.

Figure 17 presents the total number of both major and minor procedures performed per infant during each week of hospitalisation, plotted alongside the use of opioid or other strong analgesics and oral sucrose. As shown, most procedures occurred during the first two weeks of hospitalisation, followed by a downward trend until week 18 of hospitalisation. The number of days in each week where sucrose and opioid analgesics were administered followed the same trend, with the least number of days on analgesics occurring by week 18. The increase in both sucrose administration and number of procedures per infant from week 20 may reflect the fact that data for weeks 20 and beyond was only available for two infants with complex medical conditions.
Figure 17. Percentage of total data collection days when strong analgesics and oral sucrose were administered, plotted next to the number of procedures performed per infant

Calculated over successive weeks of hospitalisation.
Documentation of number of attempts for minor procedures

One component of the minor procedural-pain record kept by bedside nurses for documentation of all minor invasive procedures was information regarding the number of attempts required for completion of each procedure. This information was considered to be important as high failure rates for successful completion of procedures has previously been reported and acknowledged as an important source of procedure-related pain (Simons, van Dijk et al., 2003). This information however, was not always recorded. Such data were missing in 646 (18%) of the four procedures where the number of attempts was relevant (heel lance, intravenous catheter insertion or venepuncture, peripheral arterial line or arterial stab and lumbar puncture). For the procedures where this information had been recorded, results showed that the majority of heel lances required one attempt only. However, only 39% of intravenous catheter insertions or venepunctures, and 45% of peripheral arterial line insertions or arterial stabs were successfully completed on the first attempt. These data demonstrate that procedures may require multiple attempts until completion and are therefore a significant potential source of under-estimated pain in the neonatal setting.

Documentation of pain assessment scores

One component of the investigator’s pain diary collected on a daily basis, was the number of Pain Assessment Tool (PAT) scores documented for each infant in the cohort. The PAT is the score utilised in the NNU, RCH to score pain in infants (Hodgkinson et al., 1994). When PAT scores are performed, they are routinely documented in one of two records; either a designated post-operative PAT scoring sheet, or the daily patient observation chart. Both these charts were checked on a daily basis to ascertain the total number of PAT scores documented by clinicians for the 55 infants in the cohort over the course of their hospitalisation.

Results showed that 36 of the 55 infants (65%) had PAT scores documented during their hospitalisation. For these 36 infants, documentation of PAT scores was infrequent. PAT scores were only documented on 159 days in total; five percent of the total 3384 data collection days.

As the PAT tool was originally introduced to the NNU, RCH in December 2001 to specifically document post-operative pain, the number of PAT scores documented
post-operatively was examined in detail. In the first 48 hours following the 98 episodes of surgery, more than one PAT score was documented on only 33 (34%) occasions. As the PAT score includes behaviours indicative of pain which may be masked by high doses of morphine, and unable to be assessed in infants receiving muscle relaxants, the documentation of PAT scores in the first 48 hours post-operatively when such medications were in use, was specifically examined. On 21 (21%) occasions where less than one PAT score was documented, muscle relaxants had in fact been administered during the post-operative period, and on ten further occasions, continuous morphine was being infused at sedative doses of 30 µg/Kg/hour or higher. Both of these treatments may have precluded reliable pain scoring using the multi-dimensional tool within the first 48 hours post-operatively. However, there remained 34 episodes of surgery where no such medications had been administered post-operatively to account for the failure to document PAT scores in the post-operative period.

*Summary of findings*

In summary, the findings of this second phase of the study showed that the infants in the cohort were exposed to multiple painful procedures. Oral sucrose was administered during more than half of the minor painful procedures, and during 45% of minor procedures, morphine or other strong analgesics was being administered as part of medical management. There were 539 (15%) minor painful procedures where neither sucrose nor strong analgesics were administered. Heel lancing was the most commonly performed minor painful procedure, accounting for 71% of recorded minor procedures. Procedures such as venepuncture or intravenous catheter insertion, or insertion of intra-arterial lines frequently required more than one attempt until successful completion of the procedure, highlighting that multiple attempts at such procedures are potentially significant sources of under-estimated pain.

There was substantial use of a variety of analgesics and sedatives throughout the infants’ hospitalisation, yet there was infrequent documentation of pain scores. This illustrates that, in this cohort of infants, documented pain assessment scores were not utilised in either the evaluation of the effectiveness or otherwise of analgesics and sedatives, or in making decisions regarding the need for, or the weaning and cessation of, analgesics or sedatives.
The next chapter, Chapter 5, presents results of the third aim of the study; that of describing the effectiveness of oral sucrose over the course of the hospitalisation in the same cohort of infants by mapping the successive pain responses to the commonly performed painful procedure of heel lance.
CHAPTER 5. RESULTS: THE EFFECTIVENESS OF ORAL SUCROSE; MAPPING THE SUCCESSIVE PAIN RESPONSES TO A ROUTINE PAINFUL PROCEDURE

Chapter 5 presents results of the third phase of the study; that of describing the effectiveness of oral sucrose in reducing procedural pain during the course of an infant's prolonged hospitalisation. This was accomplished by mapping successive pain responses of the same cohort of 55 infants as presented in Chapter 4, to a routine painful procedure over the course of the hospitalisation. Results of demographic data in terms of the infants’ age, gestation, gender, diagnoses and length of stay are presented in Chapter 4.

Pain assessments during heel lances, performed for routine pathology testing (laboratory sampling of blood), were conducted over the course of the infants’ hospitalisation. As described in the Methods chapter, pain assessments were conducted weekly or more frequently if possible, subject to the infants’ medical requirement for pathology testing. No heel lance procedures were performed for the purposes of the study. The method used to assess pain during and in the three minutes following completion of the heel lance procedure was the same method as used in previous neonatal pain studies conducted in the same setting (Harrison et al., 2002; Harrison et al., 2003a), comprising a combination of behavioural (facial expression scores and crying duration) and physiological parameters (heart rate and oxygen saturation levels). Oral sucrose was administered prior to and during observed heel lance procedures as per the NNU oral sucrose protocol (Harrison, 2001), and as described in the Methods chapter. Two minutes prior to lancing of the heel, sucrose at volumes of 0.25 mL, or 0.05 mL if the infant was nil orally, was syringed onto the infant’s tongue. A pacifier was offered if the infant was able to suck. Sucrose continued to be given in the same small increments, upon commencement of the procedure, and every two minutes if the procedure continued beyond this time.

The first part of this chapter presents a summary of the responses of all 55 infants to observed heel lance procedures. An analysis of changes in responses to successive heel lances occurring over the course of the hospitalisation is subsequently presented.
Responses of all infants to heel lancing

Baseline demographic information collected at the commencement of each observation period included a proxy severity of illness score, using the Neonatal Therapeutic Intervention Scoring System (NTISS), enteral feeding status, including time of most recent feed, number of episodes of handling within the previous hour, ventilation status, behavioural state, and a baseline PAT score. Corrected gestational age and post-natal age were also calculated.

A total of 446 assessments were conducted during routine pathology testing in the cohort of 55 infants. One infant in the cohort had no pain assessments performed during the study. This infant had an arterial catheter in situ for much of the time, precluding the need for capillary blood sampling, and also received muscle relaxants for 51 of the 86 days of hospitalisation precluding the opportunity for studying responses to a heel lance procedure. There were also two infants who only had one pain assessment performed and two infants who had two pain assessments performed. The remaining 50 infants had three or more assessments performed during heel lancing throughout their hospitalisation. The median number of assessments conducted for these 50 infants was seven (IQR, 4-10).

In the majority of cases, corrected gestational age at the time of pain assessment during heel lancing was more than 37 weeks. There were only two infants younger than 28 weeks corrected gestational age on the day of an assessment. The median NTISS score was 14 (IQR, 11-19) of a maximum possible score up to 60. The maximum NTISS score depends on the number of medications and therapies prescribed. The highest NTISS score assigned during the study was 38. Behavioural state at baseline was predominantly scored as State 1 (Eyes closed, regular respiration, no movements) although on 37 (8%) occasions, the infants’ behavioural state at baseline was State 5, indicative of crying. The median PAT score at baseline was zero and the maximum score assigned was nine, out of a possible score of 20.

In the majority of assessments, the infants were not handled in the hour preceding the commencement of the heel lance procedure. In terms of feed status, during 122 (27%) assessments the infants were nil by mouth, and on 133 (30%) occasions the infants
were on continuous gavage or gastrostomy feeds. On the remaining 191 (43%) occasions, the majority of infants had been fed within the previous three-hour period.

Oral sucrose was administered prior to, and during, all heel lance procedures assessed, except for three occasions. On one occasion, an infant was on high doses of both intravenous morphine and midazolam, and in addition, had received three bolus doses of morphine in the previous 24 hours. As per the NNU oral sucrose protocol (Harrison, 2001), this infant was consequently considered to be sedated to the point that administration of oral sucrose was deemed unnecessary. The other two occasions in which oral sucrose was not administered prior to the heel lance procedure, were both in one infant following complications of a tracheo-oesophageal fistula repair. This particular infant’s medical orders specified no oral medications of any nature, including the 0.1 mL of oral sucrose routinely used for procedural pain management in infants ordered nil by mouth (Harrison, 2001). The pain scores during these three heel lance procedures in which oral sucrose was not administered, were removed from further analysis leaving a total of 443 heel lance procedures in the data analysis.

The non-pharmacological pain reduction strategies of NNS and swaddling were used in addition to oral sucrose during the majority of the 443 observed heel lance procedures. In 294 (66%) procedures, the infants were sucking on a pacifier as part of their routine care. NNS alone was used on 90 (20%) occasions and both NNS and swaddling was used on 204 (46%) occasions. Swaddling alone was used on 88 (20%) occasions and neither swaddling nor NNS was used during 61 (14%) heel lances. In terms of pharmacological agents being administered at the time of, or within the corresponding 24 hour epoch for each pain assessment, on 79 (18%) of assessments, one or more opioid analgesic was being administered. On 45 (57%) of these 79 occasions, the infants were receiving a continuous opioid infusion as part of their medical management. On 80 (18%) occasions, one or more sedative medication was being administered and on 21 (26%) of these occasions, a continuous sedative infusion (midazolam) was being administered. A combination of opioid analgesics and sedatives was being administered in 37 (8%) of the 443 pain assessments.
Behavioural responses: crying characteristics

Of the 443 pain assessments conducted during heel lancing, there were 88 (20%) occasions where infants had no capacity to cry audibly due to the presence of either an endotracheal tube or tracheostomy. During the 355 (80%) occasions where infants had the capacity to cry, crying actually occurred on only 179 (50%) of these occasions. The median proportion of crying time whilst the procedure was in progress for these 179 procedures was 16% of the blood collection phase (Figure 18). Crying in the three-minute period following completion of the heel lance procedure occurred on only 37 (10%) of the 355 occasions where infants had an audible cry. As seen in Figure 18, in the majority of occasions in which crying did occur, the duration of crying was for less than 10% of the three-minute recovery period.

A first cry until a five-second pause occurring within 10 seconds of the heel lance was present in only 123 occasions, and on the majority (59%) of these occasions where an audible cry occurred, the duration of the first cry was ten seconds or less. During 11 assessments, the duration of the first cry was longer than 60 seconds. The longest first cry until a five-second pause lasted for 275 seconds, or almost five minutes.
Figure 18. Proportion of crying time during and following heel lance procedures

(N = 355)

Data presented as percentage of crying time occurring during the heel lance procedure and in the three-minute observation period following completion of the procedure (Y axis). Empty circles represent individual observations, circles with shadows represent more than one observation and solid bars represent multiple observations.
Behavioural responses: face scores

The facial expression score used in this study to assess pain responses during heel lancing in the cohort of 55 infants comprised a zero to four scale, scoring the presence or absence of brow bulge, eye squeeze, nasolabial furrow and open mouth (Grunau & Craig, 1987; Harrison et al., 2002).

In the majority of assessments, at all time points throughout the heel lance procedure and in the three-minute period following completion of the procedure, the lowest score of zero was most frequently assigned. To illustrate, Figures 19, 20 and 21 show the distribution of facial expression scores throughout the procedure, at the following times: time point of the initial heel lance, considered the most painful part of the heel lance procedure (Grunau & Craig, 1987; Craig et al., 1993); at 30 seconds; and at the final observation point, three minutes following completion of the blood collection. At the point upon heel lance the maximum score of four was assigned during 89 (20%) procedures, whilst the lowest score of zero was assigned in 284 (64%) assessments (Figure 19). By the 30-second time point, the maximum score of four was assigned only 55 (12%) times, scores of one, two or three were assigned 64 (15%) times, whilst the lowest score of zero was assigned 324 (73%) times (Figure 20). For each subsequent observation point during and following completion of the heel lance procedure thereafter, the lowest facial score of zero was assigned more frequently. As shown in Figure 21, by the final observation point at three minutes following completion of the procedure, the score of zero was assigned for all except six pain assessments.
Figure 19. Distribution of facial scores upon heel lance

The bars represent the percentage of each facial score assigned during observed assessments (N = 443). The actual number of times each score was assigned is presented above each bar.
Figure 20. Distribution of facial scores at the 30-second time point

The bars represent the percentage of each facial score assigned during observed assessments (N = 443). The actual number of times each score was assigned is presented above each bar.
Figure 21. Distribution of facial scores at three minutes following completion of the heel lance procedure

The bars represent the percentage of each facial score assigned during all pain assessments (N = 443). The actual number of times each score was assigned is presented above each bar.
**Physiological responses**

The physiological responses recorded at baseline, prior to commencement of the heel lance procedures, during, and in the three-minute period following completion of the heel lance procedures were heart rate and oxygen saturation levels. As shown in Figure 22, mean heart rate rose steadily throughout the heel lance procedure from a baseline of $149 \pm 18$ (SD) beats per minute (bpm), up to a maximum of $167 \pm 19$ (SD) bpm at the one-minute observation point. The mean heart rate then steadily decreased upon completion of the procedure, although remained elevated four bpm above baseline at the final observation point.

The mean oxygen saturation level ($\text{SpO}_2$) decreased slightly from a baseline of 97%, to 96% upon heel lance and decreased to 95% at the two-minute observation point. Thereafter, $\text{SpO}_2$ increased and by the two-minute observation point following completion of the procedure, the mean $\text{SpO}_2$ had returned back to the baseline level of 97%. The mean oxygen saturation level, with minus standard deviation bars, at each of the ten observation points during the 443 pain assessments, is presented in Figure 23.
**Figure 22.** Mean heart rate at each observation point throughout the heel lance procedure

Y error bars represent standard deviations around the mean values

(N = 443)
Figure 23. Mean oxygen saturation levels at each observation point throughout the heel lance procedure

Minus Y error bars represent standard deviations around the mean values

(N = 443)
Effect of concomitant opioid analgesics

There were 79 (18%) heel lance assessments conducted in which the infants, in addition to receiving oral sucrose, were receiving opioid or other strong analgesics as part of their medical management. The data were examined to determine if the measured pain responses during heel lancing during these 79 assessments differed to that noted during the 364 assessments in which oral sucrose only, with no concomitant opioid analgesic was administered. In terms of the behavioural parameter of facial scores, the facial expression scores at the time point upon heel lance are presented only, as facial scores other than zero, scored at other times throughout the heel lance procedure, were infrequently assigned. Results showed that the distribution of facial expression scores at the time point upon heel lance, in the infants who were receiving opioid analgesics concomitantly with oral sucrose was different to those assessments where sucrose only was administered. As shown in Figure 24, when opioid or other strong analgesics were administered concomitantly with sucrose, the lowest score of zero was assigned in 55% of assessments, whilst a score of zero was assigned in 66% of assessments when sucrose only was administered. The maximum score of four was assigned during 23% of assessments where concomitant opioid analgesics were administered, compared to 20% of the assessments in which sucrose only was administered.
Figure 24. Distribution of facial scores upon heel lance: concomitant opioid analgesics compared to sucrose alone

Numbers of assessments in which each score was assigned is presented above each bar. During 79 assessments, sucrose with concomitant opioid analgesics was being administered, and in 364 assessments, sucrose only was administered.
Thirty-two pain assessments were performed on infants who had an ability to cry and who were receiving opioid analgesics at the time of assessment. The median crying time during the blood collection for these 32 assessments was 13 seconds (IQR, 0-42). The median duration of crying during the 323 assessments where sucrose only was administered was zero seconds (IQR, 0-13).

An attenuation in the heart rate response was observed during the assessments where concomitant opioid analgesics were being administered, compared to when oral sucrose only was administered. Although the mean heart rate at baseline was only three beats per minute lower during those assessments in which there was concomitant administration of opioid analgesics, at the point upon heel lance, this difference increased to eight beats per minute, and increased further to eleven beats per minute difference at the 30-second observation point. This difference in mean heart rate was sustained to the one-minute observation point (Figure 25).

The mean oxygen saturation levels in those assessments where concomitant opioid analgesics were being administered was two to three percent lower compared to the assessments where sucrose only was administered (Figure 25).

The median NTISS score for those 79 assessments in which opioid analgesics were administered was 24 (IQR, 20-27). The median NTISS score on the day of the 364 assessments where no opioid analgesics were administered was 14 (IQR, 11-19).
Sucrose and concomitant opioids  Sucrose only

Figure 25. Mean heart rates of assessments where sucrose and concomitant opioid analgesics administered compared to sucrose only

Data presented at each observation point during and following completion of the heel lance procedure. Y error bars represent standard deviation around the mean values.
Figure 26. Mean oxygen saturation levels during pain assessments in which concomitant opioid analgesics were administered, compared to sucrose only.

Minus Y error bars represent standard deviations around the mean values.
In summary, during the majority of the 443 observed heel lance procedures, the lowest facial score of zero was most frequently assigned, and for the procedures where crying occurred, crying duration occurred predominantly for short periods only. The mean heart rate increased from baseline throughout the procedure and remained elevated above baseline levels three minutes following completion of the blood collection, whilst the mean oxygen saturation level initially decreased from baseline but returned quickly to baseline levels. Concomitant opioid or other strong analgesics were being administered with oral sucrose during 79 observed procedures. Pain responses during these 79 procedures were different to that when sucrose only was administered, with the main effects being an increase in behavioural responses, yet an attenuation of the mean heart rate during the blood collection phase of the procedure.

Changes in successive responses
This section presents the results of pain responses to successive heel lance procedures. In order to examine successive behavioural and physiological responses to procedure-related pain, only those infants who had three or more observed pain assessments conducted during heel lancing were included in the analysis. Fifty infants were included in the analysis who had the minimum of three assessments performed over the course of the hospitalisation. A total of 437 heel lance assessments for these 50 infants were included in the analyses.

A slope calculation of the linear regression line was obtained from each of the 50 individual infants who had three or more pain assessments performed. Each of the 50 regression calculations for the behavioural and physiological responses gave a slope estimate, which reflected whether the response for that individual infant was generally decreasing, remaining steady, or increasing over successive assessments conducted over the course of the hospitalisation. An increase in the slope estimate would signify an increase in pain responses over the period of hospitalisation, whilst a decrease would signify a decrease in pain responses over the course of the hospitalisation.

To illustrate, the individual regression slopes for facial scores at the observation point upon heel lance, for infants numbered one through to eight, are presented in Appendix 11. The regression slopes for infants numbered one through to eight, based on the zero to four facial expression score, were 0.74, -0.11, -0.31, 0.30, 1.2, 1.0, -0.01 and 0
respectively. Inferences about the sample of 50 individual infants’ regression slopes, based on the two behavioural and the two physiological parameters at each observation point, were calculated to test whether the population average was zero.

As illustrated in Figure 27, when the regression coefficients for the facial expression scores upon heel lance were analysed for the 50 infants in the cohort who had three or more pain assessments performed, results showed no linear change in scores over the course of the hospitalisation. The mean regression line was -0.02 with a 95% confidence interval of -0.18 to 0.14 (t = -.27, p = .79). As the mean regression slope of -0.02 is close to zero, this indicates almost no change in facial scores, based on the zero to four facial expression scale, at the point upon heel lance, over successive observed heel lance procedures.

Facial expression scores during the remainder of the observation points during the blood collection were aggregated, and a regression analysis was performed on the mean scores for each of the 50 infants and 437 observed assessments. Results also showed no change in mean facial scores during successive heel lance procedures over the period of hospitalisation. The mean regression slope was -0.07 with a 95% confidence interval of -0.159 to 0.014 (t = -1.68, p = .10).

Similarly, the face scores occurring at the observation point upon completion of the blood collection through to the final observation point at three minutes following completion of the procedures were aggregated, and a regression analysis performed on the mean scores. Results also showed no significant changes in mean facial scores over successive heel lance procedures. The mean regression slope was -0.04 with a 95% confidence interval of -0.08 to 0.01 (t = -1.17, p = .08).
Figure 27. Regression slope for successive changes in face scores upon heel lance

Data presented as the regression slope depicting the percentage of infants with successive changes in facial expression scores. Analysis calculated for 50 infants over 437 observed assessments.

The X axis depicts the change of facial expression scores, based on the zero to four facial expression score. As no infant’s regression slope was more or less than two points the X axis scale ranges from -2 to +2.
The same regression coefficient analyses were performed on the duration of crying during the heel lance procedure, as well as duration of the first cry until a five-second pause. Regression analysis was not performed for the duration of crying in the three-minute period following completion of the heel lance procedure due to there being so few assessments where infants cried for any time (10% of occasions where infants had an audible cry).

Forty-five infants had the capacity to audibly cry at the time of three or more assessments. A total of 353 observed assessments for these 45 infants were included in the analysis. As demonstrated in Figure 28, results for all 45 infants’ regression slopes combined showed no significant change in crying duration during the heel lance procedure over the course of the hospitalisation. The mean regression coefficient was -0.23% with a 95% confidence interval of -2.38% to 1.91% (t = -2.1, p = .03).

The regression coefficient for the duration of the first cry until a five-second pause also showed no significant differences over the course of the hospitalisation as the large majority of the infants’ individual slopes were centred around zero (Figure 29). The mean regression coefficient was -1.18 seconds with a 95% confidence interval of -3.46 to 1.10 seconds (t = -1.04, p = .30).
Figure 28. Regression slope for successive changes in crying duration during heel lancing

Data presented as regression slope calculated for changes in crying duration over successive assessments. Analysis included 45 infants with three or more audible cries.

The X axis depicts the successive change in crying duration, expressed as a percentage.
Figure 29. Regression slope for successive changes in duration of first cry

Data presented as of regression slope calculated for the 45 infants.

The X axis depicts the successive change in duration if first cry (seconds).
Regression coefficient analyses were performed on both heart rate and oxygen saturation changes occurring from baseline, for the 50 infants who had three or more pain assessments conducted during heel lancing. As shown in Figure 30, the heart rate change from baseline, expressed as a percentage change, at the time point immediately upon heel lance did not show any significant upward or downward changes over successive observations. The mean regression slope from baseline was 0.26% with a 95% confidence interval of -0.48 to 1% (t = 0.70, p = 0.48).
Figure 30. Regression slope for successive changes in percentage heart rate change from baseline upon heel lance

Data presented as percentage heart rate change from baseline upon heel lance, calculated for the 50 infants.

The X axis depicts the successive change in mean heart rate change from baseline, expressed as a percentage.
The mean percentage heart rate change from baseline occurring at the observation points of 30 seconds, and one minute were also examined for the slope estimates. These were the time points during the heel lance procedures where the maximum heart rate change from baseline occurred. There were no statistically significant changes in the heart rate response at either time point over successive heel lance procedures. At the 30-second period, the mean slope estimate was 0.45% heart rate change from baseline, with a 95% confidence interval of -0.49% to 1.29% (t = .97, p = .34), and at the one-minute observation period, the mean slope estimate was 0.51% with a 95% confidence interval of -0.28% to 1.31% heart rate change from baseline (t = 1.30, p = .20).

The percentage heart rate change from baseline was aggregated for the time points in the period following completion of the heel lance procedure and examined for the slope estimates. This included the observation points at the time of completion of the blood collection, and at one, two and three minutes following completion. Results also showed no trend for the heart rate response to change over successive assessments. The mean slope estimate was 0.23% with a 95% confidence interval of -0.46 to 0.92% (t = 0.68, p = 0.50).

The analysis of the slope estimates for oxygen saturation changes from baseline occurring upon heel lance, and during and following completion of the heel lance procedures also showed that at no time were there any statistically significant differences in changes occurring over the successive heel lance procedures observed. At the time point upon heel lance, the mean slope estimate was -0.13% with a 95% confidence interval of -0.39 to 0.13% (t = -1.03, p = 0.31). When the aggregated oxygen saturation changes from baseline occurring at the time periods of 30 seconds, one, two and three minutes during the blood collection were analysed, results showed a mean slope estimate of -0.41% with a 95% confidence interval of -0.92 to 0.09% (t = -1.66, p= 0.10) and similarly, in the three minute period following completion of the blood collection, the mean slope estimate was -0.38% with a 95% confidence interval of -0.18 to 0.10% (t = -1.66, p= 0.10).
Summary of mapping the successive pain responses

In conclusion, key findings of Chapter 5 were that, following administration of small volumes of oral sucrose, behavioural responses indicative of acute pain during the majority of the 443 observed heel lance procedures were infrequently observed. In only 50% of the assessments in which the infants had a capacity to cry, did any crying actually occur, and the lowest facial expression score of zero was assigned in the majority of assessments, at all observation points during and following the heel lance procedure. An increase in mean heart rate from baseline occurred throughout the procedure and remained elevated above baseline levels at the final observation point, indicative of a sustained physiological response to an acute painful procedure. The mean oxygen saturation level initially decreased from baseline but returned to baseline levels by the two-minute observation point. Pain responses differed if opioid or other strong analgesics were being administered in addition to oral sucrose, with the effects being an attenuation of the mean heart rate yet an increase in behavioural response to the procedure.

The analysis of mapping of successive pain responses over the course of the hospitalisation, for the 50 infants who had three or more pain assessments available for analysis, showed no significant changes in the pooled slope estimates for either of the two behavioural responses, nor of the physiological responses of heart rate and oxygen saturation levels. The following chapter provides a discussion and interpretation of the results obtained from all three phases of this thesis within the context of previous relevant research and current literature.
CHAPTER 6. DISCUSSION

The aims of this thesis were threefold; to ascertain pain assessment and procedural pain management strategies utilised in Australian neonatal units; to map painful procedures, use of sucrose and other pharmacological pain reduction strategies and frequency of documentation of pain assessment scores in a single neonatal intensive care unit and in a specific cohort of infants throughout the entire period of hospitalisation, and to describe the effectiveness of oral sucrose in the reduction of pain during successive heel lance procedures performed over the period of hospitalisation in the same cohort of infants. By exploring these three inter-related aims, significant pre-existing knowledge gaps concerning the assessment and management of pain in infants nursed in neonatal units were addressed.

The first aim of the thesis was to ascertain pain assessment and procedural pain management strategies utilised in Australian neonatal units. A postal survey of the 181 Level Two and Level Three neonatal units and the newborn emergency transport services in Australia was conducted to ascertain whether an articulated procedural pain management policy existed, whether routine pain assessments were conducted, and how frequently various pain reduction strategies were used during commonly performed minor painful procedures. As reported in Chapter 3 of this thesis, the results showed that most units did not have an articulated procedural pain management policy and only six percent of units reported using a pain assessment score on a routine basis. Pain reduction strategies reported most frequently during minor painful procedures were non-nutritive sucking and other non-pharmacological comfort measures, whilst infrequent routine use of oral sucrose was reported. These results highlight that health professionals working in neonatal care in Australia are not utilising the best research evidence in terms of assessment of pain and reduction of procedural pain in hospitalised newborn infants (Harrison, Loughnan, & Johnston, 2006).

The second aim of the thesis was to examine in more detail, painful procedures, analgesic and sedative use, and frequency of documentation of pain scores in a single tertiary referral Level Three NICU, in a cohort of infants with a predicted length of stay of 28 days or more, throughout the entire period of hospitalisation. The method
used was a prospective, observational, longitudinal, cohort study, and included 55 infants with lengths of stay ranging from 28 to 181 days. The results presented in Chapter 4 highlighted that infants in the cohort were exposed to a large number of painful procedures, were administered a wide variety of analgesic and sedative medications, yet there was infrequent documentation of the effect of these medications using the validated pain assessment score already in use in the NICU where this study took place. Many of the analgesic and sedative agents used in this study, as well as other neonatal units around the world, have inadequate evidence to support their routine and prolonged use in clinical practice (Ng et al., 2002; Bellu, de Waal, & Zanini, 2005; Ng, Taddio, & Ohlsson, 2005), highlighting the difficulties clinicians face in their attempts to humanely, effectively and safely reduce pain in sick infants within an evidential base.

The third aim of this thesis was to describe the effectiveness of oral sucrose in pain reduction during successive heel lance procedures performed over the duration of the hospitalisation in the same cohort of infants. Pain assessments during routine heel lancing, at weekly, or more or less frequent intervals depending on the requirement for pathology testing, were conducted in the same cohort of infants. Prior to, and during observed heel lance procedures, oral sucrose was administered as per routine clinical practice in the NICU setting where this study was conducted. The pain assessment method used comprised beside assessment of a combination of behavioural and physiological parameters. Crying duration and a four-point facial expression score comprised the behavioural measures, whilst the physiological parameters measured were heart rate and oxygen saturation.

As oral sucrose was given prior to all heel lance procedures, the analgesic effects of oral sucrose throughout the hospitalisation could be ascertained. As reported in Chapter 5 of this thesis, there was no significant increase or decrease in the behavioural parameters of facial expression scores and crying duration, or in physiological responses, over successive heel lance procedures assessed over the course of the hospitalisation. In the majority of pain assessments, behavioural responses to pain were infrequently observed. At the time-point of the initial heel lance, considered to be the most painful part of the procedure (Grunau & Craig, 1987; Craig et al., 1993), the maximum facial score of four was assigned in only 89 (20%)
assessments, whilst the lowest score of zero was assigned in 64% of assessments. The consistently low behavioural pain responses coupled with the lack of changes in both behavioural and physiological responses, indicates that the analgesic effects of oral sucrose were sustained throughout the course of the infants’ hospitalisation.

The findings of this research contribute valuable knowledge concerning nationwide neonatal pain management practices, pain management practices in a specific cohort of infants with complex health needs, and the analgesic effects of repeated and prolonged use of oral sucrose. Importantly, this thesis is the first to describe ongoing use of oral sucrose in sick infants over the full course of a prolonged hospitalisation. In the following three sections of this Discussion chapter, these findings are discussed in further detail and within the context of current research and the existing body of knowledge.

Pain assessment and procedural pain management practices in Australian neonatal units

The findings of the cross-sectional pain assessment and pain management survey conducted in Australian neonatal units contribute important information regarding the management of procedural pain, the use of pain assessment tools in clinical practice and the extent to which pain management policies have been implemented in Australia. One of the key findings was of infrequent use of oral sucrose or other sweet tasting solutions during commonly performed minor painful procedures. This finding is despite the large body of evidence, including a systematic review, demonstrating the efficacy of small amounts of sucrose for reducing pain in diverse populations of infants (Stevens et al., 2004).

Non-nutritive sucking (NNS) and other comfort measures were the strategies reportedly used most frequently for all minor painful procedures, despite the substantial body of evidence demonstrating that sucrose or other sweet tasting solutions, is more effective in reducing pain in infants than both NNS alone (Blass & Hoffmeyer, 1991; Blass & Ciaramitaro, 1994; Blass & Watt, 1999; Stevens, Johnston, Franck et al., 1999; Gibbins et al., 2002; Stevens et al., 2004) and other
developmentally supportive comfort measures (Johnston, Stremler et al., 1997; Stevens, Johnston, Franck et al., 1999). In a study published almost 20 years ago, NNS, along with other comfort measures, was shown to be the most frequently used strategy by neonatal nurses to reduce pain in infants (Franck, 1987). The 20-year old practice of using comfort measures during painful procedures, instead of the more effective strategy of oral sucrose, still remains evident today in Australian neonatal care settings, as well as in other neonatal settings around the world (Dodds, 2003; Rohrmeister et al., 2003; Gray, Trotter, Langbridge, & Doherty, 2006).

**Sucrose utilisation**

Low utilisation of oral sucrose for pain management during minor painful procedures, as reported in this current nationwide survey was found despite the fact that almost two-thirds of the respondents were aware of the analgesic benefits of oral sucrose. Similar low rates of sucrose utilisation despite high levels of knowledge concerning sucrose analgesia have also been reported in other neonatal settings (Heaton & Herd, 2000; Rohrmeister et al., 2003; Gray et al., 2006). In a survey of pain management practices in neonatal units in Austria, 12 of 28 (42%) respondents were aware of the analgesic effects of oral sucrose, yet sucrose was routinely used in only four units (Rohrmeister et al., 2003). A survey, which described the use of oral sucrose in neonatal units in New Zealand, showed that 13 of 15 (87%) medical directors of NICUs were aware of the analgesic efficacy of oral sucrose during painful procedures (Heaton & Herd, 2000); yet, sucrose was only used in one NICU. In addition, Heaton and Herd reported that, in the one unit which did use sucrose for procedural pain management, sucrose was only used infrequently. On a similar note, a recent telephone survey of neonatal pain management practices in Australian maternity hospitals reported that although 54% of staff in Level Two special care nurseries and 83% of staff in Level Three neonatal intensive care units were aware of the analgesic effects of oral sucrose, only ten percent of units reported using oral sucrose during minor painful procedures (Gray et al., 2006).

Reasons for low utilisation of sucrose as a pain reduction strategy in various neonatal units around the world are undoubtedly numerous. In this nationwide postal survey, a perceived lack of availability of sucrose may have contributed to the low use of sucrose in the clinical setting, as 60% of respondents either answered that sucrose or
other sweet tasting solutions were unavailable for use in the clinical setting, or they were unsure of the availability. Sucrose syrup (Syrup British Pharmacopeia, David Craig Galenicals, Carole Park, Queensland, Australia) is however, readily available in Australia. This syrup is an 88% (wt/vol) solution which is diluted with sterile water to make the more commonly used sucrose solutions between 12 and 50% (wt/vol). Oral administration of the intravenous glucose solutions, of concentrations greater than ten percent, have also been shown to be effective in reducing procedural pain in infants (Ramenghi, Griffith et al., 1996; Skogsdal et al., 1997; Carbajal et al., 1999; Eriksson et al., 1999; Bellieni et al., 2002; Carbajal, Lenclen, Gajdos, Jugie, & Paupe, 2002; Carbajal et al., 2003; Lindh et al., 2003; Bauer et al., 2004; Eriksson & Finnstrom, 2004; Gradin et al., 2004). Intravenous glucose solutions, which can be given orally, are readily available in most neonatal settings. Of interest, nine units in Australia reported using the sweet tasting Glycerin British Pharmacopeia (BP) 10%, which is readily available commercially. There have however, been no published studies demonstrating the safety of Glycerin or other Glycerol solutions in infants.

Another possibility for low utilisation of sucrose in both Australian neonatal units and other neonatal settings is the uncertainty regarding the safety of sucrose for infants. As reported in Chapter 3 of this thesis, 44% of the survey respondents answered that they were unsure of the safety of sucrose. However there has been no reported short-term safety concerns associated with oral sucrose in infants per se (Gibbins et al., 2002). Oral sucrose has not been associated with hyperglycemia (Gunning & Garber, 1978; Bucher et al., 1995; Gormally et al., 2001; Johnston, Filion et al., 2002; Stevens et al., 2005), and there have been no reports of an association with necrotising enterocolitis (Ramenghi, Wood et al., 1996; Acharya et al., 2004; Stevens et al., 2005). As reported in Chapter 4 of this thesis, in the longitudinal observational study, only one infant in the cohort developed necrotising enterocolitis after admission to the NICU. Necrotising enterocolitis was diagnosed at seven weeks of age and required conservative treatment only. This infant was at high risk of developing necrotising enterocolitis due to a large gastroschisis, requiring a staged surgical repair (Oldham et al., 1988).

Another factor which may account for only 49% of respondents to this pain assessment and management survey reporting that sucrose was safe, was a previous
report of significant bacterial contamination of a ten percent oral sucrose solution used in a study of pain reduction in newborn infants (Abu-Arafeh et al., 1998). This finding is in contrast to sucrose being well known for its preservative properties (Chirife et al., 1983; Long, Han, Tuleu, & Wong, 2006). A recent examination of bacterial growth in the 33% (wt/vol) sucrose solution routinely used in the NICU where the longitudinal cohort study took place, failed to indicate any significant bacterial growth (Harrison et al., In Press). The failure to support bacterial growth in the solutions was despite the bottles of sucrose being accessed multiple times over a four-week period of clinical use. The dissemination of these recent findings may allay fears regarding the risk of bacterial growth in concentrated sucrose solutions recommended for procedural pain reduction in infants.

Another possible reason for low utilisation of oral sucrose may have been due to the fact that, at the time this nationwide survey was conducted, there had only been one study published which had examined repeated doses of oral sucrose for procedural pain management (Johnston, Filion et al., 2002), however the primary outcome measure was neurobehavioral development rather than analgesic efficacy. That study randomised premature infants less than 32 weeks gestation to receive either oral sucrose or water during all distressing and painful procedures in the first week of life. There were no differences in safety outcomes between the two groups of infants, poorer neurobehavioural scores in the infants who had received the largest number of sucrose doses, compared with those infants who had received less sucrose, was found. Although Johnston, Filion et al. (2002) acknowledged the possibility of this finding being due to chance due to small numbers of infants included in the sub-analysis, the publication of such concerning findings may have impacted on the implementation of oral sucrose for procedural pain reduction in NICUs.

More recently, the repeated and consistent use of oral sucrose over the first month of life in premature infants less than 30 weeks gestational age was evaluated (Stevens et al., 2005). A total of 66 infants were randomised to one of three groups for all painful procedures performed during the first 28 days of life. Infants randomised to the sucrose group received 0.1 mL of 24% sucrose, with a pacifier, and were nursed in a flexed and contained manner for all minor invasive procedures. Infants in the two other groups were also positioned in a flexed and contained manner, and infants
randomised to a water plus pacifier group were also given 0.1 mL of water with a pacifier to suck. Pain assessments were conducted during heel lancing at weekly intervals. Results showed ongoing efficacy of the combination of oral sucrose and NNS, at each of the weekly assessments, demonstrated by lower Premature Infant Pain Profile (PIPP) scores compared with the PIPP scores of the infants in the standard care group (Stevens et al., 2005). Importantly, in terms of safety outcomes, no differences between the sucrose group and the other groups on the neurodevelopmental outcome assessments were found. Dissemination of such research findings to health professionals caring for sick infants needs to occur in order for wide-spread acceptance and implementation of oral sucrose for procedural pain reduction in infants.

**Utilisation of topical anaesthetic agents**

Also evident from the findings of the survey, was the reported infrequent use of topical anaesthetic agents for procedural pain reduction. However, topical anaesthetic agents have been shown to have no analgesic effects during heel lancing in infants (McIntosh, van Veen, & Brameyer, 1994; Rushforth et al., 1995; Larsson et al., 1996; Taddio et al., 1998; Stevens, Johnston, Taddio et al., 1999), no analgesic effects when used alone during insertion of peripherally inserted percutaneous central lines (Ballantyne et al., 2003; Lemyre et al., 2006; Taddio et al., 2006), and there is inconsistent evidence with respect to analgesic effects during lumbar puncture (Enad et al., 1995; Taddio et al., 1998; Kaur et al., 2003). Although analgesic benefits have been shown in studies of immunisation in older infants (Taddio et al., 1994; Lindh et al., 2003) and during venepuncture (Taddio et al., 1998; Abad et al., 2001), sucrose was shown to be more effective in reducing pain during venepuncture than EMLA®, and the combination of EMLA® and sucrose was no more effective than sucrose alone (Abad et al., 2001). The infrequent use of topical anaesthetics reported in this survey is therefore justified, both on the basis of inadequate evidence to support its efficacy in neonates, as well as recommendations that topical anaesthetics agents such as EMLA® are not used in infants younger than six months of age (Donohoo, 2004).
Utilisation of breastfeeding

The use of breastfeeding during minor painful procedures was one of the pain reduction strategy options included in the survey. The results demonstrated that this practice was infrequently used during minor painful procedures. Analgesic effects of breastfeeding medically stable infants prior to, or during, venepuncture or heel lancing had been demonstrated in two studies at the time the survey was conducted (Gray et al., 2002; Carbajal et al., 2003), and has since been further demonstrated in three randomised, controlled trials (Gradin et al., 2004; Phillips, Chantry, & Gallagher, 2005; Shendurnikar & Gandhi, 2005) and a Cochrane Systematic Review (Shah, Aliwalas, & Shah, 2006). However, the feasibility of mothers breastfeeding their sick infants during procedures has not been systematically evaluated, and is highly questionable. For breastfeeding during painful procedures to occur, infants need to be allowed to receive enteral nutrition, have the ability to orally feed, and need the breastfeeding mother to be present. These conditions are unlikely to be frequently met in settings which care primarily for sick infants, such as the Level Two and Level Three neonatal units included in this survey. Different results may have been obtained if pain management practices during routinely performed painful procedures, such as heel lancing performed for newborn screening, were to be examined in settings which primarily care for healthy, newborn infants.

Other surveys of pain management strategies used for reduction of procedural pain in neonates which have been published over many years have also shown that pharmacologic or non-pharmacologic pain reduction strategies for minor painful procedures were either never used (Porter & Anand, 1998) or rarely used (Johnston, Collinge et al., 1997; Porter et al., 1997; Rohrmeister et al., 2003; Simons, van Dijk et al., 2003; Rennix et al., 2004; Gray et al., 2006). Such a gap between research evidence, and what is utilised in clinical practice, is also evident in the routine use of pain assessment tools in clinical practice. Despite recommendations arising from guidelines from national and international committees concerned with pain management in neonates and infants, to routinely document pain assessment scores (American Academy of Pediatrics & Canadian Paediatric Society, 2000; American Academy of Pediatrics, Committee on Psychosocial Aspects of Child and Family Health, & Task Force on Pain in Infants, 2001; Anand & International Evidence-
Based Group for Neonatal Pain, 2001), findings of this survey, as well as numerous other published reports, have shown infrequent utilisation of pain assessment tools in clinical practice (Debillon et al., 2002; Reyes, 2003; Rohrmeister et al., 2003; Lago et al., 2005).

**Utilisation of pain assessment scores**

Findings of the current survey showed that only six percent of neonatal units in Australia routinely used a pain assessment tool. This is a far lower rate of utilisation of pain assessments tools than that reported in other recently conducted surveys. Pain assessment tools were routinely used in only 11% of neonatal intensive care units in Austria (Rohrmeister et al., 2003) and in 19% of neonatal units in Italy (Lago et al., 2005). A higher proportion of neonatal units in France reported routine use of pain assessment scores, with 60% of units reporting routine use of pain scores for acute pain and 53% for chronic pain (Debillon et al., 2002). In that study, for those units where pain scores were not routinely used, the reasons for not using pain assessment scores were sought (Debillon et al., 2002). The most frequently reported reason was a lack of knowledge about pain scores. Other reasons included an acknowledged failure to include pain management as a priority of care, a belief that available pain scores were not valid, and a lack of time to complete pain scores (Debillon et al., 2002).

**Research utilisation**

Reasons for not routinely documenting pain scores or using pain assessment tools were not sought in the nationwide survey conducted for this study. However, lack of knowledge of relevant research as well as time constraints have previously been shown to be two of the five most frequently reported barriers to utilisation of research in the clinical area (Hutchinson & Johnston, 2004). The slow uptake of knowledge in terms of low frequency of use of oral sucrose, as well as low utilisation of pain assessment scores as reported in the current survey of pain assessment and pain management practices in Australian neonatal units, may conceivably be attributed to inadequate knowledge and time constraints, or a number of other multifactorial reasons. Other barriers to implementing relevant research in the clinical area reported by nurses have included factors such as insufficient authority to change practice, inadequate skills in critical appraisal, and lack of support for implementation of
research findings (Hutchinson & Johnston, 2004). Various strategies designed to increase uptake of relevant research and to facilitate changes in clinical practice have been proposed (Hutchinson & Johnston, 2006; Schechter, 2006).

Strengths and limitations of the nationwide pain assessment and pain management survey

One of the successful strategies for implementing change in clinical practice is by the dissemination of locally relevant and accessible policies (Schechter, 2006). The strengths of this survey therefore lie in the fact that there is now a sound information base of pain assessment and pain management practices in Australian neonatal units which was previously unavailable. Findings have already been used to inform the development of position statements relating to neonatal pain assessment and pain management, which have been endorsed by the Australian College of Neonatal Nurses (Harrison & Australian College of Neonatal Nurses, 2006b, 2006a). The survey results can also be used as a benchmark against which to gauge future policy and practice changes. Such gathering of baseline information on current clinical practices, along with the subsequent dissemination of findings, facilitates the driving of important widespread improvements in clinical practices. Important policy changes for neonatal units in Australia would be targeted at increasing use of evidence relating to neonatal pain assessment and pain management in clinical practice, such as implementation of routine pain assessments in the clinical setting, implementation of oral sucrose for procedural pain and breastfeeding during procedures when feasible. The conduct of a follow-up survey would be an important means of establishing if such practice and policy changes had in fact been implemented.

The main limitation to this survey concerns the response rate, with just over half of the posted surveys being returned. The response rate of 58% of the 181 eligible units limits the generalisability of the survey findings; the final sample size of only 108 units may not be representative of all neonatal units in Australia. The average response rate for postal surveys reported in medical journals is 60% (Asch, Jedrziewski, & Christakis, 1997) or, following up to four reminder notices, a final response rate to a postal survey was reported to be 67% (Barclay, Todd, Finlay, Grande, & Wyatt, 2002). These response rates reflect the widespread difficulties in
obtaining data from a representative target sample. In this nationwide survey, all returned surveys were anonymous, precluding the posting of reminder notices to units who had not responded to the survey. However, in an attempt to increase the response rate, a recommendation for future postal surveys, would be that a follow up letter be sent to all the eligible units, including both a reminder to the target audience to complete and return the survey, and a message thanking those who had already responded.

Another limitation of the survey was that there was no verification of data with the respondents. Therefore it was not possible to be assured that what was reported was what actually occurred. However, due to all responses being anonymous, such verification of data with each individual unit surveyed was not possible.

Questions in this survey were also largely limited to practices relating to pain assessment and pain reduction, with no focus on attitudes, beliefs, barriers to implementing change, or decision-making. Such questions may have added insight into the issue of low utilisation of pain assessment tools and low frequency of use of oral sucrose during painful procedures. Another limitation of the study was that the surveys were sent to neonatal care settings only. In many institutions, young infants, especially those requiring surgical intervention, are nursed in paediatric intensive care units or paediatric wards. It is not known whether inclusion of such settings may have resulted in similar or different findings. However it is important to ensure that recommendations arising from studies of neonatal unit practices are disseminated to such paediatric settings caring for sick newborns and young infants.

The history of an infant's prolonged hospitalisation with respect to painful procedures and pain management practices

Following the completion of the survey of pain assessment and pain management practices in Australian neonatal units, an in-depth examination of such practices in a specific cohort of sick infants in one Australian neonatal intensive care unit was conducted. The Level Three neonatal intensive care unit, where the study took place, is a tertiary referral centre, and cares primarily for infants with complex health needs, many of whom require surgery and multiple other painful procedures, and
administration of opioid analgesics. There is a dearth of information and research evidence concerning pain assessment, pain management, and effectiveness of analgesics in such infants. The aims therefore, were to map all analgesic medications administered, all skin-breaking invasive painful procedures performed, with the addition of ophthalmology examinations, as well as to establish the extent to which pain assessment scores were documented over the duration of a hospitalisation. In addition, although sedatives have little or no analgesic effects, their concomitant use with analgesics in the management of pain and agitation in NICUs has been increasingly reported (Ng et al., 2002; Ng et al., 2005). All sedative use throughout the period of hospitalisation was therefore included in this study.

A prospective, observational, longitudinal study of a cohort of 55 infants with complex health needs nursed in the Neonatal Unit (NNU) at the Royal Children’s Hospital (RCH), Melbourne, Australia for periods ranging from 28 days to five months was conducted. As reported in Chapter 4 of this thesis, 45 infants in the cohort underwent 98 surgical procedures, and all infants were exposed to repeated minor painful procedures throughout the duration of their hospitalisation. In the large majority of minor procedures, infants were given either oral sucrose for pain reduction, or were receiving intravenous morphine as part of their ongoing medical care. There was infrequent documentation of pain assessment scores, yet substantial use of a wide variety of analgesic and sedative agents administered throughout the hospitalisation. The analgesic and sedative agents administered have an inadequate evidence base in terms of both efficacy and safety in newborn infants, to support prolonged use in clinical practice (Ng et al., 2002; Bellu et al., 2005; Ng et al., 2005). These findings add important knowledge to the complex issues of pain management in sick infants. This is the only study identified which has described analgesic and sedative use in detail over the full course of a neonatal intensive care hospitalisation. It is also the only study to have recorded actual rates of analgesic use in conjunction with minor painful procedures throughout the full course of a neonatal intensive care stay. This study also highlights the negligible role that documented pain scores have in determining the apparent need for analgesic or sedatives, or in evaluating effectiveness or otherwise of these medications.
Prolonged use of analgesics and sedatives

Over five years ago, national and international guidelines recommended the administration of opioid analgesics, with or without the addition of sedatives, to critically ill infants for management of pain and distress post-operatively and during intensive care and associated invasive procedures (American Academy of Pediatrics & Canadian Paediatric Society, 2000; Anand & International Evidence-Based Group for Neonatal Pain, 2001). These recommendations were based on research conducted over a span of almost 20 years, which highlighted multiple potential consequences of withholding opioid analgesics in sick infants experiencing both acute and prolonged pain and distress (Anand, 2000b; Anand & Soriano, 2004). However, caution was recommended in the guidelines, in relation to the prolonged use of opioid analgesics and sedatives, and specifically in relation to the administration of the sedative agent, midazolam (American Academy of Pediatrics & Canadian Paediatric Society, 2000; Anand & International Evidence-Based Group for Neonatal Pain, 2001). The prolonged use of opioid analgesics and the substantial use of both midazolam and chloral hydrate as observed in this longitudinal cohort study, are not therefore in accordance with these guidelines. Yet, as reported in Chapter 4 of this thesis, more than 3800 procedures, both major and minor, were recorded for the infants in the cohort, and in addition, 50 of the 55 infants required assisted ventilation during the course of their hospitalisation. The judicious use of opioid analgesics has been recommended to reduce pain, distress, agitation, risk of intraventricular haemorrhage and ventilation asynchrony associated with mechanical ventilation (Pokela, 1994; Anand & International Evidence-Based Group for Neonatal Pain, 2001; Taddio, 2002; Aranda et al., 2005). In addition, the use of analgesics during painful procedures has been recommended on ethical and humane grounds (Pinheiro, Furdon, & Ochoa, 1993; Pokela, 1994; Menon et al., 1998; Anand et al., 2004; Bellu et al., 2005).

Since the 1980s, substantial evidence has also shown improved clinical outcomes and reduced morbidity and mortality in infants when opioid analgesics were administered during and following single episodes of surgery (Anand & Aynsley-Green, 1985; Anand et al., 1987; Anand & Hickey, 1987; Anand, 1990; Anand & Hickey, 1992). The abundant evidence resulting from these trials subsequently led to widespread implementation of opioid analgesia for infants in the intra-operative and post-operative period (De Lima et al., 1996; Johnston, Collinge et al., 1997). The practice
of administering opioid analgesics during the intra-operative and post-operative period was also evident in this current study. As reported in Chapter 4, opioid analgesics were administered intra-operatively during the majority of surgical procedures performed, with the exception of a small number of more minor surgical procedures in which inhalational anaesthesia was administered. In addition, following the majority of surgical procedures, opioid analgesics were continued during the first two days post-operatively.

The more pressing and unresolved issues of both analgesic and sedative use lie in the lack of evidence to support the prolonged administration of such agents for alleviation of pain and distress occurring during the course of medical and nursing care and as a result of large numbers of repeatedly occurring minor painful procedures. As reported in this study, there were 3605 minor procedures recorded. Although procedures were performed most frequently on the infants in this cohort in the first two weeks following admission to the neonatal unit, substantial numbers of procedures also continued to occur throughout the remainder of the hospitalisation. The most frequently performed minor painful procedure was heel lancing, accounting for 71% of the total 3605 minor procedures recorded for the 55 infants. Similarly, other authors have reported that, with the exception of suctioning of the airways, heel lances comprise the most frequently performed invasive painful procedure that hospitalised infants undergo (Barker & Rutter, 1995; Porter & Anand, 1998; Simons, van Dijk et al., 2003; Stevens et al., 2003; Evans, McCartney, Lawhon, & Galloway, 2005). A total of 1849 heel lances over a three-month period in a cohort of 54 infants were reported in one study (Barker & Rutter, 1995) and 3019 heel lances in a cohort of 81 premature infants were reported in another (Evans et al., 2005). In addition, in a study of 144 infants, 7000 procedures were recorded of which 6000 were noted to be heel lances (Porter & Anand, 1998).

Pain management during such frequently occurring, yet short lasting events, is problematic. One strategy recommended has been to avoid heel lancing, and to employ venepuncture as the method of blood collection. Evidence from four trials included in a systematic review showed that venepuncture, when performed by a skilled phlebotomist, was a less painful method of blood collection than heel lancing (Shah & Ohlsson, 2004). However, as shown in this cohort study, as well as other
studies conducted since the systematic review of venepuncture versus heel lance for blood sampling was first published in 2000, substantially more heel lances than venepuncture continue to be performed (Simons, van Dijk et al., 2003; Stevens et al., 2003). For many sick infants, difficulties in obtaining intravenous access for administration of medication, fluids and parenteral nutrition, probably deter health professionals from attempting to introduce venepuncture as the standard method of blood sampling. Heel lancing, despite being shown to be a more painful procedure than venepuncture, therefore continues to remain the principal method of blood collection in NICUs.

The discussion concerning safe and effective pain reduction in sick infants therefore returns to the difficulties in ensuring effective pain management during the large numbers of heel lances and other such frequently occurring, yet short lasting procedures, performed over the course of a hospitalisation. The use of analgesics to abolish all pain and distress at all times in infants remains controversial and problematic. Campbell, in 1989, identified this as an issue of concern and it has still not been resolved today (Campbell, 1989).

Although the issues relating to the use of analgesics to abolish all pain and distress at all times remain unresolved, the use of oral sucrose to reduce pain during minor procedures has been widely studied and there is now abundant evidence to support its use during single painful procedures in both premature and full-term neonates (Stevens et al., 2004; Anand, Johnston et al., 2005) as well as some evidence to support the use in infants beyond the neonatal period (Barr et al., 1995; Lewindon et al., 1998; Harrison et al., 2003a; Lindh et al., 2003; Reis et al., 2003; Mucignat et al., 2004). However, despite the combination of evidence to support the need for pain reduction during painful procedures (Anand & International Evidence-Based Group for Neonatal Pain, 2001) and the effectiveness of single doses of oral sucrose in reducing pain during procedures (Stevens et al., 2004), there remain numerous current reports of heel lances and other minor painful procedures being performed with no analgesic cover (Johnston, Collinge et al., 1997; Porter et al., 1997; Heaton & Herd, 2000; Sabrine & Sinha, 2000; Fernando et al., 2001; Rohrmeister et al., 2003; Simons, van Dijk et al., 2003; Rennix et al., 2004; Gray et al., 2006; Harrison, Loughnan et al., 2006). The low rates of use of oral sucrose reported in a number of surveys of pain
management practices (Heaton & Herd, 2000; Fernando et al., 2001; Rohrmeister et al., 2003; Rennix et al., 2004; Gray et al., 2006; Harrison, Loughnan et al., 2006) may be explained by the paucity of evidence concerning repeated and prolonged use of oral sucrose. Only a small number of studies have previously examined the issue of multiple doses of oral sucrose (Johnston, Filion et al., 2002; Mucignat et al., 2004; Stevens et al., 2005), and only in the recent randomised, controlled trial by Stevens et al. was the analgesic efficacy of repeated doses of oral sucrose over an extended period, reported in detail (Stevens et al., 2005). The dearth of published evidence concerning repeated doses of oral sucrose may have precluded widespread implementation of oral sucrose in the clinical setting. In this current thesis, which examined the use of oral sucrose throughout the duration of the infants’ hospitalisation, substantial numbers of sucrose doses were given, as evidenced by a total of 2322 sucrose doses recorded for the 55 infants in the cohort; a mean of 42 doses of sucrose per infant. This finding of such considerable use of oral sucrose in sick infants significantly contributes to the body of evidence concerning utilisation of oral sucrose in the clinical setting during the multitude of painful or noxious procedures performed over a prolonged hospitalisation.

Findings of this current cohort study showed that in the majority of heel lance procedures, as well as other minor procedures performed, either oral sucrose was given, or infants were receiving morphine as part of their ongoing management. During heel lancing, for example, there were only 14% (361) of heel lances reported, where morphine, or other strong analgesics, sucrose or a combination of both, were not administered. It must be highlighted that opioid or other strong analgesics were not administered specifically for pain reduction during minor procedures, but were being administered for ongoing medical management in situations such as post-operative pain or for critically ill infants requiring mechanical ventilation. Oral sucrose however, was specifically recorded for management of procedural pain, and was either administered alone or concomitantly with an opioid analgesic during 59% of all heel lance procedures. This degree of utilisation of oral sucrose could be attributed to the previous implementation of a policy, in 2001, endorsed by both medical and nursing staff, directing use of sucrose during painful procedures (Harrison, 2001 Appendix 9). In addition, the NNU, RCH has a small number of local champions promoting the use of oral sucrose during minor painful procedures and
there have been numerous educational sessions held regarding the evidence of sucrose-induced analgesia. In addition, through signage and poster presentations in the NNU and around the hospital, parents and staff are encouraged to ask about pain management, including use of sucrose, during procedures. This combination of strategies encompassing local champions, locally relevant and accessible policies, collaborative medical and nursing relationships, ongoing educational efforts and consumer involvement, has been shown to have an effect on changing culture and behaviours (Schechter, 2006).

The moderate to high frequency of use of oral sucrose for management of procedural pain as observed in this longitudinal cohort study demonstrates to some degree, uptake of an evidence-based practice. However, the evidence base supporting the prolonged use of other administered analgesics, as well as sedatives as described in this cohort study, is significantly weaker. Despite the paucity of knowledge and research to inform long-term use of opioid and other analgesics as well as sedative agents in sick infants (Bellu et al., 2005; Ng et al., 2005), the majority of the infants in this cohort were administered morphine and paracetamol for prolonged periods and codeine was given to almost half of the infants in the cohort for a median of three days. In terms of administration of sedatives, either midazolam or chloral hydrate was administered to 76% of infants on 24% of total data collection days. On many days, combinations of these agents were given to an individual infant.

As previously discussed, although there is there is a solid evidential base to support the use of morphine for sick infants following surgery (Anand & Aynsley-Green, 1985; Anand et al., 1987; Anand & Hickey, 1987; Anand, 1990; Anand & Hickey, 1992), there is conflicting evidence regarding the effectiveness of morphine for the management of pain and distress associated with mechanical ventilation and minor procedures. Some studies showed reduced pain responses in mechanically ventilated neonates, during procedures such as suctioning of airways and heel lancing, associated with the administration of morphine (Pokela, 1993, 1994; Moustogiannis et al., 1996; Anand, Barton et al., 1999). Yet, results of other studies showed that continuous infusions of morphine had only minor or no effects on pain scores associated with either heel lancing or airway suctioning (Simons, van Dijk et al., 2003; Anand et al., 2004; Carbajal et al., 2005). The analgesic effects of morphine
during periods of acute pain associated with minor procedures therefore remains questionable. In this current cohort study, a substantial number (n = 988) of minor procedures recorded for the infants were performed when morphine was being administered as part of the infants’ medical care, without the additional use of oral sucrose. The analgesic effectiveness of morphine during these acute minor painful procedures must therefore be questioned.

The analgesic effect of codeine in neonates and infants is also debatable, due to immaturity of the enzymes that are necessary to convert codeine to its active metabolite morphine, which is necessary for analgesia (Williams, Patel, & Howard, 2002). In fact, Anderson and Palmer (2006) reported that codeine has been removed from some hospitals’ formularies as nearly half of all children under 12 years of age lack the necessary maturity of the enzyme required for morphine conversion (Anderson & Palmer, 2006). Codeine is noted also to be a “weak” opioid, and is usually administered in conjunction with other analgesics (Cunliffe, 2001). In this current study, a total of 91 doses of codeine were administered to 23 (42%) of the infants in this cohort within three days following major surgery. The actual effectiveness of codeine administered post-operatively could not be ascertained in this study due to the infrequent documentation of pain scores. However, on the majority of days when codeine was administered to the 23 infants, other analgesics were also used. Paracetamol was given on 94% of the days when any codeine was given, and an intravenous infusion of morphine was being administered on 11% of the days when codeine was administered.

**Utilisation of ketamine**

Many questions relating to the safety and efficacy of other strong analgesic agents, such as tramadol, clonidine, or the anaesthetic and analgesic agent, ketamine, when administered to neonates and young infants, remain unanswered. In the meantime, the introduction of these agents to NICUs, especially for management of intra-operative and post-operative pain has been reported (Berde et al., 2005; Anderson & Palmer, 2006). As reported in this current study, ketamine was administered to five infants for management of post-operative pain, for relatively short periods of time. The median duration of days ketamine was administered for the five infants was only one day.
However, one infant received a continuous intravenous infusion of ketamine for seven consecutive days following surgical repair of an oesophageal atresia. In addition, the same infant, on day five post-operatively, was given seven bolus doses of ketamine in addition to the continuous infusion. This example illustrating extensive use of ketamine, albeit in one infant only, is worrisome in the context of lack of safety information concerning such substantial use of ketamine. Animal studies of ketamine administration used for anaesthesia in neonatal rodents have shown concerning findings of widespread neural cell death, neurological abnormalities and long-term memory deficits (Ikonomidou et al., 1999; Fredriksson, Archer, Alm, Gordh, & Eriksson, 2004; Olney, Young, Wozniak, Ikonomidou, & Jevtovic-Todorovic, 2004; Wang et al., 2005). Whether these same clearly demonstrated adverse neurological effects equally apply to human neonates and infants is not certain and continues to be debated (Anand & Soriano, 2004; Soriano, Anand, Rovnaghi, & Hickey, 2005; Soriano & Loepke, 2005). In the meantime, although further research on the use of ketamine in infants has been recommended (Berde et al., 2005), there is currently little information to guide such use of multiple doses of ketamine, as illustrated in the example of the one infant.

**Utilisation of paracetamol**

Further research on the use of paracetamol (acetaminophen) for analgesia in sick infants is also vital. As reported in Chapter 4 of this thesis, there was substantial use of enterally administered paracetamol observed in this study. This use of paracetamol is despite not only the dearth of research to support its use in neonates and infants, but also that the research which has been done, has generally shown either a lack of, or minimal, analgesic benefits [Macke, 2001 #853; van Lingen, 2001 #632; Shah, 1998 #73; Howard, 1994 #633; Bremerich, 2001 #697; van Lingen, 1999 #852]. Ubiquitous use of enteral paracetamol in infants and children has also been reported in a number of other studies (Penna et al., 1993; Dawson et al., 1996; Lamb & Henry, 2004). In fact, a statement has been made that paracetamol is probably the most commonly used drug in the Western World (Arana et al., 2001) and Dawson et al., questioned whether the prescribing patterns of paracetamol in all ages, but especially in infants less than one year of age were “near epidemic proportions” (Dawson et al., 1996) (p.180).
The use of paracetamol observed in this current study, without the evidence to support such use, is of concern. Also concerning is that, despite the institutional requirement to specify the route of administration of medications, the route of administration of paracetamol was not specified on the infants’ medication chart on 403 (39%) occasions. In 349 (34%) of cases, paracetamol was documented as administered orally and in 279 (27%) instances, paracetamol was documented as administered rectally. Due to erratic rectal absorption of paracetamol in neonates and children, recommendations have been made that larger doses are required when paracetamol is administered rectally, to achieve adequate paracetamol levels for analgesia [Anand, 2005 #781; Birmingham, 1997 #875; Bremerich, 2001 #697; Hansen, 1999 #698; Lin, 1997 #700; Anderson, 1998 #699; van Lingen, 1999 #136]. As reported in Chapter 4 of this thesis, the mean dose of paracetamol administered per kilogram did not differ whether the specific route was un-recorded, or was either recorded as rectal or oral. These prescribing and administering practices therefore had the potential to further impact upon the anticipated analgesic effects of paracetamol in the infants in this cohort. It is vital that health professionals responsible for prescribing and administering paracetamol for hospitalised infants are made aware of such findings of extensive use of paracetamol, without specified rectal or oral doses prescribed and negligible use of pain assessment scores to evaluate analgesic effects. It is through such detailed auditing of practices that awareness can be raised and areas for improvement can be identified.

**Utilisation of sedatives**

In addition to the frequent use of analgesics observed in this study, the sedative agents, midazolam and chloral hydrate were also administered to the majority of infants for variable periods during their hospitalisation. The common use of midazolam for sedation of critically ill infants has also been reported in other NICUs despite the paucity of safety and efficacy data to promote such use (Ng et al., 2002; Ng et al., 2005). Moreover, findings arising from randomised, controlled trials of continuous intravenous midazolam compared to placebo in premature newborn infants showed little clinical benefits yet risk of significant adverse effects (Jacqz-Aigrain, Daoud, Burtin, Desplanques, & Beaufils, 1994; Anand, Barton et al., 1999; Arya & Ramji, 2001). In fact, findings of a pilot study of analgesia and sedation in 67 preterm neonates requiring ventilatory support were that 32% of neonates randomised
to receive continuous intravenous midazolam had poor neurological outcomes compared to 24% of neonates in the placebo group, and 4% in the morphine group (Anand, Barton et al., 1999). The key recommendation from a systematic review of midazolam for sedation of infants in the neonatal intensive care setting was that midazolam could not be recommended for routine use in neonates undergoing intensive care (Ng et al., 2005).

The increasing use of sedatives in NICUs is a complex issue. In the case of the cohort of infants enrolled in this longitudinal cohort study with heterogeneous medical and surgical conditions, there may be high requirements for sedation which may not be comparable to the population of primarily premature infants with respiratory illnesses included in the majority of such studies of midazolam use. It is not known whether the same recommendations against the long-term use of sedatives should equally apply to such infants with complex health needs. There remains little research to guide the use of sedatives in all infants nursed in NICUs, especially unique populations of infants such as those included in this cohort study. Numerous recommendations have recently been made following extensive reviews of available literature concerning analgesic and sedative use in neonatal intensive care settings, including the need for further well-designed and adequately powered clinical trials to establish the safety, efficacy, and short and long-term outcomes of analgesia and sedation in the mechanically ventilated newborn undergoing painful procedures (Anand, Aranda et al., 2005; Anand, Johnston et al., 2005; Aranda et al., 2005). Health professionals caring for sick infants have a responsibility to act on such recommendations in a timely manner with the aim of improving the evidential base in which to guide current analgesic and sedative prescribing practices in neonatal units.

The other commonly used sedative in many NICUs is chloral hydrate (McCarver-May et al., 1996). In this current study, 36 of the 55 infants (65%) received a total of 1217 doses of chloral hydrate. This substantial use of chloral hydrate is despite recommendations against routine and prolonged use (Alexander & Todres, 1998) and from recommendations arising from a small number of case reports of adverse events associated with the administration of chloral hydrate in young infants (Laptook & Rosenfeld, 1984; Hartley, Franck, & Lundergan, 1989; McCarver-May et al., 1996; Allegaert, Daniels, Naulaers, Tibboel, & Devlieger, 2005). Chloral hydrate toxicity
resulting from chloral hydrate given at doses considered to be appropriate and safe, which subsequently resulted in paradoxical agitation was reported in two infants (Hartley et al., 1989) and in another report, chloral hydrate toxicity resulted in respiratory failure, lethargy, decreased activity and hypotonia (Laptook & Rosenfeld, 1984). In a small cross-over study of chloral hydrate and midazolam for neuroimaging studies, four of the seven infants had oxygen desaturation episodes to levels below 90% following administration of both chloral hydrate and midazolam. A significant decrease in blood pressure also occurred following chloral hydrate administration in four infants and following midazolam administration in three infants (McCarver-May et al., 1996). More recently, a study of procedural sedation in former premature infants had to be terminated due to the high rate of severe bradycardic events following administration of chloral hydrate (Allegaert, Daniels et al., 2005). Cautionary use of chloral hydrate in former premature infants was subsequently recommended.

Although the case report describing paradoxical agitation as a result of chloral hydrate administration was published over 15 years ago (Hartley et al., 1989), concerns relating to the lack of critical evaluation of safety and efficacy of chloral hydrate as well as other sedatives, for routine sedation in the NICU population currently remain unresolved. In this study, there was no systematic documentation of incidence of adverse events following administration of either midazolam or chloral hydrate, nor were there routine documented assessments of either agitation or sedation levels to permit systematic evaluation of the effectiveness of either sedative agent. Findings arising from this study do not therefore contribute to the prevailing knowledge gap relating to the safety and effectiveness of sedative use in sick infants. Similarly, as there was infrequent documentation of pain scores, the effectiveness of the various analgesic medications administered to the infants in this study also could not be systematically ascertained. The important knowledge that this study does contribute however, is a detailed description of the extent of use of such agents in sick infants. Recommendations for practice, consistent with those made by international bodies (Anand, Johnston et al., 2005; Aranda et al., 2005; Bellu et al., 2005; Ng et al., 2005), can therefore justifiably be made concerning the need for careful evaluation of both the effectiveness and safety of analgesics and sedatives used for the management of pain and distress in the NICU.
Assessment of pain and distress

The careful evaluation of effective pain, distress and agitation management in critically ill infants nursed for prolonged periods in NICUs is however, complicated by difficulties with reliable assessment of pain, sedation levels, distress and agitation. Although there are now over 35 pain assessment tools developed for use in infants (Duhn & Medves, 2004), reliable assessment remains problematic in certain populations of sick infants; especially in infants requiring assisted ventilation, infants who are irritable or agitated, or those infants with established and ongoing pain (Anand, Aranda et al., 2005; Hummel & van Dijk, 2006). The pain scoring method used in the NICU where the current study took place is the Pain Assessment Tool (PAT), which was introduced over four years ago into the NICU (Hodgkinson et al., 1994). This tool was initially developed for assessment of post-operative pain in the neonate but a further report of establishment of reliability, validity and clinical utility in a diverse population of sick hospitalised infants was published (Spence et al., 2005). The PAT was not originally designed, nor specifically tested for, assessing distress and agitation, and it is not known whether the implementation of a different scoring system, one developed specifically for assessing levels of sedation, or agitation would make any difference to the frequency of documentation of pain or distress.

Although difficulties with assessing distress and agitation were identified as problematic almost 20 years ago (Franck, 1987), the same issues remain unresolved today (Anand, Aranda et al., 2005; Hummel & van Dijk, 2006; Boyle, Freer, Wong, McIntosh, & Anand, 2006). Systematic evaluation of pain, distress and agitation management is further complicated as, despite the considerable amount of work that has gone into the development and subsequent reliability and validity testing of many of the 35 pain assessment tools, there is limited utilisation of these tools in clinical practice (Rohrmeister et al., 2003; Lago et al., 2005; Harrison, Loughnan et al., 2006). As previously shown, in this study there was infrequent documentation of PAT scores for the infants in the cohort. In fact, PAT scores were only documented on 5% of total data collection days, despite the substantial use of analgesics and sedatives and the large numbers of painful procedures performed. The infrequent documentation of PAT scores highlights that, in this cohort of infants, there was minimal recorded
systematic evaluation of effectiveness or otherwise of analgesic and sedative medications, and that decisions regarding administration, dosing, or weaning of analgesic and sedative agents were not therefore, guided by documented pain scores.

With the exception of the findings of the survey of pain assessment and pain management practices in neonatal units in France, which showed that 60% of units reported routinely using pain scores for acute pain and 53% for chronic pain (Debillon et al., 2002), numerous other reports in the literature have also shown low rates of utilisation of pain scores (Rohrmeister et al., 2003; Lago et al., 2005; Harrison, Loughnan et al., 2006). Interestingly, a study which took place in a NICU within a tertiary paediatric centre in the United States of America, showed that the majority of nurses believed they were assessing pain frequently, yet a retrospective chart review of pain assessment scores showed otherwise (Reyes, 2003). Reyes reported that less than 10% of minor procedures had a pain assessment score concomitantly documented, pain assessments during the administration of morphine rarely occurred, and only 37% of infants on a day shift and 44% of infants on a night shift had any documented pain scores. At the time that study took place the NICU was the only large centre in the area which had implemented a pain assessment policy and “utilised” a pain assessment tool. In another study, low compliance was also noted with using a new scale to measure distress, which had recently been introduced in a paediatric surgical intensive care unit in the Netherlands (van Dijk, Peters, van Deventer, & Tibboel, 2005). The authors reported that poor compliance might have been low due to the lack of effect of scores on actual pain management practices. The lack of integration of pain assessment with decisions regarding pain management has been cited as an important factor underpinning poor utilisation of pain scores in the clinical setting (Franck, 2002; Hummel & van Dijk, 2006). Difficulties with establishing clinical utility of pain assessment methods in infants have also been acknowledged (Stevens & Gibbins, 2002). In a review of pain assessment in infants, Stevens and Gibbins (2002) stated that, without clinically useful pain measures, clinicians are unable, and unlikely, to assess pain or the effectiveness of pain-relieving interventions.

Despite possible shortcomings of available methods of assessing pain, distress and agitation in sick infants, and the currently observed lack of integration of pain scores
with pain management, it is important for clinicians to change their practices and to strive to apply the most appropriate pain assessment score for their particular setting. By attempting to consistently use the most relevant tool in clinical practice, nursing, medical and allied health clinicians caring for sick infants will potentially have the means to guide dosing of analgesic and sedative medications, and to systematically evaluate the effectiveness of such medications as well as the effectiveness of non-pharmacological pain relieving interventions.

**Strengths and limitations**

This study was conducted in a single centre which has a well-defined pain management policy in relation to use of sucrose for procedural pain. This limits the external generalisability of the study, consequently the results may not be applicable to other similar neonatal settings. In addition, the criteria of minor painful procedures was defined for the purpose of this study, as skin breaking invasive procedures (Grunau, Weinberg et al., 2004) with the addition of eye examinations. As this definition excluded non-cutaneous pain, the true number of painful and stressful procedures that sick infants undergo is vastly underestimated. In addition, the use of analgesia during non-cutaneous pain remains unexplored in this thesis. Missing data relating to painful procedures also contributes to the underestimation of painful procedures sick infants undergo during the course of a prolonged hospitalisation.

The sample of infants enrolled in this cohort study with heterogeneous medical and surgical conditions may also not be comparable to the population of premature infants whom make up the large majority of infants admitted to Level Three NICUs (Laws & Sullivan, 2005), and therefore included in the majority of published studies concerning pain management practices in NICUs. This potentially limits the generalisability of the findings of this study to similar unique populations of infants, with complex medical conditions, who have had surgery, and who may have higher requirements for analgesics and sedatives for adequate management of pain and distress. Conversely, the strength of this study lies in that there is now detailed information on pain assessment and management practices in such a cohort of sick infants, for the entire duration of their hospitalisation which was not previously available. These sick infants have been excluded from the majority of studies of
analgesic and sedative use in neonates (Stevens et al., 2004; Bellu et al., 2005; Ng et al., 2005).

Due to the paucity of research in such infants, it is not known whether recommendations against the long-term use of opioid analgesics and sedatives, which have arisen from large randomised, controlled trials, systematic reviews and guideline statements (American Academy of Pediatrics & Canadian Paediatric Society, 2000; Anand & International Evidence-Based Group for Neonatal Pain, 2001; Anand et al., 2004; Bellu et al., 2005) equally apply to sick infants. The information from this longitudinal cohort study affords an increased understanding of the utilisation of opioid analgesics, sedatives and oral sucrose in a population of infants, which was previously unavailable. This in-depth history of pain management practices was also vital in informing the findings of the third aim of this study, that of describing the effectiveness of oral sucrose in reducing procedural pain during the course of a prolonged hospitalisation, by means of mapping the successive responses to a routine painful procedure in the same cohort of infants with complex health needs.

The effectiveness of oral sucrose in reducing procedural pain during the course of an infant's prolonged hospitalisation

The third aim of this study was to describe the effectiveness of oral sucrose in reducing procedural pain during the course of an infant's prolonged hospitalisation, by means of mapping the successive pain responses to the routinely and commonly performed painful procedure of heel lance. As oral sucrose was given prior to all heel lance procedures, the sustained, or otherwise, analgesic effects of oral sucrose throughout the hospitalisation could be ascertained.

Pain assessments during heel lancing were conducted weekly if possible, or more or less frequently, subject to the medical requirement for pathology testing by capillary blood sampling. As reported in Chapter 2, the method used to assess pain during, and following completion of the heel lance procedure was a combination of previously validated behavioural and physiological parameters assessed at the bedside, which included a facial expression score, duration of crying, heart rate and oxygen
saturations (Harrison et al., 2002). Oral sucrose was administered prior to and during all observed heel lance procedures as per the NNU oral sucrose protocol (Harrison, 2001), with the exception of three occasions. The three procedures where oral sucrose was not given were removed from subsequent data analysis.

As reported in Chapter 5, in the majority of heel lance procedures assessed, the lowest facial expression score of zero was assigned at all observation points. In addition, crying occurred in only half of the observed assessments where infants had the capacity to have an audible cry, and the median crying time was of a short duration. Responses to the heel lance procedure differed if opioid analgesics were administered concomitantly with oral sucrose at the time of the observed procedures. During the blood collection phase of the procedure, for those assessments where opioid analgesics had been administered, the heart rate change from baseline, in response to the heel lance procedure was reduced and the mean oxygen saturation was two to three percent lower compared to when sucrose only had been administered. In contrast, during the observed procedures where opioid analgesics were administered, crying duration was increased and there were proportionally less assessments where the lowest facial expression score of zero was assigned.

**Analgesic effects of repeated doses of oral sucrose**

Of the 55 infants in the cohort, 50 infants had three or more pain assessments during heel lancing performed, which were used in the analysis of successive pain responses. Results showed that there was no increase or decrease in facial expression scores, crying duration, or physiological responses over consecutive heel lance procedures. This lack of an increase in pain responses, coupled with the consistently low facial scores and crying duration observed in the majority of assessments, adds important evidence to persisting sucrose-induced analgesia following repeated and consistent use during multiple painful procedures throughout the neonatal period and the first few months of infancy. Previously, the abundant evidence supporting sucrose-induced analgesia arose from randomised, controlled trials examining pain responses during a single painful procedure (Stevens et al., 2004), with only one study evaluating the efficacy of multiple doses of oral sucrose in premature infants over an extended period, of one month (Stevens et al., 2005). This current study is the first to describe ongoing use of oral sucrose in sick infants over the full course of a hospitalisation,
ranging from one to five months duration. This study is also the first to describe the concomitant use of sucrose in conjunction with opioid analgesics.

These findings have important clinical implications for pain management of sick infants who are exposed to multiple and repeated painful procedures over a prolonged period of time. As reported previously, in most neonatal settings, oral sucrose is infrequently administered for pain reduction during the frequently occurring multitude of minor procedures (Heaton & Herd, 2000; Fernando et al., 2001; Rohrmeister et al., 2003; Harrison, Loughnan et al., 2006; Gray et al., 2006). The findings of this study now provide further evidence to support the use of oral sucrose for reduction of procedural pain in sick hospitalised infants during repeated exposure to painful procedures.

As one of the foremost knowledge and research gaps concerning the use of oral sucrose in the reduction of procedural pain has been the issue of analgesic benefits of repeated doses of sucrose over a prolonged period in sick infants, these findings substantially contribute to this knowledge gap. An important issue which must also be further considered is the fact that, during many of the pain assessments conducted, the infants in this cohort were receiving analgesic medications as part of their medical care, in addition to the oral sucrose given specifically for pain reduction during the heel lance procedure. As reported in Chapter 5, during 79 (18%) pain assessments during heel lances, opioid analgesics were already being administered as part the infants’ medical management. Both the behavioural and physiological responses of infants during these heel lance procedures differed from the procedures where sucrose only, without concomitant opioid analgesics, was being administered. Although facial expression scores and crying times were increased during those 79 procedures in which opioid analgesics were being administered, there was a reduction in the heart rate change from baseline in response to the heel lance procedure. The reasons for this are unclear, but could relate to the different mechanisms involved in physiological stress and behavioural pain responses. Opioid analgesics, given concomitantly with oral sucrose, appeared to have the capacity to reduce the physiological stress associated with the painful procedure, yet the behavioural pain responses were not reduced.
Pain responses during concomitant opioid analgesic administration

Attenuation of physiological responses with morphine or other opioid analgesics during and following operative procedures in sick premature and term infants has been well documented (Anand & Aynsley-Green, 1985; Anand et al., 1987; Anand et al., 1988; Anand & Hickey, 1992). In addition, attenuation of various physiological, behavioural or metabolic parameters with opioid analgesics during more prolonged pain and stress during mechanical ventilation in newborn infants has also been well demonstrated in a number of studies (Bellu et al., 2005). However, there have been no previous studies examining the analgesic effects of oral sucrose when administered concomitantly to opioid analgesics. This limits the degree of comparison that can be made with results of this study to that of other studies of pain reduction during minor painful procedures.

There is conflicting evidence of the effectiveness of morphine or other opioid analgesics in reducing pain during acute minor painful procedures. Although Menon et al. (1998) suggested that background cover with systemic analgesics alone was unlikely to provide adequate analgesia for acute painful events, a number of studies have demonstrated a reduction in either physiological and/or behavioural responses to acute procedural pain following administration of morphine (Pokela, 1994; Moustogiannis et al., 1996; Anand, Barton et al., 1999; Scott et al., 1999; Taddio et al., 2006). Scott et al. (1999) reported that facial expression scores in premature newborn infants undergoing heel lancing were reduced whilst they were receiving a continuous intravenous morphine infusion compared to when morphine was no longer being administered. Similarly, although an entirely different procedure, (endotracheal tube suctioning compared with heel lancing), a continuous intravenous infusion of morphine resulted in a significant reduction in PIPP scores during endotracheal tube suctioning in premature infants compared to the PIPP scores of infants receiving a placebo (Anand, Barton et al., 1999). In a recently published blinded, randomised, controlled trial in premature infants, analgesic effects of intravenous morphine and a topical anaesthetic agent during central line placement were examined (Taddio et al., 2006). Results showed that infants receiving morphine with or without concomitant topical anaesthetic demonstrated a significant reduction in both behavioural and physiological parameters compared with no treatment, and compared with topical
anaesthetic alone. Furthermore, results of a small descriptive study showed that a single dose of intravenous morphine given prior to placement of a peripherally inserted central line, significantly attenuated skin blood flow changes from baseline compared to those procedures where morphine was not administered (Moustogiannis et al., 1996).

The painful stimuli in all these studies differed, impeding more rigorous comparison of these findings. In addition, due to the different outcome measures used, direct comparison of the findings arising from these studies (Moustogiannis et al., 1996; Anand, Barton et al., 1999; Scott et al., 1999; Taddio et al., 2006), with findings of the longitudinal cohort study, of an attenuated heart rate response without an associated behavioural pain reduction is problematic. For example, no physiological parameters were reported in the study by Scott et al. (1999) and the PIPP score used by Anand and Barton et al. (1999) is a multidimensional pain assessment tool, precluding separate analysis of physiological and behavioural responses. In addition, the mechanism of skin blood flow in response to pain is dissimilar to that of heart rate response (Nath, Raju, & Griffin, 1990; McCulloch et al., 1995). Despite these differences, findings of these previous studies, and the attenuated heart rate response to heel lancing as reported in this study, do contribute to the evidence supporting the effectiveness of morphine in attenuating responses to acute procedural pain. However, contrasting findings from other studies have been reported.

A single dose of intravenous pethidine (meperidine), a synthetic opioid analgesic similar to morphine, given to premature infants 15 minutes prior to endotracheal suctioning or nursing cares did not result in any attenuation of heart rate change from baseline during the procedures, when compared with placebo, yet reduced behavioural pain scores and duration of hypoxaemia in the group of infants who received opioid analgesics were reported (Pokela, 1994). In contrast, findings from another study showed that a single intravenous dose of morphine given to premature infants within the first hour following surgery performed for ligation of a patent ductus arteriosus, had no effect on attenuating either behavioural, physiological, or stress hormone levels (Franck et al., 2000). Two more recent studies showed that pain scores recorded for premature infants requiring mechanical ventilation and randomised to receive a continuous intravenous infusion of morphine during either endotracheal tube
suctioning (Simons, van Dijk et al., 2003) or heel lancing (Carbajal et al., 2005) did not differ to the pain scores recorded for the infants randomised to receive a placebo. Although the inconsistent findings from these studies highlight that the role of opioid analgesics in acute procedural pain reduction remains unclear, the accumulating and recent evidence suggests that intravenous morphine does not reduce acute procedural pain in infants (Anand et al., 2004; Anand, Johnston et al., 2005; Carbajal et al., 2005).

As additional confounding issue relating to the effectiveness of opioid analgesics in reducing physiological responses to procedural pain in sick infants may be the impact of severity of illness. It must firstly be acknowledged that any interpretations relating to pain responses and NTISS scores, as alluded to in this current study, must be made with caution, as the NTISS score is simply an indicator of the number of therapies required, and as such, is a proxy severity of illness measure only (Gray et al., 1992). However, as reported in this current study, the NTISS scores on the day of observed pain assessments in those infants receiving concomitant opioid analgesics were higher than the scores for when sucrose only was administered. A reduced ability of sicker infants to mount a vigorous response to painful or distressing procedures has been described previously (Field & Goldson, 1984; Craig et al., 1993; Johnston, Stremler et al., 1997; Johnston, Stevens et al., 1999), including the report of the randomised, controlled trial of sucrose which was conducted in the same neonatal unit as this cohort study (Harrison et al., 2003a). In contrast, a number of other studies have shown that severity of illness is not a factor which impacts on infants’ ability to respond physiologically to procedural pain (Stevens et al., 1993; Stevens & Johnston, 1994; Johnston & Stevens, 1996). These conflicting findings highlight the difficulties in clearly identifying factors which predominantly influence sick infants’ responses to procedural pain. However, as previously stated, regardless of whether the infants were receiving opioid analgesics concomitantly with oral sucrose, in the majority of assessments conducted, the behavioural pain responses were infrequently exhibited, suggestive of the effectiveness of sucrose in blunting behavioural responses to procedural pain.

Of note is the disparate role of oral sweet tasting solutions to that of intravenous opioid analgesics, in the attenuation of physiological and behavioural responses to
acute procedural pain in newborn infants. As reported in the systematic review of sucrose for analgesia in newborn infants undergoing painful procedures, administration of oral sucrose, compared to placebo, resulted in reduced behavioural pain responses and multidimensional pain scores in all included studies except those which used less concentrated, and therefore less sweet tasting solutions (Stevens et al., 2004). However, the evidence to support the effectiveness of sweet tasting solutions in reducing physiological responses to procedural pain is conflicting. As reported in the systematic review, there was a statistically significant reduction in heart rate responses in infants in the sucrose groups, compared to the placebo groups in eight of the 15 included studies which measured heart rate. Results of two studies only could be pooled for meta-analysis, with results showing no difference in the heart rate response to procedural pain between the infants who received sucrose compared to those who received placebo. This lack of effect was also highlighted in the randomised, controlled trial undertaken in the same setting as this study, and which included a similar heterogeneous population of primarily term infants with a history of surgical procedures (Harrison et al., 2003a). Although Harrison et al. showed that oral sucrose resulted in reduced behavioural responses compared to placebo, especially in the period following completion of the blood sampling, there was no such attenuation of heart rate response in the sucrose group.

There is thus a large body of evidence to support the efficacy of oral sucrose in reducing behavioural responses to pain, but conflicting evidence as to whether physiological responses are also reduced by sucrose (Harrison et al., 2003a; Stevens et al., 2004). In addition, there is conflicting evidence regarding the effectiveness of opioid analgesics in attenuating behavioural and physiological responses to acute procedural pain (Anand, Johnston et al., 2005). Reasons for conflicting results are not known, but in all likelihood, are multifactorial and depend on complex individual variability in pain responses.

**Efficacy of repeated doses of oral sucrose**

Despite the large body of evidence to support the efficacy of sucrose in reducing behavioural responses to a single episode of pain, there had, until recently been limited information on the efficacy and safety of repeated doses of sucrose over a prolonged period. Although one study examined pain responses in premature infants
during repeated subcutaneous injections over a period of five months, statistical analysis was purely based on a comparison of aggregated mean pain scores between four treatment groups, rather than any changes in pain scores over the period of the study (Mucignat et al., 2004). While the results clearly added to the evidence relating to sucrose-induced analgesia, the findings did not significantly contribute to the knowledge gap concerning the effectiveness of long-term use of oral sucrose.

Johnston and Fillion et al. (2002), were the first to examine repeated use of oral sucrose in human infants. However, the study period was seven days only, and the primary focus was on neurobehavioural outcomes following multiple doses of sucrose, rather than analgesic effects of oral sucrose in procedural pain reduction (Johnston, Filion et al., 2002). In the small number of assessments conducted during painful procedures, sucrose remained more effective than water in reducing facial expression scores. However, a subgroup analysis of the infants in the sucrose group who had received the highest number of sucrose doses showed an increased incidence of lower neurobehavioural assessment scores at two of the three test sessions, compared to the infants who had received a smaller number of sucrose doses. Although in all likelihood, the study was not powered to appropriately perform this sub-analysis, cautionary use of repeated doses of sucrose in premature infants was recommended (Johnston, Filion et al., 2002). As all use of sucrose ceased after the seven-day study period in that study, the important question regarding repeated use of sucrose for painful procedures remained unanswered.

Since the commencement of this longitudinal cohort study, further evidence relating to the safety and efficacy of repeated use of sucrose in premature infants has been published (Stevens et al., 2005). Stevens et al. reported ongoing efficacy of the combination of oral sucrose and NNS, as demonstrated by lower Premature Infant Pain Profile (PIPP) scores during weekly heel lancing compared to PIPP scores of the infants randomised to the control group. Importantly, in terms of safety outcomes, no differences between the sucrose group and the other groups on the neurobiological risk scores were found. Although a power calculation based on detecting differences in neurobiological outcomes was not performed, and the study may not have been sufficiently powered to determine differences in the neurobiological risk status
outcomes, the lack of an observed difference in neurobiological risk status scores was nonetheless reassuring.

The design and participants of the study by Stevens et al. (2005) and this current longitudinal cohort study were dissimilar. Stevens and colleagues conducted a randomised, controlled trial, including premature infants only and excluding those requiring surgery or those with major congenital anomalies, whilst this current cohort study was of a non-experimental design, with a large proportion of the infants in the cohort being born at, or near, term. Included in this cohort study were infants requiring surgery and those with major congenital anomalies. A significant proportion of the infants were also receiving other analgesics and sedatives at the time the pain assessments were conducted. In addition, the use of oral sucrose was studied over the entire duration of a NICU hospitalisation, whereas the study by Stevens et al. (2005), followed the infants for the first 28 days of hospitalisation only. However, the findings of both studies, of ongoing low pain scores during heel lancing, following repeated use of oral sucrose, add important evidence to support the use of oral sucrose in the reduction of repeated painful procedures over a prolonged period in sick hospitalised infants. Prior to the publication of the randomised, controlled trial by Stevens et al. (2005), the substantial knowledge gaps in relation to long term use of oral sucrose may have deterred the widespread implementation of sucrose analgesia for frequently occurring minor procedures in NICUs. The increased body of evidence of ongoing effectiveness of oral sucrose in the continuing reduction of procedural pain can be used to recommend the routine use of oral sucrose in clinical practice in NICUs for management of acute pain during minor invasive procedures.

Analgesics and the prevention of altered pain responses
There is now further evidence of the immediate benefits of analgesic effects of oral sucrose in the reduction of repeated episodes of procedural pain. An important question remains concerning whether oral sucrose, if consistently given during painful procedures, can protect infants from developing abnormal responses to subsequent pain. Only one study, which was conducted in an animal laboratory, was identified which specifically evaluated the preventative role of oral sucrose in development of abnormal pain responses. Anseloni et al. (2002), in a study of pain responses in newborn rat pups, suggested that the provision of oral sucrose during early neonatal
pain exposure not only alleviated acute pain in response to noxious thermal and mechanical stimuli, but also effectively reduced the risk of subsequent development of heightened pain responses. Such abnormally heightened pain responses in animals, subsequent to pain exposure occurring in the newborn period had previously been reported (Woolf, 1983; Reynolds & Fitzgerald, 1995; Anand, Coskun et al., 1999; De Lima et al., 1999; Ruda et al., 2000; Fitzgerald & Beggs, 2001; Torsney & Fitzgerald, 2002; Torsney & Fitzgerald, 2003; Fitzgerald, 2004; Ren et al., 2004).

In the human infant, increased responses to subsequent mechanical or painful stimuli, following earlier acute painful procedures or tissue injury has also been well demonstrated (Fitzgerald et al., 1988; Fitzgerald et al., 1989; Andrews & Fitzgerald, 1994; Taddio et al., 1995; Taddio et al., 1997; Anand, 2000a; Taddio et al., 2002). However, as demonstrated in the current longitudinal cohort study, no increases in pain responses over successive heel lance procedures occurring over a period ranging from 28 days to almost five months were observed. Possibly, similar to the findings of Anseloni et al., this finding may suggest that the provision of either oral sucrose or opioid analgesics, given for the large majority of painful procedures, may have assisted in protecting the infants from developing increased responses to subsequent painful procedures occurring within the period of follow-up during the NICU hospitalisation. As no follow-up of sucrose-induced analgesia and pain responses during painful procedures occurred following discharge, it is not known whether heightened responses to procedural pain, such as that occurring during routine immunisation, compared with infants with no such pain exposure, developed later in infancy or childhood.

The research by Anseloni et al. (2002) is the only study identified which has specifically evaluated long-term analgesic effects of sucrose beyond the immediate pain exposure. However, there is emerging evidence in human infants that routine and consistent use of appropriate analgesics during exposure to painful procedures in the neonatal and early infancy period may also have the potential to prevent the development of altered pain responses and subsequent altered behaviours (Taddio et al., 1997; Peters, Koot, de Boer et al., 2003; Allegaert, Devlieger et al., 2005). In these studies, long-term impact of early pain exposure was evaluated over a period of one to three years, whereas this current longitudinal cohort study was concerned only
with pain responses over the course of a single, lengthy hospitalisation. However, findings from the studies of long-term responses to neonatal pain, and this study, do inform the potential capacity of appropriate analgesics during early exposure to painful procedures to provide protection from development of subsequent abnormal pain responses. Further research on the routine and consistent use of oral sucrose and other appropriate analgesics during exposure to all painful procedures in the neonatal and early infancy period throughout hospitalisation and following discharge is still required to unequivocally show if altered behaviours and pain responses in later infancy and throughout childhood, can be prevented.

Sucrose tolerance

One of the potential risks of repeated doses of oral sucrose which has been suggested, is the development of a tolerance to sweet-tasting solutions, resulting in a reduction of analgesia subsequent to large numbers of sucrose doses administered (Eriksson & Finnstrom, 2004). Animal studies have shown that repeated doses of sweet-tasting solutions or a prolonged uninterrupted period of sweet solution consumption could induce either sucrose tolerance, as demonstrated by reduced thermal pain thresholds (Holder & Bolger, 1988) or morphine tolerance (Lieblich et al., 1983; Fidler et al., 1993). However, the sweet taste-induced opioid tolerance reported in these animal studies was as a result of the rats consuming either large volumes of sweet solutions, up to 50 mLs daily for up to 28 days, or having an uninterrupted supply of sweet solution for three to six hours. These doses and duration of sucrose consumption are far in excess of what would ever be conceivably given to any infant in a NICU. In addition, in the study by Lieblich et al., the same sweet taste-induced opioid tolerance was not evident in a different strain of ten rats which consumed an average of 24 mLs of the sweet fluid, daily for 28 days; an amount still vastly in excess of what would be administered to infants for pain reduction. Even in this current study, in which large numbers of sucrose doses were given, the volumes given were substantially less than those in the animal study (Lieblich et al., 1983). As previously discussed, in the analysis of the 437 assessments during successive heel lance procedures in 50 infants with three or more pain assessments, there was no increase in behavioural or physiological pain responses over successive assessments, suggestive of a lack of development of sucrose tolerance over the period of hospitalisation.
In reality, the actual sucrose consumption for the infants in the cohort is underestimated as the administration of oral sucrose also occurs outside the prescribed sucrose solution specified for pain reduction. Medications administered to infants in the NICU are frequently suspended in a sucrose solution, including most preparations of the frequently prescribed antifungal medication, nystatin. In the NNU, RCH where this current study took place, the oral antifungal preparation, nystatin is administered orally three times each day, to all infants, to reduce the risk of systemic Candida infection. This has been an established practice in the NNU, RCH for over a decade, despite recommendations arising from a systematic review, that there is insufficient evidence to support the routine use of oral prophylactic antifungals in premature infants (Austin & Darlow, 2004). The sugar content in different nystatin preparations may vary widely, and, in fact, due to changing costs and availability, during the 15-month data collection period for this study, four different nystatin preparations were used in the NNU, RCH. All preparations used had varying concentrations of sucrose, and included a sugar-free solution, one suspended in a 12.5% (wt/vol) sucrose solution, and one containing 50% sucrose (wt/vol). In addition, one of the infants in the cohort was specifically prescribed a more concentrated formulation of nystatin for a period of three weeks, which was suspended in a preparation containing 62.5% sucrose. Despite the substantial numbers of sucrose doses given to the infants in the cohort, in addition to other sources of sucrose contained within frequently administered oral medications, no increase in pain responses over successive heel lance procedures were observed, suggestive of a lack of evidence to support development of sucrose tolerance.

*Declining sucrose-induced analgesia with increasing age*

In terms of both effectiveness and safety of routine and consistent use of oral sucrose in the reduction of procedural pain, there do remain several issues to be explored. One important issue is related to the age of the infant, at which oral sucrose remains effective. One of the findings of an animal study by Anseloni et al. was that sucrose analgesia in the rat model began to decline from 15 days of age, and was ineffective beyond 17 days of life (Anseloni et al., 2002). The approximate maturity of the rat at 17 days of age is suggested to be equivalent to early infancy in humans (Fitzgerald & de Lima, 2001), therefore the decline and loss of sucrose-induced analgesia with increasing age in rodents, requires further investigation if sucrose is to be
recommended for use in sick infants throughout a prolonged hospitalisation. Such a decline in sucrose-induced analgesia during heel lancing was not apparent in this longitudinal cohort study (median length of stay 50 days), as evident by the lack of increase in pain scores, crying duration and physiological responses over successive heel lance procedures.

A previous blinded, randomised, controlled trial, conducted in the same setting as this cohort study, also included infants beyond the neonatal period (Harrison et al., 2003a). Results also demonstrated sucrose efficacy during heel lancing, however, the analgesic effect was reported to be more modest than that observed in younger infants (Harrison et al., 2003a). Additional evidence of sucrose-induced analgesia in older infants has primarily come from studies involving pain during routine immunisation (Barr et al., 1995; Allen et al., 1996; Lewindon et al., 1998; Lindh et al., 2003; Reis et al., 2003). However, the analgesic effects of oral sucrose have either been reported to be more modest than that seen in newborn infants (Barr et al., 1995; Allen et al., 1996), or higher volumes or concentrations of sucrose were used than described in studies including newborn infants (Lewindon et al., 1998; Reis et al., 2003).

Of note, a recently published study showed that 24% (wt/vol) sucrose did not result in reduced pain responses when administered two minutes prior to urethral bladder catheterisation, in infants aged up to 90 days (Rogers, Greenwald, Deguzman, Kelley, & Simon, 2006). The results demonstrated effective sucrose analgesia only in a subgroup of infants aged less than 30 days, whilst, for the infants older than 30 days of age, sucrose was reported to be no more effective than water in reducing behavioural pain responses. However, the authors acknowledged that their study was not adequately powered to detect differences within subgroups of infants, and the limited numbers of infants in the older age groups, aged between 30 and 90 days, may have been too small to detect any such differences in pain scores (Rogers et al., 2006). Nevertheless, these results add to the evidence suggesting that sucrose analgesia beyond the first month of life may be less evident than that observed in the neonatal period, and, that larger volumes of sweet tasting solutions, or higher concentrations than that used in the neonatal period, may be required for the same analgesic effect. A sucrose concentration of 33% (wt/vol) was used throughout this study, as per the NNU, RCH oral sucrose guidelines (Harrison, 2001; Harrison et al., 2005).
solution is more concentrated than the solutions used in the majority of trials included in the systematic review of sucrose for analgesia in newborn infants undergoing painful procedures (Stevens et al., 2004), and higher than the 24% solution used in the 2006 study by Rogers et al. Although the lack of any increase in pain responses over time demonstrated in this descriptive longitudinal cohort study is suggestive of ongoing sucrose analgesia, at concentrations of 33% (wt/vol), further adequately powered randomised, controlled trials of sucrose efficacy in older infants undergoing painful procedures, are warranted to resolve the continuing uncertainty regarding sucrose analgesia beyond the neonatal period, and throughout infancy.

In summary, the results of the mapping of successive pain responses to the routinely and frequently performed invasive painful procedure of heel lancing showed that there were no changes in either behavioural or physiological responses over the course of the hospitalisation. Oral sucrose was given prior to, and during, all assessments, and on the majority of occasions, the behavioural responses to pain showed consistently low facial expression scores, and short crying durations. It appears that the analgesic effects of sucrose in reducing behavioural responses to pain were sustained throughout successive procedures occurring over a hospitalisation period ranging from one to five months. These findings contribute valuable knowledge to the issue of effective sucrose-induced analgesia, despite repeated doses, during and in the first few months beyond the neonatal period.

Strengths and limitations
There are limitations to the design of this non-experimental, observational cohort study which preclude making claims regarding conclusive evidence of continued sucrose-induced analgesia which can be generalised to a wider population of infants. The particular population of infants included was a unique heterogenous cohort of infants with complex medical and surgical conditions, the likes of whom are excluded from the large majority of studies involving neonatal pain management. The majority of infants were born at or near term, a high proportion of the infants had congenital abnormalities and a high proportion of the infants required surgery. These conditions, along with the myriad of analgesics and sedatives used over the course of the hospitalisation, may have impacted on the infants’ successive responses to pain and sucrose-induced analgesia, and may not be comparable to that of premature infants.
who make up the largest population of infants nursed in Level Three NICUs (Abeywardana, 2006).

There are also a multitude of possible confounding factors influencing individual pain responses during acute minor painful procedures. As highlighted by the variability within and between infants’ facial expression scores, as shown on the figures presented in Appendix 12, responses to pain are not uniform. Potential confounding variables on the day of study may include severity of illness, corrected gestational age, post-natal age, feed status, presence and degree of pain at baseline, as well as a multitude of other less understood factors which were not included in the data collection, such as stress hormone levels, or endorphin levels. In addition, in this study, differences in pain responses were seen between the heel lance procedures in which concomitant use of opioid analgesics with oral sucrose were being administered compared with when sucrose only was administered. Such a descriptive study design as this is not appropriate to confirm if these observed differences were true factors in influencing pain responses. A further well-powered randomised, controlled trial of oral sucrose with or without concomitant morphine would be required to confirm these results.

This study did not include any long-term monitoring of pain-related outcomes following discharge. Although it would have been desirous to evaluate and report on a number of outcomes including sucrose-induced analgesia during responses to subsequent painful procedures such as routine immunisation throughout infancy and early childhood, this extent of systematic follow-up following discharge is not routinely performed and, as such, was outside the scope of this study.

Clinical implications

Despite the limitations to each of the three inter-related questions within this thesis, the findings of the three questions collectively and independently have important clinical implications for health professionals caring for sick hospitalised infants. There is now baseline information on current pain assessment and management practices in neonatal units on a nationwide level which was previously unavailable. One of the major findings of the nationwide pain assessment and pain management survey was infrequent use of oral sucrose during painful procedures. As this
longitudinal cohort study provided further confirmation of the analgesic effects of repeated use of oral sucrose in sick infants, there is now further evidence to recommend that oral sucrose be implemented during painful procedures throughout the duration of a NICU hospitalisation. In addition, infrequent utilisation of pain assessment scores, both on a nationwide scale and in the particular neonatal unit where the longitudinal cohort study took place, was evident. As substantial use of analgesics and sedatives in sick infants was demonstrated, the lack of documented evaluation of the effectiveness or otherwise of such medications in the clinical setting is of concern. The dissemination of these important disparities between the evidence and best practice recommendations, and what is practiced in the clinical area, provides a platform to raise awareness. In addition, the nationwide survey findings can be used as a baseline to ascertain future changes in pain assessment and management practices in Australian neonatal units.

Recommendations for further research

A number of recommendations for further research can be generated from this study. One of the most critical questions that require further work in relation to sucrose analgesia relates to the effectiveness of sucrose administered concomitantly with opioid analgesia to sick infants nursed in neonatal intensive care units. The conduct of an appropriately powered, randomised, controlled trial of oral sucrose with concomitant morphine, or an alternative opioid analgesic, compared with oral sucrose alone, during commonly performed painful procedures is important to ascertain if opioid use is a true factor in influencing pain responses during minor procedures. There is currently conflicting evidence concerning the role of maintenance opioid analgesics in the reduction of acute minor procedural pain. With the exception of this descriptive study, there is no other research examining concomitant use of opioid analgesia with oral sucrose.

This study highlighted that a great deal of further research into the safety and efficacy of most analgesic and sedative agents used in neonatal intensive care units is warranted. As a large majority of analgesics used in the neonatal setting have not been labelled for use in newborns (Conroy & Peden, 2001; Tan, Cranswick, Rayner, & Chapman, 2003; Anand, Aranda et al., 2005), clinicians caring for sick hospitalised
infants need to collaborate with the pharmaceutical industry to ensure that well conducted studies of both safety and efficacy of new and existing analgesic and sedative agents are planned. In the meantime, further descriptive studies of such use of analgesic and sedative agents, along with systematic evaluation of effectiveness or otherwise of such agents using appropriate pain assessment tools, would further inform future trials. This leads onto a further critical question that requires research in the clinical arena. This is in relation to the urgent need for evaluation of effectiveness, or otherwise, of the variety of analgesics and sedatives used during the course of sick infants’ hospitalisation. Results of both the survey and the cohort study clearly showed that documented pain assessments play a negligible role in evaluating the need for, and effectiveness of analgesia. Hence health professionals are not systematically developing knowledge concerning the effectiveness or otherwise of the variety of analgesics and sedatives administered to sick infants. The conduct of a study to promote change, and monitor and measure such a change, within a knowledge translation framework, with the outcome being consistent use of appropriate pain and/or sedation assessment tools would enable systematic evaluation of effectiveness of the variety of analgesic and sedative agents used in neonatal intensive care units.

Another important recommendation would be to conduct a follow-up Australia-wide survey of pain assessment and procedural pain management practices in neonatal units. Results of such a succeeding survey would determine if recommendations arising from the first survey, regarding practice and policy changes (Harrison, Loughnan et al., 2006) had been implemented. In addition, as sick neonates may be cared for in paediatric settings, the survey could also be sent to paediatric intensive care units, with the aim of establishing baseline neonatal pain assessment and procedural pain management practices in such units. Practices between the two different types of units could be compared. This information would further add to the knowledge base concerning pain management in sick neonates and infants in Australian neonatal and paediatric settings.

Also warranted is a program of systematic follow-up of infants requiring surgery and prolonged hospitalisation following discharge from the NICU. Such follow-up would assist in the ascertainment of the degree to which the hospitalisation experience and
associated pain exposure and analgesic and sedative use impacts on the growing infant. One such specific project recommended is a comparative study of responses during subsequent acute pain during routine infant and childhood immunisation between infants with a previous NICU hospitalisation and infants with no such previous hospitalisation exposure. Such studies as these would further contribute valuable information regarding outcomes of sick infants following discharge from the NICU environment. Such a follow-up programme, focussing on outcomes of sick infants with complex heterogeneous medical conditions, would supplement the research programme by Grunau and colleagues, of pain and stress related outcomes of extremely low birth weight infants following discharge from a NICU (Grunau, Whitfield, & Petrie, 1994; Grunau, Whitfield, Petrie et al., 1994; Grunau, Whitfield et al., 1998; Grunau, 2002; Grunau et al., 2005).

Further research to determine sucrose efficacy throughout infancy is also required. Well conducted randomised, controlled trial studies of sucrose efficacy in both healthy and sick infants up to two years of age undergoing routine infant and childhood immunisation would assist in resolving the research gap concerning age-related analgesic effects of oral sucrose.
CONCLUSION

Findings of this thesis have highlighted important issues concerning pain assessment and pain management in sick neonates and infants. Firstly, many institutions caring for premature and sick neonates have not implemented the simple yet effective strategy of oral sucrose for procedural pain management, despite the abundant evidence of the efficacy of sucrose in reducing pain in neonates undergoing a single procedure. Low utilisation of pain assessment tools was also found in both the nationwide survey and the longitudinal cohort study. This thesis also demonstrated ubiquitous and prolonged use of analgesic and sedative agents, despite the limited evidence base to support prolonged use of such agents in neonates and infants, and despite infrequent documentation of evaluation of effectiveness of such agents. Yet this study also highlighted the multitude of painful procedures that sick infants are exposed to over the course of a hospitalisation. Despite the limited evidence base to support prolonged use of analgesics and sedatives, clinicians caring for sick infants have a moral and ethical responsibility to avoid, prevent, and minimise pain to the best of their ability. In fact, the majority of the painful procedures recorded were performed following sucrose administration, or whilst the infants were receiving opioid analgesics as part of their ongoing medical care. Lastly, the findings of a lack of increased pain responses during heel lancing occurring over the duration of the hospitalisation adds important evidence to the apparent effectiveness of repeated doses of oral sucrose in sick infants.

Health professionals caring for sick, hospitalised infants have the challenge of endeavouring to effectively and humanely manage pain, distress and agitation as well as weighing up the benefits and risks of prolonged use of analgesic and sedative agents, with the risks associated with withholding such agents. As clinicians have little evidence to guide them in many of the decisions regarding long-term use of analgesics and sedatives, practice needs to be guided by expert opinion and experience, as well as a universal aim to provide pain management systematically to attempt to reduce the acute and long-term impact of pain experienced in the NICU. As there is currently little documented evaluation of the effectiveness of analgesic and sedative agents administered to sick infants, it is imperative that the utilisation of pain
assessment tools improve, and that pain assessment becomes integral to the prescribing, dosing and subsequent weaning of analgesics and sedatives.

In conclusion, the findings arising from the nationwide pain assessment and pain management survey provide a broad information base which can be used to benchmark against further individual or similar large scale audits. The survey findings have already been used to inform the development of nationally endorsed pain assessment and pain management position papers for the Australian College of Neonatal Nurses (Harrison & Australian College of Neonatal Nurses, 2006b, 2006a). The in-depth mapping of painful procedures, pain assessment scores and pain reduction strategies as well as the mapping of pain scores during heel lancing, in the cohort of 55 sick infants nursed in one tertiary referral Level Three NICU, has provided a detailed basis for the understanding of pain management practices and pain responses in sick infants over the full course of a NICU hospitalisation. In addition, these findings make a significant contribution to the knowledge-research gap concerning analgesic effectiveness of repeated use of oral sucrose. The results reported in this thesis can be used to inform future clinical practice changes and future research with the aim of continuing to improve world-wide pain management in infants.
## ABBREVIATIONS

<table>
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<tr>
<th>Abbreviation</th>
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<tr>
<td>BPM</td>
<td>Beats per minute</td>
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<td>HRV</td>
<td>Heart rate variability</td>
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<td>IBCS</td>
<td>Infant Body Coding System</td>
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<td>IQR</td>
<td>Interquartile range</td>
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<td>Kg</td>
<td>Kilogram</td>
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<td>KC</td>
<td>Kangaroo Care</td>
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<td>µg</td>
<td>Microgram</td>
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<td>mL</td>
<td>Millilitre</td>
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<td>NETS</td>
<td>Newborn Emergency Transport Service</td>
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<td>NFCS</td>
<td>Neonatal Facial Coding System</td>
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<td>NICU</td>
<td>Neonatal Intensive Care Unit</td>
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<td>NNS</td>
<td>Non-nutritive sucking</td>
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<td>NNU</td>
<td>Neonatal Unit</td>
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<td>PAT</td>
<td>Pain Assessment Tool</td>
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<td>PIPP</td>
<td>Premature Infant Pain Profile</td>
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<td>RCH</td>
<td>Royal Children’s Hospital</td>
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<td>SCN</td>
<td>Special Care Nursery</td>
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<td>SD</td>
<td>Standard deviation</td>
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<td>SpO₂</td>
<td>Oxygen saturation</td>
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<td>Wt/vol</td>
<td>Weight per volume</td>
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Abbreviations
REFERENCES

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evidenced by increase in oxygen consumption, energy expenditure, and heart rate. *Pediatric Research,* 55(4), 695-700.


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Appendices

APPENDICES

Appendix 1. Pain assessment and pain management survey

Survey of Pain Assessment and Procedural Pain Management in Neonatal Intensive Care, Special Care Units and Newborn Emergency Transport Teams

Pain Assessment Practices

1. Does your unit use any pain assessment scores on a regular basis? If the answer is no, proceed to question 6.

Yes ☐ No ☐

2. If so, in what situations are pain scores routinely performed? (Please tick all that apply)

- During regular documentation of vital observations ☐
- Post-operatively ☐
- During procedures ☐
- For research purposes ☐
- When on analgesic medications ☐
- Other (Please specify) ☐
3. If pain assessments are routinely performed, are they documented on a permanent record?

Yes ☐ No ☐ Not Applicable ☐

4. If so, please tick where pain assessments are documented (Please tick all that apply)

Nursing notes ☐ Separate pain assessment chart ☐ Observation chart ☐

Medical notes ☐ Other (Please state) ☐

5. Please state what pain assessment method or scores are used? (Please tick all that apply)

- Pain Assessment Tool (PAT) ☐
- Premature Infant Pain Profile (PIPP) ☐
- Neonatal Facial Coding System ☐
- FLACC ☐
- Asking parents opinion ☐
- Comfort ☐
- Pain assessment score developed by staff in your unit/nursery ☐
- A visual analogue scale ☐
- Others; Please specify ☐
- Neonatal Infant Pain Scale (NIPS) ☐

6. Does your unit have a policy or guideline directing pain management practices during minor procedures? (Please tick appropriate box)

Yes ☐ No ☐
7. When the following procedures are undertaken, please indicate current practice in your unit regarding the administration of analgesia and/or provision of comfort measures by placing a tick in the most appropriate box.

**Heel Lance:**

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Occasionally</th>
<th>Often</th>
<th>Always</th>
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</thead>
<tbody>
<tr>
<td>Oral sucrose alone</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Non-nutritive sucking with oral sucrose</td>
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<tr>
<td>Non-nutritive sucking alone</td>
<td></td>
<td></td>
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<tr>
<td>Breastfeeding</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Topical Amethocaine (EMLA®/ANGEL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No analgesia/comfort measures used</td>
<td></td>
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<tr>
<td>Other, eg: cuddling, nesting, injected local anaesthetic. (Please specify)</td>
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</table>

**Venepuncture/Peripheral venous catheter placement:**

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<th>Never</th>
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<td>Non-nutritive sucking with oral sucrose</td>
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<td>Non-nutritive sucking alone</td>
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<tr>
<td>Breastfeeding</td>
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<tr>
<td>Topical Amethocaine (EMLA®, /ANGEL)</td>
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<tr>
<td>No analgesia/comfort measures used</td>
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<tr>
<td>Other, eg: cuddling, nesting, injected local anaesthetic. (Please specify)</td>
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</table>
### Lumbar Puncture:

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<th>Occasionally</th>
<th>Often</th>
<th>Always</th>
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</thead>
<tbody>
<tr>
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<tr>
<td>Non-nutritive sucking with oral sucrose</td>
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<tr>
<td>Non-nutritive sucking alone</td>
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<tr>
<td>Topical Amethocaine (EMLA®/ANGEL)</td>
<td>☐</td>
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<td>☐</td>
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<tr>
<td>No analgesia/comfort measures used</td>
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<tr>
<td>Other, eg: cuddling, nesting, injected local anaesthetic. (Please specify)</td>
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### Eye Examination:

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<th>Never</th>
<th>Occasionally</th>
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<tr>
<td>Oral sucrose alone</td>
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<tr>
<td>Non-nutritive sucking with oral sucrose</td>
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<tr>
<td>Non-nutritive sucking alone</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
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<tr>
<td>Local anaesthetic eye drops</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
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<tr>
<td>No analgesia/comfort measures used</td>
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<td>☐</td>
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<tr>
<td>Other, eg: nesting (Please specify)</td>
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</table>
### Peripheral arterial stab/peripheral arterial catheter placement:

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<th>Method</th>
<th>Never</th>
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<th>Often</th>
<th>Always</th>
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<tr>
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<tr>
<td>Non-nutritive sucking with oral sucrose</td>
<td>☐</td>
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<tr>
<td>Non-nutritive sucking alone</td>
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<tr>
<td>Topical Amethocaine (EMLA®/ANGEL)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
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<tr>
<td>Breastfeeding</td>
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<td>☐</td>
<td>☐</td>
<td>☐</td>
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<tr>
<td>No analgesia/comfort measures used</td>
<td>☐</td>
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<tr>
<td>Other, eg: cuddling, nesting, injected local anaesthetic. (Please specify)</td>
<td>☐</td>
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</table>

### Intramuscular or subcutaneous injection:

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<tr>
<th>Method</th>
<th>Never</th>
<th>Occasionally</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral sucrose alone</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Non-nutritive sucking with oral sucrose</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
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<tr>
<td>Non-nutritive sucking alone</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
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<tr>
<td>Topical Amethocaine (EMLA®, /ANGEL)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>No analgesia/comfort measures used</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Other, eg: cuddling, nesting, injected local anaesthetic. (Please specify)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

8. **If you use sucrose or other sweet tasting solutions, please tick which solution is used, plus state volume and concentration.**

<table>
<thead>
<tr>
<th>Solution</th>
<th>Concentration</th>
<th>Volume given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sucrose</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Glucose</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Other</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
9. If you use sucrose or other sweet tasting solutions, do you have any contraindications to their use for any groups of infants?

Yes ☐  No ☐

10. If so, for which conditions do these contraindications apply? (Please tick all relevant).

<table>
<thead>
<tr>
<th>Condition</th>
<th>☐</th>
<th>☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nil by mouth for any reason</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Confirmed necrotising enterocolitis</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Infants on opioid infusions</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Altered conscious state</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Infants of mothers taking methadone</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Suspected necrotising enterocolitis</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Parental refusal</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Below a specified gestational age (Please specify)</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>&gt; 2 months corrected post-natal age</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>&gt; 4 months corrected post-natal age</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>&gt; 6 months corrected post-natal age</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

11. Who is responsible for ordering sucrose or other sweet tasting solutions?

Not Applicable ☐  Medical officer ☐  Nursing Staff ☐  No written order required ☐
The following two questions relate to the safety, efficacy and utility of oral sucrose and topical anaesthetic creams. Please tick your response to the following statements.

12. **Oral sucrose or other sweet tasting solutions:**

<table>
<thead>
<tr>
<th></th>
<th>True</th>
<th>False</th>
<th>Unsure</th>
</tr>
</thead>
<tbody>
<tr>
<td>have been shown in clinical trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>to be effective in reducing pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>are safe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>are readily available for use in the</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ward setting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>work almost immediately</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

13. **EMLA®/AnGEL/amethocaine creams:**

<table>
<thead>
<tr>
<th></th>
<th>True</th>
<th>False</th>
<th>Unsure</th>
</tr>
</thead>
<tbody>
<tr>
<td>have been shown in clinical trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>to be effective in reducing pain</td>
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<td>are safe</td>
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<td></td>
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<td>are readily available for use in the</td>
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</tr>
<tr>
<td>ward setting</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>work almost immediately</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

14. **Please specify your type of unit.**

- Level 3 Neonatal Intensive Care: [ ]
- Level 2 Special Care Nursery: [X]
- Newborn Emergency Transport Team: [ ]
Thank you for completing this survey.

If you would like a copy of the results of this survey sent to you, please enclose this sheet of paper in the separate stamped self addressed envelope to that of the questionnaire with the name of your hospital/contact address. Alternatively email request for results to: denise.harrison@rch.org.au

For any further information, please contact:
Denise Harrison
Neonatal Unit, Royal Children's Hospital,
Flemington Road, Parkville, 3052,
Australia
(03) 93455000
Email: denise.harrison@rch.org.au
Appendix 2. Pain assessment and pain management survey: Plain language statement

SURVEY OF ASSESSMENT OF PAIN AND PROCEDURAL PAIN MANAGEMENT PRACTICES IN NEONATAL AND SPECIAL CARE NURSERIES and NEWBORN EMERGENCY TRANSPORT TEAMS

You are invited to participate in a study about pain assessment and procedural pain management practices in neonatal and special care nurseries in Australia. Nurse Unit Managers of all neonatal intensive care units and level 2 special care nurseries in Australia have been sent this survey.

The survey is being conducted by staff from the Department of Neonatology, at the Royal Children’s Hospital, Melbourne. Denise Harrison; a Clinical Nurse Educator in the Neonatal Unit, Professor Linda Johnston; Chair of Neonatal Nursing Research at the Royal Children’s Hospital and The University of Melbourne, and Dr Peter Loughnan, deputy director, Neonatal Unit, Royal Children’s Hospital. The three investigators have a special interest in the assessment and management of pain in sick infants. The study has been approved by the Royal Children’s Hospital Ethics in Human Research Committee

Should you agree to participate, we would ask you or your nominee to complete the enclosed survey. The survey comprises 14 questions. We estimate that this will take no more than ten minutes of your time to complete.

Once the project has been completed, a brief summary of the findings will be available to you if requested. If you would like a summary, please complete the final page of the survey, and send separately to the completed survey in the reply paid envelope provided. Alternatively, you may email the investigators with your request for a summary of the findings.

Please be advised that your participation in this survey is completely voluntary. Consent is implied by return of the survey.

Please fill in the enclosed survey, and return it in the envelope provided. Should you require any further information, or have any concerns, please do not hesitate to contact any of the investigators.
Appendices

Denise Harrison: 03 9345 5000.
Email: denise.harrison@rch.org.au

Associate Professor Linda Johnston: 03 8344 0768.
Email: lj1@unimelb.edu.au

Dr Peter Loughnan: 03 9345 5007.
Email: peter.loughnan@rch.org.au

Should you have any concerns about the conduct of the project, you are welcome to contact the Consumer Liaison, Clinical Support Services Team at the Executive Office, RCH Unit.
Telephone 9345 5676 (Monday to Friday 9am-5pm)
Appendix 3. Royal Children’s Hospital ethics approval

(EHRC 23123 A)
Appendices

Put survey ethics here
Appendices

Appendix 4. Minor procedural pain diary

Include:
- Heel Lance (HL)
- IV insertion and venepuncture (IV or VP)
- Lumbar Puncture (LP)
- IA line or arterial stab (IA)
- Eye examination (Eye)
- IM/SC injection (IM)
- SPA

<table>
<thead>
<tr>
<th>Date of procedure</th>
<th>Procedure description</th>
<th>Time of procedure</th>
<th>No. attempts until completion of procedure</th>
<th>Sucrose</th>
<th>Dummy used during most of procedure?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
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<td></td>
<td></td>
<td></td>
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<td>Total amt. (mL)</td>
<td>Yes</td>
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</tbody>
</table>
## Appendix 5. Investigator’s daily pain diary (0800-0800)

<table>
<thead>
<tr>
<th>Dates</th>
<th>N MRs</th>
<th>N sucr doses</th>
<th>HFOV /Jet</th>
<th>CMV</th>
<th>CPAP</th>
<th>Airway no</th>
<th>Supp 0₂</th>
<th>Nil</th>
<th>Nitric Oxide</th>
<th>Feeds</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0₂</td>
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</table>

<table>
<thead>
<tr>
<th>Dates</th>
<th>Opiods</th>
<th>Dose/Kg</th>
<th>N. boluses</th>
<th>Route</th>
<th>Cont/intermittent</th>
<th>If int. n. doses</th>
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</thead>
<tbody>
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<table>
<thead>
<tr>
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<th>Sedatives, anticonvulsants</th>
<th>Dose/Kg</th>
<th>N. boluses</th>
<th>Route</th>
<th>Cont/intermittent</th>
<th>If int. n. doses</th>
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<thead>
<tr>
<th>Dates</th>
<th>Paracetamol or equivalent</th>
<th>Dose/Kg</th>
<th>Route:PR, O, or Not specified</th>
<th>Max dose specified?</th>
<th>No. doses</th>
<th>No. PAT scores</th>
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<thead>
<tr>
<th>Major procedures &amp; dates</th>
<th>Surgery</th>
<th>Chest drain</th>
<th>Long line</th>
<th>Intubation</th>
<th>Other</th>
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<tbody>
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<thead>
<tr>
<th>CPR required?</th>
<th>Date</th>
<th>Regional anaesthetic and dates: site</th>
<th>drug</th>
</tr>
</thead>
</table>
Appendix 6. The University of Melbourne ethics approval

(HREC Project 040641)
Appendices

Put approval here
Appendix 7. Royal Children’s Hospital, clinical audit approval

(AUD/2001-)
Appendices

Put RCH clinical audit here
Appendices

Appendix 8. Plain language statement: Pain management practices

The Royal Children’s Hospital, Melbourne

Flemington Road,
Parkville, Victoria,
Australia, 3052

Telephone (03) 9345 5522
ISD (+613) 9345 5522
Facsimile (03) 9345 5789
Web www.rch.org.au

Research Project: A study of pain management practices during the prolonged hospitalisation of infants

Dear Parents,

My name is Denise Harrison. I am one of the nurses in the Neonatal Unit, and a PhD student at The University of Melbourne. I am working on projects relating to measuring and treating pain in sick babies. I am undertaking one of these projects as part of my PhD studies through The University of Melbourne. The title of this project is, “A study of pain management practices during the prolonged hospitalisation of infants”. All babies in the Neonatal Unit, unless their stay is expected to be very short, are included in this study. This study involves measuring your baby’s response to some of their blood tests whilst they are in the Neonatal Unit at the Royal Children’s Hospital. I would be observing your baby during their blood tests about once a week, when their blood tests are ordered. This observation involves looking at your baby’s face and audio-taping your baby’s cry. I will ensure this does not inconvenience you or your baby. If your baby is not already monitored, a heart rate monitor will be put on your baby for the duration of the blood test and for a short period following the test.

There are no extra blood tests ordered for this study. There is no change in the normal care given to your baby during their blood test. I will be giving your baby a small amount of sugar solution before the blood test as per the normal care of babies during such procedures in the Neonatal Unit. Also, if your baby usually sucks on a dummy, I will give your baby their dummy to suck during the blood test.

I will also be collecting information which has been written in your baby’s medical records such as doses of Panadol and other pain reducing medications, as well as details of procedures such as if new drips are inserted, or if nasogastric tubes are put in. This information will assist us in understanding more about how pain and distress in babies is managed in the Neonatal Unit.
All information collected will be stored in a secure place and only myself and my supervisors, Professor Linda Johnston and Dr Peter Loughnan, will have access to it. If the study is subsequently published, no information identifying you or your baby will be included. All information will be destroyed five years following the final publication relating to this project.

If you would like to speak to myself, the Unit Manager, or my supervisors about this project, please contact any of the following people, or ask the nurse caring for your baby to contact one of us.

Denise Harrison: 0438672005  
Nurse Unit Manager: Sheri Waldron. Extension 5318  
Principle Supervisor: Professor Linda Johnston. 83440768  
Co-supervisor: Dr Peter Loughnan: Extension 5007

If you have any concerns about the conduct of this research project, you are welcome to contact the Consumer Liaison, Clinical Support Services Team at the Executive Office, RCH Unit.  
Telephone: 9345 5676 (Monday to Friday 9am-5pm)

Yours sincerely,

Denise Harrison  
Neonatal Unit, Royal Children’s Hospital
Appendices

Appendix 9. Neonatal Unit Oral Sucrose for Procedural Pain Guideline
Appendices
### Appendix 10. Procedural pain data collection tool

<table>
<thead>
<tr>
<th>Date of study</th>
<th>Time of study</th>
<th>Corrected GA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### BASELINE DATA

<table>
<thead>
<tr>
<th>Sucrose during procedure</th>
<th>NNS during procedure</th>
<th>Fed during procedure</th>
<th>Wrapped during procedure</th>
<th>NTISS</th>
<th>PAT score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Behavioural State:

1. On feeds?
2. Hours since fed:
   - Continuous
   - Within previous 30 mins
   - 30 min - 1 hr
   - 1-2 hrs
   - 2-3 hrs
   - 3-4 hrs
   - >4 hrs
3. Number of periods of handling within previous hour

#### PHYSIOLOGICAL

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Lance</th>
<th>30 secs</th>
<th>1 min</th>
<th>2 min</th>
<th>3 min</th>
<th>Comp</th>
<th>1 min</th>
<th>2 min</th>
<th>3 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen Saturation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### FACIAL EXPRESSIONS

- Baseline
- Lance
- 30 secs
- 1 min
- 2 min
- 3 min
- Comp
- 1 min
- 2 min
- 3 min

| Brow Bulge/brow furrow |
| Eye Squeeze |
| Nasolabial Furrow |
| Stretch Open Mouth |
| CRY |
| Ability to cry? |
| Duration of first cry until 5 second pause. | Throughout Procedure | % | 3 minutes following completion | % |

#### Scoring:

- State: 5 Crying: Active/awake eyes open, facial movts.
- 4 Quie/awake, eyes open, no facial movts.
- 3 Quie/awake, eyes closed, no facial movts.
- 2 Active/sleep, eyes closed facial movts.
- 1 Quiet sleep, eyes closed no movts.

#### Comments

Eg Regarding comfort measures used throughout procedure, condition of baby not captured on other data collected.
### Appendix 11. NTISS and adaptations

(Adaptations in brackets)

<table>
<thead>
<tr>
<th>Item</th>
<th>Subscore</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
</tr>
<tr>
<td>Supplemental oxygen</td>
<td>1(^a)</td>
</tr>
<tr>
<td>Surfactant administration (in last 2 weeks)</td>
<td>1</td>
</tr>
<tr>
<td>Tracheostomy care</td>
<td>1(^b)</td>
</tr>
<tr>
<td>Tracheostomy placement (or intubation, change of tubes)</td>
<td>1(^b)</td>
</tr>
<tr>
<td>Continuous positive airway pressure administration</td>
<td>2(^a)</td>
</tr>
<tr>
<td>Endotracheal intubation</td>
<td>2</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>3(^a)</td>
</tr>
<tr>
<td>Mechanical ventilation with muscle relaxant</td>
<td>4(^a)</td>
</tr>
<tr>
<td>High-frequency ventilation</td>
<td>4(^a)</td>
</tr>
<tr>
<td>Extracorporeal membrane oxygenation</td>
<td>4</td>
</tr>
<tr>
<td>(Nitric Oxide</td>
<td>4</td>
</tr>
<tr>
<td><strong>Cardiovascular (All within previous 24 hours)</strong></td>
<td></td>
</tr>
<tr>
<td>Indomethacin administration</td>
<td>1</td>
</tr>
<tr>
<td>Volume expansion; ≤15ml/Kg</td>
<td>1(^c)</td>
</tr>
<tr>
<td>Vasopressor administration ; 1 agent</td>
<td>2(^d)</td>
</tr>
<tr>
<td>Volume expansion; &gt;15ml/Kg</td>
<td>3(^c)</td>
</tr>
<tr>
<td>Vasopressor administration &gt;1 agent</td>
<td>3(^d)</td>
</tr>
<tr>
<td>Pacemaker on standby</td>
<td>3(^e)</td>
</tr>
<tr>
<td>Pacemaker used</td>
<td>4(^e)</td>
</tr>
<tr>
<td>Cardiopulmonary resuscitation</td>
<td>4</td>
</tr>
<tr>
<td><strong>Drug therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Antibiotic administration; ≤ 2 agents</td>
<td>1(^f)</td>
</tr>
<tr>
<td>Diuretic administration; enteral</td>
<td>1(^g)</td>
</tr>
<tr>
<td>Steroid administration; postnatal</td>
<td>1</td>
</tr>
<tr>
<td>Anticonvulsant administration</td>
<td>1</td>
</tr>
<tr>
<td>Aminophylline administration</td>
<td>1</td>
</tr>
<tr>
<td>Other unscheduled medication (all other scheduled medications)</td>
<td>1</td>
</tr>
<tr>
<td>including vitamins, nystatin, sucrose, intravenous saline flushes etc: score of 1</td>
<td>2(^f)</td>
</tr>
<tr>
<td>Antibiotic administration; &gt;2 agents</td>
<td>2(^g)</td>
</tr>
<tr>
<td>Diuretic administration; parenteral</td>
<td>3</td>
</tr>
<tr>
<td>Treatment of metabolic acidosis</td>
<td>3</td>
</tr>
<tr>
<td>Potassium binding resin administration</td>
<td></td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td></td>
</tr>
<tr>
<td>Frequent vital signs</td>
<td>1</td>
</tr>
<tr>
<td>Cardiorespiratory monitoring</td>
<td>1</td>
</tr>
<tr>
<td>Phlebotomy; 5-10 blood draws (in past 7 days)</td>
<td>1(^h)</td>
</tr>
<tr>
<td>Thermoregulated environment</td>
<td>1</td>
</tr>
<tr>
<td>Non-invasive oxygen monitoring (plus extra point for TCM)</td>
<td>1</td>
</tr>
<tr>
<td>Arterial pressure monitoring</td>
<td>1</td>
</tr>
<tr>
<td>Central venous pressure monitoring</td>
<td>1</td>
</tr>
<tr>
<td>Urinary catheter (all catheters, inc. nephrostomy, ureteric)</td>
<td>1</td>
</tr>
<tr>
<td>Quantitative intake and output</td>
<td>1</td>
</tr>
<tr>
<td>Extensive phlebotomy; &gt;10 blood draws (in past 7 days)</td>
<td>2(^h)</td>
</tr>
<tr>
<td>Metabolic/nutrition</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>---</td>
</tr>
<tr>
<td>Gavage feeding</td>
<td>1</td>
</tr>
<tr>
<td>Intravenous fat emulsion</td>
<td>1</td>
</tr>
<tr>
<td>Intravenous amino acid solution (TPN)</td>
<td>1</td>
</tr>
<tr>
<td>Phototherapy</td>
<td>1</td>
</tr>
<tr>
<td>Insulin administration</td>
<td>2</td>
</tr>
<tr>
<td>Potassium Infusion</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transfusion (All within past 24 hours)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous gamma globulin</td>
<td>1</td>
</tr>
<tr>
<td>Red blood cell transfusion; ≤15ml/Kg</td>
<td>(^2i)</td>
</tr>
<tr>
<td>Partial volume exchange transfusion</td>
<td>2</td>
</tr>
<tr>
<td>Red blood cell transfusion; &gt;15ml/Kg</td>
<td>(^3i)</td>
</tr>
<tr>
<td>Platelet transfusion</td>
<td>3</td>
</tr>
<tr>
<td>White blood cell transfusion</td>
<td>3</td>
</tr>
<tr>
<td>Double volume exchange transfusion</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Procedural</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Transport of patient. (Score 2 for each transport occurring within past 24 hours)</td>
<td>2</td>
</tr>
<tr>
<td>Single chest tube in place</td>
<td>(^2l)</td>
</tr>
<tr>
<td>(Score 2 for any ostomies, gastrostomy, NGT on FD, drainage tubes other than urinary catheters, dressings which need to be done, etc)</td>
<td>2</td>
</tr>
<tr>
<td>Minor operation (Within previous 7 days; Inguinal hernia, CVL)</td>
<td>(^2k)</td>
</tr>
<tr>
<td>Multiple chest tubes in place</td>
<td>(^3k)</td>
</tr>
<tr>
<td>Thoracentesis</td>
<td>3</td>
</tr>
<tr>
<td>Major operation (All surgery in previous 7 days other than minor)</td>
<td>(^4k)</td>
</tr>
<tr>
<td>Pericardiocentesis</td>
<td>(^4l)</td>
</tr>
<tr>
<td>Pericardial tube in place</td>
<td>4</td>
</tr>
<tr>
<td>Dialysis</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular access (1 for each catheter present)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral intravenous line</td>
<td>1</td>
</tr>
<tr>
<td>Arterial line</td>
<td>2</td>
</tr>
<tr>
<td>Central venous line</td>
<td>2</td>
</tr>
</tbody>
</table>

* Superscript letters represent mutually exclusive variables
Appendices

Appendix 12. Individual infants’ regression slopes: Facial score upon heel lance (illustration of plots of the first eight infants).
Appendices

Appendix 13. Copies of publications arising from this thesis

Bacterial contamination of oral sucrose solutions
Appendices

*Nationwide pain assessment and pain management survey*
Appendices

Abstracts of the 7th International Symposium of Pediatric Pain
Appendices

*Australian College of Neonatal Nurses position statements*
Appendices
Author/s:  
HARRISON, DENISE MARGARET

Title:  
A study of pain management practices during the prolonged hospitalisation of infants.

Date:  
2007-05

Citation:  

Publication Status:  
Unpublished

Persistent Link:  
http://hdl.handle.net/11343/39289

File Description:  
A study of pain management practices during the prolonged hospitalisation of infants.

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