Apnea after Awake Regional and General Anesthesia in Infants

The General Anesthesia Compared to Spinal Anesthesia Study—Comparing Apnea and Neurodevelopmental Outcomes, a Randomized Controlled Trial

Andrew J. Davidson, M.D., Neil S. Morton, M.D., F.R.C.A., Sarah J. Arnup, M.Biostat., Jurgen C. de Graaff, Ph.D., Nicola Disma, M.D., Davinia E. Withington, B.M., Geoff Frawley, M.B.B.S., Rodney W. Hunt, Ph.D., Pollyanna Hardy, M.Sc., Magda Khotcholava, M.D., Britta S. von Ungern Sternberg, Ph.D., Niall Wilton, M.B.B.S., Pietro Tuo, M.D., Ida Salvo, M.D., Gillian Ormond, M.Sc., Robyn Stargatt, Ph.D., Bruno Guido Locatelli, M.D., Mary Ellen McCann, M.D.; the General Anesthesia compared to Spinal anesthesia (GAS) Consortium*

ABSTRACT

Background: Postoperative apnea is a complication in young infants. Awake regional anesthesia (RA) may reduce the risk; however, the evidence is weak. The General Anesthesia compared to Spinal anesthesia study is a randomized, controlled trial designed to assess the influence of general anesthesia (GA) on neurodevelopment. A secondary aim is to compare rates of apnea after anesthesia.

Methods: Infants aged 60 weeks or younger, postmenstrual age scheduled for inguinal herniorrhaphy, were randomized to RA or GA. Exclusion criteria included risk factors for adverse neurodevelopmental outcome and infants born less than 26 weeks gestation. The primary outcome of this analysis was any observed apnea up to 12 h postoperatively. Apnea assessment was unblinded.

Results: Three hundred sixty-three patients were assigned to RA and 359 to GA. Overall, the incidence of apnea (0 to 12 h) was similar between arms (3% in RA and 4% in GA arms; odds ratio [OR], 0.63; 95% CI, 0.31 to 1.30, $P = 0.2133$); however, the incidence of early apnea (0 to 30 min) was lower in the RA arm (1 *vs.* 3%; OR, 0.20; 95% CI, 0.05 to 0.91; $P = 0.0367$). The incidence of late apnea (30 min to 12 h) was 2% in both RA and GA arms (OR, 1.17; 95% CI, 0.41 to 3.33; $P = 0.7688$). The strongest predictor of apnea was prematurity (OR, 21.87; 95% CI, 4.38 to 109.24), and 96% of infants with apnea were premature.

Conclusions: RA in infants undergoing inguinal herniorrhaphy reduces apnea in the early postoperative period. Cardiorespiratory monitoring should be used for all ex-premature infants. **(Anesthesiology 2015; 123:38-54)**

POSTOPERATIVE apnea is a complication in young infants; the risk being greater in neonates who were premature.[1–3] Reducing the risk of apnea and identifying infants at risk of apnea may reduce morbidity and guide clinicians on the optimal age for surgery and the length and intensity of postoperative observation. Spinal anesthesia is a technique that may reduce the risk of apnea. Three small trials comparing spinal and general anesthesia (GA) have reported a reduced risk of apnea in high-risk infants receiving spinal anesthesia.[1,4,5] These studies are difficult to interpret because of small numbers, different ways of defining

What We Already Know about This Topic

- Whether awake regional anesthesia reduces the risk of apnea compared to general anesthesia in infants is unclear

What This Article Tells Us That Is New

- In a secondary analysis of over 700 infants less than 60 weeks postmenstrual age randomized to regional or general anesthesia for inguinal herniorrhaphy, there was no difference in the incidence apnea in the first 12 postoperative hours (primary outcome measure), although early apnea in the first 30 min was less with regional

This article is featured in "This Month in Anesthesiology," page 1A. Corresponding article on page 15.

Submitted for publication September 1, 2014. Accepted for publication February 14, 2015. From the Anaesthesia and Pain Management Research Group, Murdoch Childrens Research Institute, Melbourne, Victoria, Australia (A.J.D., G.F., G.O.); Department of Anaesthesia and Pain Management, The Royal Children's Hospital, Melbourne, Victoria, Australia (A.J.D., G.F.); Department of Paediatrics, University of Melbourne, Melbourne, Victoria, Australia (A.J.D., G.F., R.W.H.); Academic Unit of Anaesthesia, Pain and Critical Care, University of Glasgow, Glasgow, United Kingdom (N.S.M.); Department of Anaesthesia, Royal Hospital for Sick Children, Glasgow, United Kingdom (N.S.M.); Clinical Epidemiology and Biostatistics Unit, Murdoch Childrens Research Institute, Melbourne, Victoria, Australia (S.J.A.); Department of Anaesthesia, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands (J.C.d.G.); Department of Anesthesia, Istituto Giannina Gaslini, Genoa, Italy (N.D., P.T.); Department of Anaesthesia, Montreal Children's Hospital, Montreal, Quebec, Canada (D.E.W.); Department of Anesthesia, McGill University, Montreal, Quebec, Canada (D.E.W.); Department of Neonatal Medicine, The Royal Children's Hospital, Melbourne, Victoria, Australia (R.W.H.); Neonatal Research Group, Murdoch Childrens Research Institute, Melbourne, Victoria, Australia (R.W.H.);

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

 Anesthesiology 2015; 123:38-54

and identifying apnea, and different GA agents used.[6] A 2003 Cochrane review called for a large, well-designed randomized trial to address this issue.[7]

The General Anesthesia compared to Spinal anesthesia (GAS) study, comparing apnea and neurodevelopmental outcomes, is a prospective randomized trial where 722 infants undergoing inguinal herniorrhaphy were randomized to regional anesthesia (RA) or GA. The trial was designed primarily to address the long-term effect of GA on the developing brain with the primary outcome being neurodevelopmental outcome at 5 yr. An important secondary aim of the GAS study is to compare the immediate postoperative benefits of RA with GA, in particular, reduction in apnea. This article compares the incidence of apnea in each group and identifies other factors associated with apnea; specifically, we hypothesized that RA would reduce the risk of apnea. Other short-term outcomes in each group are also described.

Materials and Methods

Study Design and Participants

In a multinational prospective randomized trial with 2 parallel arms, we enrolled patients in 7 countries and 28 sites (table 1). Institutional review board or human research ethics committee approval was obtained for each site, and written informed consent was obtained from parents or guardians. Eligibility criteria included infants up to 60 weeks postmenstrual age (PMA) scheduled for unilateral or bilateral inguinal herniorrhaphy (with or without circumcision) born at greater than 26 weeks gestation. Exclusion criteria included any contraindication for either anesthetic technique, a history of congenital heart disease requiring surgery or pharmacotherapy, mechanical ventilation immediately before surgery, known chromosomal abnormalities or other known acquired or congenital abnormalities that might affect neurodevelopment, previous exposure to volatile GA or benzodiazepines as a neonate or in the third trimester *in utero*, any known neurologic injury such as cystic periventricular leukomalacia or grade 3 or 4 intraventricular hemorrhage, any social or geographic factor that may make follow-up difficult, or having a primary language at home where neurodevelopmental tests are not available. Eligible infants were identified from operating room schedules or at preadmission clinics and recruited in the clinic or in the preadmission areas of the operating floor.

The GAS study is registered in Australia and New Zealand at ANZCTR: ACTRN12606000441516 first registered on October 16, 2006, principal investigators: Andrew Davidson, Mary Ellen McCann, and Neil Morton; in the United States at ClinicalTrials.gov: NCT00756600 first registered on September 18, 2008, principal investigators: Andrew Davidson, Mary Ellen McCann, and Neil Morton; and in the United Kingdom at UK Clinical Research Network: 6635 (International Standard Randomised Controlled Trial Number, 12437565; Multi-Centre Research Ethics Committee No, 07/S0709/20), principal investigator: Neil Morton. The protocol for the GAS study has been previously published by *The Lancet*.[8]

Randomization and Blinding

A 24-h web-based randomization service was managed by The Data Management & Analysis Centre, Department of Public Health, University of Adelaide, South Australia. Children were randomized with a 1:1 allocation ratio to either RA or GA. Randomization was in random permuted 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 and more. The anesthesiologist, surgeon, and nurses in the postoperative care units were aware of group allocation; therefore, the study was unblinded for type of anesthetic given.

Procedures

The RA arm received regional nerve blocks: spinal alone, spinal with caudal, spinal with ilioinguinal, or caudal alone. The local anesthetic used was bupivacaine or levobupivacaine. In addition, some patients received caudal chloroprocaine intraoperatively to prolong the block. The type of regional technique and the local anesthetic used were at the discretion of the anesthesiologist. In the RA arm, all forms of sedation or GA were avoided if possible; however, if any sedation or GA was required, this was regarded as a protocol violation. Oral sucrose drops were permitted in the RA arm and paracetamol in both arms. The GA arm received sevoflurane for induction and maintenance in an air/oxygen mixture along with nerve blockade with caudal or ilioinguinal bupivacaine or levobupivacaine. The form of airway support and use of neuromuscular-blocking agents was at the discretion of the anesthesiologist. No opioids or nitrous oxide was allowed intraoperatively. Blood pressure, heart rate, oxygen saturation, and temperature were recorded every 5 min intraoperatively.

Postoperatively children were observed closely and constantly by the research assistant for at least the first hour or until discharge if discharged before 1 h. The research assistant was a nurse, scientist, or physician. All were trained to detect apnea and familiar with the definition of a significant

National Perinatal Epidemiology Unit, Clinical Trials Unit, University of Oxford, Oxford, United Kingdom (P.H.); Department of Anaesthesia, Ospedale Papa Giovanni XXIII, Bergamo, Italy (M.K., B.G.L.); Pharmacology, Pharmacy, Anaesthesiology Unit, School of Medicine and Pharmacology, The University of Western Australia, Perth, Western Australia, Australia (B.S.v.U.S.); Department of Anaesthesia and Pain Management, Princess Margaret Hospital for Children, Perth, Western Australia, Australia (B.S.v.U.S.); Department of Paediatric Anaesthesia and Operating Rooms, Starship Children's Hospital, Auckland District Health Board, Auckland, New Zealand (N.W.); Department of Anesthesiology and Paediatric Intensive Care, Ospedale Pediatrico Vittore Buzzi, Milan, Italy (I.S.); School of Psychology and Public Health, Department of Psychology and Counselling, La Trobe University, Melbourne, Victoria, Australia (R.S.); Child Neuropsychology, Murdoch Childrens Research Institute, Melbourne, Victoria, Australia (R.S.); and Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts (M.E.M.).

Table 1. Randomization by Site

Country	Site	Allocated to RA	Allocated to GA
Australia	Royal Children's Hospital Melbourne	57	58
	Monash Medical Centre, Melbourne*	26	25
	Princess Margaret Hospital for Children, Perth	16	15
	Women's and Children's Hospital, Adelaide	6	5
Italy	Istituto Giannina Gaslini, Genoa	42	39
	Ospedale Vittore Buzzi, Milan	25	23
	Ospedale Papa Giovanni XXIII, Bergamo	18	20
United States	Boston Children's Hospital, Boston	29	31
	Seattle Children's Hospital, Seattle	11	14
	Children's Hospital Colorado, Denver	9	9
	University of Iowa Hospital, Iowa	8	8
	Children's Medical Center, Dallas	7	7
	Anne and Robert H. Lurie Children's Memorial Hospital, Chicago	2	3
	Dartmouth Hitchcock Medical Center, Lebanon	2	2
	Vanderbilt University Medical Center, Nashville	1	2
	Children's Hospital of Philadelphia, Philadelphia	1	1
	The University of Vermont/Fletcher Allen Health Care, Burlington	1	0
United Kingdom	Royal Hospital for Sick Children, Glasgow	27	25
	Birmingham Children's Hospital, Birmingham	7	6
	Sheffield Children's Hospital, Sheffield	5	4
	Bristol Royal Hospital for Children, Bristol	2	2
	Royal Belfast Hospital for Sick Children, Belfast	2	2
	Royal Liverpool Children's Hospital Alder Hey, Liverpool	1	1
Canada	Montreal Children's Hospital, Quebec	21	21
	CHU Sainte-Justine, Quebec	3	5
The Netherlands	Wilhelmina Children's Hospital, University Medical Center Utrecht	15	14
	University Medical Center Groningen	6	5
New Zealand	Starship Children's Hospital, Auckland	13	12

* Including Casey hospital.
GA = general anesthesia; RA = regional anesthesia.

apnea. Electronic monitoring and the alarm settings on monitors were not standardized. During this period, any apnea was noted. Respiratory support and oxygen saturation were also recorded every 5 min. After the first hour, children were observed as per the usual routine at each hospital. The level of observation and monitoring was not standardized beyond the first hour. Hospital records were reviewed to identify apnea events. The management and significance of any apnea during this period was determined from the hospital record. Hemoglobin was measured either preoperatively or during anesthesia. Intraoperative end-tidal carbon dioxide is not reported as it is not an accurate measure of arterial carbon dioxide in the presence of large leaks around the tracheal tube or face mask.

The prespecified primary outcome for this analysis was observed apnea within 12 h of surgery or until discharge. Apnea was defined as a pause in breathing for more than 15 s or more than 10 s if associated with oxygen saturation less than 80% or bradycardia (20% decrease in heart rate). Early apnea was defined *a priori* as an apnea occurring within the first 30 min postoperatively in the postanesthesia care unit (PACU), and late apnea was defined as an observed apnea occurring between 30 min and 12 h postoperatively. A *post hoc* sensitivity analysis was also performed describing late apnea where children were excluded if discharged before 12 h. Level of intervention for postoperative apnea, methylxanthine administration, and other respiratory complications were also noted. A significant intervention was defined *a priori* as any intervention greater than simple tactile stimulation and included providing oxygen by mask (with or without positive pressure ventilation) or cardiopulmonary resuscitation with external chest compressions.

Statistical Analysis

Sample Size Considerations. The sample size for the GAS study was based on the 5-yr neurodevelopmental outcome; the 5 yr follow-up Wechsler Preschool and Primary Scale of Intelligence, Third Edition, full-scale intelligence quotient score, a standardized score with mean 100 and SD 15. Assuming an expected difference of one standardized score point and a 90% chance that a 95% CI will exclude a difference of more than five (the largest difference acceptable to demonstrate equivalence), the trial needed 598 infants in total. Enrolling approximately 720 allowed for 10% loss to follow-up and 10% with a major protocol violation.

Given that this article presents data on a secondary aim of the trial, an *a priori* power calculation was not conducted for these secondary outcomes. In line with Consolidated

Standards of Reporting Trials recommendations, we do not believe that *post hoc* power calculations are useful, and instead, we present our results along with CIs, which capture the uncertainty in our findings that reflect the sample size. During recruitment, a Data Monitoring Committee met at planned 6 mo intervals. Summary data by allocation were presented to the Data Monitoring Committee, and no formal group comparisons were performed.

Analysis Populations. The primary analysis for apnea included participants as randomized, excluding participants who withdrew consent or were randomized after surgery. Although the future neurodevelopmental outcomes are to be based on an equivalence design, the apnea data are analyzed as a superiority design. This analysis is reported as intention to treat (ITT). A secondary analysis was performed as per-protocol (APP), which excludes cases where surgery was cancelled, and in the RA arm, any child who received any sevoflurane or sedative medication.

Partial GA/sedation is defined as those in the RA group who received sevoflurane for only some of the surgery or received some other sedative medication during surgery. Full GA is defined as receiving sevoflurane from before knife to skin to the end of surgery.

Data Analysis. The unit of analysis is the participant. Apnea outcomes were analyzed if a participant is recorded as having at least one event. Categorical data are summarized using counts and percentages, and continuous data are summarized using means (SD) or medians (interquartile range). For binary outcomes, a comparison between arms is presented as an odds ratio (OR) as estimated from a logistic regression model. For continuous outcomes, a comparison between arms 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. Any missing data were not explored because the percentage of missing data was less than 5% for all outcomes. Descriptive analyzes were performed on prespecified subgroups. All outcomes were adjusted for (1) stratified gestational age at birth as a fixed effect and (2) site of randomization using the generalized estimating equation approach with robust SEs.[9,10] Sites with less than 20 randomized infants were combined as a single site in the model. An exchangeable correlation structure was assumed between any two children from the same site.

The early and late apnea outcomes were modeled together by including an additional fixed time effect (early or late time) and a fixed interaction between time and study arm. Because the generalized estimating equation approach only allows for one level of clustering, we tested two different exchangeable correlation structures for this model: (1) first, we accounted for the correlation between two apnea outcomes taken from the same child and (2) second, between outcomes from any two children from the same site. Because almost no difference was observed in the results from the two correlation structures, we show results from the second approach, so that the same correlation structure is used for all presented analyses. We judged that the interaction term provided sufficient evidence ($P = 0.03$ for ITT analysis and $P = 0.09$ for APP analysis) to present the effect of the study arm separately for early and late apnea, given the study was not powered to make this comparison.

The predictors of apnea were identified by constructing a logistic regression model adjusted for site of randomization using the generalized estimating equation approach as described in Data Analysis and including allocated study arm as a covariate. An interaction between time and covariate was included for the combined analysis of the early and late apnea outcomes.

When presenting these results to peers, we have been specifically asked for the risk reduction between RA and GA for term and ex-premature infants; thus, we also present a post hoc analysis calculating the absolute risk reduction (ARR) in term and ex-premature infants (less than 37 weeks gestational age at birth). The association between early and late apnea was assessed by constructing a logistic regression model adjusted for site of randomization using the generalized estimating equation approach as described earlier and including allocated study arm and stratified gestational age at birth as covariates. All analyses were carried out using Stata 13 (Stata Corp LP., USA).

Results

Seven hundred twenty-two infants were recruited into the trial between February 9, 2007, and January 31, 2013. Three were withdrawn from analysis. For the ITT analysis, 361 were in the RA arm and 358 in the GA arm (fig. 1). Baseline, demographic, anesthetic, and surgical data are summarized in table 2. There were 394 premature infants and 325 term infants. Outcome data are missing for five RA cases and two GA cases because surgery was cancelled and one RA case because no data were collected. In the RA arm, 70 had a protocol violation involving exposure to sevoflurane or sedation. Thus, for the APP analysis, 286 were in the RA arm and 356 in the GA arm (RA, 355 and GA, 356 in the ITT analysis).

Twenty-five participants (3%; 10 in the RA and 15 in the GA arm) were recorded as having at least one apnea. Most apnea occurred in the early postoperative period (fig. 2), especially in the GA group. Most infants with apnea had a single event; however, one infant had 18 events. The proportions of infants with apnea-related outcomes in each group are presented in table 3 and the adjusted ORs for those outcomes in table 4. There was little evidence that allocation to RA or GA altered the odds of apnea in the overall period up to 12 h after surgery (OR, 0.63 with 95% CI, 0.31 to 1.30, $P = 0.2133$ by ITT). However, for early apnea, there was evidence that the odds of apnea were less in the RA arm (OR, 0.20; 95% CI, 0.05 to 0.91; $P = 0.0367$ by ITT). The odds for needing a significant intervention for early apnea were also less in the RA arm (OR, 0.09; 95% CI, 0.01 to 0.64; $P = 0.0164$). These

effects were seen for both ITT and APP analyses, the effects being greater in the APP analysis. The level of intervention for apnea was also less in the RA arm (table 5). Of the infants with postoperative apnea, 86% in the GA arm and 50% in the RA arm received an intervention as tactile stimulation, supplemental oxygen, bag mask ventilation, or CPR to treat apnea. Details of the nine (1.3%) children requiring the positive pressure ventilation or cardiopulmonary resuscitation within 5 days of surgery are shown in table 6. Of these nine children, six children who had this event within 30 min of surgery were in the GA arm (1.7% of the GA arm). However, 2 infants in the RA group did not have apnea in PACU, yet experienced multiple apneic episodes starting 6 to 7 h postoperatively on the inpatient ward, which was treated with continuous positive airway pressure or bag and mask ventilation with transfer to intensive care.

A brief exposure to anesthesia or sedation in the RA arm was not observed to increase apnea incidence; however, if a full GA was administered, the risk of apnea approached the risk associated with a planned GA (table 3).

The apnea rate was relatively low, and this is reflected in a low ARR. In all infants, the ARR for early apnea with allocation to RA was 0.03 (95% CI, 0.004 to 0.05). In preterm infants, the ARR for early apnea with allocation to RA was 0.04 (95% CI, 0.004 to 0.08), and in term infants, the ARR for early apnea with allocation to RA was 0.006 (95% CI, −0.006 to 0.02).

Characteristics of infants who had early and late apnea are listed in table 7 along with logistic regression models for determining the factors associated with apnea (table 8). Indeed all apnea occurred in ex-premature infants except one case. This one infant was born at 37 weeks and 1 day, had an unremarkable history, had a general anesthetic at approximately 44 weeks PMA, and two apneas 20 min postoperatively that responded to gentle stimulation. Thus, the incidence of apnea among preterm infants was 6.1% compared with 0.3% in term infants. After adjusting for group allocation, there was evidence for an association between apnea and the following risk factors: prematurity, decreasing gestational age at birth, decreasing weight, decreasing PMA, a history of recent apnea, ever receiving methylxanthine, ever receiving ventilation through a tracheal tube, and ever needing oxygen support. Factors associated with late apnea were similar. Factors associated with early apnea were also similar, albeit with less evidence for an association with a history of recent apnea or ever requiring ventilation with a

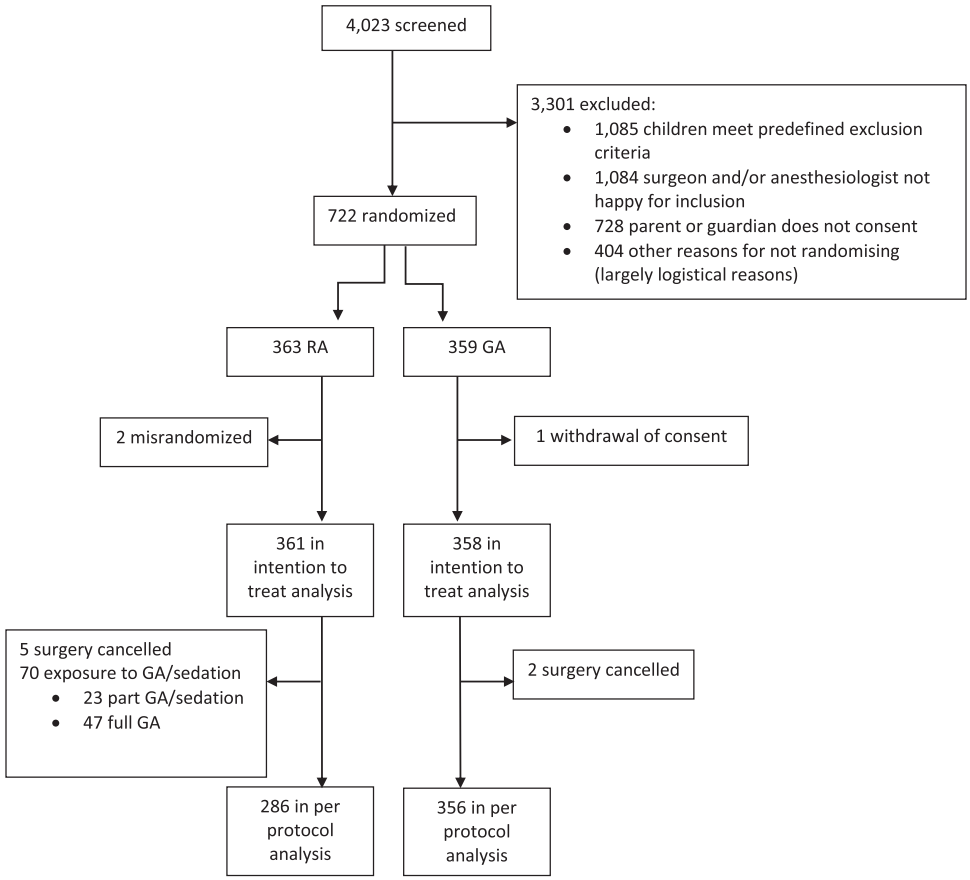

Fig. 1. Consort flow diagram. Of the 70 protocol violations in the RA arm, 10 infants had a full GA with no awake regional attempted, 37 had a full GA after complete block failure, and 23 infants had a partly successful block requiring a short period of GA or sedation. Participants who withdrew consent (n = 1) or were randomized after surgery (n = 2) were excluded from intention-to-treat analyses. GA = general anesthesia; RA = regional anesthesia.

Table 2. Baseline, Demographic, Anesthetic, and Surgical Data

Demographics	RA Arm as Intention to Treat (N = 361)	GA Arm as Intention to Treat (N = 358)	RA Arm as per Protocol (N = 286)
Male, n (%)	294 (82)	306 (85)	231 (81)
Gestational age at birth (wk), mean (SD)	35.5 (4.1)	35.5 (3.9)	35.5 (4.1)
Premature (born <37 weeks gestation), n (%)	198 (55)	196 (55)	160 (56)
Chronological age at surgery (wk), mean (SD)	10.0 (4.5)	10.1 (4.5)	9.8 (4.4)
Postmenstrual age at surgery (wk), mean (SD)	45.5 (4.7)	45.6 (4.6)	45.3 (4.6)
Birth weight (kg)	2.4 (0.9)	2.3 (0.9)	2.3 (0.9)
Weight at time of surgery (kg), mean (SD)	4.2 (1.1)	4.3 (1.1)	4.2 (1.1)
Median Apgar at 1 min	9 (7–9)	9 (7–9)	9 (7–9)
Median Apgar at 5 min	9 (9–10)	9 (9–10)	9 (9–10)
One of multiple pregnancy, n (%)	62 (17)	62 (17)	52 (18)
Child ever discharged from hospital, n (%)	332 (93)	336 (94)	266 (93)
Smoker in the household, n (%)	104 (29)	115 (32)	83 (29)
Ever treated with CPAP, n (%)	91 (25)	90 (25)	70 (24)
Ever treated with a methylxanthine, n (%)	60 (17)	54 (15)	49 (17)
Ever ventilated with a tracheal tube, n (%)	47 (13)	45 (13)	37 (13)
Ever required supplemental oxygen (apart from at birth), n (%)	95 (26)	81 (23)	76 (27)
Supplemental oxygen immediately before surgery, n (%)	6 (2)	6 (2)	4 (1)
Electronic monitoring for apnea in previous 24 h, n (%)	17 (5)	17 (5)	13 (5)
Observed apnea previous 24 h, n (%)	6 (2)	8 (2)	6 (2)
Fasting time (min), mean (SD)	368.2 (146.4)	367.3 (155.1)	370.7 (152.6)
Preoperative intravenous fluid, n (%)	46 (13)	45 (13)	36 (13)
Hemoglobin (g/100 ml), mean (SD)	10.3 (2.1)	10.2 (2.0)	10.3 (2.0)
Baseline oxygen saturation, median (IQR)	99 (98–100)	99 (98–100)	99 (98–100)
Baseline heart rate, mean (SD)	152.4 (19.7)	149.9 (16.3)	153.4 (19.9)
Surgical details, n (%)			
Bilateral hernia exploration/repair	162 (46)	161 (45)	127 (44)
Anesthesia details, n (%)			
Suxamethonium given	0	1 (<1)	0
Nondepolarizing neuromuscular blocker given	20 (6)	125 (35)	0
Spinal without caudal*	222 (64)	0	193 (67)
Caudal without spinal*	7 (2)	332 (93)	4 (1)
Caudal plus spinal*	117 (34)	0	89 (31)
Ilioinguinal block	3 (1)	16 (4)	2 (1)
Field bock	51 (14)	40 (11)	36 (13)
Laryngeal mask airway used	7 (2)	60 (17)	0
Tracheal tube used	40 (11)	281 (79)	0
Details of monitoring for apnea for all of the first 30 min postoperatively, n (%)			
Pulse oximetry	319 (90)	314 (88)	254 (82)
ECG	124 (35)	111 (31)	89 (31)
Respiratory rate monitor	123 (35)	128 (36)	91 (32)
Pneumograph	6 (2)	7 (2)	4 (1)

Data are presented as mean (SD), median (interquartile range), or frequencies (%) of nonmissing data.

* Note these data refer to all cases where the listed blocks were attempted before start of surgery whether the blocks were effective or not. GA as per-protocol data are not presented as only two children in the GA arm had surgery cancelled, so the data are very similar to the intention-to-treat data.

CPAP = continuous positive airway pressure; ECG = electrocardiogram; GA = general anesthesia; IQR = interquartile range; RA = regional anesthesia.

tracheal tube. The strongest risk factor for apnea was a history of prematurity (OR, 21.87; 95% CI, 4.38 to 109.24). In appropriate subpopulations, there was no evidence for an association between intraoperative use of tracheal tube or neuromuscular-blocking agent and apnea (tables 9 and10).

Early apnea was also a strong predictor of late apnea. In a model with late apnea as the outcome and including gestational age and type of anesthetic, the ORs for early apnea were 24.21 (95% CI, 5.88 to 99.66, $P < 0.0001$) for the ITT analysis and 46.52 (95% CI, 7.71 to 280.59, $P < 0.0001$) for APP analysis. For the APP analysis, of the 13 children who had late apnea, only 5 had an early apnea, giving a low sensitivity of 0.38. Although early apnea is a strong predictor of late apnea, it is not a sensitive measure for late apnea.

Other outcome data are shown in table 11. Anesthesia time was shorter in the RA arm (51 *vs.* 66 min) with little evidence for any difference in surgical times (28 min each). Infants randomized to RA had a substantially greater mean

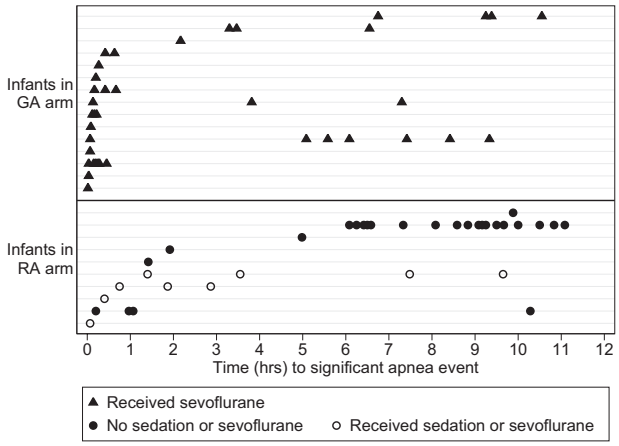

Fig. 2. Time to apnoea events in RA and GA. Times of all apnoea events in all infants in RA and GA allocated groups with RA group further divided into those with no sedation or sevoflurane (*closed circles*) and those exposed to sevoflurane or sedation (*closed squares*). Each *horizontal dashed line* represents one infant. GA = general anesthesia; RA = regional anesthesia.

minimum systolic blood pressure (70.7 *vs.* 54.8 mmHg) and were less likely to need an intervention for hypotension during anesthesia (7 *vs.* 19%). Infants randomized to RA had a slightly higher minimum intraoperative heart rate (133.9 *vs.* 127.6 beats per min) and were slightly warmer (36.1° *vs.* 36.0°C). Infants randomized to RA were less likely to have a significant oxygen desaturation postoperatively (1 *vs.* 4%) and slightly shorter times to first feed (31 *vs.* 36 min). Approximately 20% of children were discharged before 12 h; discharge times were similar in each arm (table 12).

Discussion

In this trial, there was no evidence that RA reduced the overall risk of observed apnea. In subgroup analyses, RA did reduce the risk of early postoperative apnea; however, there was no evidence that RA reduced the risk of late apnea. RA also reduced the degree of postoperative oxygen desaturation and the level of intervention for apnea, implying that apnea after RA was not only less frequent but also of lesser clinical importance. However, overall the incidence of bedside intervention for postoperative apnea was appreciable by current standards of patient safety in pediatric anesthesia.[11–13] Infants in the GA arm also had lower minimum blood pressures intraoperatively. The strongest risk factor for apnea was prematurity.

Strengths of this trial include the size of the study, being multinational, and hence increasing external validity and the use of modern anesthetic agents. The trial does have a number of limitations. First, the GAS study was primarily designed to address the issue of potential neurotoxicity of GA. Exclusion criteria reflect this aim. The trial excluded infants born extremely premature and some infants with significant comorbidity. It is possible that benefits of RA and risk factors for apnea are different in these populations. Second, in this trial, we relied on staff and researchers to identify apnea. Apnea incidence depends on the type of monitoring used.[3] In our trial, few sites used impedance pneumography, and none used more sensitive techniques such as thermistry or capnography. It would not have been feasible to obtain and standardize this monitoring across all sites. Similarly, the infants were only constantly monitored for the first hour. After that, monitoring was as per routine or clinical judgment. Therefore, our results likely underestimate the true rate of apnea, especially late apnea. We are also unable to comment on apnea that occurred after discharge; thus, we performed a *post hoc* analysis for late apnea where we only included children who were not discharged before 12 h. Given the uncertainty surrounding the significance of brief apnea and the likelihood that our trial may

Table 3. Proportion of Children with Apnea-related Outcomes in Each Group

Outcome	Intention to Treat		As per Protocol—RA (N = 286)	RA to Partial GA/Sedation (N = 23)	RA to Full GA (N = 46)
	RA (N = 355)	GA (N = 356)			
Any apnea (0–12 h)	10 (3)	15 (4)	6 (2)	0	4 (9)
Any early apnea (0–30 min)	3 (1)	12 (3)	1 (<1)	0	2 (4)
Any late apnea (30 min–12 h)	8 (2)	7 (2)	6 (2)	0	2 (4)
Any late apnea if discharged ≥12 h postoperatively	8 (3)	6 (2)	6 (3)	0	2 (5)
Required significant intervention for apnea (0–5 d)*	7 (2)	18 (5)	4 (1)	0	3 (7)
Required significant intervention for apnea (0–30 min)*	1 (<1)	12 (3)	0	0	1 (2)
Required significant intervention for apnea (30 min–12 h)*	5 (1)	5 (1)	3 (1)	0	2 (4)
Required significant intervention for late apnea if discharged ≥12 h postoperatively	5 (2)	5 (2)	3 (1)	0	2 (5)
Required significant intervention for apnea after 12 h (12 h–5 d)*	2 (1)	4 (1)	2 (1)	0	0
Any caffeine administered postoperatively (0–5 d)	2 (1)	4 (1)	2 (1)	0	0

Data are presented as n (%) of nonmissing data. Partial GA/sedation is defined as receiving sevoflurane for only some of the surgery or receiving sedation. Full GA is defined as receiving sevoflurane from before knife to skin to the end of surgery.

* Significant intervention for apnea is any intervention greater than simple tactile stimulation. GA as per-protocol data are not presented as only two children in the GA arm had surgery cancelled, so the data are very similar to the intention-to-treat data.

GA = general anesthesia; RA = regional anesthesia.

Table 4. Odds Ratios for Apnea-related Outcomes in Regional Anesthesia Compared with General Anesthesia

	Intention to Treat		As per Protocol	
Outcome	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Any apnea (0–12 h)	0.63 (0.31–1.30)	0.2133	0.47 (0.17–1.32)	0.1518
Any early apnea (0–30 min)	0.20 (0.05–0.91)	0.0367	0.07 (0.01–0.84)	0.0359
Any late apnea (30 min–12 h)	1.17 (0.41–3.33)	0.7688	1.17 (0.44–3.14)	0.7521
Any apnea (30 min–12 h, if discharged ≥12 h postoperatively)	1.42 (0.53–3.79)	0.4857	1.46 (0.52–4.12)	0.4713
Any significant intervention for apnea (0–5 d)*	0.38 (0.21–0.69)	0.0016	0.25 (0.11–0.57)	0.0009
Any significant intervention for early apnea (0–30 min)*	0.09 (0.01–0.64)	0.0164	n/a	
Any significant intervention for late apnea (30 min–12 h)*†	1.00 (0.26–3.84)	0.9973	0.70 (0.18–2.67)	0.5979
Any significant intervention for apnea (30 min–12 h, if discharged ≥12 h postoperatively)	0.93 (0.23–3.73)	0.9237	0.73 (0.19–2.77)	0.6387
Any significant intervention for apnea after 12 h (12 h—5 d)*	0.51 (0.10–2.70)	0.4292	0.62 (0.12–3.27)	0.5741
Any caffeine for apnea (0–5 d)	0.45 (0.10–2.11)	0.3098	0.50 (0.09–2.77)	0.4255

* Significant intervention for apnea is any intervention greater than simple tactile stimulation. † Note that any significant intervention for late apnea in the as per-protocol analysis is modeled separately from early apnea, because there were no events in the RA arm for early apnea.

RA = regional anesthesia.

Table 5. Level of Intervention

	Intention to Treat		As per Protocol—RA, n (%)	RA to Partial GA/Sedation, n (%)	RA to Full GA, n (%)
Intervention	–RA, n (%)	GA, n (%)			
0–5 d	N = 18	N = 28	N = 11	N = 1	N = 6
Self-limiting	9 (50)	4 (14)	5 (45)	1 (100)	3 (50)
Tactile stimulation	2 (11)	6 (21)	2 (18)	0	0
Oxygen with no PPV	5 (28)	11 (39)	2 (18)	0	3 (50)
PPV, bag and mask, or CPAP	2 (11)	5 (18)	2 (18)	0	0
CPR	0	2 (7)	0	0	0
0–30 min	N = 7	N = 17	N = 2	N = 1	N = 4
Self-limiting	5 (71)	2 (12)	1 (50)	1 (100)	3 (75)
Tactile stimulation	1 (14)	3 (18)	1 (50)	0	0
Oxygen with no PPV	1 (14)	6 (35)	0	0	1 (25)
PPV, bag and mask, or CPAP	0	5 (29)	0	0	0
CPR	0	1 (6)	0	0	0
30 min–12 h	N = 15	N = 13	N = 11	N = 1	N = 3
Self-limiting	8 (53)	3 (23)	6 (55)	1 (100)	1 (33)
Tactile stimulation	2 (13)	5 (38)	2 (18)	0	0
Oxygen with no PPV	4 (27)	5 (38)	2 (18)	0	2 (67)
PPV, bag and mask, or CPAP	1 (7)	0	1 (9)	0	0
CPR	0	0	0	0	0
30 min–12 h*	N = 15	N = 12	N = 11	N = 1	N = 3
Self-limiting	8 (53)	3 (25)	6 (55)	1 (100)	1 (33)
Tactile stimulation	2 (13)	4 (33)	2 (18)	0	0
Oxygen with no PPV	4 (27)	5 (42)	2 (18)	0	2 (67)
PPV, bag and mask, or CPAP	1 (7)	0	1 (9)	0	0
CPR	0	0	0	0	0
12 h–5 d	N = 4	N = 6	N = 4	N = 0	N = 0
Self-limiting	1 (25)	2 (33)	1 (25)	0	0
Tactile stimulation	1 (25)	0	1 (25)	0	0
Oxygen with no PPV	1 (25)	3 (50)	1 (25)	0	0
PPV, bag and mask, or CPAP	1 (25)	0	1 (25)	0	0
CPR	0	1 (17)	0	0	0

These data include interventions for all events, including pauses in breathing that do not meet the criteria for apnea. Partial GA/sedation is defined as receiving sevoflurane for only some of the surgery or receiving sedation. Full GA is defined as receiving sevoflurane from before knife to skin to the end of surgery.

* The denominator in this group is restricted to those who were discharged ≥12 h.

CPAP = continuous positive airway pressure; CPR = cardiopulmonary resuscitation; GA = general anesthesia; PPV = positive pressure ventilation; RA = regional anesthesia.

Table 6. Details of Children Who Required Positive Pressure Ventilation and/or CPR for Postoperative Apnea

Child	Gestational Age at Birth (wk)	Postmenstrual Age at Surgery (wk)	Group Allocation	Relevant History	Description of Event
A	29.1	40.4	GA	Required 2 d CPAP after birth, uneventful anesthesia.	Brief apnea on arrival in PACU requiring stimulation, 10 min oxygen saturation was 74% with heart rate 80, brief CPR and adrenaline given twice, tracheal tube inserted, rapid reoxygenation and return of heart rate, tracheal tube removed 24 h later, normal ECG and cardiac echo. Discharged home 6 d after surgery.
B	33.1	49.0	GA	Was having apnea preoperatively, had 4 d with tracheal tube after birth and supplemental oxygen for 9 d. Uncomplicated anesthesia. No apnea in PACU. Four apnea on ward between 6 and 10 h after surgery—requiring no intervention, discharged home next day with apnea monitor.	Day 3 after discharge had an apnea at home and an aunt performed brief CPR. Full and rapid recovery. Paramedics not called and child not readmitted to hospital.
C	29.1	41.1	RA	Child never discharged from hospital, required 62 d CPAP after birth, no respiratory support before surgery, uneventful surgery, discharged back to NICU post surgery.	18 apneas, starting 6 h after surgery, some with oxygen saturation <50% requiring bag and mask positive pressure ventilation, transferred to a neonatal unit at another hospital and nasal CPAP commenced, treated for suspected sepsis, given caffeine, and discharged home 7 d after surgery.
D	29.0	39.6	GA	Child never discharged from hospital, required 8 d CPAP and 69 d supplemental oxygen after birth, no respiratory support before surgery, uneventful surgery.	Apnea shortly after arrival in PACU, treated with bag and mask positive pressure ventilation, transferred to PICU where had two further self-limiting apnea, discharged home 9 d after surgery.
E	31.9	37.0	GA	Unremarkable history. No previous requirement for respiratory support. Uncomplicated anesthesia.	Oxygen saturation 59 on arrival to PACU—given bag and mask positive pressure ventilation. No further apnea or complications.
F	30.0	39.7	RA	Required 42 d of CPAP after birth, no respiratory support preoperatively, uncomplicated spinal, several apneas intraoperatively, no apnea in recovery. Given tramadol before discharge from PACU.	Five apneas starting on the ward 7 h after surgery, transferred to NICU, 12 h after surgery further apnea and low oxygen saturation, given nasal CPAP and caffeine, discharged home 2 d after surgery, readmitted 2 wk later with bronchiolitis.
G	28.4	41.9	GA	Two days CPAP after birth, uneventful anesthesia.	Apnea on arrival in PACU requiring bag and mask positive pressure ventilation, no further apnea, discharged home next day.
H	34.9	53.4	GA	Uneventful postnatal period, uneventful anesthesia.	Apnea on arrival in PACU requiring bag and mask positive pressure ventilation, no further apnea, discharged home next day.
I	26.6	37.6	GA	Required 22 d CPAP after birth, uneventful anesthesia.	Six apneas in PACU requiring bag and mask positive pressure ventilation, given caffeine, discharged home 2 d after surgery.

Note for the entire study, the mean gestational age at birth was 35.4 weeks, and the mean postmenstrual age at surgery was 45.6 weeks.

CPAP = continuous positive airway pressure; CPR = cardiopulmonary resuscitation; ECG = electrocardiogram; GA = general anesthesia; NICU = neonatal intensive care unit; PACU = postanesthesia care unit; PICU = pediatric intensive care unit; PPV = positive pressure ventilation; RA = regional anesthesia.

Table 7. Summary Data of Children with and without Apnea

	ITT					APP				
	Any Apnea (0–12 h)	No Apnea	Early Apnea (0–30 min)	Late Apnea (30 min–12 h)	Late Apnea (30 min–12 h, if discharged ≥12 h postop)	Any Apnea (0–12 h)	No Apnea	Early Apnea (0–30 min)	Late Apnea (30 min–12 h)	Late Apnea (30 min–12 h, if discharged ≥12 h postop)
N	25	686	15	15	14	21	621	13	13	12
Regional anaesthesia, n (%)	10 (40)	345 (50)	3 (20)	8 (53)	8 (57)	6 (29)	280 (55)	1 (8)	6 (46)	6 (50)
Age (PMA) at surgery (wk)	41.2 (3.9)	45.7 (4.5)	41.5 (4.3)	40.6 (3.2)	40.3 (3.1)	41.1 (4.1)	45.7 (4.5)	41.4 (4.5)	40.6 (3.4)	40.3 (3.3)
Weight at surgery (kg)	3.3 (1.2)	4.3 (1.1)	3.6 (1.3)	3.1 (0.9)	3.0 (0.7)	3.4 (1.2)	4.3 (1.1)	3.7 (1.3)	3.2 (1.0)	3.0 (0.8)
Hemoglobin level (g/100 ml)	9.8 (1.2)	10.3 (2.0)	10.1 (1.8)	9.8 (2.0)	9.7 (2.0)	9.9 (1.8)	10.3 (2.0)	10.0 (1.8)	10.0 (1.9)	10.0 (2.0)
Gestational age at birth (wk)	30.8 (2.8)	35.7 (3.9)	31.4 (3.3)	31.0 (2.6)	30.6 (2.1)	31.1 (2.9)	35.6 (3.9)	31.7 (3.3)	31.3 (2.8)	30.8 (2.3)
Less than 37 wk gestational age, n (%)	24 (96)	365 (53)	14 (93)	14 (93)	14 (100)	20 (95)	335 (54)	12 (92)	12 (92)	12 (100)
Blood glucose (mmol/l)	6 (1.6)	5.8 (1.9)	6.0 (1.1)	6.0 (1.8)	6.1 (1.8)	6.2 (1.6)	5.8 (1.9)	6.1 (1.1)	6.2 (1.8)	6.3 (1.8)
Apnea in previous 24 h, n (%)	4 (16)	10 (1)	1 (7)	4 (27)	4 (29)	4 (19)	10 (2)	1 (8)	4 (31)	4 (33)
Ever treated with a methylxanthine, n (%)	14 (56)	98 (14)	7 (47)	10 (67)	10 (71)	12 (57)	91 (15)	6 (46)	9 (69)	9 (75)
Ever ventilated with a tracheal tube preoperatively, n (%)	8 (32)	83 (12)	3 (20)	6 (40)	6 (43)	6 (29)	76 (12)	3 (23)	4 (31)	4 (33)
Ever needed oxygen therapy (apart from at birth) , n (%)	18 (72)	156 (23)	9 (60)	13 (87)	13 (93)	15 (71)	141 (23)	8 (62)	11 (85)	11 (92)
Smoker in the household, n (%)	6 (24)	212 (31)	4 (27)	4 (27)	3 (21)	6 (29)	191 (31)	4 (31)	4 (31)	3 (25)
Any opioids given before apnea, n (%)*	1 (4)	14 (2)	0 (0.0)		1 (7)	1 (5)	12 (2)	0 (0.0)		1 (8)
Minimum intraoperative temperature	36.0 (0.8)	36.0 (0.8)	36.0 (0.6)	36.0 (1.0)	36.0 (1.0)	36.0 (0.8)	36.1 (0.8)	36.0 (0.6)	36.1 (0.9)	36.2 (1.0)
Surgery duration (min)	30 (22–39)	28 (20–39)	29 (24–39)	26 (20–41)	28 (20–41)	29 (22–32)	27 (20–38)	28 (24–32)	26 (20–31)	28 (20–36)

Data are represented as frequency (%) of nonmissing data or mean (SD).

* Note that the data are incomplete with respect to opioid administration after 1 h, so only early apnea data are shown.

APP = as per protocol; ITT = intention to treat; PMA = postmenstrual age.

Table 8. Logistic Regression Analysis of Factors Associated with Apnea by Intention to Treat and as per Protocol

Variable	Any Apnea (0–12 h)		Early Apnea (0–30 min)		Late Apnea (30 min–12 h)		Late Apnea (30 min–12 h, if discharged ≥12 h postop)	
	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Intention-to-treat analysis								
Age (PMA) at surgery (increase per week)	0.73 (0.63–0.83)	<0.0001	0.75 (0.64–0.89)	0.0008	0.69 (0.65–0.74)	<0.0001	0.74 (0.66–0.83)	<0.0001
Weight at surgery (increase per kg)	0.33 (0.18–0.61)	0.0003	0.48 (0.25–0.93)	0.0294	0.26 (0.16–0.43)	<0.0001	0.24 (0.15–0.38)	<0.0001
Hemoglobin level (increase per unit)	0.90 (0.78–1.04)	0.1618	0.98 (0.77–1.24)	0.8517	0.88 (0.74–1.04)	0.1381	0.89 (0.75–1.05)	0.1589
Gestational age (increase per week)	0.73 (0.68–0.79)	<0.0001	0.76 (0.71–0.83)	<0.0001	0.75 (0.67–0.84)	<0.0001	0.74 (0.66–0.83)	<0.0001
Less than 37 wk gestational age	21.87 (4.38–109.24)	0.0002	13.02 (2.22–76.45)	0.0045	12.16 (3.14–47.08)	0.0003	1.00 (1.00–1.00)	
Apnea in previous 24 h	12.60 (3.13–50.73)	0.0004	3.46 (0.73–16.51)	0.1189	26.72 (7.50–95.24)	<0.0001	24.94 (6.70–92.77)	<0.0001
Ever treated with a methylxanthine	8.74 (5.05–15.12)	<0.0001	6.16 (2.86–13.29)	<0.0001	14.44 (6.56–31.77)	<0.0001	13.28 (4.83–36.52)	<0.0001
Ever ventilated with a tracheal tube	3.55 (1.77–7.11)	0.0004	1.83 (0.54–6.21)	0.3339	5.39 (1.95–14.89)	0.0012	4.51 (1.72–11.78)	0.0021
Ever needed oxygen therapy (apart from at birth)	9.10 (4.84–17.14)	<0.0001	5.23 (1.84–14.87)	0.0019	23.02 (7.44–71.17)	<0.0001	33.47 (4.76–235.39)	0.0004
Smoker in the household	0.66 (0.32–1.35)	0.2519	0.71 (0.25–2.01)	0.5238	0.74 (0.20–2.73)	0.6571	0.58 (0.17–1.92)	0.3726
Blood glucose level (increase per unit)	1.03 (0.92–1.15)	0.6298	1.02 (0.87–1.18)	0.8477	1.02 (0.87–1.20)	0.7958	1.03 (0.90–1.19)	0.6551
Minimum intraoperative temperature (increase per degree)	0.93 (0.46–1.88)	0.8321	1.01 (0.54–1.90)	0.9675	0.93 (0.20–4.44)	0.9308	1.03 (0.17–6.09)	0.9755
Surgery duration (increase per min)	0.99 (0.98–1.01)	0.3827	0.99 (0.97–1.01)	0.3995	0.99 (0.96–1.01)	0.2388	0.99 (0.97–1.01)	0.1793
As per-protocol analysis								
Age (PMA) at surgery (increase per week)	0.73 (0.63–0.84)	<0.0001	0.75 (0.63–0.88)	0.0005	0.70 (0.66–0.76)	<0.0001	0.69 (0.63–0.76)	<0.0001
Weight at surgery (increase per kg)	0.38 (0.22–0.66)	0.0006	0.52 (0.29–0.94)	0.0295	0.27 (0.14–0.53)	0.0001	0.24 (0.13–0.45)	<0.0001
Hemoglobin level (increase per unit)	0.93 (0.78–1.12)	0.4632	0.97 (0.75–1.27)	0.8433	0.96 (0.79–1.17)	0.6973	0.98 (0.80–1.19)	0.8062
Gestational age (increase per week)	0.75 (0.68–0.81)	<0.0001	0.77 (0.69–0.87)	<0.0001	0.76 (0.68–0.86)	<0.0001	0.75 (0.65–0.86)	<0.0001
Less than 37 wk gestational age	17.26 (3.54–84.05)	0.0004	10.85 (1.75–67.32)	0.0105	9.76 (3.02–31.53)	0.0001	1.00 (1.00–1.00)	
Apnea in previous 24 h	14.65 (3.62–59.22)	0.0002	3.79 (0.71–20.32)	0.1204	27.86 (9.19–84.47)	<0.0001	26.33 (8.36–82.96)	<0.0001
Ever treated with a methylxanthine	8.81 (4.86–15.98)	<0.0001	5.91 (2.16–16.19)	0.0005	15.05 (7.64–29.68)	<0.0001	14.97 (6.07–36.62)	<0.0001
Ever ventilated with a tracheal tube	2.98 (1.28–6.92)	0.0112	2.24 (0.60–8.30)	0.2286	3.36 (1.22–9.25)	0.0192	2.80 (1.03–7.60)	0.0429
Ever needed oxygen therapy (apart from at birth)	8.98 (4.02–20.06)	<0.0001	5.69 (1.65–19.63)	0.0060	19.39 (6.52–57.65)	<0.0001	30.25 (3.63–252.18)	0.0016
Smoker in the household	0.83 (0.37–1.89)	0.664	0.88 (0.27–2.90)	0.8337	0.94 (0.27–3.28)	0.9168	0.70 (0.23–2.12)	0.5187
Blood glucose level (increase per unit)	1.06 (0.96–1.17)	0.23	1.02 (0.87–1.21)	0.7781	1.08 (0.98–1.19)	0.1348	1.09 (0.99–1.20)	0.0712
Minimum intraoperative temperature (increase per degree)	1.14 (0.37–3.52)	0.8216	1.12 (0.38–3.29)	0.8423	1.38 (0.23–8.31)	0.7240	1.68 (0.19–14.67)	0.6386
Surgery duration (increase per min)	0.99 (0.97–1.01)	0.3497	0.99 (0.97–1.01)	0.2513	0.98 (0.96–1.01)	0.2704	0.99 (0.96–1.01)	0.2673

The bivariable regression analyses were adjusted for treatment allocation in addition to each factor listed in the table. We planned to include the use of opioid administration before apnea as a predictor of apnea, but the number of apnea events was too low.

PMA = postmenstrual age.

Table 9. Association between the Use of a Tracheal Tube and Apnea

Outcome	Tracheal Tube (N = 281), n (%)	No Tracheal Tube (N = 73), n (%)	Odds Ratio (95% CI)	*P* Value
Any apnea (0–12 h)	11 (4)	4 (5)	0.72 (0.18–2.85)	0.6406
Any early apnea (0–30 min)	8 (3)	4 (5)	0.44 (0.09–2.08)	0.2981
Any late apnea (30 min–12 h)	6 (2)	1 (1)	1.37 (0.06–30.22)	0.8413
Any apnea (30 min–12 h, if discharged ≥12 h postop)	5 (2)	1 (2)	1.39 (0.71–14.63)	0.9873

In the GA arm, 281 (79%) of infants had a tracheal tube. There were four cases where use of a tracheal tube was not recorded. There was no evidence for an association between tracheal tube and apnea in the 354 infants in the GA arm without protocol violation.

GA = general anesthesia.

Table 10. Association between the Use of Neuromuscular-blocking Agents and Apnea

Outcome	Neuromuscular-blocking Agent Used (N = 122), n (%)	No Neuromuscular-blocking Agent Used (N = 159), n (%)	Odds Ratio (95% CI)	*P* Value
Any apnea (0–12 h)	5 (4)	6 (4)	0.96 (0.29–3.13)	0.9473
Any early apnea (0–30 min)	3 (2)	5 (3)	0.75 (0.21–2.67)	0.6579
Any late apnea (30 min–12 h)	4 (3)	2 (1)	2.87 (0.88–9.36)	0.0798
Any apnea (30 min–12 h, if discharged ≥12 h postoperatively)	4 (4)	1 (1)	6.73 (0.62–55.60)	0.1235

In the GA arm that had a tracheal tube, 122 (43.6%) of infants had a neuromuscular-blocking agent administered. There was one case where a tracheal tube was used, but it was not recorded whether a neuromuscular-blocking agent was used. There was no evidence for an association between tracheal tube and apnea in the 280 infants who had a tracheal tube in the GA arm without protocol violation.

GA = general anesthesia.

have missed brief apnea, it is important to consider not only the recorded apnea but also the incidence of the significant clinical interventions. Our trial was large enough to give some indication of relative frequency of these events; RA reducing the odds for such events. Recording and comparing these events may be more clinically relevant than capturing all brief self-resolving apnea events. The incidence of positive pressure ventilation or CPR occurred in nine infants overall (1.3%) and in six infants (0.8%) in PACU. The events occurred in these six children within 30 min of the end of surgery and all these were in the GA arm, and all were ex-premature infants. This nontrivial event rate underscores the need for close monitoring in this population.[11–13] Another limitation to the trial was lack of blinding. It was impossible to blind nursing staff because an infant recovering from spinal would often have no lower limb motor function; in the GA arm, the airway is often secured by tape that leaves a distinctive mark on the infant's sensitive skin, and in the RA arm, a puncture site would be visible in the infant's back. Failure of the RA technique may also confound some of the outcome measures, and thus, it is important that both ITT and APP data and analyses are considered. Importantly some advantage was still seen with the ITT analysis, implying the failure rate does not substantially diminish the advantage of planning to perform an awake regional technique. The factors associated with failure are complex and are described in another publication in Anesthesiology. Finally, the frequency of apnea was low. Although there were enough events to draw some conclusions, the low event rate precluded identifying independent risk factors in multivariable models.

The overall rate of apnea in our trial was 3%. Coté *et al.* performed a combined analysis of apnea in ex-premature infants from five previous studies. He reported a combined apnea rate of 25%; however, the rate in the contributing studies varied from 5 to 49%.[3] Reported rates of apnea vary depending on its definition, the detection method used, and the population studied. Although the definition used by the National Institute of Health, United States, for serious apnea is 20 s duration for apnea of prematurity, most (but not all) studies examining postoperative apnea have used a duration of more than 15 s or more than 10 s if accompanied by either hypoxia or bradycardia.[14] For consistency, we chose the definition used most widely for postoperative apnea. The relatively low rate of apnea in our study may be due to the method used to detect apnea. Those who defined apnea using continuous recording devices (impedance pneumography with or without nasal thermistry) found rates of 31 to 49%.[5,15–19] Those studies that relied on nursing observation and/or responding to alarming from impedance pneumography found rates of 5 to 10%.[2,20] Also in our study, only half the infants in our trial were ex-premature. All bar one infant with apnea was premature, giving a rate of apnea in ex-premature infants as 6%. This is consistent with previous studies that have failed to identify apnea in term infants.[21,22] Coté *et al.* found that anemia was a strong predictor of apnea. In contrast, we found no evidence for an association between anemia and apnea.

Table 11. Non-apnea–related Outcomes in Each Group

Outcome	Intention to Treat		As per Protocol	Intention to Treat		As per Protocol	
	RA (N = 355)	GA (N = 356)	RA (N = 286)	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Intraoperative data (events in operating theatre)							
Minimum oxygen saturation, median (IQR)*	97 (95–98)	97 (95–99)	97 (95–98)				
Oxygen saturation <95%, n (%)†	77 (22)	75 (21)	63 (22)	1.05 (0.66–1.67)	0.8290	1.04 (0.62–1.75)	0.8744
Minimum systolic blood pressure (mmHg)	70.7 (15.3)	54.8 (11.7)	73.2 (14.3)	15.90 (13.21–18.58)	<0.0001	18.33 (15.29–21.37)	<0.0001
Intervention for hypotension, n (%)	26 (7)	69 (19)	19 (7)	0.34 (0.21–0.53)	<0.0001	0.29 (0.17–0.50)	<0.0001
Minimum heart rate (beats/min), mean (SD)	133.9 (16.4)	127.6 (15.2)	134.3 (16.8)	6.29 (2.26–10.32)	0.0022	6.67 (2.64–10.71)	0.0012
Minimum temperature (°C), mean (SD)	36.1 (0.9)	36.0 (0.6)	36.2 (0.9)	0.16 (0.04–0.28)	0.0109	0.19 (0.07–0.32)	0.0024
Anesthesia time: from start skin prep for regional or induction of GA, to out of operating theatre (min), median (IQR)‡	51 (40–69)	66 (52–85)	47 (39–61)	0.81 (0.75–0.87)	<0.0001	0.75 (0.71–0.81)	<0.0001
Surgery time: from knife to skin to last stitch (min), median (IQR)‡	28 (20–38)	28 (20–40)	26 (19–35)	0.98 (0.92–1.03)	0.3863	0.94 (0.87–1.01)	0.0840
Postanesthesia care data							
Time to first feed (min), median (IQR)‡	31 (16–66)	36 (19–95)	29 (15–60)	—	0.0507	0.69 (0.51–0.92)	0.0132
Received opioid analgesia within 1 h of surgery, n (%)	3 (1)	9 (3)	1 (<1)	—	0.0866	0.15 (0.02–0.96)	0.0452
Oxygen saturation <80% in first hour after surgery, n (%)	4 (1)	13 (4)	1 (<1)	—	0.0402	0.10 (0.02–0.49)	0.0046
Oxygen saturation <95% in first hour after surgery, n (%)†	70 (20)	98 (28)	50 (17)	—	0.0004	0.55 (0.42–0.71)	<0.0001
Minimum oxygen saturation within 1 h of surgery*	96 (95–98)	96 (94–98)	97 (95–98)	—			
Requiring any respiratory support at 1 h after surgery, n (%)	15 (4)	15 (4)	8 (3)	0.99 (0.49–2.00)	0.9808	0.63 (0.31–1.29)	0.2092
Requiring nasal CPAP within 12 h of surgery, n (%)	2 (1)	2 (1)	2 (1)	1.01 (0.18–5.60)	0.9884	N/A	
Requiring any positive pressure mask ventilation within 12 h of surgery, n (%)	5 (1)	20 (6)	2 (1)	0.21 (0.09–0.51)	0.0006	0.11 (0.01–0.84)	0.0333
Tracheal intubation within 12 h of surgery, n (%)	0	1 (<1)	0	N/A		N/A	
Any stridor within 5 d of surgery, n (%)	1 (<1)	4 (1)	1 (<1)	0.27 (0.03–2.11)	0.2119	0.32 (0.04–2.74)	0.2982

GA as per-protocol summary data are not presented as only two children in the GA arm had surgery cancelled; so in most instances, the data are very similar to the intention-to-treat data.

* Data strongly skewed so no comparative statistics performed. † Odds ratio for child ever having at least one measurement < 95% oxygen saturation during surgery. This measure was defined post-hoc since the distribution of the minimum oxygen saturation was strongly skewed. The investigators who defined the 95% cut off were blind to the oxygen saturation data. ‡ Median and IQR are presented, treatment effect is estimated for the log-transformed variable and thus gives the multiplicative increase in outcome in the GA arm.

CPAP = continuous positive airway pressure; GA = general anesthesia; IQR = interquartile range; N/A = insufficient number of events to estimate treatment effect with logistic regression model; RA = regional anesthesia.

Table 12. Postanesthesia Care Location and Discharge Times in Each Group

	Intention to Treat		As per Protocol RA (N = 286), n (%)
	RA (N = 355), n (%)	GA (N = 356), n (%)	
Postoperative recovery location			
Postanesthesia care unit	304 (88)	301 (88)	247 (87)
Step-down facility	1 (<1)	0	1 (<1)
Neonatal ward	1 (<1)	3 (1)	1 (<1)
General ward	14 (4)	20 (6)	13 (5)
Neonatal intensive care	11 (3)	7 (2)	9 (3)
General pediatric intensive care	15 (4)	13 (4)	12 (4)
Discharge from hospital times			
30 min–2 h	20 (6)	17 (5)	15 (5)
>2–6 h	37 (10)	41 (12)	32 (11)
>6–<12 h	14 (4)	10 (3)	12 (4)
12 h–5 d	275 (78)	279 (79)	217 (77)
>5 d	7 (2)	8 (2)	7 (2)

GA = General Anesthesia; RA = Regional Anesthesia.

Differentiating early and late apnea is important as the etiology and management may differ. Determining which infants are at risk of late apnea may help identify those that require extended observation. When considering late apnea, we found a similar and low rate in both groups. It is not possible from our results to determine how much this apnea rate is related to the surgery and how much they reflect the "background" rate of apnea in these children.

In our trial, we found that early apnea is a strong predictor of late apnea. However, early apnea is an insensitive measure. Thus, although any infant with early apnea is at an increased risk of subsequent apnea, absence of early apnea is not a guarantee that the infant will not have a late apnea—more than half of the infants with late apnea had no early apnea, confirming previous study results.[18]

In this trial, the GA arm had a substantially lower average minimum systolic blood pressure. The ideal blood pressure for infants undergoing surgery is unknown. These data will be further described in a subsequent publication. The first implication of our trial is that aiming to perform an awake regional anesthetic has distinct benefits in reducing the odds for apnea that required significant intervention in the PACU. If the surgeon and family agree, if there are no contraindications, and if the anesthetist is familiar with the technique, then awake RA is potentially the preferred technique in this population. However, our study highlights the importance of a back-up plan for GA because the incidence of failure of RA is appreciable (20%). The second implication of our trial relates to which children should be monitored for an extended period postoperatively. To reduce the risk of late apnea, surgery should be delayed as long as safe and feasible, and extended monitoring should be considered for at least those children who are premature and those who have early postoperative apnea. The monitoring should occur in a location where healthcare providers are trained in neonatal apnea intervention and will be able to respond quickly to an alarm. However, although awake RA may still be preferable for reasons mentioned earlier, we found no evidence that it reduces the risk of late apnea in this population.

Our study excluded many infants who were extremely premature or had significant comorbidity. Further studies are required to quantify the benefits of awake RA in these high-risk groups. Although our study recruited more participants than all previous similar studies combined, it may still be too few to identify rare and serious complications such as death from apnea after discharge, or subdural hematoma or central nervous system infection from awake RA. Larger ongoing surveillance studies are needed to quantify these risks.

Acknowledgments

The authors would like to acknowledge all of these collaborators for their assistance and advice with the GAS study: Mark Fajgman, M.B.B.S., F.A.N.Z.C.A., Department of Anaesthesia, Monash Medical Centre, Melbourne, Australia; Daniela Tronconi, R.N., Department of Anesthesia, Istituto Giannina Gaslini, Genoa, Italy; David C. van der Zee, M.D., Ph.D., Department of Pediatric Surgery, Wilhelmina Children's Hospital, University Medical Centre, Utrecht, The Netherlands; Jan B. F. Hulscher, M.D., Ph.D., Department of Surgery, University Medical Center Groningen, Groningen University, Groningen, The Netherlands; Rob Spanjersberg, R.N., Department of Anesthesiology, University Medical Center Groningen, Groningen University, Groningen, The Netherlands; Michael J. Rivkin, M.D., Department of Neurology, Children's Hospital Boston, Boston, Massachusetts; Michelle Sadler-Greever, R.N., Department of Anesthesia and Pain Medicine, University of Washington, Seattle, Washington, and Department of Anesthesia and Pain Medicine, Seattle Children's Hospital, Seattle, Washington; Debra Faulk, M.D., Department of Anesthesiology, Children's Hospital Colorado, Denver, Colorado, and Department of Anesthesiology, University of Colorado School of Medicine, Denver, Colorado; Danai Udomtecha, M.D., Sarah Titler, M.D., Susan Stringham, R.N., Pamela Jacobs, R.N., and Alicia Manning, A.D.N., Department of Anesthesia, The University of Iowa Hospital and Clinics, Iowa City, Iowa; Roxana Ploski, B.S., and Alan

Farrow-Gillespie, M.D., Department of Anesthesiology, Children's Medical Center Dallas, Dallas, Texas, Department of Anesthesiology, University of Texas Southwestern Medical Center, Dallas, Texas, and Dallas and Children's Medical Center at Dallas and Outcome Research Consortium, Dallas, Texas; Timothy Cooper, M.A., Psy.D., Division of Developmental Medicine and the Center for Child Development, Monroe Carell Jr Children's Hospital at Vanderbilt, Nashville, Tennessee; Elizabeth Card, M.S.N., A.P.R.N., R.N., F.N.P.-B.C., C.P.A.N., C.C.R.P., Perioperative Clinical Research Institute, Vanderbilt University Medical Center, Nashville, Tennessee; Wendy A. Boardman, B.A., Department of Anesthesiology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; Theodora K. Goebel, R.N., B.S.N., C.C.R.C., Department of Anesthesiology and Critical Care Children's Hospital of Philadelphia, Philadelphia, Pennsylvania.

All hospitals and centers were generously supported by anesthesiology departmental funding. In addition to this funding, specific grants received for this study are as follows: Australia and New Zealand: The Australian National Health & Medical Research Council, Canberra, Australian Capital Territory, Australia; Australian and New Zealand College of Anesthetists, Melbourne, Victoria, Australia; Murdoch Childrens Research Institute, Melbourne, Victoria, Australia. This study was supported by the Victorian Government's Operational Infrastructure Support Program in Melbourne, Victoria, Australia; Department of Anaesthesia and Pain Management, Royal Children's Hospital, Melbourne, Victoria, Australia; Department of Anaesthesia, Monash Medical Centre, Melbourne, 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 Institute 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. Davidson: Anaesthesia and Pain Management Research Group, Murdoch Childrens Research Institute, The Royal Children's Hospital, Flemington Road, Parkville, Victoria 3052, Australia. andrew.davidson@rch.org.au. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

References

1. Krane EJ, Haberkern CM, Jacobson LE: Postoperative apnea, bradycardia, and oxygen desaturation in formerly premature infants: Prospective comparison of spinal and general anesthesia. Anesth Analg 1995; 80:7–13
2. Malviya S, Swartz J, Lerman J: Are all preterm infants younger than 60 weeks postconceptual age at risk for postanesthetic apnea? Anesthesiology 1993; 78:1076–81
3. Coté CJ, Zaslavsky A, Downes JJ, Kurth CD, Welborn LG, Warner LO, Malviya SV: Postoperative apnea in former preterm infants after inguinal herniorrhaphy. A combined analysis. Anesthesiology 1995; 82:809–22
4. Somri M, Gaitini L, Vaida S, Collins G, Sabo E, Mogilner G: Postoperative outcome in high-risk infants undergoing herniorrhaphy: Comparison between spinal and general anaesthesia. Anaesthesia 1998; 53:762–6
5. Welborn LG, Rice LJ, Hannallah RS, Broadman LM, Ruttimann UE, Fink R: Postoperative apnea in former preterm infants: Prospective comparison of spinal and general anesthesia. Anesthesiology 1990; 72:838–42
6. Fisher DM: When is the ex-premature infant no longer at risk for apnea? Anesthesiology 1995; 82:807–8
7. Craven PD, Badawi N, Henderson-Smart DJ, O'Brien M: Regional (spinal, epidural, caudal) versus general anaesthesia in preterm infants undergoing inguinal herniorrhaphy in early infancy. Cochrane Database Syst Rev 2003:CD003669.
8. http://www.thelancet.com/protocol-reviews/09PRT-9078. Accessed January 27, 2015.
9. Liang K-Y, Zeger SL: Longitudinal data analysis using generalized linear models. Biometrika 1986; 73:13–22.
10. Huber PJ: The behavior of maximum likelihood estimates under nonstandard conditions, Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and

Probability, Volume 1: Statistics. Berkeley, University of California Press, 1967, pp 221–33. http://projecteuclid.org/euclid.bsmsp/1200512988. Accessed August 28, 2014

11. Kurth CD, Tyler D, Heitmiller E, Tosone SR, Martin L, Deshpande JK: National pediatric anesthesia safety quality improvement program in the United States. Anesth Analg 2014; 119:112–21
12. Murat I, Constant I, Maud'huy H: Perioperative anaesthetic morbidity in children: a database of 24,165 anaesthetics over a 30-month period. Paediatr Anaesth 2004; 14:158–66
13. Tiret L, Nivoche Y, Hatton F, Desmonts JM, Vourc'h G: Complications related to anaesthesia in infants and children. A prospective survey of 40240 anaesthetics. Br J Anaesth 1988; 61:263–9
14. National Institutes of Health Consensus Development Conference on Infantile Apnea and Home Monitoring, Sept 29 to Oct 1, 1986. Pediatrics 1987; 79:292–9.
15. Welborn LG, de Soto H, Hannallah RS, Fink R, Ruttimann UE, Boeckx R: The use of caffeine in the control of post-anesthetic apnea in former premature infants. Anesthesiology 1988; 68:796–8
16. Welborn LG, Hannallah RS, Fink R, Ruttimann UE, Hicks JM: High-dose caffeine suppresses postoperative apnea in former preterm infants. Anesthesiology 1989; 71:347–9
17. Welborn LG, Hannallah RS, Luban NL, Fink R, Ruttimann UE: Anemia and postoperative apnea in former preterm infants. Anesthesiology 1991; 74:1003–6
18. Kurth CD, LeBard SE: Association of postoperative apnea, airway obstruction, and hypoxemia in former premature infants. Anesthesiology 1991; 75:22–6
19. Kurth CD, Spitzer AR, Broennle AM, Downes JJ: Postoperative apnea in preterm infants. Anesthesiology 1987; 66:483–8
20. Warner LO, Teitelbaum DH, Caniano DA, Vanik PE, Martino JD, Servick JD: Inguinal herniorrhaphy in young infants: Perianesthetic complications and associated preanesthetic risk factors. J Clin Anesth 1992; 4:455–61
21. Liu LM, Coté CJ, Goudsouzian NG, Ryan JF, Firestone S, Dedrick DF, Liu PL, Todres ID: Life-threatening apnea in infants recovering from anesthesia. Anesthesiology 1983; 59:506–10
22. Andropoulos DB, Heard MB, Johnson KL, Clarke JT, Rowe RW: Postanesthetic apnea in full-term infants after pyloromyotomy. Anesthesiology 1994; 80:216–9

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; Department of Anaesthesia and Pain Management, The Royal Children's Hospital, Melbourne, Australia; 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; 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; 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, Texas; 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 & 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; 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. (HB), 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. (UK), 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, M.D., Mary Ellen McCann, M.D., Neil S. Morton, M.D., F.R.C.A., Nicola Disma, M.D., Davinia E. Withington, B.M., Jurgen C. de Graaff, Ph.D., Geoff Frawley, M.B.B.S., Rodney W. Hunt, Ph.D., Dr. David Bellinger, Dr. Charles Berde, Prof. Andy Wolf, Prof. Neil McIntosh, Prof. John Carlin, and Prof. Kate Leslie; Attendees: Gillian Ormond, M.Sc., Pollyanna Hardy, M.Sc., Sarah J. Arnup, M.Biostat., Robyn Stargatt, Ph.D., Ms Suzette Sheppard, and Dr. Katherine Lee.

Data Monitoring Committee: Dr. Jonathan de Lima (Chair), Prof. Greg Hammer, Prof. David Field, Prof. Val Gebski, and Prof. Dick Tibboel.