Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

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

Published in final edited form as:

Anesthesiology. 2015 July ; 123(1): 55–65. doi:10.1097/ALN.0000000000000708.

Predictors of failure of awake regional anesthesia for neonatal hernia repair: data from the General Anesthesia compared to Spinal anesthesia (GAS) study: comparing apnoea and neurodevelopmental outcomes

Geoff Frawley, MBBS[1,2,3], **Graham Bell, MB, ChB**[4], **Nicola Disma, MD**[5], **Davinia E. Withington, BM**[6,7], **Jurgen C. de Graaff, PhD**[8], **Neil S. Morton, MD**[4,9], **Mary Ellen McCann, MD**[10], **Sarah J. Arnup, MBiostat**[11], **Oliver Bagshaw, MB, ChB, FRCA, FFICM**[12], **Andrea Wolfler, MD**[13], **David Bellinger, PhD**[14], **Andrew J. Davidson, MD**[1,2,3], and **the GAS Consortium**

[1]Anaesthesia and Pain Management Research Group, Murdoch Childrens Research Institute, Melbourne, Victoria, Australia [2]Department of Anaesthesia and Pain Management, The Royal Children's Hospital, Melbourne, Victoria, Australia [3]Department of Paediatrics, University of

Corresponding Author: Geoff Frawley, Department of Anaesthesia and Pain Management, The Royal Children's Hospital, Parkville, Victoria, Australia 3052. geoff.frawley@rch.org.au Phone Number: +613 9345 6213; Fax Number: +613 9345 6003.

The authors declare no competing interests.

Funding Institutions:

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 Institute 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; 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 & Paediatric Intensive Care, Ospedale Vittore Buzzi, Milan, Italy and Department of Anaesthesia, Ospedale Papa Giovanni XXIII, Bergamo, Italy. **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.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Melbourne, Melbourne, Victoria, Australia [4]Department of Anaesthesia, Royal Hospital for Sick Children, Glasgow, United Kingdom [5]Department of Anesthesia, Istituto Giannina Gaslini, Genoa, Italy [6]Department of Anaesthesia, Montreal Children's Hospital, Montreal, Canada [7]Department of Anesthesia, McGill University, Montreal, Canada [8]Department of Anaesthesia, Wilhelmina Children's Hospital, University Medical Center Utrecht, the Netherlands [9]Academic Unit of Anaesthesia, Pain and Critical Care, University of Glasgow, Glasgow, United Kingdom [10]Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts [11]Clinical Epidemiology and Biostatistics Unit, Murdoch Childrens Research Institute, Melbourne, Victoria, Australia [12]Department of Anaesthesia, Birmingham Children's Hospital, Birmingham, United Kingdom [13]Department of Anesthesiology & Paediatric Intensive Care, Ospedale Pediatrico 'Vittore Buzzi', Milan, Italy [14]Department of Neurology, Boston Children's Hospital, Boston, Massachusetts

Abstract

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

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

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

Conclusions—The failure rate of spinal anesthesia was low. Variability in application of combined spinal caudal anesthetic limited attempts to compare the success of this technique to spinal alone.

Introduction

Since its initial description at the start of the twentieth century infant spinal anesthesia has occupied a significant place in the history of pediatric regional anesthesia. During the 1970s a new role was proposed for spinal anesthesia with the recognition that this method may

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

reduce the risk of postoperative apnea, periodic breathing and desaturation after general anesthesia in ex-premature infants.[1–3] In centers with experience in performing herniorrhaphy under spinal anesthesia, success rates of close to 100% have been reported to complete the operation.[4,5] However many authors report a higher failure rate, often due to failed access to the subarachnoid space, bloody taps and blocks requiring supplementation. In a study evaluating the ease of neonatal spinal tap with or without local anesthetic, the rates of failed access to cerebrospinal fluid were 17 % and bloody tap 46%.[6] Williams *et al.* reported a 20% traumatic tap and failure rate and Shenkman *et al.* reported a 16% failure rate where spinal fluid could not be obtained in ex-premature infants.[7,8] While many authors allude to factors associated with an increased risk of failure, there are no data describing the increase in the risk of failure for specific factors such as age, weight and operator experience. Understanding these factors could improve the success rate.

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

Materials and Methods

Study design and participants

In this multinational prospective randomized controlled equivalence trial, members from the GAS consortium (Appendix 1) enrolled 722 patients from 28 centers in Australia, the United States, the United Kingdom, Italy, the Netherlands, Canada and New Zealand between February 9, 2007 and January 31, 2013. Institutional review board or human research ethics committee approval was obtained from each site. Eligible patients included any children scheduled for unilateral or bilateral herniorrhaphy (with or without circumcision). Exclusion criteria included any child > 60 weeks postmenstrual age or born ≤ 26 weeks gestational age. Further exclusion criteria included contraindications to general or regional anesthesia, preoperative ventilation immediately prior to surgery, congenital heart disease, known chromosomal abnormalities or other known acquired or congenital abnormalities (other than prematurity) which might affect development, children whose primary language was not that of the country they were recruited in, previous exposure to volatile general anesthesia or benzodiazepines as a neonate or in the third trimester in utero, or any known neurologic injury such as cystic periventricular leukomalacia or grade 3 or 4 intraventricular hemorrhage. Patients were enrolled after obtaining written informed consent from the child's parents and permission from the treating anesthesiologist and surgeon.

The GAS study protocol was approved by the following: Royal Children's Hospital Human Research Ethics Committee, Melbourne, Victoria, Australia; Southern Health Human Research Ethics Committee "B" meeting, Melbourne, Victoria, Australia; Women's and

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Children's Health Network Human Research Ethics Committee, Adelaide, South Australia, Australia; Princess Margaret Hospital for Children Ethics Committee, Perth, Western Australia, Australia; Northern X Regional Ethics Committee and Auckland District Health Board, Auckland, New Zealand; Comitato di Etica Istituto Giannina Gaslini, Genoa, Italy; Comitato Etico dell'Azienda Ospedaliera Istituti Clinici di Perfezionamento di Milano; Milan, Italy; Comitato Etico Ospedali Riuniti Bergamo, Bergamo, Italy; West Glasgow Ethics Committee 2, Glasgow, United Kingdom; Comité d'éthique de la recherche CHU Sainte-Justine, Montreal, Quebec, Canada; Montréal Children's Hospital Research Ethics Board, Montreal, Quebec, Canada; The Medical Ethical Committee – Universitair Medisch Centrum Utrecht, Utrecht, the Netherlands; The Medical Ethical Committee – Universitair Medisch Centrum Groningen, Groningen, the Netherlands; Boston Children's Hospital Committee on Clinical Investigations, Boston, Massachusetts; Ann & Robert H Lurie Children's Hospital of Chicago Institutional Review Board, Chicago, Illinois; The Children's Hospital of Philadelphia Institutional Review Board, Philadelphia, Pennsylvania; Institutional Review Board at University of Texas Southwestern Medical Center, Dallas, Texas; Committee for the Protection of Human Subjects Dartmouth-Hitchcock Medical Center, Hanover, New Hampshire; Colorado Multiple Institutional Review Board Children's Hospital Colorado, Denver, Colorado; The University of Iowa Hospitals and Clinics Institutional Review Board, Iowa City, Iowa; Seattle Children's Hospital Institutional Review Board, Seattle, Washington; Monroe Carell Jr. Children's Hospital at Vanderbilt Institutional Review Board, Nashville, Tennessee; Fletcher Allen Health Care Institutional Review Board, Burlington, Vermont. 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 United Kingdom Clinical Research Network (UKCRN) ID#: 6635 (ISRCTN ID#: 12437565; MREC No: 07/S0709/20) Principal Investigator Neil Morton.

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. Patients were randomised with a 1:1 allocation ratio to either General Anesthesia (GA) or Regional Anesthesia (RA). Randomization was in blocks of two or four and stratified by site and gestational age at birth: 26 to 29 weeks and 6 days, 30 to 36 weeks and 6 days and 37 weeks or more. The anesthesiologist and anesthetic team were aware of group allocation and the perioperative assessments were not blinded. Parents were not informed of the group allocation but were told if they asked.

Procedures

Preoperative fasting was in accordance with institutional guidelines. Premedication with acetaminophen 15- 20mg/kg was optional as was use of topical local anesthetics (EMLA). Intravenous infusion of Ringer's lactate solution, saline or dextrose saline was delivered at 4ml/kg/hr during surgery. Oral sucrose was used for sedation/analgesia but no other sedation

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

or volatile anesthetic agents were given at any stage. Patient warming was in accordance with institutional practice.

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

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

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

Rescue treatments—There were rescue protocols for hypoglycemia, hypotension and hypoxemia. If the blood pressure fell > 20% below baseline (measured in a comforted, non-distressed child) an intravenous bolus of $20ml.kg^{-1}$ Ringers lactate solution was administered. Vasoactive drugs were given if deemed necessary by the anesthetist. Hypoglycemia (blood sugar < $3.0mmol.L^{-1}$) was treated with a bolus of $5ml.kg^{-1}$ of 10% dextrose. Oxygen by face mask or blow-by was used at the discretion of the anesthetist to maintain arterial oxygen saturation > 95%. Hypoxemia (SpO2 < 90%) was managed by oxygen delivered by Hudson mask, face mask or intubation.

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

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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Statistical Analysis

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

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

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

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

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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

because the effect of experience may only be evident in sites with some prior RA experience. The outcomes assessed for a difference between CSCA and spinal only anesthesia were failure and total anesthesia time.

All analyses were performed using Stata 13 (Stata Corp LP., College Station, Texas).

Results

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

Success rate of awake RA

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

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

Success rate of spinal only and CSCA technique

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

After initial failure at spinal anesthesia there were 28 second attempts of which 10 (36%) failed, 18 (64%) were successful, including one in which awake caudal was successfully attempted. In the 10 failed second blocks 4 of the anesthesiologists were more experienced

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

than the primary anesthesiologists. In the 18 successful blocks 2 (11%) of the anesthesiologists were more experienced than the first anesthesiologist. Bloody taps occurred in 30% of spinal attempts and 44% of CSCA attempts. Bloody taps occurred in 35% of first attempts, 11% in second attempts and 7% of third attempts; therefore a bloody tap is less likely with subsequent attempts. There were 52 cases in the CSCA group with at least one bloody tap. Of these 44(85%) had a bloody tap in one of the spinal attempts, 3 had a bloody tap in the caudal attempt and 5 had bloody taps in both spinal and caudal attempts.

Predictors of failure

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

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

Comparison of spinal only and CSCA techniques

Total anesthetic time, included the time to perform the block and duration of surgical time, had a median value for CSCA of 63 min (IQR 46 to 90) and 45 min (IQR 38 to 57) for spinal block. The total anesthesia time was estimated to be 36% (95% CI: 20% to 55%, $p < 0.001$) longer for CSCA than spinal blocks. How much longer the anesthetic time is in the CSCA group depends on how long the time would be in the spinal group. For example, if the median anesthetic time is 45 min in the spinal group, we would expect the CSCA time to be 45 * 1.36 = 61.2 min, an increase of 16.2 min. However for a long anaesthetic time of 57min (the 75th percentile), we would expect the anaesthetic time to be 77.5 min in the CSCA group, an absolute increase of 20.5 min. Surgical times were 62 (IQR 48–86) minutes for bilateral hernia repair and 46 (IQR 39–61) minutes for unilateral repairs. In no cases did surgical time exceed the regional anesthesia.

Perioperative events are described in table 5. Awake RA was associated with a low incidence of respiratory or hemodynamic compromise. Bradycardia occurred in five (1.5%) patients, and the need for any intervention for hypotension occurred in 23 (6.8%) patients.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Apart from a lower minimum systolic blood pressure in the CSCA group, no other outcomes showed evidence for a difference between spinal and CSCA.

Discussion

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

The clinical implications of the 17% failure rate in the GAS study is that awake spinal anesthesia has a relevant failure rate and that use of caudal anesthesia in addition to spinal anesthesia does not reduce this failure to zero. As a result it may not be possible to avoid volatile anesthetics or sedatives during early neonatal life in all infants having herniorrhaphy under RA. We were also not able to identify those infants at higher risk of failure of awake techniques in this series. Gestational age, current age, weight, drugs used, anesthetic technique and experience of the anesthetist were not predictive of successful completion of the surgery under RA alone. This is in contrast to other series describing awake regional anesthesia in ex-premature infants which have implied; but not specifically tested; the theory that heavier and older infants are associated with lower spinal anesthesia success rates.[15,16] Reports of spinal anesthesia in older children would suggest that patient factors are less important in units with greater experience in infant spinal anesthesia and with the use of sedation for placement of the block.[11,14] While prior experience with neonatal spinal anesthesia was expected to increase success rates we were not able to demonstrate a significant learning curve. The use of awake spinal techniques was not common in many of the centers in the GAS consortium at the start of the trial but there was no difference in the failure rate when the first six months of recruitment was compared to the last 12 months. It is likely that other factors confounded the association including changes in personnel as the trial continued.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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

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

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

The low incidence of bradycardia, hypotension requiring more than fluid bolus, intraoperative hypoxemia or airway interventions would suggest considerable physiological stability during surgery with awake regional techniques. The only significant event related to awake regional anesthesia was an infant who demonstrated signs of high block height and required bag mask ventilation. It was felt this was due to rapid injection of local anesthetic rather than unexpected head down positioning.

Awake regional anesthesia still represents only a small percentage of all pediatric regional anesthetic techniques and is often reserved for neonates.[18] Opponents of awake regional techniques suggest the techniques have an excessive failure rate, inadequate duration of anesthesia and an unacceptably high rate of unsettled infants requiring intraoperative sedation. Similarly surgeons may express concerns that only some procedures can be safely and efficiently conducted under spinal anesthesia. While 55% of herniorrhaphies in the GAS

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

were unilateral the median anesthetic times for both awake spinal and CSCA would be expected to be more than adequate for both unilateral and bilateral herniorrhaphy.

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

Limitations

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

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

Conclusions

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

Acknowledgments

We would like to acknowledge all of these collaborators for their assistance and advice with the GAS study: Mark Fajgman MBBS, FANZCA Department of Anaesthesia, Monash Medical Centre, Melbourne, Australia; Daniela Tronconi RN Department of Anesthesia, Istituto Giannina Gaslini, Genoa, Italy; David C van der Zee MD, PhD Department of Pediatric Surgery, Wilhelmina Children's Hospital, University Medical Centre Utrecht, The Netherlands; Jan BF Hulscher MD, PhD Department of Surgery, University Medical Center Groningen, Groningen University, Groningen, The Netherlands; Rob Spanjersberg RN Department of Anesthesiology, University Medical Center Groningen, Groningen University, Groningen, The Netherlands; Michael J Rivkin MD Department of Neurology, Children's Hospital Boston, Boston, Massachusetts; Michelle Sadler-Greever RN Department of

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Anesthesia and Pain Medicine, University of Washington, Seattle, Washington and Department of Anesthesia and Pain Medicine, Seattle Children's Hospital, Seattle, Washington; Debra Faulk MD Department of Anesthesiology, Children's Hospital Colorado, Denver, Colorado and Department of Anesthesiology, University of Colorado School of Medicine, Denver, Colorado; Danai Udomtecha MD, Sarah Titler MD, Susan Stringham RN, Pamela Jacobs RN and Alicia Manning and Department of Anesthesia, The University of Iowa Hospital and Clinics, Iowa City, Iowa; Roxana Ploski BS and Alan Farrow-Gillespie MD Department of Anesthesiology, Children's Medical Center Dallas, Dallas, Texas and 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 MA, PsyD Division of Developmental Medicine & the Center for Child Development, Monroe Carell Jr Children's Hospital at Vanderbilt, Nashville, Tennessee; Elizabeth Card MSN, APRN, RN, FNP-BC, CPAN, CCRP Perioperative Clinical Research Institute, Vanderbilt University Medical Center, Nashville, Tennessee; Wendy A Boardman BA Department of Anesthesiology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire; Theodora K Goebel RN, BSN, CCRC Department of Anesthesiology and Critical Care Children's Hospital of Philadelphia, Philadelphia, Pennsylvania.

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. [PubMed: 7802303]
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. [PubMed: 8512100]
3. Cote 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. [PubMed: 7717551]
4. Rice LJ, DeMars PD, Whalen TV, Crooms JC, Parkinson SK. Duration of spinal anesthesia in infants less than one year of age. Comparison of three hyperbaric techniques. Reg Anesth. 1994; 19:325–9. [PubMed: 7848931]
5. Frumiento C, Abajian JC, Vane DW. Spinal anesthesia for preterm infants undergoing inguinal hernia repair. Arch Surg. 2000; 135:445–51. [PubMed: 10768710]
6. Pinheiro JM, Furdon S, Ochoa LF. Role of local anesthesia during lumbar puncture in neonates. Pediatrics. 1993; 91:379–82. [PubMed: 8424014]
7. William JM, Stoddart PA, Williams SA, Wolf AR. Post-operative recovery after inguinal herniotomy in ex-premature infants: Comparison between sevoflurane and spinal anaesthesia. Br J Anaesth. 2001; 86:366–71. [PubMed: 11573526]
8. Shenkman Z, Hoppenstein D, Litmanowitz I, Shorer S, Gutermacher M, Lazar L, Erez I, Jedeikin R, Freud E. Spinal anesthesia in 62 premature, former-premature or young infants--technical aspects and pitfalls. Can J Anaesth. 2002; 49:262–9. [PubMed: 11861344]
9. Liang KY, Zeger SL. Longitudinal data analysis using generalised linear models. Biometrika. 1986; 73:13–22.
10. Williams RK, Adams DC, Aladjem EV, Kreutz JM, Sartorelli KH, Vane DW, Abajian JC. The safety and efficacy of spinal anesthesia for surgery in infants: The Vermont Infant Spinal Registry. Anesth Analg. 2006; 102:67–71. [PubMed: 16368805]
11. Puncuh F, Lampugnani E, Kokki H. Use of spinal anaesthesia in paediatric patients: A single centre experience with 1132 cases. Paediatr Anaesth. 2004; 14:564–7. [PubMed: 15200653]
12. Kim GS, Song JG, Gwak MS, Yang M. Postoperative outcome in formerly premature infants undergoing herniorrhaphy: Comparison of spinal and general anesthesia. J Korean Med Sci. 2003; 18:691–5. [PubMed: 14555822]
13. Webster AC, McKishnie JD, Kenyon CF, Marshall DG. Spinal anaesthesia for inguinal hernia repair in high-risk neonates. Can J Anaesth. 1991; 38:281–6. [PubMed: 2036689]
14. Kokki H, Tuovinen K, Hendolin H. Spinal anaesthesia for paediatric day-case surgery: A double-blind, randomized, parallel group, prospective comparison of isobaric and hyperbaric bupivacaine. Br J Anaesth. 1998; 81:502–6. [PubMed: 9924220]
15. Abajian JC, Mellish RW, Browne AF, Perkins FM, Lambert DH, Mazuzan JE Jr. Spinal anesthesia for surgery in the high-risk infant. Anesth Analg. 1984; 63:359–62. [PubMed: 6703353]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

16. Sartorelli KH, Abajian JC, Kreutz JM, Vane DW. Improved outcome utilizing spinal anesthesia in high-risk infants. J Pediatr Surg. 1992; 27:1022–5. [PubMed: 1403527]
17. Kokki H, Hendolin H. No difference between bupivacaine in 0. 9% and 8% glucose for spinal anaesthesia in small children. Acta Anaesthesiol Scand. 2000; 44:548–51. [PubMed: 10786740]
18. 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. [PubMed: 2187377]
19. Ecoffey C, Lacroix F, Giaufré E, Orliaguet G, Courrèges P. Association des Anesthésistes Réanimateurs Pédiatriques d'Expression Française (ADARPEF). Epidemiology and morbidity of regional anesthesia in children: A follow-up one-year prospective survey of the French-Language Society of Paediatric Anaesthesiologists (ADARPEF). Paediatr Anaesth. 2010; 20:1061–9. [PubMed: 21199114]
20. Rochette A, Dadure C, Raux O, Troncin R, Mailheé P, Capdevila X. A review of pediatric regional anesthesia practice during a 17-year period in a single institution. Paediatr Anaesth. 2007; 17:874–80. [PubMed: 17683407]
21. Lacroix F. Epidemiology and morbidity of regional anaesthesia in children. Curr Opin Anaesthesiol. 2008; 21:345–9. [PubMed: 18458552]
22. Polaner DM, Taenzer AH, Walker BJ, Bosenberg A, Krane EJ, Suresh S, Wolf C, Martin LD. Pediatric Regional Anesthesia Network (PRAN): A multi-institutional study of the use and incidence of complications of pediatric regional anesthesia. Anesth Analg. 2012; 115:1353–64. [PubMed: 22696610]

GAS study Consortium

Australia

Andrew J Davidson MD and Geoff Frawley MBBS (Anaesthesia and Pain Management Research Group, Murdoch Childrens Research Institute, Melbourne, Australia and Department of Anaesthesia and Pain Management, The Royal Children's Hospital, Melbourne, Australia and Department of Paediatrics, University of Melbourne, Melbourne, Australia); Pollyanna Hardy MSc (National Perinatal Epidemiology Unit, Clinical Trials Unit, University of Oxford, Oxford, United Kingdom); Sarah J Arnup MBiostat and Katherine Lee PhD (Clinical Epidemiology and Biostatistics Unit, Murdoch Childrens Research Institute, Melbourne, Australia); Rodney W Hunt PhD (Department of Neonatal Medicine, The Royal Children's Hospital, Melbourne, Australia and Neonatal Research Group, Murdoch Childrens Research Institute, Melbourne, Australia and Department of Paediatrics, University of Melbourne, Melbourne, Australia); Robyn Stargatt PhD (School of Psychological Science, La Trobe University, Melbourne, Australia and Child Neuropsychology Research Group, Murdoch Childrens Research Institut e, Melbourne, Australia); Suzette Sheppard BSc, Gillian Ormond MSc, and Penelope Hartmann B Psych (Hons) (Department of Anaesthesia and Pain Management, Murdoch Childrens Research Institute, Melbourne, Australia); Philip Ragg MBBS (Department of Anaesthesia and Pain Management, The Royal Children's Hospital, Melbourne, Australia); Marie Backstrom RN Cert (Department of Anaesthesia, Monash Medical Centre, Melbourne, Australia); David Costi BMBS (Department of Paediatric Anaesthesia, Women's and Children's Hospital, Adelaide, Australia); Britta S von Ungern-Sternberg MD PhD (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)

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

New Zealand

Niall Wilton MRCP and Graham Knottenbelt MBBCH (Department of Paediatric Anaesthesia and Operating Rooms, Starship Children's Hospital, Auckland, New Zealand)

Italy

Nicola Disma MD, Giovanni Montobbio MD, Leila Mameli MD, Pietro Tuo MD, and Gaia Giribaldi MD (Department of Anesthesia, Istituto Giannina Gaslini, Genoa, Italy); Alessio Pini Prato MD (Department of Pediatric Surgery, Istituto Giannina Gaslini, Genoa, Italy); Girolamo Mattioli MD (DINOGMI Department, University of Genoa, Genoa, Italy); Andrea Wolfler MD, Francesca Izzo MD, and Ida Salvo MD (Department of Anesthesiology & Paediatric Intensive Care, Ospedale Pediatrico 'Vittore Buzzi', Milan, Italy); Valter Sonzogni MD, Bruno Guido Locatelli MD, and Magda Khotcholava MD (Department of Anaesthesia, Ospedale Papa Giovanni XXIII, Bergamo, Italy)

The Netherlands

Jurgen C de Graaff MD PhD, Jose TDG van Gool RN, Sandra C Numan MSc, and Cor J Kalkman MD PhD (Department of Anesthesiology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, The Netherlands); JHM Hagenaars BSc, Anthony R Absalom MBChB FRCA MD, Frouckje M Hoekstra MD, and Martin J Volkers MD (Department of Anesthesiology, University Medical Center Groningen, Groningen University, Groningen, The Netherlands)

Canada

Davinia E Withington BM (Department of Anesthesia, Montreal Children's Hospital, Montreal, Canada and McGill University, Montreal, Canada); Koto Furue MD (Département d'Anesthésie, Centre Hospitalier Universitaire Sainte-Justine, Montreal, Canada); Josee Gaudreault MScA (Department of Anesthesia, Montreal Children's Hospital, Montreal, Canada)

USA

Mary Ellen McCann MD, Charles Berde MD, Sulpicio Soriano MD, Vanessa Young RN, BA, Navil Sethna MD, Pete Kovatsis MD, and Joseph P Cravero MD (Department of Anesthesiology, Perioperative and Pain Medicine, Children's Hospital Boston, Boston, Massachusetts); David Bellinger PhD and Jacki Marmor M.Ed (Department of Neurology, Children's Hospital Boston, Boston, Massachusetts); Anne Lynn MD, Iskra Ivanova MD, Agnes Hunyady MD, and Shilpa Verma MD (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 MD, FAAP (Department of Anesthesiology, Children's Hospital Colorado, Denver, Colorado and Department of Anesthesiology, University of Colorado, Denver, Colorado); Joss Thomas MD, Martin Meuller MD, and Denisa Haret MD (Department of Anesthesia, The University of Iowa Hospitals and Clinics, Iowa City, Iowa); Peter Szmuk MD, Jeffery Steiner DO, and

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Brian Kravitz MD (Department of Anesthesiology, Children's Medical Center Dallas, Texas and Department of Anesthesiology, University of Texas Southwestern Medical Center, Dallas, Texas and Children's Medical Center at Dallas and Outcome Research Consortium, Dallas, Texas); Santhanam Suresh MD (Department of Pediatric Anesthesiology, Ann & Robert H Lurie Children's Hospital of Chicago, Northwestern University, Chicago, Illinois); Stephen R Hays MD (Department of Pediatric Anesthesia, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, Tennessee); Andreas H Taenzer MD MS (Department of Anesthesiology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire); Lynne G Maxwell MD (Department of Anesthesiology and Critical Care Children's Hospital of Philadelphia, Philadelphia, Pennsylvania); Robert K Williams MD (Department of Anesthesia and Pediatrics, College of Medicine, University of Vermont, Vermont Children's Hospital, Burlington, Vermont)

UK

Neil S Morton MD FRCA (Academic Unit of Anaesthesia, Pain and Critical Care, University of Glasgow, Glasgow, UK and Department of Anaesthesia, Royal Hospital for Sick Children, Glasgow, UK); Graham T Bell MBChB (Department of Anaesthesia, Royal Hospital for Sick Children, Glasgow, UK); Liam Dorris DClinPsy and Claire Adey MA(Hons) (Fraser of Allander Unit, Royal Hospital for Sick Children, Glasgow, UK); Oliver Bagshaw MB ChB, FRCA, FFICM (Department of Anaesthesia, Birmingham Children's Hospital, Birmingham, UK); Anthony Chisakuta BSc (HB), MB ChB, MSc, MMEDSc, FFARCSI (Department of Anaesthetics, Royal Belfast Hospital for Sick Children, Belfast, UK); Ayman Eissa MD (Anaesthetic Department, Sheffield Children's Hospital, Sheffield, UK); Peter Stoddart MB BS, BSc, MRCP (UK), FRCA (Department of Paediatric Anaesthesia, Bristol Royal Hospital for Children, Bristol, UK); Annette Davis MB ChB, FRCA (Department of Anaesthesia, Pain Relief and Sedation, Alder Hey Childrens' NHS Foundation Trust, Liverpool, UK)

Trial Steering Committee

Prof Paul Myles (chair); Members – AJD, MEMcC, NSM, ND, DW, JCdeG, GF, RWH, Dr David Bellinger, Dr Charles Berde, Prof Andy Wolf, Prof Neil McIntosh, Prof John Carlin, Prof Kate Leslie, Attendees- GO, PH, SA, RS, Ms Suzette Sheppard, Dr Katherine Lee.

Data Monitoring Committee

Dr Jonathan de Lima (chair), Prof Greg Hammer, Prof David Field, Prof Val Gebski, Prof Dick Tibboels

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Final Box Summary Statement

What we already know about this topic

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

What this article tells us that is new

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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1

Demographics

		Awake Regional n=339	Spinal n=222	CSCA n=117
Gender	Male (%)	275 (81.1%)	179 (80.6%)	96 (82.1%)
Multiple Pregnancy	Yes (%)	59 (17.4%)	31 (14.0%)	28 (24.0%)
Gestational Age	Wks	35.4 (4.1)	35.5 (4.2)	35.3 (3.9)
Birth Weight	Kg	2.34 (0.92)	2.34 (0.90)	2.35 (0.95)
Post Menstrual Age	Wks	45.5 (4.6)	45.4 (4.7)	45.7 (4.5)
Current Weight	Kg	4.21 (1.09)	4.14 (1.06)	4.36 (1.14)
Age at surgery	Wks	10.0 (4.6)	9.9 (4.4)	10.4 (4.8)
Ever Home from Hospital since birth	Yes (%)	313 (92.3%)	208[a] (93.7%)	105 (89.7%)
Sent Home with supplementary	Yes (%)	7 (2.1%)	5[b] (2.3%)	2[c] (1.7%)
Oxygen Surgery Type	Unilateral/Bilateral Herniorrhaphy(% Unilateral)	186 (54.9%)	122 (55%)	64 (54.7%)

CSCA= combined spinal caudal anesthetic

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

[a] One patient is excluded as was a home birth.

[b] Eight patients were not included as were still in hospital at time of surgery and variable was recorded as unknown in four patients.

[c] Seven patients were not included as were still in hospital at time of surgery.

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

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Awake regional techniques

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

CSCA= combined spinal caudal anesthetic

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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 3

Failure rates by technique and recruitment site.

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

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

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

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

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

Table 4

Factors associated with Failure.

	Variable		Failure	No failure	Odds Ratio	95% CI	P value
Patient factors	Gestational Age (wks)		35.5 (4.1)	35.4 (4.1)	1.01	0.93 – 1.08	0.86
	Post Menstrual Age (wks)		10.7 (5.4)	9.9 (4.4)	1.03	0.95 – 1.12	0.41
	Current Weight (kg)		4.37 (1.11)	4.18 (1.08)	1.16	0.87 – 1.57	0.31
Technique	CSCA *vs* Spinal	Spinal	29 (13.1%)	193 (86.9%)	1 (Reference)		
		CSCA	28 (23.9%)	89 (76.1%)	2.82	0.72 – 11.0	0.14
	Bloody tap	No	27 (12.3%)	193 (87.7%)	1 (Reference)		
		Yes	30 (25.2%)	89 (74.8%)	2.46	1.24 – 4.87	0.01
Experience #	Time of site in study when performing block (per 6 months)	All			0.91	0.81 – 1.02	0.11
		Exp			0.94	0.80 – 1.10	0.44
	Number of blocks (per 5 blocks)	All			0.88	0.77 – 1.00	0.06
		Exp			0.92	0.80 – 1.05	0.21
	Seniority of person performing first block	Other	6 (24%)	19 (76%)	1 (Reference)		
		Consultant	51 (16.2%)	263 (83.8%)	0.58	0.31 – 1.07	0.08
Local Anesthetic *	Dose of Bupivacaine (mg)		3.9 (0.9)	4.1 (1.2)	0.87	0.60 – 1.27	0.47
	0.75% *vs* 0.5% Bupivicaine	0.5%	11 (6.2%)	167 (93.8%)	1 (Reference)		
		0.75%	4 (28.6%)	10 (71.4%)	5.66	1.59 – 20.1	0.007
	0.5% Levobupivacaine *vs* 0.5% Bupivacaine	Bupivacaine	11 (6.2%)	167 (93.8%)	1 (Reference)		
		Levobupivacaine	1 (20%)	4 (80%)	3.55	0.81 – 15.5	0.09

CSCA = combined spinal caudal anesthetic; Exp = Centres which performed more than 20 awake regional blocks.

The odds ratio as estimated from univariable logistic regression model for each predictor adjusted for site of randomization using the generalized estimating equation approach with robust standard errors. For factors with a binary outcome (Technique, Bloody tap) the odds ratio represents the presence or absence of the factor. For continuous data the estimate is the odds ratio for a unit increase for the factor (per 1 kilogram, per 1 mg local anesthetic, per block of 5 regionals or per 6 month time period).

Centers which performed more than 20 awake regional blocks (exp) were compared to all centers (all).

* Of 222 patients allocated to Spinal anaesthesia concentration information was not recorded in 25 cases so dose was not calculated.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 5

Perioperative complications.

		Awake Regional n=339	Spinal (REF) n= 222	CSCA n=117	Odds Ratio/# Mean % change	95% CI	p value
Anesthetic time(min)[a]	Median (IQR)	50 [40 – 68]	45 [38 – 57]	63 [46 – 90]	1.36[#]	(1.20 – 1.55)	<0.001
Bradycardia	Any Bradycardia	5 (1.6%)	3 (1.5%)	2 (1.8%)	1.19	0.21 – 7.01	0.84
	Minimum Heart Rate	133.8 (16.5)	133.7 (17.6)	134.2(14.2)	2.26	−1.55 – 6.07	0.25
Hypotension	Any Hypotension	23 (6.8%)	10 (4.5%)	13 (11.1%)	1.97	0.79 – 4.89	0.14
	Minimum Systolic BP	71.1 (15.1)	73.0 (14.2)	67.7 (16.0)	−6.43	−12.29 – −0.58	0.03
	Minimum Diastolic BP	32.0 (9.1)	33.3 (8.5)	29.5 (9.5)	−3.57	−7.44 – 0.30	0.07
	Any intravenous bolus	19 (5.6%)	8(3.6%)	11(9.4%)	1.81	0.60 – 5.42	0.29
	Any vasoactive drug	5(1.5%)	3(1.4%)	2 (1.7%)	1.33	0.28 – 6.41	0.72
	Bolus +Vasoactive drug	1	1	0	N/A[*]		
Hypoxemia	During performance of block	4 (1.3%)	4 (2.1%)	0 (0%)	N/A[*]		
	SpO2 <90% during surgery	19 (5.6%)	15 (6.8%)	4 (3.4%)	0.75	0.3–1.85	0.54
	Bag Mask Ventilation during case	8 (2.3%)	3 (1.3%)	5 (4.3%)	3.27	0.37–28.5	0.28
Intraoperative restraint		132 (39.1%)	89 (40.3%)	43 (36.8%)	0.72	0.20 – 2.55	0.61

BP = Blood Pressure; CSCA = combined spinal caudal anesthetic; IQR = Interquartile Range; Min = Minute; N/A = Not Applicable; Mean diff = mean difference.

For binary variables raw counts and percentage of total of the first catergory presented are shown. For continuous data mean and standard deviation are shown. The odds ratio as estimated from a univariable logistic regression and for # anesthetic time only, the mean percentage change is estimated from a linear regression model after applying a log-transformation to the anesthetic times.

[a] Mean increase between groups,

[*] OR cannot be estimated using generalized estimating equation approach because of the zero cell.

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