Predictors of Failure of Awake Regional Anesthesia for Neonatal Hernia Repair

Data from the General Anesthesia Compared to Spinal Anesthesia Study—Comparing Apnea and Neurodevelopmental Outcomes

Geoff Frawley, M.B.B.S., Graham Bell, M.B., Ch.B., Nicola Disma, M.D., Davinia E. Withington, B.M., Jurgen C. de Graaff, Ph.D., Neil S. Morton, M.D., Mary Ellen McCann, M.D., Sarah J. Arnup, M.Biostat., Oliver Bagshaw, M.B., Ch.B., F.R.C.A., F.F.I.C.M., Andrea Wolfler, M.D., David Bellinger, Ph.D., Andrew J. Davidson, M.D.; the General Anesthesia compared to Spinal anesthesia (GAS) Consortium*

ABSTRACT

Background: Awake regional anesthesia (RA) is a viable alternative to general anesthesia (GA) for infants undergoing lower abdominal surgery. Benefits include lower incidence of postoperative apnea and avoidance of anesthetic agents that may increase neuroapoptosis and worsen neurocognitive outcomes. The General Anesthesia compared to Spinal anesthesia study compares neurodevelopmental outcomes after awake RA or GA in otherwise healthy infants. The aim of the study is to describe success and failure rates of RA and report factors associated with failure.

Methods: This was a nested cohort study within a prospective, randomized, controlled, observer-blind, equivalence trial. Seven hundred twenty-two infants 60 weeks or less postmenstrual age scheduled for herniorrhaphy under anesthesia were randomly assigned to receive RA (spinal, caudal epidural, or combined spinal caudal anesthetic) or GA with sevoflurane. The data of 339 infants, where spinal or combined spinal caudal anesthetic was attempted, were analyzed. Possible predictors of failure were assessed including patient factors, technique, experience of site and anesthetist, and type of local anesthetic.

Results: RA was sufficient for the completion of surgery in 83.2% of patients. Spinal anesthesia was successful in 86.9% of cases and combined spinal caudal anesthetic in 76.1%. Thirty-four patients required conversion to GA, and an additional 23 patients (6.8%) required brief sedation. Bloody tap on the first attempt at lumbar puncture was the only risk factor significantly associated with block failure (odds ratio = 2.46).

Conclusions: The failure rate of spinal anesthesia was low. Variability in application of combined spinal caudal anesthetic limited attempts to compare the success of this technique to spinal alone. **(ANESTHESIOLOGY 2015; 123:55-65)**

SINCE its initial description at the start of the 20th century, infant spinal anesthesia has occupied a significant place in the history of pediatric regional anesthesia (RA). During the 1970s, a new role was proposed for spinal anesthesia with the recognition that this method may reduce the risk of postoperative apnea, periodic breathing, and desaturation after GA in expremature infants.[1–3] In centers with experience in performing herniorrhaphy under spinal anesthesia, success rates of approximately 100% have been reported to complete the operation.[4,5] However, many authors report a higher failure rate, often due to failed access to the subarachnoid space, bloody taps, and blocks requiring supplementation. In a study evaluating the ease of neonatal

What We Already Know about This Topic

- Spinal and caudal anesthesia for surgery in infants may avoid exposure to general anesthetic and carry clinical advantages
- The failure rate of spinal and caudal anesthesia in this age group has not been studied in a multicenter, prospective fashion

What This Article Tells Us That Is New

- In a secondary analysis of the General Anesthesia compared to Spinal anesthesia study, data from 339 infants less than 60 weeks postmenstrual age receiving spinal or caudal anesthesia for herniorrhaphy were examined
- Failure of regional anesthesia requiring general anesthesia occurred in 10% of cases, and its only predictor was bloody tap on the first attempt at lumbar puncture

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* Members of the General Anesthesia compared to Spinal anesthesia (GAS) Consortium are listed in the appendix.

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spinal tap with or without local anesthetic, the rates of failed access to cerebrospinal fluid and for bloody tap were 17 and 46%, respectively.[6] William *et al.*[7] reported a 20% traumatic tap and failure rate, and Shenkman *et al.*[8] reported a 16% failure rate where spinal fluid could not be obtained in expremature infants. Although many authors allude to factors associated with an increased risk of failure, there are no data describing the increase in the risk of failure for specific factors such as age, weight, and operator experience. Understanding these factors could improve the success rate.

The General Anesthesia compared to Spinal anesthesia (GAS) study is a prospective, randomized, controlled trial designed to compare the effect of GA to RA in infancy on neurodevelopmental outcome. Early postoperative outcomes of RA and GA in the GAS study have been described elsewhere. The aim of this article is to examine the infant subpopulation randomized to awake regional in the GAS study, first to report the failure rate in a large multinational population and second to identify the patient and operator characteristics associated with failure. Last, we aim to evaluate whether the addition of caudal block to spinal block increases the likelihood of successful completion of surgery.

Materials and Methods

Study Design and Participants

In this multinational, prospective, randomized, controlled, equivalence trial, members from the GAS consortium (appendix) enrolled 722 patients from 28 centers in Australia, the United States, the United Kingdom, Italy, The Netherlands, Canada, and New Zealand between February 9, 2007 and January 31, 2013. Institutional review board or human research ethics committee approval was obtained from each site. Eligible patients included any children scheduled for unilateral or bilateral herniorrhaphy (with or without circumcision). Exclusion criteria included any child older than 60 weeks postmenstrual age or born 26 weeks or less gestational age. Further exclusion criteria included contraindications to GA or RA, preoperative ventilation immediately before surgery, congenital heart disease, known chromosomal abnormalities or other known acquired or congenital abnormalities (other than prematurity) that might affect development, children whose primary language was not that of the country they were recruited in, previous exposure to volatile GA or benzodiazepines as a neonate or in the third trimester *in utero*, or any known neurologic injury such as cystic periventricular leukomalacia or grade 3 or 4 intraventricular hemorrhage. Patients were enrolled after obtaining written informed consent from the child's parents and permission from the treating anesthesiologist and surgeon.

The GAS study protocol was approved by the following: Royal Children's Hospital Human Research Ethics Committee, Melbourne, Victoria, Australia; Southern Health Human Research Ethics Committee "B" meeting, Melbourne, Victoria, Australia; Women's and Children's Health Network Human Research Ethics Committee, Adelaide, South Australia, Australia; Princess Margaret Hospital for Children Ethics Committee, Perth, Western Australia, Australia; Northern X Regional Ethics Committee and Auckland District Health Board, Auckland, New Zealand; Comitato di Etica Istituto Giannina Gaslini, Genoa, Italy; Comitato Etico dell'Azienda Ospedaliera Istituti Clinici di Perfezionamento di Milano; Milan, Italy; Comitato Etico Ospedali Riuniti Bergamo, Bergamo, Italy; West Glasgow Ethics Committee 2, Glasgow, United Kingdom; Comité d'éthique de la recherche CHU Sainte-Justine, Montreal, Quebec, Canada; Montréal Children's Hospital Research Ethics Board, Montreal, Quebec, Canada; The Medical Ethical Committee—Universitair Medisch Centrum Utrecht, Utrecht, The Netherlands; The Medical Ethical Committee—Universitair Medisch Centrum Groningen, Groningen, The Netherlands; Boston Children's Hospital Committee on Clinical Investigations, Boston, Massachusetts; Ann & Robert H Lurie Children's Hospital of Chicago Institutional Review Board, Chicago, Illinois; The Children's Hospital of Philadelphia Institutional Review Board, Philadelphia, Pennsylvania; Institutional Review Board at University of Texas Southwestern Medical Center, Dallas, Texas; Committee for the Protection of Human Subjects Dartmouth-Hitchcock Medical Center, Hanover, New Hampshire; Colorado Multiple Institutional Review Board Children's Hospital Colorado, Denver, Colorado; The University of Iowa Hospitals and Clinics Institutional Review Board, Iowa City, Iowa; Seattle Children's Hospital Institutional Review Board, Seattle, Washington; Monroe Carell Jr. Children's Hospital at Vanderbilt Institutional Review Board, Nashville, Tennessee; and Fletcher Allen Health Care Institutional Review Board, Burlington, Vermont. The GAS study is registered in Australia and New Zealand at Australian New Zealand Clinical Trials Registry: ID ACTRN12606000441516 first registered on October 16, 2006, principal investigators: A.J.D., M.E.M., and N.S.M.; in the United States at ClinicalTrials.gov: ID: NCT00756600 first registered on September 18, 2008, principal investigators: A.J.D., M.E.M., and N.S.M.; and in the United Kingdom at United Kingdom Clinical Research Network ID: 6635 (International Standard Registered Clinical/Social Study Number ID: 12437565; MREC No.: 07/S0709/20) principal investigator: N.S.M.

Randomization and Blinding

A 24-h Web-based randomization service was managed by The Data Management and Analysis Centre, Department of Public Health, University of Adelaide, Adelaide, South Australia, Australia. Patients were randomized with a 1:1 allocation ratio to either GA or RA. Randomization was in blocks of two or four and stratified by site and gestational age at birth: 26 to 29 weeks and 6 days, 30 to 36 weeks and 6 days, and 37 weeks or more. The anesthesiologist and anesthetic team were aware of group allocation, and the perioperative assessments were not blinded. Parents were not informed of the group allocation but were told if they asked.

Procedures

Preoperative fasting was in accordance with the institutional guidelines. Premedication with acetaminophen 15 to 20 mg/kg was optional as was use of topical local anesthetics (EMLA). Intravenous infusion of Ringer's lactate solution, saline, or dextrose saline was delivered at 4 ml kg^{-1} h^{-1} during surgery. Oral sucrose was used for sedation/analgesia, but no other sedation or volatile anesthetic agents were given at any stage. Patient warming was in accordance with institutional practice.

The RA group received a spinal or combined spinal caudal anesthetic (CSCA) according to institutional protocols. Spinal anesthesia was performed with a 25- or 22-gauge needle between L3 and L5 in lateral or sitting position. The dose of bupivacaine was 0.2 ml/kg 0.5% isobaric bupivacaine with a minimum volume of 0.5 ml. Due to unavailability of isobaric bupivacaine at some sites, other agents were used (in the United States, 0.75 mg/kg of hyperbaric 0.75% bupivacaine, and in the United Kingdom, 0.5% levobupivacaine).

Caudal anesthesia was performed with 2.5 mg/kg of 0.25% bupivacaine *via* needle or cannula at the discretion of anesthetist. In the United Kingdom, 0.25% levobupivacaine was used. In the United States, if surgery was likely to take more than 1 h, some patients were given a loading dose of 3% chloroprocaine (1 ml/kg in divided doses of no greater than 0.25 ml/kg per 15 s) *via* a caudal cannula and then an infusion of 1 to 2 ml kg^{-1} h^{-1}.

At the end of surgery, a caudal block or an ilioinguinal block could be administered by the anesthetist to provide postoperative analgesia. Alternatively, the surgeons could perform a field block provided the total dose of bupivacaine did not exceed 2.5 mg/kg. Infants received acetaminophen 20 mg/kg orally or intravenously postoperatively if not given preoperatively and intravenous fluids until feeding commenced.

Rescue Treatments. There were rescue protocols for hypoglycemia, hypotension, and hypoxemia. If the blood pressure decreased more than 20% below baseline (measured in a comforted, nondistressed child), an intravenous bolus of 20 ml/kg Ringer's lactate solution was administered. Vasoactive drugs were given if deemed necessary by the anesthetist. Hypoglycemia (blood sugar < 3.0 mmol/l) was treated with a bolus of 5 ml/kg of 10% dextrose. Oxygen by face mask or blow-by was used at the discretion of the anesthetist to maintain arterial oxygen saturation greater than 95%. Hypoxemia (Spo_2 < 90%) was managed by oxygen delivered by Hudson mask, face mask, or intubation.

Inadequate Anesthesia. If a spinal anesthetic was attempted and there was no evidence of effective motor block (after 5 min the infant continued to vigorously spontaneously move both legs and withdraw both legs to gentle pinch of the thigh), then a second attempt at a spinal anesthetic could be performed with another 1 mg/kg bupivacaine. If the block still appeared ineffective, a general anesthetic was administered.

If there was good evidence of motor block initially, but the child became unsettled intraoperatively (such as during spermatic cord or hernia sac traction), then the first-line treatment was soothing maneuvers with a pacifier. Second-line treatment involved oral glucose and third-line treatment involved infiltration of additional local anesthetic by the surgeon (field block). If the child remained distressed for prolonged periods, then sevoflurane was administered. A GA was also administered in the event of respiratory compromise or if prolonged or more extensive surgery was required.

Statistical Analysis

Sample Size Considerations. The sample size for the GAS study was based on the neurodevelopmental outcome at 5 yr of age. Given that this article presents data on a secondary outcome of the study, an *a priori* power calculation was not conducted for this outcome. We do not believe *post hoc* power calculations are useful and instead we present our results along with CIs that capture the uncertainty in our findings reflecting the sample size.

Data Analysis. Patients were excluded from analysis if they were randomized to RA, but a regional anesthetic was never attempted, or they received only an awake caudal with no spinal block. No analysis of risk factors for failure associated with awake caudal anesthesia was attempted because of the small number of awake caudal-only cases.

Failure was defined as the use of any sevoflurane or sedative in infants randomized to RA and can be categorized as either a complete failure or a partial failure. Complete failure was defined as when sevoflurane was given from before, or at the moment of knife to skin, and given continuously until the last stitch. A partial failure was defined when patients received sevoflurane or any sedative agent (apart from glucose) for any part of the period between knife to skin and last stitch, and/or for part of the period between arriving in the operating room and knife to skin. A success was defined as an RA that required no supplementation with GA for any phase of the operation.

Categorical data are summarized using counts and percentages and continuous data using means (with SD) or medians (with interquartile range [IQR], 25 to 75%). For binary outcomes, a comparison between groups is presented as an odds ratio (OR) as estimated from a logistic regression model. For continuous outcomes, a comparison between groups is presented as a difference in means as estimated from a linear regression model. The distribution of continuous outcomes was examined for normality, and log transformations were applied where appropriate. All estimates are presented with 95% CIs and two-sided *P* values. All outcomes were adjusted for site of randomization using the generalized estimating equation approach with robust standard errors.[9] Sites with less than 20 participants were treated as a single cluster. An exchangeable correlation structure was assumed between any two children from the same site.

The following factors were identified *a priori* as potential risk factors for any failure (partial or complete): patient factors (gestational age at birth, postmenstrual age at surgery, and weight), clinician and site factors (site experience and anesthesiologists seniority), and technique factors (spinal *vs.* CSCA, drug type, drug dose, and presence of bloody tap). The association between each factor and any failure was assessed separately. Site experience was defined by (1) number of blocks performed and (2) time since first randomization in study because it was expected that there would be a significant learning curve at those centers where awake RA was not common before the GAS trial. Anesthesiologists' experience was dichotomized as senior if the most senior person performing the first block was a consultant or attending anesthesiologist or other if the most senior person performing the first block was a fellow, registrar, resident or senior house officer, nurse anesthetist, or surgeon. In a sensitivity analysis, assessment of site experience was restricted to sites with greater than 20 randomizations because the effect of experience may only be evident in sites with some prior RA experience. The outcomes assessed for a difference between CSCA and spinal-only anesthesia were failure and total anesthesia time. All analyses were performed using Stata 13 (Stata Corp LP, USA).

Results

Of the 363 cases randomized to RA, 339 (93.4%) were analyzed in this article. No surgery was performed in five patients (1.4%), and two patients (less than 1%) were misrandomized. No attempt at RA was made in 10 patients (2.8%), due to miscommunication among staff, lack of staff availability on the day of surgery, and the child no longer being eligible for RA on the day of surgery. In seven cases (1.9%), an awake caudal only was attempted. Spinal anesthesia alone was attempted in 222 patients (65.5%), and CSCA was attempted in 117 patients (34.5%). The demographics of the analyzed patients are presented in table 1.

Success Rate of Awake RA

Awake RA was successful in 282 of 339 patients (83.2%). A partial failure occurred in 23 patients (6.8%) and complete failure occurred in 34 (10.0%) of cases (table 2). Ilioinguinal nerve blocks or wound infiltration at the end of surgery was used to prolong the duration of analgesia in 51 of 339 (15.0%) of patients. An ilioinguinal nerve block was performed at the end of surgery in three patients (1%), and a field block was performed by the surgeon in another 48 patients (14.2%).

Hypoxemia during performance of the block occurred in four cases (1.3%), and desaturation (less than 90%) at any time during the anesthetic occurred in 19 cases (5.7%). Eight infants (2.4%) required bag-mask ventilation in the operating room (three spinal and five CSCA). One infant had clinical evidence of high spinal block with inadequate ventilation and received assisted ventilation for the majority of the procedure, whereas two other infants had brief apneas requiring stimulation and brief assisted mask ventilation. Of the five CSCA infants, a failed spinal block was converted to GA in three and GA plus caudal in two infants. There was no evidence of systemic toxicity in any infant. Reintubation was not required for any infants.

Success Rate of Spinal-only and CSCA Technique

Spinal was sufficient on its own for the completion of surgery in 193 of the 222 cases (86.9%), and CSCA was sufficient in 89 of 117 cases (76%) (table 2). In 66 of the 222 cases (29.7%), some form of anesthesia was required after the first attempt at spinal anesthesia. A second spinal was attempted in 28 patients (12.6%), an awake caudal in 8 patients (3.6%), and conversion to GA occurred in 30 patients (13.5%). Conversion to GA occurred for a number of reasons that were not completely described during data collection. In some cases, successful blocks were converted to GA because the team felt the patient's distress was not compatible with completion of surgery.

Table 1. Demographics of Infants Enrolled in the General Anesthesia Compared to Spinal Anesthesia Study and Randomized to Awake Regional Anesthesia for Inguinal Hernia Repair

	Awake Regional, n = 339	Spinal, n = 222	CSCA, n = 117
Gender, male (%)	275 (81.1%)	179 (80.6%)	96 (82.1%)
Multiple pregnancy, yes (%)	59 (17.4%)	31 (14.0%)	28 (24.0%)
Gestational age, wk	35.4 (4.1)	35.5 (4.2)	35.3 (3.9)
Birth weight, kg	2.34 (0.92)	2.34 (0.90)	2.35 (0.95)
Postmenstrual age, wk	45.5 (4.6)	45.4 (4.7)	45.7 (4.5)
Current weight, kg	4.21 (1.09)	4.14 (1.06)	4.36 (1.14)
Age at surgery, wk	10.0 (4.6)	9.9 (4.4)	10.4 (4.8)
Ever home from hospital since birth, yes (%)	313 (92.3%)	208 (93.7%)*	105 (89.7%)
Sent home with supplementary oxygen, yes (%)	7 (2.1%)	5 (2.3%)†	2 (1.7%)‡
Surgery type (unilateral/bilateral) herniorrhaphy (% unilateral)	186 (54.9%)	122 (55%)	64 (54.7%)

Mean (SD) are shown for continuous variables and n (%) for binary variables.

* One patient is excluded as was a home birth. † Eight patients were not included as were still in hospital at time of surgery and variable was recorded as unknown in four patients. ‡ Seven patients were not included as were still in hospital at time of surgery.

CSCA = combined spinal caudal anesthetic.

Table 2. Awake Regional Techniques

Technique Attempted	Success, n (%)	Partial Failure, n (%)	Complete Failure, n (%)
Spinal (n = 222)	193 (86.9%)	16 (7.2%)	13 (5.9%)
CSCA (n = 117)	89 (76.1%)	7 (6%)	21 (17.9%)
Total	282 (83.2%)	23 (6.8 %)	34 (10%)

Anesthetic techniques included spinal or a CSCA. Success was defined as completion of surgery with awake regional anesthesia alone. Complete failure was defined as when any sevoflurane or sedative was given from before, or at the moment of knife to skin, and given continuously until last stitch. A partial failure was defined when patients received sevoflurane or any sedative agent (apart from glucose) for any part of the period between knife to skin and last stitch, and for part of the period between arriving in the operating room and knife to skin.

CSCA = combined spinal caudal anesthetic.

After initial failure at spinal anesthesia, there were 28 second attempts of which 10 (36%) failed and 18 (64%) were successful, including the one in which awake caudal was successfully attempted. In the 10 failed second blocks, 4 of the anesthesiologists were more experienced than the primary anesthesiologists. In the 18 successful blocks, 2 (11%) of the anesthesiologists were more experienced than the first anesthesiologist. Bloody taps occurred in 30% of spinal attempts and 44% of CSCA attempts. Bloody taps occurred in 35% of first attempts, 11% in second attempts, and 7% of third attempts; therefore, a bloody tap is less likely with subsequent attempts. There were 52 cases in the CSCA group with at least one bloody tap. Of these, 44 (85%) had a bloody tap in one of the spinal attempts, 3 had a bloody tap in the caudal attempt, and 5 had bloody taps in both spinal and caudal attempts.

Predictors of Failure

The failure rate of awake regional techniques by recruitment center and by experience at that center is presented in table 3. The strength of each risk factor as predictor of failure is presented in table 4. There was moderate evidence that the incidence of bloody tap at first spinal attempt is a risk factor for failure (OR = 2.46; 95% CI, 1.24 to 4.87; $P = 0.01$). There is very weak evidence that the failure rates for pediatric staff anesthesiologist consultants (16.2%) was lower than for other anesthesiologists (24%) (OR = 0.58; 95% CI, 0.31 to 1.07; $P = 0.08$). There was weak evidence for a decrease in failure rate with time. The association between the number of regional anesthetics attempted since first randomization and failure of the block was OR = 0.88 per five patients recruited (95% CI, 0.77 to 1.00; $P = 0.06$). There may have been reasons other than experience for a reduction in failure including changes in patient recruitment and changes in anesthetic personnel. In contrast, there was little evidence that the odds of failure of awake RA was associated with the duration of time since the site commenced recruiting patients into the study. When the analysis was restricted to sites where at least 20 patients were recruited, the ORs were similar to when all sites were included.

Failure rates for spinal anesthesia with 0.5% isobaric bupivacaine were lower (6.2%) than hyperbaric 0.75% bupivacaine (28.6%) or 0.5% levobupivacaine (20%).

Comparison of Spinal-only and CSCA Techniques

Total anesthetic time, included the time to perform the block and duration of surgical time, had a median value for CSCA of 63 min (IQR, 46 to 90) and 45 min (IQR, 38 to 57) for spinal block. The total anesthesia time was estimated to be 36% (95% CI, 20 to 55%; $P < 0.001$) longer for CSCA than for spinal blocks. How much longer the anesthetic time is in the CSCA group depends on how long the time would be in the spinal group. For example, if the median anesthetic time is 45 min in the spinal group, we would expect the CSCA time to be $45 \times 1.36 = 61.2$ min, an increase of 16.2 min. However, for a long anesthetic time of 57 min (the 75th percentile), we would expect the anesthetic time to be 77.5 min in the CSCA group, an absolute increase of 20.5 min. Surgical times were 62 min (IQR, 48 to 86 min) for bilateral

Table 3. Failure Rates by Technique and Recruitment Site

		Sites	Spinal (n)	Failure Rate, n (%)	Combined Spinal Caudal Anesthesia (n)	Failure Rate, n (%)	Overall Failure, n (%)
Sites recruiting > 20 patients	Australia	2	70	3 (4.3%)	9	8 (88.9%)	11 (13.9%)
	United Kingdom	1	3	1 (33.3%)	24	0 (0%)	1 (3.7%)
	Italy	2	64	12 (18.8%)	2	2 (100%)	14 (21.2%)
	United States	1	2	1 (50%)	26	3 (11.5%)	4 (14.3%)
Sites recruiting < 20 patients	Australia	2	19	1 (5.3%)	3	2 (66.7%)	3 (13.6%)
	New Zealand	1	5	0 (0%)	4	0 (0%)	0 (0%)
	United Kingdom	4	6	4 (66.7%)	9	1 (11.1%)	5 (33.3%)
	Italy	1	16	2 (12.5%)	0	0 (0%)	2 (12.5%)
	The Netherlands	2	5	0 (0%)	16	1 (6.2%)	1 (4.8%)
	United States	8	15	4 (26.7%)	22	9 (40.9%)	13 (35.1%)
	Canada	2	17	1 (5.9%)	2	2 (100%)	3 (15.8%)

Failure was defined as either complete or partial. Complete failure was when any sevoflurane or sedative was given from before, or at the moment of knife to skin, and given continuously until last stitch. A partial failure was defined when patients received sevoflurane or any sedative agent (apart from glucose) for any part of the period between knife to skin and last stitch, and or for part of the period between arriving in the operating room and knife to skin.

Table 4. Factors Associated with Failure

Variables			Failure	No Failure	OR	95% CI	*P* Value
Patient factors	Gestational age (wk)		35.5 (4.1)	35.4 (4.1)	1.01	0.93–1.08	0.86
	Postmenstrual age (wk)		10.7 (5.4)	9.9 (4.4)	1.03	0.95–1.12	0.41
	Current weight (kg)		4.37 (1.11)	4.18 (1.08)	1.16	0.87–1.57	0.31
Technique	CSCA *vs.* spinal	Spinal	29 (13.1%)	193 (86.9%)	1 (Reference)	0.72–11.0	0.14
		CSCA	28 (23.9%)	89 (76.1%)	2.82		
	Bloody tap	No	27 (12.3%)	193 (87.7%)	1 (Reference)	1.24–4.87	0.01
		Yes	30 (25.2%)	89 (74.8%)	2.46		
Experience*	Time of site in study when performing block (per 6 months)	All			0.91	0.81–1.02	0.11
		Exp			0.94	0.80–1.10	0.44
	Number of blocks (per five blocks)	All			0.88	0.77–1.00	0.06
		Exp			0.92	0.80–1.05	0.21
	Seniority of person performing first block	Other	6 (24%)	19 (76%)	1 (Reference)	0.31–1.07	0.08
		Consultant	51 (16.2%)	263 (83.8%)	0.58		
Local anesthetic†	Dose of bupivacaine (mg)	0.5%	3.9 (0.9)	4.1 (1.2)	0.87	0.60–1.27	0.47
	0.75 *vs.* 0.5% bupivacaine	0.75%	11 (6.2%)	167 (93.8%)	1 (Reference)		
			4 (28.6%)	10 (71.4%)	5.66	1.59–20.1	0.007
		Bupivacaine	11 (6.2%)	167 (93.8%)	1 (Reference)		
	0.5% levobupivacaine *vs.* 0.5% bupivacaine	Levobupivacaine	1 (20%)	4 (80%)	3.55	0.81–15.5	0.09

The odds ratio as estimated from univariable logistic regression model for each predictor adjusted for site of randomization using the generalized estimating equation approach with robust standard errors. For factors with a binary outcome (technique and bloody tap), the odds ratio represents the presence or absence of the factor. For continuous data, the estimate is the odds ratio for a unit increase for the factor (per 1 kg, per 1 mg local anesthetic, per block of five regionals, or per 6-month time period).

* Centers that performed greater than 20 awake regional blocks (exp) were compared with all centers (all). † Of 222 patients allocated to spinal anesthesia, concentration information was not recorded in 25 cases, so dose was not calculated.

CSCA = combined spinal caudal anesthetic; Exp = centers that performed greater than 20 awake regional blocks; OR = odds ratio.

hernia repair and 46 min (IQR, 39 to 61 min) for unilateral repairs. In no cases did surgical time exceed the RA.

Perioperative events are described in table 5. Awake RA was associated with a low incidence of respiratory or hemodynamic compromise. Bradycardia occurred in five patients (1.5%), and the need for any intervention for hypotension occurred in 23 patients (6.8%). Apart from a lower minimum systolic blood pressure in the CSCA group, no other outcomes showed evidence for a difference between spinal and CSCA.

Discussion

The overall success rate of RA in the GAS study was 83%; the block failed completely in 10% of cases; and the block required some supplemental sedation or a limited exposure to sevoflurane in 7% of cases. The overall failure rate is higher than other studies of RA techniques, but these series use a less stringent definition of success. The Vermont Infant Spinal Study reported success rates of 98% for a wide range of neonatal surgical procedures but also report that up to 24% of these patients were given sedation at some point during the procedure. The nonsedated success rate of 76% is then consistent with the GAS study.[10] Older series have reported high success rates but do not detail sedation or restraint used.[5,11] In contrast to other studies, the GAS study protocol precluded routine sedative premedication nor were infants allowed any sedation (including nitrous oxide benzodiazepines or ketamine) for institution of the regional block.[12–14] In previous case series, it has been a common practice to use sedation to allow the block to be performed as this removes some technical difficulties in performing neuraxial procedures with a moving and often crying infant. In the GAS study, intraoperative restraint was required in 40% of infants. Although this was largely to prevent the infant contaminating the sterile field, there was a small proportion in which infant distress was such that conversion to GA was required to complete surgery. The premise of avoiding sedation in infants on account of neuronal apoptosis is new, and the practice of premedication in previous series varies from nil to universal.[8,14] The GAS study protocol adopted an approach whereby any exposure to a drug associated with the potential for apoptosis was avoided.

The clinical implications of the 17% failure rate in the GAS study is that awake spinal anesthesia has a relevant failure rate and that use of caudal anesthesia in addition to spinal anesthesia does not reduce this failure to zero. As a result, it may not be possible to avoid volatile anesthetics or sedatives during the early neonatal life in all infants having herniorrhaphy under RA. We were also not able to identify those infants at higher risk of failure of awake techniques in this series. Gestational age, current age, weight, drugs used, anesthetic technique, and experience of the anesthetist were not predictive of successful completion of the surgery under RA alone. This is in contrast to other series describing awake RA in expremature infants which have implied; but not specifically tested; the theory that heavier and older infants

Table 5. Perioperative Complications

		Awake Regional, n = 339	Spinal (REF), n = 222	CSCA, n = 117	Odds Ratio/Mean % Change*	95% CI	*P* Value
Anesthetic time (min)†	Median (IQR)	50 (40 to 68)	45 (38 to 57)	63 (46–90)	1.36*	(1.20 to 1.55)	< 0.001
Bradycardia	Any bradycardia	5 (1.6%)	3 (1.5%)	2 (1.8%)	1.19	0.21 to 7.01	0.84
	Minimum heart rate	133.8 (16.5)	133.7 (17.6)	134.2 (14.2)	2.26	–1.55 to 6.07	0.25
Hypotension	Any hypotension	23 (6.8%)	10 (4.5%)	13 (11.1%)	1.97	0.79 to 4.89	0.14
	Minimum systolic blood pressure	71.1 (15.1)	73.0 (14.2)	67.7 (16.0)	–6.43	–12.29 to –0.58	0.03
	Minimum diastolic blood pressure	32.0 (9.1)	33.3 (8.5)	29.5 (9.5)	–3.57	–7.44 to 0.30	0.07
	Any intravenous bolus	19 (5.6%)	8 (3.6%)	11 (9.4%)	1.81	0.60 to 5.42	0.29
	Any vasoactive drug	5 (1.5%)	3 (1.4%)	2 (1.7%)	1.33	0.28 to 6.41	0.72
	Bolus + vasoactive drug	1	1	0	N/A‡		
Hypoxemia	During performance of block	4 (1.3%)	4 (2.1%)	0 (0%)	N/A‡		
	Spo_2 < 90% during surgery	19 (5.6%)	15 (6.8%)	4 (3.4%)	0.75	0.3 to 1.85	0.54
	Bag-mask ventilation during case	8 (2.3%)	3 (1.3%)	5 (4.3%)	3.27	0.37 to 28.5	0.28
Intraoperative restraint		132 (39.1%)	89 (40.3%)	43 (36.8%)	0.72	0.20 to 2.55	0.61

For binary variables, raw counts and percentage of total of the first category presented are shown. For continuous data, mean and SD are shown.

The odds ratio as estimated from a univariable logistic regression and for *anesthetic time only, the mean percentage change is estimated from a linear regression model after applying a log transformation to the anesthetic times. † Mean increase between groups. ‡ Odds ratio cannot be estimated using generalized estimating equation approach because of the zero cell.

CSCA = combined spinal caudal anesthetic; IQR = interquartile range; mean diff = mean difference; N/A = not applicable.

are associated with lower spinal anesthesia success rates.[15,16] Reports of spinal anesthesia in older children would suggest that patient factors are less important in units with greater experience in infant spinal anesthesia and with the use of sedation for placement of the block.[11,14] Although prior experience with neonatal spinal anesthesia was expected to increase success rates, we were not able to demonstrate a significant learning curve. The use of awake spinal techniques was not common in many of the centers in the GAS consortium at the start of the trial, but there was no difference in the failure rate when the first 6 months of recruitment was compared with the last 12 months. It is likely that other factors confounded the association including changes in personnel as the trial continued.

The influence of dose and concentration of local anesthetic on success was confounded by differences in regional availability of local anesthetics in this trial. For spinal anesthesia, isobaric 0.5% bupivacaine was used in Australasia, Europe, and one Canadian site, whereas 0.5% levobupivacaine was used in the United Kingdom and 0.75% bupivacaine with 8.25% glucose ("heavy" or hyperbaric bupivacaine) in the United States and the second Canadian site. To maintain a total dose of 1 mg/kg, the sites using hyperbaric solutions used a lower volume of local anesthetic (0.133 ml/kg). This may have contributed to the lower success rates in these centers. Kokki and Hendolin[17] reported no difference in success rates between isobaric or hyperbaric bupivacaine solutions for infant spinal anesthesia; however, their cohort included older infants.

A number of centers in the GAS consortium consider a CSCA, the technique of choice for infant herniorrhaphy. They believe intraoperative analgesia is superior and the extended duration of anesthesia compensates for unexpectedly prolonged surgery. As a result, CSCA was used in 34.5% of cases with national differences in the preferred awake regional technique between centers. There was a tendency for higher failure rates for the infants who received a CSCA anesthetic due to the fact that in some infants the caudal component of a CSCA technique was performed electively after a successful spinal before surgery, whereas in others it was a rescue technique for a failed spinal or electively at the end of the case to extend postoperative analgesia. In those patients where one or two attempts at spinal anesthesia were followed by caudal anesthesia, failure could be related to the restrictions on the epidural local anesthetic dose required if the total dose is to remain within safe total doses. Awake caudal anesthesia alone was performed in a small number of cases but was not included in the analysis as the comparisons with spinal only would have large uncertainty.

The local anesthetic effect on success could be affected by regional or national practices. In some U.S. sites and one Canadian site, caudal chloroprocaine was used to prolong the block. In contrast, caudal anesthesia with isobaric 0.25% bupivacaine was used for this purpose in Australasia, Europe, and one Canadian site, and 0.25% levobupivacaine was used in the United Kingdom. The limited number of CSCA cases with each dose and local anesthetic precluded assessment of each agent's success rate.

The low incidence of bradycardia, hypotension requiring more than fluid bolus, intraoperative hypoxemia, or airway interventions would suggest considerable physiological stability during surgery with awake regional techniques. The only significant event related to awake RA was an infant who demonstrated signs of high block height and required bag-mask

ventilation. It was felt this was due to rapid injection of local anesthetic rather than unexpected head down positioning.

Awake RA still represents only a small percentage of all pediatric regional anesthetic techniques and is often reserved for neonates.[18] Opponents of awake regional techniques suggest that the techniques have an excessive failure rate, inadequate duration of anesthesia, and an unacceptably high rate of unsettled infants requiring intraoperative sedation. Similarly, surgeons may express concerns that only some procedures can be safely and efficiently conducted under spinal anesthesia. Although 55% of herniorrhaphies in the GAS were unilateral, the median anesthetic times for both awake spinal and CSCA would be expected to be more than adequate for both unilateral and bilateral herniorrhaphy.

It remains to be seen if the proportion of infants undergoing neonatal surgery under awake RA increases. A 1-yr study of 24,409 regional blocks in children suggested that spinal anesthesia represents only 3.7% of all cases but 18% of all regional blocks in premature infants and 5% of blocks in term infants currently less than 30 days of age.[19] Rochette *et al.*[20] reported that 10,929 pediatric regional anesthetic blocks of which the 1,042 neonatal spinal anesthetics represented 30% of all infant neuraxial blocks. Lacroix[21] reported significant decreases in the use of caudal anesthesia from 1994 to 2006, but spinal anesthesia use increased from 2.1 to 3.2% of all regional procedures. More recently, the Pediatric Regional Anesthesia Network series documents that infant spinals represent only 1.3% of all central neuraxial blocks.[22]

Limitations

Our group of patients does not encompass the full spectrum of infants normally presenting for herniorrhaphy. In addition to the usual contraindications for RA, we also excluded patients with cardiac defects and chromosomal anomalies or neurological injury as, collectively, these findings were likely to have an influence on the second and fifth year neurodevelopmental score and thus their inclusion would weaken the power of the study with respect to the primary outcome. It could be argued that these infants would benefit most from avoidance of GA.

The fact that center experience with spinal anesthesia had no impact on the success rate needs to be considered with caution. It is entirely conceivable that while two centers performed 20 spinal anesthetics each in this series, their experience before this study could be vastly different. One center may have completed hundreds of spinals before this series and the other none, yet they were both analyzed as being experienced. Furthermore, experience with other regional techniques in children that may have contributed to expertise, or the use of imaging techniques, such as the use of ultrasound for spinal placement, could not be assessed.

Conclusions

In the GAS study, RA had a failure rate of 17% with a lower failure rate for awake spinal anesthesia. The marked variation in preferred techniques and local anesthetics between sites in this series, however, is extremely likely to have contributed to variable failure rates. Predicting which infants are likely to be unsuitable for awake techniques remains difficult.

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bourne, Victoria, Australia; Department of Anaesthesia and Pain Management, Princess Margaret Hospital for Children, Perth, Western Australia, Australia; Department of Paediatric Anaesthesia, Women's Children's Hospital, Adelaide, South Australia, Australia; and Department of Paediatric Anaesthesia and Operating Rooms, Starship Children's Hospital, Auckland, New Zealand. United States: National Institutes of Health, Bethesda, Maryland; Food and Drug Administration, Silver Spring, Maryland; Department of Anesthesiology, Perioperative, and Pain Medicine, Boston Children's Hospital, Boston, Massachusetts; Department of Anesthesia and Pain Medicine, Seattle Children's Hospital, Seattle, Washington; Department of Anesthesiology, Children's Hospital Colorado, Denver, Colorado; Department of Anesthesia, University of Iowa Hospital, Iowa City, Iowa; Department of Anesthesiology, Children's Medical Center Dallas, Dallas, Texas; Department of Pediatric Anesthesiology, Anne and Robert H. Lurie Children's Memorial Hospital, Chicago, Illinois; Department of Anesthesiology, Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire; Department of Pediatric Anesthesia, Vanderbilt University Medical Center, Nashville, Tennessee; Department of Anesthesiology and Critical Care, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; and Department of Anesthesia and Pediatrics, The University of Vermont/Fletcher Allen Health Care, Burlington, Vermont. Italy: Italian Ministry of Health, Rome, Italy; Department of Anesthesia, Istituto Giannina Gaslini, Genoa, Italy; Department of Anesthesiology and Paediatric Intensive Care, Ospedale Vittore Buzzi, Milan, Italy; and Department of Anaesthesia, Ospedale Papa Giovanni XXIII, Bergamo, Italy. The Netherlands: Fonds NutsOhra, Amsterdam, The Netherlands; Department of Anesthesiology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands; and Department of Anesthesiology, University Medical Center Groningen, Groningen, The Netherlands. Canada: Canadian Institute of Health Research, Ottawa, Ontario, Canada; Canadian Anesthesiologists' Society, Toronto, Ontario, Canada; Pfizer Canada Inc., Kirkland, Quebec, Canada; Department of Anesthesia, Montreal Children's Hospital, Montreal, Quebec, Canada; and Département d'Anesthésie, CHU Sainte-Justine, Montreal, Quebec, Canada. United Kingdom: Health Technologies Assessment-National Institutes for Health Research United Kingdom, Southampton, United Kingdom. Anesthesiology Departmental Funding: Department of Anaesthesia, Royal Hospital for Sick Children, Glasgow, United Kingdom; Department of Anaesthesia, Birmingham Children's Hospital, Birmingham, United Kingdom; Anaesthetic Department, Sheffield Children's Hospital, Sheffield, United Kingdom; Department of Paediatric Anaesthesia, Bristol Royal Hospital for Children, Bristol, United Kingdom; Department of Anaesthetics, Royal Belfast Hospital for Sick Children, Belfast, United Kingdom; and Department of Anaesthesia, Pain Relief, and Sedation, Alder Hey Childrens' NHS Foundation Trust, Liverpool, United Kingdom.

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Frawley: Department Paediatric Anaesthesia, The Royal Children's Hospital, Flemington Rd., Parkville, Victoria 3052, Australia. geoff.frawley@rch.org.au. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

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Appendix: General Anesthesia Compared to Spinal Anesthesia (GAS) Study Consortium

Australia: Andrew J. Davidson, M.D., and Geoff Frawley, M.B.B.S. (Anaesthesia and Pain Management Research Group, Murdoch Childrens Research Institute, Melbourne, Australia, and Department of Anaesthesia and Pain Management, The Royal Children's Hospital, Melbourne, Australia, and Department of Paediatrics, University of Melbourne, Melbourne, Australia); Pollyanna Hardy, M.Sc. (National Perinatal Epidemiology Unit, Clinical Trials Unit, University of Oxford, Oxford, United Kingdom); Sarah J. Arnup, M.Biostat., and Katherine Lee, Ph.D. (Clinical Epidemiology and Biostatistics Unit, Murdoch Childrens Research Institute, Melbourne, Australia); Rodney W. Hunt, Ph.D. (Department of Neonatal Medicine, The Royal Children's Hospital, Melbourne, Australia, and Neonatal Research Group, Murdoch Childrens Research Institute, Melbourne, Australia, and Department of Paediatrics, University of Melbourne, Melbourne, Australia); Robyn Stargatt, Ph.D. (School of Psychological Science, La Trobe University, Melbourne, Australia, and Child Neuropsychology Research Group, Murdoch Childrens Research Institute, Melbourne, Australia); Suzette Sheppard, B.Sc., Gillian Ormond, M.Sc., and Penelope Hartmann, B.Psych. (Hons.) (Department of Anaesthesia and Pain Management, Murdoch Childrens Research Institute, Melbourne, Australia); Philip Ragg, M.B.B.S. (Department of Anaesthesia and Pain Management, The Royal Children's Hospital, Melbourne, Australia); Marie Backstrom, R.N.Cert. (Department of Anaesthesia, Monash Medical Centre, Melbourne, Australia); David Costi, B.M.B.S. (Department of Paediatric Anaesthesia, Women's and Children's Hospital, Adelaide, Australia); Britta S. von Ungern-Sternberg, M.D., Ph.D. (Department of Anaesthesia and Pain Management, Princess Margaret Hospital for Children, Perth, Australia, and Pharmacology, Pharmacy and Anaesthesiology Unit, School of Medicine and Pharmacology, The University of Western Australia, Perth, Australia). New Zealand: Niall Wilton, M.R.C.P., and Graham Knottenbelt, M.B.B.C.H. (Department of Paediatric Anaesthesia and Operating Rooms, Starship Children's Hospital, Auckland, New Zealand). Italy: Nicola Disma, M.D., Giovanni Montobbio, M.D., Leila Mameli, M.D., Pietro Tuo, M.D., and Gaia Giribaldi, M.D. (Department of Anesthesia, Istituto Giannina Gaslini, Genoa, Italy); Alessio Pini Prato, M.D. (Department of Pediatric Surgery, Istituto Giannina Gaslini, Genoa, Italy); Girolamo Mattioli, M.D. (DINOGMI Department, University of Genoa, Genoa, Italy); Andrea Wolfler, M.D., Francesca Izzo, M.D., and Ida Salvo, M.D. (Department of Anesthesiology and Paediatric Intensive Care, Ospedale Pediatrico "Vittore Buzzi," Milan, Italy); Valter Sonzogni, M.D., Bruno Guido Locatelli, M.D., and Magda Khotcholava, M.D. (Department of Anaesthesia, Ospedale Papa Giovanni XXIII, Bergamo, Italy). The Netherlands: Jurgen C. de Graaff, M.D., Ph.D., Jose T. D. G. van Gool, R.N., Sandra C. Numan, M.Sc., and Cor J. Kalkman, M.D., Ph.D. (Department of Anesthesiology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, The Netherlands); J. H. M. Hagenaars, B.Sc., Anthony R. Absalom, M.B.Ch.B., F.R.C.A., M.D., Frouckje M. Hoekstra, M.D., and Martin J. Volkers, M.D. (Department of Anesthesiology, University Medical Center Groningen, Groningen University, Groningen, The Netherlands). Canada: Davinia E. Withington, B.M. (Department of Anesthesia, Montreal Children's Hospital, Montreal, Canada, and McGill University, Montreal, Canada); Koto Furue, M.D. (Département d'Anesthésie, Centre Hospitalier Universitaire Sainte-Justine, Montreal, Canada); Josee Gaudreault, M.Sc.A. (Department of Anesthesia, Montreal Children's Hospital, Montreal, Canada). United States: Mary Ellen McCann, M.D., Charles Berde, M.D., Sulpicio Soriano, M.D., Vanessa Young, R.N., B.A., Navil Sethna, M.D., Pete Kovatsis, M.D., and Joseph P. Cravero, M.D. (Department of Anesthesiology, Perioperative, and Pain Medicine, Children's Hospital Boston, Boston, Massachusetts); David Bellinger, Ph.D., and Jacki Marmor, M.Ed. (Department of Neurology, Children's Hospital Boston, Boston, Massachusetts); Anne Lynn, M.D., Iskra Ivanova, M.D., Agnes Hunyady, M.D., and Shilpa Verma, M.D. (Department of Anesthesia and Pain Medicine, University of Washington, Seattle, Washington, and Department of Anesthesia and Pain Medicine, Seattle Children's Hospital, Seattle, Washington); David Polaner, M.D., F.A.A.P. (Department of Anesthesiology, Children's Hospital Colorado, Denver, Colorado, and Department of Anesthesiology, University of Colorado, Denver, Colorado); Joss Thomas, M.D., Martin Meuller, M.D., and Denisa Haret, M.D. (Department of Anesthesia, The University of Iowa Hospitals and Clinics, Iowa City, Iowa); Peter Szmuk, M.D., Jeffery Steiner, D.O., and Brian Kravitz, M.D. (Department of Anesthesiology, Children's Medical Center Dallas, Dallas, Texas, and Department of Anesthesiology, University of Texas Southwestern Medical Center, Dallas, Texas, and Children's Medical Center at Dallas and Outcome Research Consortium, Dallas, Texas); Santhanam Suresh, M.D. (Department of Pediatric Anesthesiology, Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University, Chicago, Illinois); Stephen R. Hays, M.D. (Department of Pediatric Anesthesia, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, Tennessee); Andreas H. Taenzer, M.D., M.S. (Department of Anesthesiology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire); Lynne G. Maxwell, M.D. (Department of Anesthesiology and Critical Care Children's Hospital of Philadelphia, Philadelphia, Pennsylvania); Robert K. Williams, M.D. (Department of Anesthesia and Pediatrics, College of Medicine, University of Vermont, Vermont Children's Hospital, Burlington, Vermont). United Kingdom: Neil S.

Morton, M.D., F.R.C.A. (Academic Unit of Anaesthesia, Pain, and Critical Care, University of Glasgow, Glasgow, United Kingdom and Department of Anaesthesia, Royal Hospital for Sick Children, Glasgow, United Kingdom); Graham T. Bell, M.B.Ch.B. (Department of Anaesthesia, Royal Hospital for Sick Children, Glasgow, United Kingdom); Liam Dorris, D.Clin.Psy., and Claire Adey, M.A.(Hons.) (Fraser of Allander Unit, Royal Hospital for Sick Children, Glasgow, United Kingdom); Oliver Bagshaw, M.B.Ch.B., F.R.C.A., F.F.I.C.M. (Department of Anaesthesia, Birmingham Children's Hospital, Birmingham, United Kingdom); Anthony Chisakuta, B.Sc. (H.B.), M.B.Ch.B., M.Sc., M.M.E.D.Sc., F.F.A.R.C.S.I. (Department of Anaesthetics, Royal Belfast Hospital for Sick Children, Belfast, United Kingdom); Ayman Eissa, M.D. (Anaesthetic Department, Sheffield Children's Hospital, Sheffield, United Kingdom); Peter Stoddart, M.B.B.S., B.Sc., M.R.C.P. (United Kingdom), F.R.C.A. (Department of Paediatric Anaesthesia, Bristol Royal Hospital for Children, Bristol, United Kingdom); Annette Davis, M.B.Ch.B., F.R.C.A. (Department of Anaesthesia, Pain Relief and Sedation, Alder Hey Childrens' NHS Foundation Trust, Liverpool, United Kingdom). Trial Steering Committee: Prof Paul Myles (chair); Members—Andrew J. Davidson, Mary Ellen McCann, Neil S. Morton, Nicola Disma, Davinia E. Withington, Jurgen C. de Graaff, Geoff Frawley, Rodney W. Hunt, David Bellinger, Charles Berde, Andy Wolf, Neil McIntosh, John Carlin, and Kate Leslie. Attendees: Gillian Ormond, Pollyanna Hardy, Sarah J. Arnup, Robyn Stargatt, Suzette Sheppard, and Katherine Lee. Data Monitoring Committee: Jonathan de Lima (chair), Greg Hammer, David Field, Val Gebski, and Dick Tibboel.