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Anesthesia management of laser photocoagulation for retinopathy of prematurity. A retrospective review of perioperative adverse events

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Abstract:

Aims

The aim of this study was to report the incidence of perioperative adverse events occurring in infants undergoing diode laser photocoagulation of retinopathy of prematurity and to identify clinical risk factors that may affect the incidence.

Methods

This was a retrospective study of anaesthetic and medical records of premature infants who were treated in the neonatal intensive care unit or an operating theatre with laser photocoagulation in our institution between January 2014 and December 2019. Infants less than 38 weeks post menstrual age or less than 2000 grams were considered high risk for complications. Electronic medical records were evaluated for clinical and demographic characteristics, co morbidities and perioperative complications of anaesthesia.

Results

Sixty-one infants (39 males, 22 females) underwent 72 laser treatments. The mean gestational age was 25.3 weeks (SD 1.6) andmean birth weight was 730 grams (SD 202). At treatment, the mean postmenstrual age was 37.5weeks (SD 2.7) and weightwas 2320 grams (SD 610) . Laser therapy was performed in an operating theatre in 66 procedures (91.7%) and in the neonatal unit in 6 cases (8.3%). Twenty-nine (40.3%) laser surgeries occurred outside normal week-day daytime operating hours.Intraoperative hypotension occurred in12 procedures (16.7%)but was not significantly different in high risk infants (16.1% vs 16.7% OR 0.94 p=0.94) or in procedures performed in hours (16.3% vs 17.2% OR 0.93 p=0.91).Post extubation apnoea occurred in 21 procedures (29%) but was not significantly different in high risk infants (29.0% vs 27.3% OR 0.98 p=0.34) or in procedures performed in hours (27.9%

vs 31.1% OR 0.86 p=0.77). Infants remained intubated at the end of the procedure in 58 (80.5%) cases and 29 (40.3%) remained ventilated more than 24 hours after the procedure.

Conclusion

The incidence of perioperative adverse events was not associated with patient's age, current weight,timing,or location of the procedure. Extubating infants at the end of the procedure is however associated with a high rate of apnoeas and bradycardia and consideration should be given to keeping low weight infants undergoing prolonged procedures out of hours intubated.
Key words: Anesthesia, general; Retinopathy of prematurity; Lasers; Infant, premature.

Clinical implications:

What is already known about the topic?

Diode laser photocoagulation for retinopathy of prematurity is associated with a high prevalence of perioperative complications.

Anaesthesia and sedation is provided by both neonatologists and anaesthetists but there are no widely accepted protocols describing appropriate anaesthetic and analgesic agents.

What new information this study adds:

The incidence of perioperative adverse events was not associated with patient's age, current weight, or location of the procedure. Extubating infants at the end of the procedure is associated with a high rate of apnoeas and bradycardia and consideration should be given to low weight infants undergoing prolonged procedures out of hoursremaining intubatedovernight.

Performing laser treatment out-of-hours by itself did not increase the risk of perioperative complications and as such this may be an important consideration when trying to treat infants as soon as possible to maximize outcomes for vision.

Background and Significance

Retinopathy of prematurity (ROP) is a vasoproliferative disease that affects the developing retinal vessels of premature infants. Severe disease can cause retinal detachment and blindness. The major risk factor forthe development of ROP is a low gestational age. Guidelines recommend that all infants born at a gestational age of 30 weeks or less, or a birth weight of less than or equal to 1500g should be screened(1). There are many other ROP risk factors including intrauterine growth restriction, hyperoxia, hyperglycaemia, neonatal

infections, multiple births, male infants, mechanical ventilation and blood transfusion(2). Infants outside these criteria but who are considered at risk of ROP include infants with hypotension requiring inotropes, infants receiving oxygen for more than a few days and infants who receive oxygen without saturation monitoring. The timing of the initial ROP screeningexamination depends on the gestational age and in our institution is based on the policy statement by the American Academy of Pediatrics and the American Academy of Ophthalmology(1).

The Early Treatment for ROP (ETROP) trial found that ablative laser treatment for type 1 ROP (high-risk ROP) reduced the risk of a poor visual outcome (3, 4) and as a result infants are presenting for treatment at a lower post menstrual age (PMA). Multiple approaches to airway and anesthetic management of these preterm infants undergoing laser treatment have been described but the technique associated with lowest risk of perioperative adverse events has not been identified. Previous surveys of ophthalmologists in the UK reported that 50% of ophthalmologists preferred general anesthesia whilst 37% used intravenous sedation combined with topical anesthesia(5). A later survey of American ophthalmologists and neonatologists reported intravenous sedation in 60%, general anaesthesia in the intensive care unit in 19% and general anaesthesia in an operating room in 20%(6). Whilst general anesthesia with intubation may be superior to intravenous sedation in providing ideal operating conditions it does introduce risk associated with intubation and ventilation of premature infants previously stabilised on non-invasive ventilation strategies. Laryngeal mask airway use has been described with variable success (7) Alternative approaches based on opiate sedation and avoidance of volatile anaesthetics have been promoted by units where the availability of ophthalmologists, operating theatre sessions and paediatric anaesthetists is limited. Other concerns include avoidance of repeated anaesthetic exposureas they may affect neurodevelopment(8).

To minimize the risk of a poor retinal outcome, treatment should be performed as soon as possible(1). Staffing issues however can create a scenario where the only option is to provide laser therapy out of normal working hours. The question is whether this alters the perioperative risk.

The primary aim of this study was to describe the incidence of perioperative adverse events in infants undergoing laser photocoagulation for retinopathy of prematurityin our institution. The secondary objectives were to determine whether patient factors (low current weight or

PMA); location of laser therapy (operating theatre or NICU) or time of day were associated with an increased incidence of adverse anaesthetic events.

Methods:

This is a single centre retrospective cohort study of all consecutive patients with ROP undergoing diode laser photocoagulation at the Royal Children's Hospital (RCH) Melbourne from January 2014 to December 2019. After institutional ethics committee approval (QA/59303/RCHM-2019) patients were identified from thehospital electronic medical record.

All infants underwent a detailed pre-anesthetic evaluation and followed standardinstitutional fasting guidelines. Intraoperative monitoring consisted of continuous electrocardiography, pulse oximetry, noninvasive blood pressure, end-tidal carbon dioxide and temperature. As well as warming the operating room, a forced air warming device was used during the entire intraoperative period.

Phenylephrine 2.5% and Cyclopentolate 0.25% eye drops were used to dilate both pupils prior to examination with two to four drops in each eye up to two hours prior to the examination. The dose was repeated 20 minutes after the initial dose. Infants with dark coloured eyes may require an extra dose. If inadequate pupillary dilatation occurred the drops were repeated intraoperatively. The laser therapies were performed by a consultant ophthalmologist with a trainee ophthalmologist assisting in all cases under a standard treatment protocol.

Data:

Information collected from patient electronic medical records included patient demographics, gestational age and weight, incidence of perinatal comorbidities, other congenital anomalies, associated syndromes, the presence of major cardiac anomalies, and age at surgery. Anaesthetic charts were reviewed for general anaesthetic complications, difficulty with ventilation and intubation, the presence of intraoperative hypotension and bradycardia and surgical duration. The duration of postoperative ventilation,incidence of post extubation apnoeas, bradycardia and stridor and any post-operative hypotension was documented.Apnoea was defined as a respiratory pause of >15 s or <15 s if the apnoea was associated with a desaturation or bradycardia. The definition of a significant desaturation was a haemoglobin saturation falling to <80% or a change of >20% of the pre-existing value. Bradycardia was defined as heart rate <100 beats per minute (bpm) requiring intervention.

Hypotension was defined as a decrease in systolic blood pressure > 20% below a baseline value and requiring anaesthetic intervention. Hypothermia was defined as a core temperature of <36^{0}C and classified as mild (34-36C), moderate (32-34C) or severe (<32C). Out-of-hours surgery was defined as any event where the anaesthetic starting time was after 6pm or on weekends.High risk infants were defined as low current age (< 38 weeks PMA) or low current weight (< 2000g)infants who were considered at increased risk of perioperative complications.

Statistics:

Calculation of skewness and kurtosis values and a Shapiro-Wilk test was performed on continuous data to test for normality of data. Continuous variables were analysed using student's t-test or Wilcoxon's rank sum test in cases of heteroscedasticity or non-normality. Categorical variables were analysed using Fisher's exact test. Binary categories were created based on location of surgery (NICU or operating theatre) and timing of procedure (in hours or out-of-hours). A univariate regression analysis was used to determine the effect of patient variables potentially associated with anaesthetic complications. The type 1 error was set at 5% (2 sided) for all statistical tests. Stata 15 (College Station Texas USA) was used for data analyses.

Results:

Sixty one infants underwent seventy two diode laser treatments. Demographic data is presented in table 1. Twenty seven (43%) infants were transferred from another neonatal unit specifically for ROP treatment and for management of other neonatal conditions in 34 patients (57%).The mean gestational age was 25.3 weeks (SD 1.6) and the mean birth weight was 728 grams (SD 202). At the time of surgery, the mean postmenstrual age was 37.5 weeks (SD 2.7) and the mean weight was 2320 grams (SD 610). The infants were predominantly male (61.1%),weighed less than 2.5kg (70.8%) and were less than 38 weeks PMA (54.2%).

The laser treatment was performed in an operating theatre in 66 (91.7%) cases and in the NICU in 6 (8.3%) cases. Infants treated in NICU were receiving complex ventilation which precluded transfer. The procedure was performed in hours in 43 (59.7%) cases and out of hours in 29 (40.3%) cases.

Airway management:For nineteen (26.4%) procedures, theinfants were intubated by a neonatologist prior to surgery either electively(11.1%), as part of airway management for other co-morbidities or for interhospital transfer.

Anaesthesia:General anaesthesia induction with sevoflurane or propofol, followed by neuromuscular blockade with atracurium, intubation and mechanical ventilation was performed in n= 53 (73.6%). If already intubated, infants were anaesthetised with sevoflurane or remifentanil infusion with neuromuscular blockade. Infants in NICU were managed with remifentanil infusions or repeat fentanyl boluses without volatile anaesthesia (Table 2).

Intraoperative adverse events: The overall incidence of any intraoperative adverse event was 25% with the commonest event being intraoperative hypotension (16.7%) and hypertension and bradycardia associated with ocular drop use (2.8%)(Table 3). Hypoxaemia on intubation occurred in two procedures (2.8%). Intraoperative hypotension occurred in 12 procedures (16.7%) but was not significantly different in high risk infants (16.1% vs 16.7% OR 0.94 p=0.94) or in procedures performed in hours compared to out of hours(16.3% vs 17.2% OR 0.93 p=0.91). Bradycardia requiring atropine treatment occurred in 9 procedures (12.5%) but was not significantly different in high risk infants(16.1% vs 9.8% OR 1.8;p=0.42).The total procedure time was 149.2 minutes (SD 46.9) with the laser component being 99.9 (35.0) minutes.

Post-operative adverse events: The overall incidence of any postoperative adverse event was 59.7% with the commonest event being postoperative hypothermia (30.6%) and post extubation apnoea (29.2%). Post extubation apnoea occurred in 21 procedures (29%) but was not significantly more frequent in high risk infants (29.0% vs 27.3% OR 0.98 p=0.34) or in procedures performed in hours (27.9% vs 31.1% OR 0.86 p=0.77). Postoperative hypothermia was predominantly mild (<36C) and transient and there was no significant difference between in hours and out of hours groups (35.5% vs 32.8%, OR 0.43 95% CI 0.15-1.2, p=0.10). Similarly, the risk of post extubation bradycardia was not increased in in hours compared to out of hours treatments (44.2% vs 24.1%,OR 2.5; 95%CI 0.88-7, p=0.08). Post extubation apnoeas were significantly more common in infants extubated at the end of the case compared to delayed extubation (1-24 hrs postoperatively) (43.8% vs 7.4% OR 9.7 (1.69-55.7) p=0.01).

Postoperative ventilation:The infants were extubated at the end of the procedure in 14 cases (19.4%), between 1 and 24 hours in 29 (40.3%) and exceeded 24 hours in 29 (40.3%) of

infants. Infants were significantly less likely to be extubated at the end of the procedure if they were high risk [12.9% vs 24.4% (OR 0.21; 95% CI 0.04-1.0), p=0.05] and if the procedure was out of hours [10.3% vs 25.6%,(OR 3.0; 95%CI 0.7-11.8), p=0.07]. In fifty eight procedures (80.6%) infants remained intubated either because of complex ventilation requirements (17.2%), inadequate respiratory effort or apnoeas (58.6%), need for further non laser therapy within the next 24 hours (13.8%) or to facilitate transfer back to the parent unit (6.9%). In some cases, extubation was delayed at the request of the treating neonatologist as the level of airway expertise overnight was suboptimal .

Post-operative ventilation data was heavily skewed. Extubation more than 24 hours after the procedure occurred in 29 (40.3%) procedures because of significant cardiorespiratory compromise (16.7%) , need for further non laser therapy (9.7%) frequent apnoeas or inadequate respiration (11.1%) or to facilitate transfer back to the parent unit (2.8%).

Discussion:

This study describes the incidence of perioperative adverse events when the preferred anaesthetic technique was sevoflurane volatile anaesthesia, neuromuscular blockade, intubation and mechanical ventilationwith a closed circuit. This study reinforces the evidence that infants undergoing laser photocoagulation for retinopathy are at high risk of intra- and post-operative adverse events(9-11). There was no evidence that current age, current weight, timing of the procedure or location of the procedure had an effect on the incidence of perioperative adverse events. In contrast many studies identify low PMA and low weight as significant risk factors for perioperative adverse events(12-14). The ETROP trial compared infants treated early (because of high risk prethreshold ROP) to infants treated at a conventional threshold. The infants treated early were two weeks younger than the comparator group and had twice the rate of apnoea, bradycardia, or new cyanosis (12.2% vs 5.9%) and rate of reintubation within 10 days of treatment (11% vs 5%). One study reporting post extubation events occurring in NICU patients recovering in the post anaesthetic care unit (PACU) describe an 11.5% risk of any post-operative event(14). In that study major respiratory events occurred in 9%, reintubation was required in 0.8% and predictors of adverse events were birth weight <1.58kg and PMA <41 weeks at the time of surgery(14).

In this study the incidence of apnoea and bradycardia is similar to other studies reporting volatile anaesthetic techniques for laser photocoagulation (9, 10, 15, 16) (Table 4). The influence of anaesthetic technique on the incidence of perioperative adverse events is

unclear. Volatile anaesthesia with halothane is associated with a 17% -34% incidence of "marked" instability(9, 10) whereas sevoflurane anaesthesia is associated with no intraoperative cardiorespiratory events but a 42% postoperative apnoea rate(11).In one observational study infants who were breathing spontaneously or with non-invasive ventilator support comparison was made between local anaesthetic alone (by an ophthalmologist), pentazocine or fentanyl (by a neonatologist) and sevoflurane anaesthesia (by an anaesthetist). Desaturations to less than 70% occurred in 33-45% of the first three groups and bradycardia in 45-54%. Neither occurred in the Sevoflurane group(11).

In contrast anaesthesia with fentanyl or remifentanil infusion have demonstrated a significant incidence of perioperative events. Fentanyl analgesia has been reported to have the same degree of cardiorespiratory stability as general anaesthesia with halothane(10). In the fentanyl group 4.2% of infants and in the halothane GA group 10.5% of infants needed mechanical ventilation for 1–2 days postoperatively. Anaesthesia with propofol and fentanyl infusion with endotracheal intubation reportssimilar findings with extubation at the end of surgery in 98% but 3% required reintubation for low saturations (17). Remifentanil anaesthesia has been reported to provide adequate anaesthesia with much lower rates of apnoea and bradycardia but the studies do not describe post-operative cardiorespiratory or extubation events(18, 19).

A number of studies have described opiate analgesia by non-anaesthetists(18, 19) often with high rates of apnoeas. A series of 64 intubated and ventilated neonates receiving remifentanil with a bolus of midazolam reported low pain scores and rapid subsequent extubation but 2 episodes of bradycardia and hypotension (18). A similar sedation protocol based on fentanyl and midazolam boluses and continuous infusion provided by a neonatologist reported at least one cardiopulmonary adverse event occurred in 65% (hypotension in 46%, apnoea in 23%, hypotension in 46% and bradycardia in 27%). Ten neonates required intubation and ventilation during the procedure all of whom were receiving non-invasive ventilation at baseline (15). By their own definition only 27% had success with 58% requiring dose modification during the procedure. There were significantly fewer adverse events noted in infants who were intubated at baseline than in those receiving non-invasive ventilation or room air at baseline (20.0% vs.76.2%).

Intravenous sedation by neonatologists has been proposed as a means of providing analgesia without the constraints of anaesthetist and operating theatre availability(15, 18) but have a significant failure rate. Its proponents state the technique decreases the need for intubation,

reduces the need for patient transfer and decreases the length of postoperative ventilation(15). Few of the studies however have demonstrated these goals consistently.

In this series scheduling of the procedure out of standard working hours did not significantly increase the risk of perioperative adverse events. It had been expected that there would be anincreased risk of perioperative morbidity especially hypothermia as transfer of the infant exposes them to ambient temperature gradients which can be significant at night(20, 21). This effect has been described in a small series where perioperative hypothermia occurred in 23% of neonates undergoing procedures in the NICU and was described as a risk factor for postoperative apnoea (12). In that study PMA, weight, type of surgery and length of surgery were not associated with increased risk of adverse events.

Limitations:

The retrospective nature of this study introduced a number of limitations. The limited sample size did not allow us to determine causality of postoperative cardiorespiratory instability. There are a number of potential biases in the comparison of out-of-hours and in-hours treatments. The different rates of complications could feasibly be due to differences in surgical techniques and experience rather than patient factors. It is possible that the incidence of bradycardia has been overestimated. There was no indication in the anaesthetic record whether the bradycardia intervention was in response to spontaneous events or secondary to surgeon induced activation of the oculocardiac reflex. The decision to treat out-of-hours was largely dependent on surgeon availability, with a view to treating as soon as possible.

There was a tendency for infants to remain intubated and ventilated post procedure regardless of the timing or location of procedure. The incidence of post-extubation apnoea and bradycardia was therefore not entirely due to the anaesthesia technique used for the laser photocoagulation.

Conclusions:

General anaesthesia with sevoflurane for laser photocoagulation of retinopathy of prematurity is associated with moderate rates of intraoperative hypotension and post extubation apnoea. The incidence of perioperative adverse events was not associated with patient's age, current weight, or location of the procedure. Extubating infants at the end of the procedure is associatedwith ahigh rate of apnoeas and bradycardia and consideration should be made to remain intubated in low weight infants undergoing prolonged procedures out of hours.

Performing laser treatment out-of-hours by itself did not increase the risk of perioperative complications and as such this may be an important consideration when trying to treat infants as soon as possible to maximize outcomes for vision.

Table Legends:

Table 1 Demographics of infants undergoing general anaesthesia for laser photocoagulation of retinopathy of prematurity. Out of hours was defined as operating after 6pm. Necrotising enterocolitis (NEC), patent ductus arteriosus (PDA),intraventricular haemorrhage (IVH).

Table 2 Demographics of infants undergoing general anaesthesia for laser photocoagulation of retinopathy of prematurity. Out of hours was defined as operating after 6pm. Neonatal Intensive Care Unit (NICU).

Table 3 Incidence of perioperative adverse events in infants undergoing general anaesthesia for laser photocoagulation of retinopathy of prematurity. Out of hours was defined as operating after 6pm. High risk is defined as being low current age (<38 weeks PMA) and low current weight (<2kg).Neonatal Intensive care Unit (NICU), odds ratio (OR),non-significant (ns).

Table 4 Literature review of anaesthesia related adverse perioperative events associated with laser photocoagulation treatment of retinopathy of prematurity. General anaesthesia (GA), local anaesthesia (LA).

Ethics statement:

This study was approved by the Human Research Ethics Committee of the Royal Childrens Hospital (QA/59303/RCHM-2019).

Disclosures:

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Any conflict of interest: all authors confirm no conflict of interest for this study.

Author contributions:

The corresponding author helped conceive, design, and conduct the study, coordinate the data, contribute to the statistical analysis plan, interpret the data, and write and revise the manuscript. All authors (BK, JW,SC and GF) were involved either in the perioperative

management of cases, collection of data or analysis of results and critically reviewing the manuscript. All authors have read and approved the final manuscript.

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		Overall	In Hours n=43 treatments	Out of Hours n=29 treatments	P value
Gender (Male)		44 (%)	25 (58%)	19 (65%)	0.53
Gestational age (wks.)		25.4(1.4)	25.5 (1.6)	25.1 (1.5)	0.35
Birth weight (kg)		0.73 (0.2)	0.70 (0.2)	0.77 (0.23)	0.17
Current Age (wks.)		37.5 (2.7)	37.6 (2.9)	37.2 (2.5)	0.50
Current weight (kg)		2.3 (2.6)	2.42 (0.68)	2.17 (0.47)	0.09
Age at Surgery (wks)		11.1 (2.4)	11.2 (2.6)	11.1 (2.2)	0.84
Co Morbidities	Chronic Lung disease	67 (93%)	40(93%)	27(93%)	0.99
	Previous NEC	30 (41.7%)	16 (37%)	14 (48%)	0.35
	PDA	49 (68.1%)	30 (69.8%)	19(65.5%)	0.70
	IVH	21 (29.2%)	13 (30.2%)	8 (27.6%)	0.81

	Previous Sepsis	21 (29.2%)	9 (20.9%)	12 (41.4%)	0.06

Table 1 Demographics of infants undergoing general anaesthesia for laser photocoagulation of retinopathy of prematurity. Out of hours was defined as operating after 6pm. Necrotising enterocolitis (NEC), patent ductus arteriosus (PDA),intraventricular haemorrhage (IVH).

		Operating Theatre n=66	NICU n=6	P value	In hours N=43	Out of Hours N=29	P value
Airway Management	Intubated by Anaesthetist	52 (78.8%)	0 (0%)	0.02	28 (65.1%)	26 (89.7%)	0.02
	Intubated by Neonatologist	14 (21.2%)	6 (100%)	ns	15 (34.9%)	3 (10.3%)	0.02
Anaesthetic	Sevoflurane	61 (92.4%)	0 (0%)	0.01	37 (86.1%)	27 (93.1%)	0.35
Neuromuscular blocking agent	Atracurium	44 (66.7%)	2 (33.3%)	0.10	30(69.8%)	16 (55.2%)	0.19
	Pancuronium	15 (22.7%)	2 (33.3%)	0.56	4 (9.3%)	11 (37.9%)	0.01
	Vecuronium	2 (3%)	0 (0%)	ns	4 (9.3%)	0%	ns
	Nil	5 (7.6%)	2(33.3%%)	0.04	5 (11.6%)	2(6.9%)	0.51
Analgesia	Fentanyl	40 (60.6%)	3 (50%)	0.61	25 (58.1%)	18 (62.1%)	0.74
	Morphine	2(15.2%)	2 (33.3%)	0.01	7 (16.3%)	5(17.2%)	0.89
	Remifentanil	5 (7.6%)	1 (16.7%)		3 (7%)	2 (6.9%)	0.91
	Nil	11(16.7%)	0 (0%)	ns	8 (18.6%)	4 (13.8%)	0.59

Pre-emptive Atropine	3 (4.6%)	0 (0%)	ns	1 (2.3%)	2 (6.9%)	0.34

Table 2 Demographics of infants undergoing general anaesthesia for laser photocoagulation of retinopathy of prematurity. Out of hours was defined as operating after 6pm. Neonatal Intensive Care Unit (NICU).

		High risk n=31	Low Risk n=41	Operating Theatre n=66	NICU n=6	In hours N=43	Out of Hours N=29
Intraoperative	Hypoxaemia on induction	1 (3.2%)	1 (2.4%)	1 (1.5%)	1(16.7%)	1 (2.3%)	1 (3.4%)
	Hypotension	5 (16.1%) OR 0.94(0.27-3.28) p=0.91	7 (17.1%)	11 (16.7%) p=0.99	1 (16.7%)	7 (16.3%) OR 0.93 (0.26-3.3) p=0.91	5 (17.2%)
	Hypertension	1 (3.2%)	1 (2.4%)	2(3%)	0 (0%)	2 (4.6%)	0 (0%)
	Bradycardia	p=0.84		p=0.66		P=0.24	
Post-Operative	Extubation at end of case	4 (12.9%) OR 0.21(0.04-1.05) p=0.05	10 (24.4%)	14 (20.9%) ns	0 (0%)	11(25.63%) OR 3.0 (0.7-11.8) p=0.07	3 (10.3%)
	Extubation 1-24 hrs post op	13 (41.9%) OR 1.1(0.44-2.9) p=0.80	16 (39%)	28 (41.8%) OR 2.9 (0.3-27.1) p=0.36	1(16.7%)	14 (32.6%) OR 0.45 (0.17-1.2) p=0.11	15 (51.7%)
	Hypothermia <36C	11 (35.5%) OR 1.5(0.55-4.1) p=0.43	11 (26.9%)	22 (32.8%)	0 (0%)	10(23.3%) OR 0.43 (0.15-1.2) p=0.10	12 (41.4%)
	Bradycardia	12 (38.7%) OR 1.2(0.46-3.2) p=0.69	14 (34.1%)	25 (37.9%) OR 2.4(0.25-22.5) p=0.44	1(16.7%)	19 (44.2%) OR 2.5 (0.88-7.1) p=0.08	7(24.1%)
	Post extubation Apnoea	9 (29.0%) OR 0.98(0.35-2.7) p=0.34	12 (29.3%)	20(27.3%)	1 (16.7%)	12(27.9%) OR 0.86 (0.31-2.4) p=0.77	9 (31.1%)

				OR 1.7 (0.18-16.2) p=0.33			
Delayed extubation	Ventilated >24hrs	14 (45.1%) OR 1.43(0.55-3.7) p=0.46	15 (36.6%)	25(37.3%) OR 0.15(0.02-1.4) p=0.09	4(66.6%)	18(41.9%) OR 1.2 (0.45-3.1) p=0.09	11(37.9%)

Table 3 Incidence of perioperative adverse events in infants undergoing general anaesthesia for laser photocoagulation of retinopathy of prematurity. Out of hours was defined as operating after 6pm. High risk is defined as being low current age (<38 weeks PMA) and low current weight (<2kg). Neonatal Intensive care Unit (NICU), odds ratio (OR),non-significant (ns).

Author	Anaesthetic	Comparator	Apnoea	Bradycardia	Comments
Haigh	Halothane	Topical amethocaine	GA 16.7%	GA 0%	
		Fentanyl Infusion	LA 25%	LA 25%	
			Fentanyl 16.7%	Sedation 16.7%	
Jiang	Halothane	proxymetacaine LA	GA 10.5%	N/R	
		Fentanyl bolus 2µg.kg^{-1}	LA 12.9%		
		Infusion 2µg.kg.hr^{-1}	Fent 4.3%		
Sato	Sevoflurane	LA oxybuprocaine	Sevoflurane 0%	Sevoflurane 0%	Sevoflurane Postop
		Pentazocine	LA 33%	LA 0 %	Apnoea
		Fentanyl 5 µg.kg^{-1}	Pentazocine 64%	Pentazocine45%	42%
			Fentanyl 45%	Fentanyl 54%	
Demirel	Remifentanil 0.4µg.kg.min^{-1}	Nil	1.5%	1.5%	
	Midazolam 0.1mg.kg^{-1}				
Sammartino	Remifentanil 0.75-5 µg.kg.min^{-1}	Nil	0 %	0%	
	Midazolam 0.1mg.kg^{-1}				
Piersigilli	Propofol 2-4mg.kg.hr-1	Nil	15.4%	0%	30.8% required CPAP
	Fentanyl 1 µg.kg^{-1}				support intra or post op
Dannelley	Fentanyl infusion 2 µg.kg.hr^{-1}	Nil	23%	27%	26% sedation success
	Midazolam infusion 0.06 µg.kg.hr^{-1}				

					65% cardiopulmonary events

Table 4 Literature review of anaesthesia for laser photocoagulation treatment of retinopathy of prematurity. General anaesthesia (GA), local anaesthesia (LA).