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An Open Label Pilot Study of a Dexmedetomidine-Remifentanil-Caudal Anesthetic for Infant Lower Abdominal/Lower Extremity Surgery:

The T REX Pilot Study

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What is already known about this subject

Animal studies provided strong evidence that general anesthesia with drugs interacting at the N-methyl-D-aspartate receptor and at the γ -aminobutyric-acid (GABA) A receptor, increased neuroapoptosis, altered synaptogenesis, and resulted in abnormal neurodevelopment and performance.

What this study adds

This feasibility study found that an anesthetic protocol based on dexmedetomidine, remifentanyl and caudal anesthesia was effective in 90% of infants studied .

Abstract

Background: Concern over potential neurotoxicity of anesthetics has led to growing interest in prospective clinical trials using potentially less toxic anesthetic regimens, especially for prolonged anesthesia in infants. Preclinical studies suggest that dexmedetomidine may have a reduced neurotoxic profile compared to other conventional anesthetic regimens; however, coadministration with either anesthetic drugs (e.g. remifentanyl) and/or regional blockade is required to achieve adequate anesthesia for surgery. The feasibility of this pharmacological approach is unknown. The aim of this study was to determine the feasibility of a remifentanyl/dexmedetomidine/ neuraxial block technique in infants scheduled for surgery lasting longer than 2 hours.

Methods: Sixty infants (age 1-12 months) were enrolled at seven centers over 18 months. A caudal local anesthetic block was placed after induction of anesthesia with sevoflurane. Next, an infusion of

dexmedetomidine and remifentanyl commenced, and the sevoflurane was discontinued. Three different protocols with escalating doses of dexmedetomidine and remifentanyl were used.

Results: One infant was excluded due to a protocol violation and consent was withdrawn prior to anesthesia in another. The caudal block was unsuccessful in 2 infants. Of the 56 infants who completed the protocol 45 (80%) had at least one episode of hypertension (Mean Arterial Pressure >80 mmHg) and/or movement that required adjusting the anesthesia regimen. In the majority of these cases the remifentanyl and/or dexmedetomidine doses were increased although six infants required rescue 0.3% sevoflurane and one required a propofol bolus. Ten infants had at least one episode of mild hypotension (Mean Arterial Pressure 40 -50 mmHg) and 4 had at least one episode of moderate hypotension (Mean Arterial Pressure <40 mmHg).

Conclusion: A dexmedetomidine/remifentanyl neuraxial anesthetic regimen was effective in 87.5% of infants. These findings can be used as a foundation for designing larger trials that assess alternative anesthetic regimens for anesthetic neurotoxicity in infants

Keywords

Anesthesia, General/adverse effects

Anesthesia, General/methods

Anesthesia, Caudal/adverse effects

Brain/drug effects

Dexmedetomidine

Remifentanyl

Introduction

There is evidence that most general anesthetics induce neuronal apoptosis in animal studies.¹ Some studies have also demonstrated long-term behavioral and functional changes in the neurodevelopment of animals exposed to prolonged anesthesia in infancy.² There is, however controversy over whether these animal data are relevant in the care of children undergoing general anesthesia.^{3,4,5}

The changes seen in preclinical studies are greatest with exposure to gamma-aminobutyric acid (GABA) agonists and N-methyl-D-aspartate (NMDA) antagonists such as volatile anesthetics (e.g. sevoflurane), propofol, midazolam, ketamine, and nitrous oxide. There is less evidence for such changes with opioids (e.g. remifentanyl) and conflicting evidence with alpha-2 agonists (e.g. dexmedetomidine), with neurodegeneration occurring with doses larger than those used clinically.⁶⁻⁸ Furthermore, these preclinical

studies showed a dose-response relation: higher doses of anesthesia (i.e. longer anesthesia) are associated with more morphologic and functional changes.

Some, but not all, human cohort studies have shown an association between exposure to anesthesia in infancy or early childhood and subsequent changes in cognitive tests, school performance, or risk of developing neurodevelopmental disorders.⁹⁻¹⁵ Results of recent studies^{16,17} are reassuring for most healthy children exposed to one brief anesthetic, but the MASK study reported evidence of an association between multiple anesthetics and decreased fine motor ability and processing speed.¹⁸ Importantly, there is strong evidence for an association between surgery and poor neurodevelopmental outcome in infants having prolonged anesthesia for major surgery.¹⁹ However in this population there is likely to be strong confounding due to disease, surgical outcomes, and surgical stress potentially influencing neurodevelopmental outcomes. Because of the potential associations, on December 14, 2016, the U.S. Food and Drug Administration issued a safety announcement regarding the potential effect of prolonged (>3 hours) or repeated anesthetics on children younger than 3 years of age.

(<http://www.fda.gov/Drugs/DrugSafety/ucm532356.htm>)

The best study design to determine the impact of various anesthetic agents on neurodevelopment are clinical trials to limit the risk of confounding. (Such trials would need to include young children having relatively lengthy procedures and compare a currently used anesthetic regimen with a clinically viable anesthetic regimen that includes agents which are plausibly less injurious based on preclinical data. Remifentanyl and dexmedetomidine emerged as suitable candidates; however, there are very few, if any, data on whether or not this combination is a clinically feasible anesthetic.

The purpose of this pilot study was to determine the feasibility of using a dexmedetomidine/remifentanyl/caudal-epidural block anesthetic in infants younger than 1 year of age, requiring 2-3 hours of urologic or lower limb surgery, in order to prepare for a definitive trial comparing neurodevelopmental outcomes after this regimen versus a volatile anesthetic based regimen. The primary aim of the study was to determine the frequency of having to abandon the protocol for any reason. Our secondary aims were to determine the frequency of having to administer low dose sevoflurane or other types of rescue treatments for signs of light anesthesia (defined as hypertension and/or movement). We also noted the frequency of having to provide rescue treatment for hypotension and/or bradycardia, the time to recovery after anesthesia, need for postoperative pain medication, and any other adverse events.

Methods

An Institutional Review Board approved the protocol in all participating institutions and written informed consent was obtained from subjects' parents.

We included infants, age 1 to 12 months (corrected for gestational age) and American Society of Anesthesiologists physical status I or II, undergoing lower abdominal/lower extremity surgery anticipated

to require at least 120 minutes of anesthesia time, where the surgical incision would be covered with a caudal or epidural block. Surgical procedures included hypospadias repair, lower abdominal surgery, or lower extremity surgery. We excluded patients ASA III or higher, those with any contraindication to caudal analgesia or inhalational anesthesia with sevoflurane, patients with planned postoperative admission to an intensive care unit, or those with planned tracheal intubation and postoperative mechanical ventilation.

Anesthetic technique

Baseline blood pressure and heart rate were recorded, and anesthesia was induced with sevoflurane (up to 8%) in air/oxygen, for the purpose of intravenous (IV) line placement. Once an IV line was inserted, sevoflurane was discontinued, loading doses of remifentanyl and dexmedetomidine were started, the airway was secured, and a caudal-epidural was placed in a sterile manner. The time of sevoflurane administration was not to exceed 10 minutes. Airway management technique was at the discretion of the anesthesiologist (endotracheal tube or laryngeal mask airway). Glycopyrrolate (5 mcg kg^{-1}) was administered before the dexmedetomidine and remifentanyl loading doses. Common neuromuscular blocking drugs (at recommended doses) were permitted for initial airway management. End-tidal CO_2 was maintained at 35-45 mmHg.

Caudal or epidural analgesia was performed after induction and airway management. The caudal block was typically performed with a 22G Angiocath, the catheter was advanced past the sacrococcygeal ligament and secured in place. Bupivacaine 0.175%-0.25% or ropivacaine 0.2% was administered through a catheter that was also available for re-dosing if required. The agent, dose, and technique were at the discretion of the anesthesiologist. Epinephrine 1/200,000 could be added to the local anesthetic, but clonidine or opioids were not allowed as adjuvants.

The protocol included a staged approach where dexmedetomidine and remifentanyl doses were reviewed by the Trial Steering Committee after the first 20 infants were recruited. We started with a low dose of remifentanyl and dexmedetomidine as our initial greatest concerns were bradycardia and hypotension. After the first review, the Committee suggested a further review after another 20 children. At each review, light anesthesia (hypertension and/or movement) was deemed to be a greater problem than hypotension and thus we ended up sequentially enrolling three sets of children with steadily increasing doses of remifentanyl and/or dexmedetomidine. Light anesthesia was defined as movement or hypertension (two subsequent recordings of mean arterial pressure (MAP) $>80 \text{ mmHg}$).

Protocol version 1

Initially, 0.6 mcg kg^{-1} of dexmedetomidine over 10 minutes and 1 mcg kg^{-1} of remifentanyl over 1-2 minutes were administered as loading doses during induction. At the completion of the loading doses, infusions of dexmedetomidine $0.6 \text{ mcg kg}^{-1} \text{ h}^{-1}$ and remifentanyl $0.1 \text{ mcg kg}^{-1} \text{ min}^{-1}$ were started. The

infusion rates could be increased or decreased within 50% of the starting dose for dexmedetomidine, and a maximum dose of $0.5 \text{ mcg kg}^{-1} \text{ min}^{-1}$ for remifentanyl.

Protocol versions 2 and 3

The Committee amended the protocol twice after 16 (version 2) and 23 subjects (version 3) had been enrolled (see Figure 1).

Dexmedetomidine was discontinued 15-30 minutes before the end of surgery and remifentanyl was stopped after the last stitch. Antiemetic agents, warming, and fluid administration were managed according to local protocols.

Management of side effects

In the case of light anesthesia with hypertension, the rescue protocol included a remifentanyl bolus of $0.25\text{-}0.5 \text{ mcg kg}^{-1}$ followed by an increase in remifentanyl infusion by $0.1 \text{ mcg kg}^{-1} \text{ min}^{-1}$. The caudal block was re-dosed if appropriate, by using 50% of the initial local anesthetic dose. If hypertension or movement persisted for 5 minutes despite these interventions, a bolus of dexmedetomidine 0.2 mcg kg^{-1} was given and the infusion rate increased by 50%. If movement or hypertension still, then 0.3% sevoflurane was added to dexmedetomidine and remifentanyl. A repeat dose of neuromuscular blocking agent was allowed for excessive movement. Finally, if movement or hypertension persisted with 0.3% sevoflurane, then the protocol was abandoned, and patient management was left at the discretion of the anesthesiologist. If treatment of light anesthesia was required for the child's immediate safety, then a propofol bolus could be given.

For mild hypotension (defined as two subsequent recordings of MAP $40\text{-}50 \text{ mm Hg}$), the protocol specified that a bolus of $10\text{-}20 \text{ mL kg}^{-1}$ of isotonic IV fluid be administered and the dose of remifentanyl or dexmedetomidine decreased. For moderate hypotension (defined as two subsequent recordings of MAP $<40 \text{ mm Hg}$), or persistent mild hypotension after fluid bolus, a bolus of phenylephrine $1\text{-}5 \text{ mcg kg}^{-1}$ or epinephrine $1\text{-}5 \text{ mcg kg}^{-1}$ or ephedrine $0.25\text{-}0.5 \text{ mg kg}^{-1}$ was specified in the protocol.

In case of mild bradycardia (defined as two subsequent recordings of a heart rate <100 but >70 beats per minute over 1 minute in duration), atropine $10\text{-}20 \text{ mcg kg}^{-1}$ or glycopyrrolate 5 mcg kg^{-1} was to be given and dexmedetomidine was to be decreased by 50% per the protocol. Moderate bradycardia was defined as HR <70 beats per min for over 1 minute and was treated with epinephrine $1\text{-}5 \text{ mcg kg}^{-1}$ if hypotensive and/or persistent significant bradycardia occurred at the discretion of the anesthesiologist. If significant bradycardia persisted after treatment, the anesthesiologist was to abandon protocol and treat the patient at his/her discretion.

Patients were observed in the recovery room for 60 minutes. Oxygen saturation and MAP were recorded continuously, and the Face, Legs, Activity, Cry, Consolability scale (FLACC) was scored every 5 minutes.

Statistical analysis

Considering a 5% failure rate and a precision of 95% confidence interval, a sample of 60 patients was deemed reasonable to estimate the proportion of participants where the protocol is abandoned (primary outcome). Continuous variables are presented as mean ($\pm$ standard deviation), and median (IQR = Interquartile Range). Categorical variables are summarized as frequency and percentages. The primary outcome, the proportion of failures, is presented as a percentage along with its 95% confidence interval calculated using the binomial exact method.

The trial was registered at ClinicalTrials.gov in Feb 2015, Reference Number NCT02353182.

Subjects were studied under U.S. Food and Drug Administration Investigational New Drug number 118058 for dexmedetomidine.

Results

Sixty patients were enrolled in this pilot, feasibility study between May 2015 and Oct 2016, from seven centers. (Table 1). Two children were excluded shortly after enrollment: one subject received midazolam premedication, one withdrew consent. No data were collected from these infants. In 2/58 infants (3%, 95% confidence interval 0.4, 11.9%), the protocol was abandoned due to failure to place the caudal block and the infant had an anesthetic given at the discretion of the anesthesiologist (primary outcome). In these cases, no intra-operative data were collected. The remaining 56 infants were treated as per protocol. In protocol version 1, 16 subjects were included. Following amendments of the study drug dose by the Trial Steering Committee, 23 and 17 subjects were subsequently enrolled in version 2 and 3 of the protocol, respectively (Figure 1). There was not an equal number of infants treated with each version of the protocol due to protocol violations and the lag in time between passing recruitment target and when the Steering Committee could meet.

The demographic and anesthetic related data for the 56 children with a functioning caudal or epidural block is presented in Table 1. FiO_2 ranged between 0.35 and 0.4. Ropivacaine 0.2% was the most frequently used local anesthetic (70%), followed by bupivacaine 0.25% (26%), and levobupivacaine (4%). Local anesthetic for the caudal block was re-dosed in 42 (72.4%) infants. Two infants received epidural blockade, both with levobupivacaine. The following neuromuscular blocking drugs were used in 53 out of 56 patients: rocuronium ($n = 41$; 77%), atracurium ($n = 2$; 4%), cisatracurium ($n = 1$; 2%), and vecuronium ($n = 9$; 17%). Three patients did not receive neuromuscular blockade. Furthermore, 20 patients received a second dose, and 9 patients a third dose.

Primary outcome

The protocol was abandoned in 2 of 58 (3.4%) patients due to caudal block placement failure. Once the block was placed, none of the remaining 56 infants required the protocol to be abandoned.

Secondary outcomes

Six of the 56 infants who completed the protocol (10.7%) received low dose rescue sevoflurane (0.2-0.9%) for a mean duration 24 ± 27 minutes (3 in protocol version one, 1 in version two, and 2 in version three). **There was no relationship between the type of local anesthetic and the need for sevoflurane rescue.** One subject received rescue propofol, but not sevoflurane (in protocol version three). Rescue treatment for light anesthesia (movement and/or hypertension) was required for the majority of infants (45/56; 80.3%). Movement without hypertension was reported in 42 (75%) infants (Table 2). Episodes of hypertension (defined as two subsequent recordings of MAP >80 mm Hg) were recorded in 20 (36%) infants (Table 3). Movement and hypertension were observed in infants receiving all three protocols.

Overall, 14 of 56 subjects (25%) experienced hypotension – most of these in protocol version 3. The hypotension was mild (MAP 40-50 mmHg) in 10 infants and was moderate (MAP <40 mm Hg) in 4 infants. All infants who had moderate hypotensive episodes also had mild hypotensive episodes (Table 4). All but one of the hypotensive patients received fluid bolus, and none received administration of phenylephrine or epinephrine. In many instances, the treating clinicians did not follow the rescue treatment exactly; vasopressors were not given with moderate hypotension or with persistent mild hypotension after fluid bolus. The dose of remifentanyl or dexmedetomidine alone or together was decreased in all infants with hypotension. Overall the mean lowest MAP was 47.7 ± 9.04 mmHg. The mean lowest MAP was 49.6 ± 6.9 mmHg in protocol version 1, 48.8 ± 8.99 mmHg in version 2, and 44.8 ± 10.63 mmHg in version 3. The absolute lowest MAP recorded in any infant was 35 mmHg in version 1, 27 mmHg in version 2, and 22 mmHg in version 3. The mean percentage of time during anesthesia where a child was hypotensive was $2 \pm 7\%$ in version 1, $3 \pm 10\%$ in version 2 and $10 \pm 17\%$ in version 3.

There were 8 (14.3%) recorded episodes of mild bradycardia and one of moderate bradycardia. All infants with bradycardia received rescue treatment (Table 5).

One patient reduced his heart rate to 53 bpm, which was considered significant bradycardia (defined as heart rate <70 bpm over 1 minute in duration). This episode occurred at the time of extubation and about 10 minutes after discontinuation of dexmedetomidine. The bradycardia resolved after atropine administration and due to its occurrence after discontinuation of dexmedetomidine, it was considered a vaso-vagal event and unrelated to the study protocol.

The time to recovery from anesthesia (defined as the time from last stitch to eye opening) was 7.7 ± 10 minutes and the mean time from last stitch to “ready for PACU discharge” was 75 ± 19 minutes.

The mean FLACC scores were <2 in all patients, but seven patients (12.5%) received postoperative analgesia. There was one episode of bradycardia observed 20 minutes after the patient arrived to PACU,

which resolved with glycopyrrolate. One patient experienced hiccups throughout the procedure. There were no other adverse events.

Discussion

This pilot study demonstrated that with a functioning caudal or epidural block, 87.5% of infants could be given satisfactory anesthesia with remifentanyl and dexmedetomidine, without the addition of other general anesthetics. We deliberately choose a conservative protocol, that was amended twice by the Steering Committee based on interim analysis. Specifically, it was decided to increase the dose of dexmedetomidine and remifentanyl to provide a certain degree of flexibility in changing the anesthetic plane when needed. However, the successful performance of a functional regional anesthesia (either caudal or epidural block) seemed to be a mandatory requisite to minimize intraoperative signs of light anesthesia.

Aproximately one third of children who completed the trial protocol had mild hypotension and bradycardia episodes requiring anesthesia depth adjustments with titration of dexmedetomidine and remifentanyl, but the clinical significance of these events remains uncertain. Many infants (80%) had signs of light anesthesia (minor movement with or without hypertension), regardless of the dosing regimens applied. A possible clinical explanation could be the suboptimal caudal block level or density, or the caudal block wearing off.

Rescue medication was triggered by clinical signs (movement, hyper or hypotension, etc.) and they happened throughout the course of anesthesia. It is possible that rescue was initiated early in some infants because caudal blockade was not totally effective. Rescue occurred later in other infants when the caudal block was wearing off.

The hypertensive and hypotensive episodes were short lived and represented 10% of the total anesthesia time. Adjusting anesthesia depth in response to signs of light or deep anesthesia is a common practice both with inhalational and intravenous anesthetics particularly in young infants. Based on our limited data, we are unable to comment whether infusion rate adjustments of remifentanyl and/or dexmedetomidine were greater or similar to that in routine clinical care.

In some instances the treating clinician did not strictly follow the rescue protocol for hypotension; e.g. vasopressors were never given. The reason for these deviations was that the treating clinicians did not consider the degree of hypotension concerning enough to warrant treatment. This divergence of opinion amongst clinicians reflects the controversy surrounding what is an acceptable blood pressure in anesthetized infants.^{20,21}

Dexmedetomidine has an elimination half-life of 2-hours in adults; but clearance is reduced in neonates²² and matures over the first year of life. These pharmacokinetics could prolong “wake-up” and recovery

times.^{23,24} The wake-up (7.7 ± 10 minutes from last stitch to eye opening) and recovery times (75 ± 19 minutes - "ready to discharge from PACU") found in our patients are in agreement with reports from previous studies that showed a small increase in recovery time that is unlikely to be clinically relevant. Positively, there was no evidence for excessive pain or slow awakening. The protocol was completely abandoned in only 2 of 58 cases (3%) due to caudal block failure, which is similar to the failure rate found in larger trials.²⁵ This could be construed as indicating that this technique could be clinically feasible for selected cases or for the comparative arm in larger trials.

Despite protocol changes (versions 2 and 3) by the Trial Steering Committee to reduce the incidences of light anesthesia by increasing the dexmedetomidine and remifentanyl doses, episodes of light anesthesia persisted. The study was not powered to determine if increasing the dexmedetomidine and remifentanyl infusion rates would lower the signs of light anesthesia and a-posteriori statistical analysis was not performed. The rate of hypotension was slightly higher in the third version of the protocol, but no formal statistical analysis was performed.

Although there were frequent signs of perceived "light anesthesia" in all three dosing protocols, these were successfully managed by increasing the doses of remifentanyl or dexmedetomidine. One of the major limitations of this pilot study was the slow recruitment rate. In spite of enrolling from several large pediatric hospitals, there were few cases scheduled to last over 2 hours where the stimulus of surgery could be covered with a caudal block. In light of this, the Trial Steering Committee decided that a regimen based solely on caudal block/remifentanyl/dexmedetomidine would not be a feasible comparator for a large trial. A larger trial (the TREX study, NCT03089905) should allow inclusion of infants where a regional block may not guarantee ablation of all stimulus; simply adding low dose sevoflurane (0.4-0.6%) to remifentanyl and dexmedetomidine, with or without regional anesthesia, could be chosen as comparator to the standard of care where higher doses of sevoflurane are used.

Conclusion

This pilot study demonstrated that with a functioning caudal or epidural block and a remifentanyl-dexmedetomidine infusion, 87.5% of infants could have their surgery completed with no sevoflurane or propofol. These findings can be used as a foundation for designing larger trials that assess alternative anesthetic regimens for anesthetic neurotoxicity in infants and young children. The pilot study does also provide evidence that this technique may be a viable anesthetic option in selected cases. However, the optimal doses of remifentanyl and dexmedetomidine remain to be determined, as well as PK/PD of both drugs during general anesthesia in the studied population.

Disclosures

- 1. An Institutional Review Board approved the protocol in all participating institutions and written informed consent was obtained from subjects' parents.**

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3. Dean Andropoulos, Jurgen De Graaf, Dean Kurth, Justin Skowno, Britta von Ungern-Sternberg, Lazlo Vutskits, Brian Anderson, and Andrew Davidson sit on the Editorial Board of the journal Pediatric Anesthesia. The authors have no other conflicts of interest to declare.

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Table 1**Patient enrollment, study centers, demographic, and anesthetic related data**

Study centers (number of patients enrolled)	Texas Children's Hospital, Houston, TX (15) Boston Children's Hospital, Boston, MA (1) Royal Children's Hospital, Parkville, Victoria, AUS (2) Oregon Health and Science University, Portland, OR (7) Cincinnati Children's Hospital Medical Centre, Cincinnati, OH (3) The Children's Hospital of Philadelphia, Philadelphia, PA (10) University of Texas Southwestern and Children's Health, Medical Centre Dallas, Dallas, TX (20) KK Women's and Children's Hospital, Singapore, Singapore (2)
Age (mean $\pm$ SD)	251 $\pm$ 62.4 days
Gender: Female/Male	3 (6%)/ 53 (94%)
Weight (mean $\pm$ SD)	8.23 $\pm$ 1.03 kg
Airway choice	55 Endotracheal Tube, 1 Laryngeal Mask Airway
Time of anesthesia (mean $\pm$ SD)	2:18 $\pm$ 0:42 hours
Type of surgery:	46 hypospadias repair 3 epispadias repair 2 orchiopexies 2 phalloplasty 1 laparoscopic cystectomy 1 colostomy closure 1 polydactyly repair

Table 2**Number of movement episodes in protocol version 1, 2, and 3**

	Version 1	Version 2	Version 3	Total Movement episodes
	No=16	No=23	No=17	

1 episode	4	5	8	17
2 episodes	4	3	3	10
3 episodes	2	4	2	8
4 episodes	0	2	0	2
5 episodes	2	0	1	3
>5 episodes	1	1	0	2
No of subjects with 1 or more episode (%)	13 (81%)	15 (65%)	14 (82%)	42 (75%)

Table 3

Number of subjects with hypertension episodes in protocol version 1, 2, and 3

	Version 1 No=16	Version 2 No=23	Version 3 No=17	Total Hypertension episodes
1 episode	1	4	3	8
2 episodes	2	2	2	6
3 episodes	0	1	3	4
4 episodes	0	0	0	0
5 episodes	0	0	0	0
>5 episodes	0	0	2	2

No of subjects with 1 or more episode (%)	3 (19%)	7 (30%)	10 (59%)	20 (36%)

Hypertension: two subsequent recordings of mean arterial pressure (MAP) >80 mmHg.

Table 4

Number of subjects with mild and moderate hypotension episodes

	Version 1 No=16		Version 2 No=23		Version 3 No=17		Total Hypotension episodes
	Mild	Moderate	Mild	Moderate	Mild	Moderate	
1 episode	0	0	1	0	0	1	2
2 episodes	0	0	2	0	0	2	4
3 episodes	0	0	0	0	0	0	0
4 episodes	0	0	0	0	0	0	0
5 episodes	0	0	0	0	0	0	0
>5 episodes	0	0	0	0	7	1	8
No of subjects with 1 or more episodes (%)	0		3 (13%)	0	7 (41%)	4(24%)	14 (25)

Mild hypotension: two subsequent recordings of mean arterial pressure (MAP) between 40 and 50 mmHg; moderate hypotension: two subsequent recordings of MAP <40 mmHg, or persistent mild hypotension after fluid bolus, or vasopressor dose.

Table 5

Number of subjects with bradycardia episodes

	Version 1 No=16		Version 2 No=23		Version 3 No=17		Total Bradycardia episodes
	Mild	Significant	Mild	Significant	Mild	Significant	
1 episode	3	1	3	0	2	0	9
2 episodes	0	0	0	0	0	0	0
3 episodes	0	0	0	0	0	0	0
4 episodes	0	0	0	0	0	0	0
5 episodes	0	0	0	0	0	0	0
>5 episodes	0	0	0	0	0	0	0
No of subjects with one or more episodes (%)	3 (19%)	1 (6%)	3(13%)	0	2 (12%)	0	9 (16%)

Mild bradycardia: two subsequent recordings of a heart rate <100 but >70 beats per minute over 1 minute in duration; moderate bradycardia: two subsequent recordings of a heart rate <70 BPM over 1 minute in duration.

Figure 1. Study profile and protocol modifications

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