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Apnea after awake-regional and general anesthesia in infants: The General Anesthesia compared to Spinal anesthesia (GAS) study: comparing apnea and neurodevelopmental outcomes, a randomized controlled trial

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Abstract

Background—Post-operative 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 (GAS) 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 ≤ 60 weeks postmenstrual age scheduled for inguinal herniorraphy were randomized to RA or GA. Exclusion criteria included risk factors for adverse neurodevelopmental outcome and infants born < 26 weeks' gestation. The primary outcome of this analysis was any observed apnea up to 12 hours post-operatively. Apnea assessment was unblinded.

Results—363 patients were assigned to RA and 359 to GA. Overall the incidence of apnea (0 to 12 hours) was similar between arms (3% in RA and 4% in GA arms, Odds Ratio (OR) 0.63, 95% Confidence Intervals (CI): 0.31 to 1.30, P=0.2133), however the incidence of early apnea (0 to 30 minutes) was lower in the RA arm (1% versus 3%, OR 0.20, 95%CI: 0.05 to 0.91, P=0.0367). The incidence of late apnea (30 minutes to 12 hours) 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 herniorraphy reduces apnea in the early post-operative period. Cardio-respiratory monitoring should be used for all ex-premature infants.

Introduction

Post-operative 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 post-operative observation. Spinal anesthesia is one 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 due to small numbers, different ways of defining 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 herniorraphy 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 five years. An important secondary aim of the GAS study is to compare the immediate post-operative benefits of RA compared to GA, in particular, reduction in apnea. This paper 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 two parallel arms, we enrolled patients in seven countries and 28 sites (table 1). Institutional review board or human research ethics committee approval was obtained for each site and written informed consent obtained from parents or guardians. Eligibility criteria included infants up to 60 weeks' postmenstrual age (PMA) scheduled for unilateral or bilateral inguinal herniorraphy (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 prior to surgery, known chromosomal abnormalities or other known acquired or congenital abnormalities which 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 peri-ventricular leukomalacia or grade three or four intra-ventricular 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 pre-admission 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: ID# ACTRN12606000441516 first registered on 16th October 2006, Principal Investigators Andrew Davidson, Mary Ellen McCann and Neil Morton; in the United States at ClinicalTrials.gov: ID#: NCT00756600 first registered on 18th September 2008, Principal Investigators Andrew Davidson, Mary Ellen McCann and Neil Morton; and in the United Kingdom at UK Clinical Research Network (UKCRN) ID#: 6635 (ISRCTN ID#: 12437565; MREC 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-hour 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 post-operative 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: either 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 intra-operatively 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 were allowed intra-operatively. Blood pressure, heart rate, oxygen saturation and temperature were recorded every 5 minutes intra-operatively.

Post-operatively children were observed closely and constantly by the research assistant for at least the first hour, or until discharge home if discharged before one hour. The research assistant was a nurse, scientist or physician. All were trained to detect apnea and familiar with the definition of a significant apnea. Electronic monitoring, and the alarm settings on monitors were not standardised. During this period any apnea was noted. Respiratory support and oxygen saturation were also recorded every five minutes. After the first hour children were observed as per the usual routine at each hospital. The level of observation and monitoring was not standardised 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 pre-operatively or during anesthesia. Intra-operative 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 pre-specified primary outcome for this analysis was observed apnea within 12 hours of surgery or until discharge. Apnea was defined as a pause in breathing >15 seconds or a pause >10 seconds if associated with oxygen saturation <80% or bradycardia (20% fall in heart rate). Early apnea was defined *a-priori* as an apnea occurring within the first 30 minutes postoperatively in the post anesthesia care unit, and late apnea was defined as an observed apnea occurring between 30 minutes and 12 hours post-operatively. A *post hoc* sensitivity analysis was also performed describing late apnea where children were excluded if discharged before 12 hours. Level of intervention for post-operative apnea, methyl-xanthine 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 five year neurodevelopmental outcome; the five year follow up Wechsler Preschool and Primary Scale of Intelligence – Third Edition full scale Intelligence Quotient score, a standardized score with mean 100 and standard deviation 15. Assuming an expected difference of one standardized score point, and a 90% chance that a 95% confidence interval 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 paper presents data on a secondary aim of the trial, an *a priori* power calculation was not conducted for these secondary outcomes. In line with CONSORT recommendations we do not believe *post-hoc* power calculations are useful and instead we present our results along with confidence intervals, which capture the uncertainty in our findings that reflect the sample size. During recruitment a Data Monitoring Committee met at planned six month 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 that received sevoflurane for only some of the surgery or received some other sedative medication during surgery Full GA is defined as receiving sevoflurane from prior to 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 using means (standard deviation (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% confidence intervals and two-sided p-values. Any missing data were not explored because the percentage of missing data was <5% for all outcomes. Descriptive analyzes were performed on pre-specified sub-groups. All outcomes were adjusted for i) stratified gestational age at birth as a fixed effect and ii) site of randomization using the generalized estimating equation approach with robust standard errors.[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 modelled 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 i) firstly we accounted for the correlation between two apnea outcomes taken from the same child, and ii) secondly between outcomes from any two children from the same site. Since 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.

Predictors of apnea were identified by constructing a logistic regression model adjusted for site of randomization using the generalized estimating equation approach as described above (Paragraph title: Data Analysis, Page 17, Paragraph 1, Line 11) 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 in term and ex premature infants (<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 above and including allocated study arm and stratified

gestational age at birth as covariates. All analyses were carried out in Stata 13 (Stata Corp LP., College Station, TX).

Results

722 infants were recruited into the trial between 9th February 2007 and 31st January 2013. Three were withdrawn from analysis. For the ITT analysis 361 were in the RA arm and 358 in the GA arm (figure 1). Baseline, demographic, anesthetic and surgical data are summarized in table 2. There were 394 premature infants and 325 term infants. Outcome data is missing for five RA cases and two GA cases because surgery was cancelled, and one RA case because no data was 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, 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 post-operative period (figure 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 odds ratios 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 hours 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 9 (1.3%) children requiring the positive pressure ventilation or cardiopulmonary resuscitation within 5 days of surgery are shown in table 6. Of these 9 children, the 6 that had this event within 30 minutes of surgery were all these 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 6–7 hours postoperatively on the inpatient ward which was treated with CPAP 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 absolute risk reduction (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 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 one day, had an unremarkable history, had a general anesthetic at approximately 44 weeks PMA and two apneas 20 minutes post-operatively that responded to gentle stimulation. Thus the incidence of apnea amongst preterm infants was 6.1% compared to 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 methyl xanthine, ever receiving ventilation via 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 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 sub-populations there was no evidence for an association between intra-operative use of tracheal tube or neuromuscular blocking agent and apnea (tables 9 & 10).

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 odds ratios 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 that had late apnea only five had an early apnea, giving a low sensitivity of 0.38. While 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 versus 66 minutes) with little evidence for any difference in surgical times (28 minutes each). Infants randomized to RA had a substantially greater mean minimum systolic blood pressure (70.7 mmHg versus 54.8 mmHg) and were less likely to need an intervention for hypotension during anesthesia (7% versus 19%). Infants randomized to RA had a slightly higher minimum intra-operative heart rate (133.9 versus 127.6 beats per minute) and were slightly warmer (36.1 versus 36.0 degrees Celsius). Infants randomized to RA were less likely to have a significant oxygen desaturation post-operatively (1% versus 4%), and slightly shorter times to first feed (31 versus 36 minutes). Approximately 20% of children were discharged prior to 12 hours; 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 post-operative apnea; however there was no evidence that RA reduced the risk of late apnea. RA also reduced the degree of post-operative oxygen desaturation and the level of intervention for apnea, implying that apnea after RA was not only less frequent but 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 intra-operatively. 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. Firstly, 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 co-morbidity. It is possible that benefits of RA and risk factors for apnea are different in these populations. Secondly, 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. Our results therefore likely underestimate the true rate of apnea, especially late apnea. We are also unable to comment on apnea that occurred after discharge from hospital – thus we performed a *post hoc* analysis for late apnea where we only included children that were not discharged prior to 12 hours. Given the uncertainty surrounding the significance of brief apnea, and the likelihood that our trial may 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 9 infants overall (1.3%) and in 6 infants (0.8%) in PACU. The events occurred in these six children within 30 minutes of the end of surgery and all these were in the GA arm, and all were ex-premature infants. This non-trivial 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%. Cote *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 seconds duration for apnea of prematurity, most (but not all) studies examining post-operative apnea have used a duration of >15 seconds or >10 seconds if accompanied by either hypoxia or bradycardia.[14] For consistency we chose the definition used most widely for post-operative apnea. The relatively low rate of apnea in our study may be due to 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] Cote *et al* found that anemia was a strong predictor of apnea. In contrast we found no evidence for an association between anemia and apnea.

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 “back ground” 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 while any infant with early apnea is at 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 post anesthesia care unit. If the surgeon and family agree, if there are no contra-indications, and if the anaesthetist is familiar with the technique, then awake-regional anesthesia is potentially the preferred technique in this population. However, our study highlights the importance of a back-up plan for GA since 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 post-operative 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, while awake-regional anesthesia may still be preferable for reasons mentioned above (Page 26, Paragraph 4), we found no evidence that it reduces the risk of late apnea in this population.

Our study excluded many infants that were extremely premature or had significant co-morbidity. Further studies are required to quantify the benefits of awake-regional anesthesia in these high risk groups. While 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 sub-dural hematoma or central nervous system

infection from awake-regional anesthesia. Larger ongoing surveillance studies are needed to quantify these risks.

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Appendix 1. GAS study Consortium

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Final Box Summary Statement

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 < 60 weeks postmenstrual age randomized to regional or general anesthesia for inguinal herniorraphy, 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

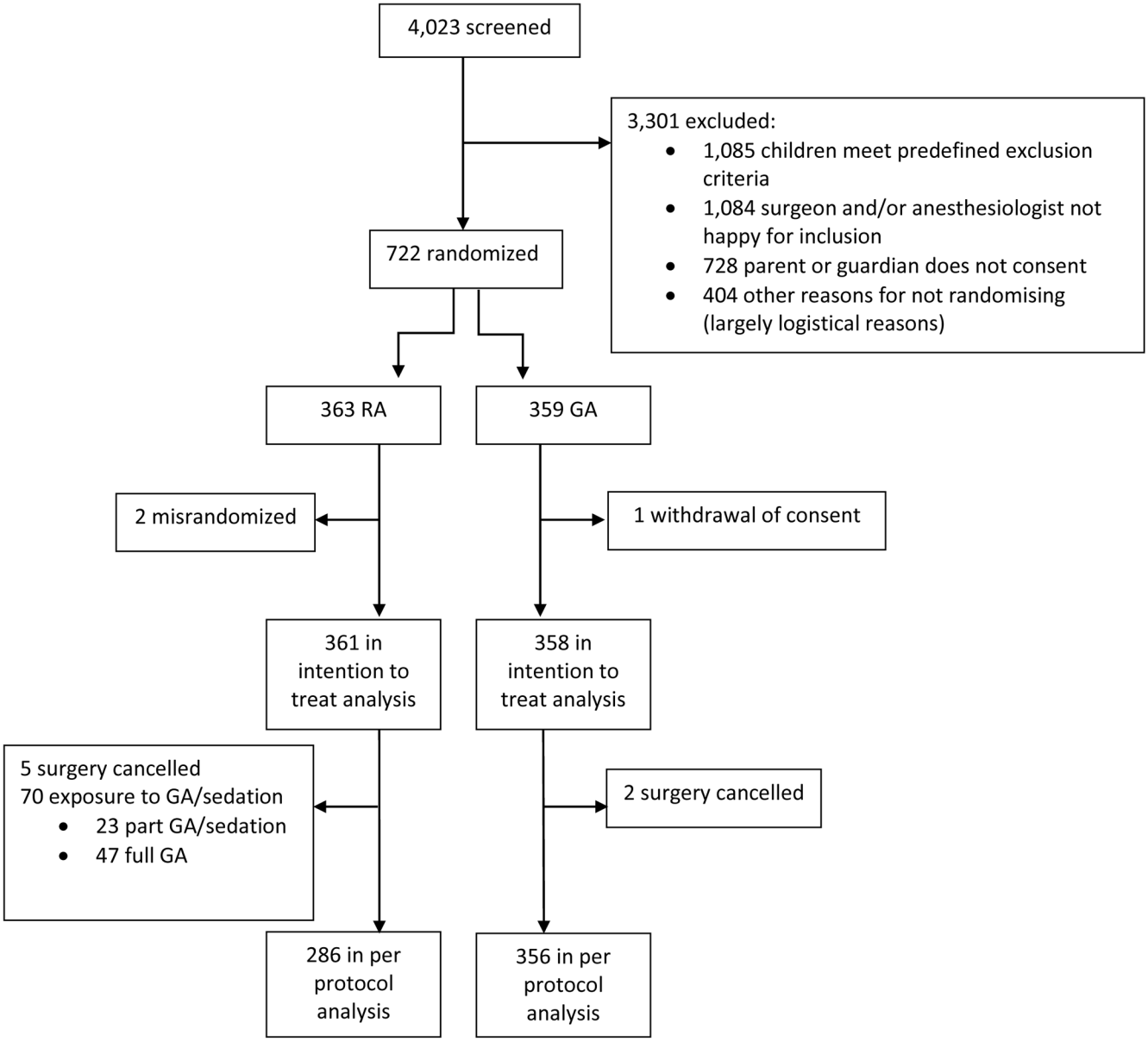

Figure 1. Consort Flow Diagram

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

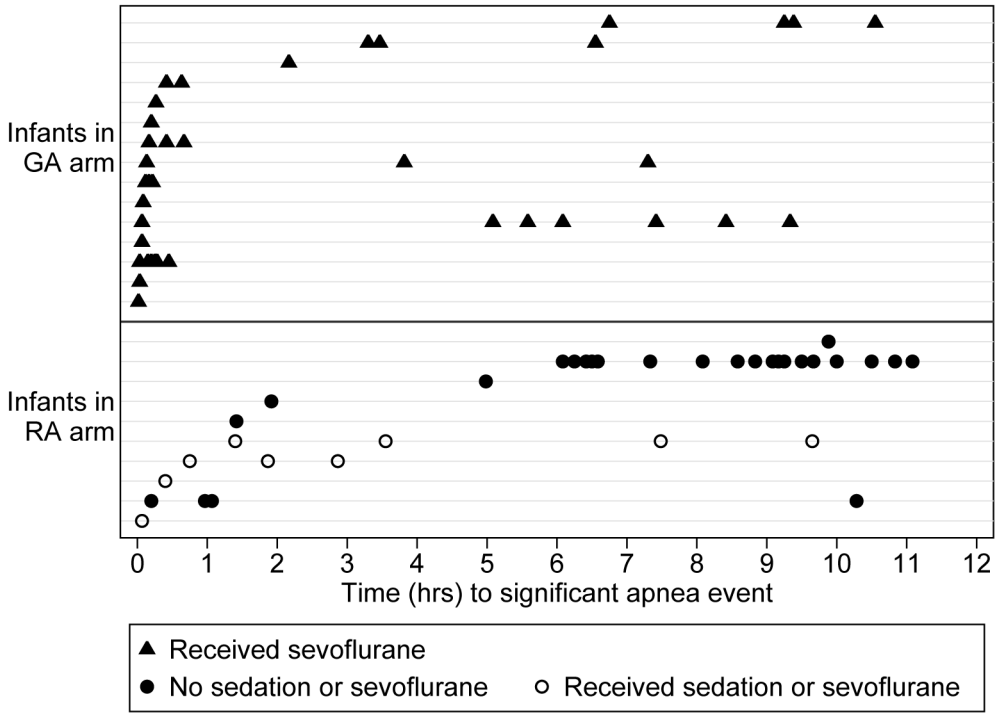

Figure 2. Time to Apnoea Events in RA and GA

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.

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.

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 gender	294 (82%)	306 (85%)	231 (81%)
Mean (SD) Gestational age at birth (weeks)	35.5 (4.1)	35.5 (3.9)	35.5 (4.1)
Premature (born <37 weeks gestation)	198 (55%)	196 (55%)	160 (56%)
Mean (SD) Chronological age at surgery (weeks)	10.0 (4.5)	10.1 (4.5)	9.8 (4.4)
Mean (SD) Post menstrual age at surgery (weeks)	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)
Mean (SD) Weight at time of surgery (kg)	4.2 (1.1)	4.3 (1.1)	4.2 (1.1)
Median Apgar at 1 minute	9 (7 to 9)	9 (7 to 9)	9 (7 to 9)
Median Apgar at 5 minutes	9 (9 to 10)	9 (9 to 10)	9 (9 to 10)
One of multiple pregnancy	62 (17%)	62 (17%)	52 (18%)
Child ever discharged from hospital	332 (93%)	336 (94%)	266 (93%)
Smoker in the household	104 (29%)	115 (32%)	83 (29%)
Ever treated with CPAP	91 (25%)	90 (25%)	70 (24%)
Ever treated with a methyl xanthine	60 (17%)	54 (15%)	49 (17%)
Ever ventilated with a tracheal tube	47 (13%)	45 (13%)	37 (13%)
Ever required supplemental oxygen (apart from at birth)	95 (26%)	81 (23%)	76 (27%)
Supplemental oxygen immediately prior to surgery	6 (2%)	6 (2%)	4 (1%)
Electronic monitoring for apnea in previous 24 hrs	17 (5%)	17 (5%)	13 (5%)
Observed apnea previous 24 hrs	6 (2%)	8 (2%)	6 (2%)
Mean (SD) Fasting time (mins)	368.2 (146.4)	367.3 (155.1)	370.7 (152.6)
Pre-operative intravenous fluid	46 (13%)	45 (13%)	36 (13%)
Mean (SD) Haemoglobin (g/100ml)	10.3 (2.1)	10.2 (2.0)	10.3 (2.0)
Median (IQR) Baseline oxygen saturation	99 (98 to 100)	99 (98 to 100)	99 (98 to 100)
Mean (SD) Baseline heart rate	152.4 (19.7)	149.9 (16.3)	153.4 (19.9)
Surgical details			
Bilateral hernia exploration/repair	162 (46%)	161 (45%)	127 (44%)
Anesthesia details			
Suxamethonium given	0	1 (<1%)	0
Non depolarising 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

Demographics	**RA arm as intention to treat N=361**	**GA arm as intention to treat N=358**	**RA arm as per protocol N=286**
Tracheal tube used	40 (11%)	281 (79%)	0
Details of monitoring for apnea for All of the first 30 minutes post-operatively			
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%)

CPAP = Continuous Positive Airway Pressure; GA = General Anesthesia; Hrs = Hours; IQR = Interquartile Range; KG = Kilograms, Mins = Minutes; RA = Regional Anesthesia; SD = Standard Deviation.

Data presented as mean and standard deviation or median and interquartile range or frequencies and percentage of non missing data.

* Note these data refer to all cases where the listed blocks were attempted prior to start of surgery whether the blocks were effective or not. GA as-per-protocol data are not presented as only 2 children in the GA arm had surgery cancelled so the data are very similar to the intention-to-treat data

Table 3

Proportion of children with apnea related outcomes in each group.

Outcome	Intention to treat - RA N=355	Intention to treat – GA N=356	As per protocol - RA N=286	RA to partial GA/ sedation N=23	RA to full GA N=46
Any apnea (0–12hr)	10 (3%)	15 (4%)	6 (2%)	0	4 (9%)
Any early apnea (0–30min)	3 (1%)	12 (3%)	1 (<1%)	0	2 (4%)
Any late apnea (30min–12hr)	8 (2%)	7 (2%)	6 (2%)	0	2 (4%)
Any late apnea if discharged >=12hrs post-op	8 (3%)	6 (2%)	6(3%)	0	2 (5%)
Required significant intervention for apnea (0–5days)*	7 (2%)	18 (5%)	4 (1%)	0	3 (7%)
Required significant intervention for apnea (0–30min)*	1 (<1%)	12 (3%)	0	0	1 (2%)
Required significant intervention for apnea (30min–12hr)*	5 (1%)	5 (1%)	3 (1%)	0	2 (4%)
Required significant intervention for late apnea if discharged >=12hrs post-op	5 (2%)	5 (2%)	3(1%)	0	2 (5%)
Required significant intervention for apnea after 12 hrs (12hr–5days)*	2 (1%)	4 (1%)	2 (1%)	0	0
Any caffeine administered post-operatively (0–5days)	2 (1%)	4 (1%)	2 (1%)	0	0

GA= General Anesthesia; Hr = Hours; Min = Minutes; RA = Regional Anesthesia.

Data are presented as percentages of non-missing 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 prior to 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 2 children in the GA arm had surgery cancelled so the data are very similar to the intention-to-treat data

Table 4

Odds ratios for apnea related outcomes regional as compared with general anesthesia

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

Hr = Hours; Min = Minutes; RA = Regional Anesthesia

*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.

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Table 5

Level of intervention

Intervention	Intention to treat - RA	Intention to treat – GA	As per protocol - RA	RA to partial GA/sedation	RA to full GA
0–5days	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
0–30min	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
30min–12hr	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–12hr*	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
12hr–5days	N=4	N=6	N=4	N=0	N=0
Self limiting	1 (25%)	2 (33%)	1 (25%)	0	0

Intervention		Intention to treat - RA	Intention to treat – GA	As per protocol - RA	RA to partial GA/sedation	RA to full GA
	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

CPAP= Continuous Positive Airway Pressure; CPR= Cardiopulmonary Resuscitation; GA = General Anesthesia; PPV= Positive Pressure Ventilation; RA = Regional Anesthesia

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 prior to knife to skin to the end of surgery.

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

Table 6

Details of children that required positive pressure ventilation and/or CPR for post-operative apnea

Child	Gestational age at birth (weeks)	Post menstrual age at surgery (weeks)	Group allocation	Relevant past history	Description of event
A	29.1	40.4	GA	Required two days CPAP after birth, uneventful anesthesia.	Brief apnea on arrival in PACU requiring stimulation, ten minutes oxygen saturation was 74% with heart rate 80, brief CPR and adrenaline given twice, tracheal tube inserted, rapid re-oxygenation and return of heart rate, tracheal tube removed 24 hours later, normal ECG and cardiac echo, Discharged home six days post surgery.
B	33.1	49.0	GA	Was having apnea pre-op, had four days with tracheal tube after birth and supplemental oxygen for nine days. Uncomplicated anesthesia. No apnea in PACU. Four apnea on ward between six and ten hours post surgery– requiring no intervention, discharged home next day with apnea monitor.	Day three 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 days CPAP after birth, no respiratory support prior to surgery, uneventful surgery, discharged back to NICU post surgery.	18 apneas, starting six hours post 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 seven days post surgery.
D	29.0	39.6	GA	Child never discharged from hospital, required eight days CPAP and 69 days supplemental oxygen after birth, no respiratory support prior to 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 nine days post surgery.
E	31.9	37.0	GA	Unremarkable past 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 days of CPAP after birth, no respiratory support pre-operatively, uncomplicated spinal, several apneas intra-operatively, no apnea in recovery. Given tramadol prior to discharge from PACU	Five apneas starting on the ward seven hours post surgery, transferred to NICU, 12 hours post surgery further apnea and low oxygen saturation, given nasal CPAP and caffeine, discharged home two days post surgery, readmitted two weeks 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 post natal 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 days CPA P after birth, uneventful anesthesia.	Six apneas in PACU requiring bag and mask positive pressure ventilation, given caffeine, discharged home two days after surgery.

CPAP= Continuous Positive Airway Pressure; CPR= Cardiopulmonary Resuscitation; ECG = Electrocardiogram; GA = General Anesthesia; NICU = Neonatal Intensive Care Unit; PACU = Post Anesthesia Care Unit; PICU = Pediatric Intensive Care Unit; PPV= Positive Pressure Ventilation; RA = Regional Anesthesia

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

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Table 7

Summary data of children with and without apnea

	ITT					APP				
	Any Apnea (0–12hrs)	**No Apnea**	**Early Apnea (0–30 min)**	**Late Apnea (30 min – 12 hrs)**	**Late Apnea (30 min – 12 hrs, if discharged ≥12hrs post-op)**	**Any Apnea (0–12hrs)**	**No Apnea**	**Early Apnea (0–30 min)**	**Late Apnea (30 min – 12 hrs)**	**Late Apnea (30 min – 12 hrs, if discharged ≥12hrs post-op)**
	N=25	**N=686**	**N=15**	**N=15**	**N=14**	**N=21**	**N=621**	**N=13**	**N=13**	**N=12**
Regional Anaesthesia	10 (40%)	345 (50%)	3 (20%)	8 (53%)	8 (57%)	6 (29%)	280 (55%)	1 (8%)	6 (46%)	6 (50%)
Age (PMA) at surgery (weeks)	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)
Haemoglobin level (g/100ml)	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 (weeks)	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 weeks gestational age	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 hours	4 (16%)	10 (1%)	1 (7%)	4 (27%)	4 (29%)	4 (19%)	10 (2%)	1 (8%)	4 (31%)	4 (33%)
Ever treated with a methyl xanthine	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 pre-operatively	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)	18 (72%)	156 (23%)	9 (60%)	13 (87%)	13 (93%)	15 (71%)	141 (23%)	8 (62%)	11 (85%)	11 (92%)
Smoker in the household	6 (24%)	212 (31%)	4 (27%)	4 (27%)	3 (21%)	6 (29%)	191 (31%)	4 (31%)	4 (31%)	3 (25%)
Any opioids given prior to apnea*	1 (4 %)	14 (2%)	0 (0.0)		1 (7%)	1 (5%)	12 (2%)	0 (0.0)		1 (8%)
Minimum intra-operative 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 (mins)	30 (22 to 39)	28 (20 to 39)	29 (24 to 39)	26 (20 to 41)	28 (20 to 41)	29 (22 to 32)	27 (20 to 38)	28 (24 to 32)	26 (20 to 31)	28 (20 to 36)

APP = As Per Protocol; ITT = Intention to Treat; Mins = Minutes; PMA = Postmenstrual Age;

Data as frequency and percentage of non-missing data or mean and standard deviation.

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

Table 8

Logistic regression analysis of factors associated with apnea by Intention-To-Treat and As-Per-Protocol

Variable	Any apnea (0–12hrs)		Early apnea (0–30 min)		Late apnea (30 min – 12 hrs)		Late apnea (30 min – 12 hrs, if discharged ≥12hrs post-op)	
	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 to 0.83)	<0.0001	0.75 (0.64 to 0.89)	0.0008	0.69 (0.65 to 0.74)	<0.0001	0.74 (0.66 to 0.83)	<0.0001
Weight at surgery (increase per kg)	0.33 (0.18 to 0.61)	0.0003	0.48 (0.25 to 0.93)	0.0294	0.26 (0.16 to 0.43)	<0.0001	0.24 (0.15 to 0.38)	<0.0001
hemoglobin level (increase per unit)	0.90 (0.78 to 1.04)	0.1618	0.98 (0.77 to 1.24)	0.8517	0.88 (0.74 to 1.04)	0.1381	0.89 (0.75 to 1.05)	0.1589
Gestational age (increase per week)	0.73 (0.68 to 0.79)	<0.0001	0.76 (0.71 to 0.83)	<0.0001	0.75 (0.67 to 0.84)	<0.0001	0.74 (0.66 to 0.83)	<0.0001
Less than 37 weeks gestational age	21.87 (4.38 to 109.24)	0.0002	13.02 (2.22 to 76.45)	0.0045	12.16 (3.14 to 47.08)	0.0003	1.00 (1.00 to 1.00)	
Apnea in previous 24 hours	12.60 (3.13 to 50.73)	0.0004	3.46 (0.73 to 16.51)	0.1189	26.72 (7.50 to 95.24)	<0.0001	24.94 (6.70 to 92.77)	<0.0001
Ever treated with a methyl xanthine	8.74 (5.05 to 15.12)	<0.0001	6.16 (2.86 to 13.29)	<0.0001	14.44 (6.56 to 31.77)	<0.0001	13.28 (4.83 to 36.52)	<0.0001
Ever ventilated with a tracheal tube	3.55 (1.77 to 7.11)	0.0004	1.83 (0.54 to 6.21)	0.3339	5.39 (1.95 to 14.89)	0.0012	4.51 (1.72 to 11.78)	0.0021
Ever needed oxygen therapy (apart from at birth)	9.10 (4.84 to 17.14)	<0.0001	5.23 (1.84 to 14.87)	0.0019	23.02 (7.44 to 71.17)	<0.0001	33.47 (4.76 to 235.39)	0.0004
Smoker in the household	0.66 (0.32 to 1.35)	0.2519	0.71 (0.25 to 2.01)	0.5238	0.74 (0.20 to 2.73)	0.6571	0.58 (0.17 to 1.92)	0.3726
Blood glucose level (increase per unit)	1.03 (0.92 to 1.15)	0.6298	1.02 (0.87 to 1.18)	0.8477	1.02 (0.87 to 1.20)	0.7958	1.03 (0.90 to 1.19)	0.6551
Minimum intra-operative temperature (increase per degree)	0.93 (0.46 to 1.88)	0.8321	1.01 (0.54 to 1.90)	0.9675	0.93 (0.20 to 4.44)	0.9308	1.03 (0.17 to 6.09)	0.9755
Surgery duration (increase per min)	0.99 (0.98 to 1.01)	0.3827	0.99 (0.97 to 1.01)	0.3995	0.99 (0.96 to 1.01)	0.2388	0.99 (0.97 to 1.01)	0.1793
As- Per-Protocol Analysis								
Age (PMA) at surgery (increase per week)	0.73 (0.63 to 0.84)	<0.0001	0.75 (0.63 to 0.88)	0.0005	0.70 (0.66 to 0.76)	<0.0001	0.69 (0.63 to 0.76)	<0.0001
Weight at surgery (increase per kg)	0.38 (0.22 to 0.66)	0.0006	0.52 (0.29 to 0.94)	0.0295	0.27 (0.14 to 0.53)	0.0001	0.24 (0.13 to 0.45)	<0.0001
Hemoglobin level (increase per unit)	0.93 (0.78 to 1.12)	0.4632	0.97 (0.75 to 1.27)	0.8433	0.96 (0.79 to 1.17)	0.6973	0.98 (0.80 to 1.19)	0.8062
Gestational age (increase per week)	0.75 (0.68 to 0.81)	<0.0001	0.77 (0.69 to 0.87)	<0.0001	0.76 (0.68 to 0.86)	<0.0001	0.75 (0.65 to 0.86)	<0.0001
Less than 37 weeks gestational age	17.26 (3.54 to 84.05)	0.0004	10.85 (1.75 to 67.32)	0.0105	9.76 (3.02 to 31.53)	0.0001	1.00 (1.00 to 1.00)	
Apnea in previous 24 hours	14.65 (3.62 to 59.22)	0.0002	3.79 (0.71 to 20.32)	0.1204	27.86 (9.19 to 84.47)	<0.0001	26.33 (8.36 to 82.96)	<0.0001
Ever treated with a methyl xanthine	8.81 (4.86 to 15.98)	<0.0001	5.91 (2.16 to 16.19)	0.0005	15.05 (7.64 to 29.68)	<0.0001	14.97 (6.07 to 36.62)	<0.0001

Variable	Any apnea (0–12hrs)		Early apnea (0–30 min)		Late apnea (30 min – 12 hrs)		Late apnea (30 min – 12 hrs, if discharged ≥12hrs post-op)	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Ever ventilated with a tracheal tube	2.98 (1.28 to 6.92)	0.0112	2.24 (0.60 to 8.30)	0.2286	3.36 (1.22 to 9.25)	0.0192	2.80 (1.03 to 7.60)	0.0429
Ever needed oxygen therapy (apart from at birth)	8.98 (4.02 to 20.06)	<0.0001	5.69 (1.65 to 19.63)	0.0060	19.39 (6.52 to 57.65)	<0.0001	30.25 (3.63 to 252.18)	0.0016
Smoker in the household	0.83 (0.37 to 1.89)	0.664	0.88 (0.27 to 2.90)	0.8337	0.94 (0.27 to 3.28)	0.9168	0.70 (0.23 to 2.12)	0.5187
Blood glucose level (increase per unit)	1.06 (0.96 to 1.17)	0.23	1.02 (0.87 to 1.21)	0.7781	1.08 (0.98 to 1.19)	0.1348	1.09 (0.99 to 1.20)	0.0712
Minimum intra-operative temperature (increase per degree)	1.14 (0.37 to 3.52)	0.8216	1.12 (0.38 to 3.29)	0.8423	1.38 (0.23 to 8.31)	0.7240	1.68 (0.19 to 14.67)	0.6386
Surgery duration (increase per min)	0.99 (0.97 to 1.01)	0.3497	0.99 (0.97 to 1.01)	0.2513	0.98 (0.96 to 1.01)	0.2704	0.99 (0.96 to 1.01)	0.2673

Hrs = Hours; Min = Minutes; PMA = Postmenstrual Age

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 prior to apnea as a predictor of apnea, but the number of apnea events was too low.

Anesthesiology. Author manuscript; available in PMC 2016 July 01.

Table 9

Association between the use of a tracheal tube and apnea

Outcome	Tracheal tube N=281	No tracheal tube N=73	OR (95% CI)	P value
Any apnea (0–12hr)	11 (4%)	4 (5%)	0.72 (0.18 to 2.85)	0.6406
Any early apnea (0–30min)	8 (3%)	4 (5%)	0.44 (0.09 to 2.08)	0.2981
Any late apnea (30min–12hr)	6 (2%)	1 (1%)	1.37 (0.06 to 30.22)	0.8413
Any Apnea (30 min–12hr, if discharged ≥12hrs post-op)	5 (2%)	1 (2%)	1.39 (0.71 to 14.63)	0.9873

GA = General Anesthesia; Hr = Hours; Min = Minutes

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.

Table 10

Association between the use of neuromuscular blocking agents and apnea

Outcome	Neuromuscular blocking agent used N= 122	No Neuromuscular blocking agent used N= 159	OR (95% CI)	P value
Any apnea (0–12hr)	5 (4%)	6 (4%)	0.96 (0.29 to 3.13)	0.9473
Any early apnea (0–30min)	3 (2%)	5 (3%)	0.75 (0.21 to 2.67)	0.6579
Any late apnea (30min–12hr)	4 (3%)	2 (1%)	2.87 (0.88 to 9.36)	0.0798
Any Apnea (30 min–12hr, if discharged ≥12hrs post-op)	4 (4%)	1 (1%)	6.73 (0.62 to 55.60)	0.1235

GA = General Anesthesia; Hr = Hours; Min = Minutes

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 if a neuromuscular blocking agent was used. There was no evidence for an association between tracheal tube and apnea in the 280 infants that had a tracheal tube in the GA arm without protocol violation.

Table 11

Non-apnea related outcomes in each group.

Outcome	Intention to treat - RA N=355	Intention to treat – GA N=356	As per protocol RA N=286	Intention-to-treat		As-per-protocol	
Intra-operative data (events in operating theatre)							
(Median (IQR))Minimum oxygen saturation **	97 (95 to 98)	97 (95 to 99)	97 (95 to 98)				
Oxygen saturation below 95% #	77 (22%)	75 (21%)	63 (22%)	1.05 (0.66 to 1.67)	0.8290	1.04 (0.62 to 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 to 18.58)	<0.0001	18.33 (15.29 to 21.37)	<0.0001
Intervention for hypotension	26 (7%)	69 (19%)	19 (7%)	0.34 (0.21 to 0.53)	<0.0001	0.29 (0.17 to 0.50)	<0.0001
Mean (SD) Minimum heart rate (beats/minute)	133.9 (16.4)	127.6 (15.2)	134.3 (16.8)	6.29 (2.26 to 10.32)	0.0022	6.67 (2.64 to 10.71)	0.0012
Mean (SD) Minimum temperature (degrees Celsius)	36.1 (0.9)	36.0 (0.6)	36.2 (0.9)	0.16 (0.04 to 0.28)	0.0109	0.19 (0.07 to 0.32)	0.0024
(Median (IQR))Anesthesia time: from start skin prep for regional or induction of GA, to out of operating theatre (mins) *	51 (40 to 69)	66 (52 to 85)	47(39 to 61)	0.81 (0.75 to 0.87)	<0.0001	0.75 (0.71 to 0.81)	<0.0001
(Median (IQR)) Surgery time: from knife to skin to last stitch (mins)*	28 (20 to 38)	28 (20 to 40)	26 (19 to 35)	0.98 (0.92 to 1.03)	0.3863	0.94 (0.87 to 1.01)	0.0840
Post anesthesia care data							
(Median (IQR)) Time to first feed (mins)*	31 (16 to 66)	36 (19 to 95)	29 (15 to 60)	0.77 (0.59 to 1.00)	0.0507	0.69 (0.51 to 0.92)	0.0132
Received opioid analgesia within 1hr of surgery	3 (1%)	9 (3%)	1 (<1%)	0.32 (0.09 to 1.18)	0.0866	0.15 (0.02 to 0.96)	0.0452
Oxygen saturation <80% in first hour after surgery	4 (1%)	13 (4%)	1 (<1%)	0.31 (0.10 to 0.95)	0.0402	0.10 (0.02 to 0.49)	0.0046
Oxygen saturation <95% in first hour after surgery#	70 (20%)	98 (28%)	50 (17%)	0.64 (0.50 to 0.82)	0.0004	0.55 (0.42 to 0.71)	<0.0001
Minimum oxygen saturation within 1hr of surgery **	96 (95 to 98)	96 (94 to 98)	97 (95 to 98)				
Requiring any respiratory support at 1hr post surgery	15 (4%)	15 (4%)	8 (3%)	0.99 (0.49 to 2.00)	0.9808	0.63 (0.31 to 1.29)	0.2092
Requiring nasal CPAP within 12 hrs of surgery	2 (1%)	2 (1%)	2 (1%)	1.01 (0.18 to 5.60)	0.9884	N/A	
Requiring any positive pressure mask ventilation within 12 hrs of surgery	5 (1%)	20 (6%)	2 (1%)	0.21 (0.09 to 0.51)	0.0006	0.11 (0.01 to 0.84)	0.0333
Tracheal intubation within 12 hrs of surgery	0	1 (<1%)	0	N/A		N/A	
Any stridor within 5 days of surgery	1 (<1%)	4 (1%)	1 (<1%)	0.27 (0.03 to 2.11)	0.2119	0.32 (0.04 to 2.74)	0.2982

CPAP= Continuous Positive Airway Pressure; GA= General Anesthesia; IQR = Interquartile Range; Mins = Minutes; RA = Regional Anesthesia; SD = Standard Deviation.

GA as-per-protocol summary data are not presented as only 2 children in the GA arm had surgery cancelled so in most instances the data are very similar to the intention-to-treat data. Percentages given as percentages of non-missing data. N/A: insufficient number of events to estimate treatment effect with logistic regression model.

*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.

**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.

Table 12

Post anesthesia care location and discharge times in each group.

	Intention to treat - RA N=355	**Intention to treat – GA N=356**	**As per protocol RA N=286**
Post-operative recovery location			
Post anesthesia 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 paediatric intensive care	15 (4%)	13 (4%)	12 (4%)
Discharge from hospital times			
30minutes – 2 hrs	20 (6%)	17 (5%)	15 (5%)
>2–6 hrs	37 (10%)	41 (12%)	32 (11%)
>6–<12 hrs	14 (4%)	10 (3%)	12 (4%)
12hrs–5days	275 (78%)	279 (79%)	217 (77%)
>5days	7 (2%)	8 (2%)	7 (2%)

GA = General Anesthesia; RA = Regional Anesthesia