Differences in Blood Pressure in Infants after General Anesthesia compared to Awake

Regional Anesthesia (GAS Study-a prospective randomized trial).

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Neil Morton. The protocol for the GAS study has been previously published by The Lancet.[13]

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Abbreviated Title: Hypotension after infant spinal or general anesthesia

Abstract:

Background: The General Anesthesia compared to Spinal anesthesia (GAS) study is a prospective randomized, controlled, multi-site, trial designed to assess the influence of general anesthesia (GA) on neurodevelopment at five years of age.   A secondary aim obtained from the blood pressure data of the GAS trial is to compare rates of intraoperative hypotension after anesthesia and to identify risk factors for intraoperative hypotension.

Methods: 722 infants $\leq$ 60 weeks postmenstrual age undergoing inguinal herniorrhaphy were randomized to either bupivacaine RA or sevoflurane GA. Exclusion criteria included risk factors for adverse neurodevelopmental outcome and infants born < 26 weeks' gestation. Moderate hypotension was defined as mean arterial pressure (MAP) measurement of < 35 mm Hg. Any hypotension was defined as mean arterial pressure (MAP) of <45 mm Hg. Epochs were defined as a 5 minute measurement periods. The primary outcome was any measured hypotension <35 mm Hg from start of anesthesia to leaving the operating room. This analysis is reported primarily as intention to treat (ITT) and secondarily as per protocol (APP).

Results: The relative risk of general anesthesia compared with regional anesthesia predicting any measured hypotension<35 mm Hg from the start of anesthesia to leaving the operating room was 2.8 (CI 2.0, 4.1, p value <0.001) by ITT analysis and 4.5 (CI 2.7,7.4, p value <0.001) by APP analysis(?).

In the GA group 87% and 49% and in the RA group 41% and 16% exhibited any or moderate hypotension by ITT, respectively. In multivariable modeling, group assignment (GA vs. RA), weight at the time of surgery and minimal intraoperative temperature were risk factors for hypotension. Interventions for hypotension occurred more commonly in the GA group compared with the RA group (Relative Risk 2.8, 95% CI:1.7,4.4 by ITT).

Conclusions: RA reduces the incidence of hypotension and chance of intervention to treat it compared with sevoflurane anesthesia in young infants undergoing inguinal hernia repair.

Keywords: Anesthesia, General; Anesthesia, Spinal; Blood Pressure; Infant

Introduction:

It is estimated that over 6 million general anesthetics are administered to young children worldwide annually.(1,2) Several studies have demonstrated an association between surgery in infancy and increased risk of poor neurobehavioral outcome, although the reason for this

association is unclear.(3-5) Since many general anesthetics cause neurotoxicity in young animals, there is concern that general anesthetics maybe neurotoxic to infants.(6-8)   Apart from neurotoxicity, there may be other modifiable peri-operative factors which impact on long term neurocognitive outcome, among them hypotension.(9)

The General Anesthesia compared to Spinal anesthesia (GAS) study, a prospective randomized equivalence trial, which was designed to determine whether GA and RA have similar long-term effects on the developing brain.{Davidson, 2016 #3031}In this study 722 infants undergoing inguinal herniorrhaphy were randomized to regional anesthesia (RA) or general anesthesia (GA). The apnea, interim 2 year neurocognitive and summary blood pressure data have been recently published elsewhere. The hypothesis of this study is that moderate hypotension is more common in infants undergoing general anesthesia compared to infants undergoing regional anesthesia as measured by the incidences of moderate hypotension. Secondary aims were to compare duration of hypotension and the incidence of interventions to treat it, and identify factors associated with hypotension.

Methods:

This manuscript adheres to the applicable Equator guidelines. 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 USA at ClinicalTrials.gov: ID#: NCT00756600 first registered on 18th September 2008, Principal Investigators Andrew Davidson, Mary Ellen McCann and Neil Morton; and in UK 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.[13]

Study participants

After institutional review board approval from each site and written informed consent from parents or guardians, infants were enrolled. (Table 1) Recruitment began in 2007 and ended in 2013. Eligibility criteria included infants up to 60 weeks' postmenstrual age (PMA) undergoing inguinal herniorrhaphy (with or without circumcision) born at greater than 26 weeks' gestation. Exclusion criteria included contraindications for either anesthetic technique, history of heart disease requiring surgery or pharmacotherapy, mechanical ventilation immediately prior to surgery, known chromosomal or congenital abnormalities known to affect neurodevelopment, previous exposure to volatile GA or benzodiazepines as a neonate or in the third trimester *in*

utero, known neurologic injury such as cystic peri-ventricular leukomalacia or grade three or four intra-ventricular hemorrhage, and social or geographic factor or language barriers that made follow up difficult. Eligible infants were identified from operating room schedules and pre-admission clinics.

Randomization and blinding

A 24-hour web-based randomization 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 by 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.

Procedures

Patients in the RA arm received regional anesthesia: either spinal, spinal with caudal, spinal with ilioinguinal nerve block, or caudal block. The anesthetic used was bupivacaine or levobupivacaine. Some patients received caudal chloroprocaine intra-operatively to prolong the block. In the RA arm, any sedation or GA given was considered a protocol violation. Oral sucrose drops were permitted in the RA arm and acetaminophen (paracetamol) in both arms. Those in the GA arm received sevoflurane in air/oxygen for induction and maintenance along with neural blockade via caudal or ilioinguinal block with bupivacaine or levobupivacaine. Airway support and use of neuromuscular blocking agents was not standardized. No opioids or

nitrous oxide were allowed intra-operatively. Blood pressure, heart rate, oxygen saturation, end-tidal CO_2 and temperature were recorded every 5 minutes intra-operatively. Because there was no airway management standardization within this study, end tidal CO2 measurements were considered unreliable. These measurements were recorded on the Case Report Forms by a research assistant and in the anesthesia record. A blood glucose measurement was obtained perioperatively.

The pre-specified primary outcome for this analysis was at least one epoch of observed moderate hypotension. Secondary outcomes include observation of at least one epoch of observed any hypotension; at least three epochs of moderate hypotension, at least three epochs of any hypotension and average intraoperative MAP as well as interventions done for blood pressures less than 80% of baseline. Moderate hypotension and any hypotension was defined as single or multiple measures of MAP of <35 mm Hg and MAP of <45 mm Hg, respectively. NIRS and Doppler evidence demonstrates that cerebral blood flow decreases at MAPs <45 mm Hg and cerebral oxygenation decreases at MAPs <35 mm Hg in infants <6 months undergoing sevoflurane anesthesia.(10) An epoch was defined as a single intraoperative measurement representing a 5 minute period. Multiple measures within a 5 minute period were averaged. Mean arterial pressures were calculated from the formula ((systolic BP) +2(diastolic BP))/3. Cuff position (calf vs arm) was not adjusted for because there is less than a 1 mm Hg difference between calf and arm pressures in infants less than 3 months.(11,12) Cuff size was determined by choice of a cuff width that was between 2/3 the length of either the humerus, femur or tibia

depending on the limb. Baseline blood pressure measurements were the first blood pressure measured in the operating room. Intraoperative and PACU interventions for blood pressure greater than 20% below baseline included lactated Ringer's bolus of 20 milliliters/kilogram and vasoactive medications at the discretion of the anesthesiologist.

Prolonged hypotension was defined as 3 or more consecutive epochs of MAP <35 mm Hg. Any hypotension and moderate hypotension rates were analyzed in three time periods: anesthesia time: time from the start of the anesthesia to time of leaving the operating room (primary analysis); pre-incision time: time from the start of anesthesia to incision and
 surgical time: time between knife to skin and last stitch. The level of intervention for intraoperative hypotension was also noted. A significant intervention was defined a-priori as a fluid bolus or the administration of a vasoactive substance.

Statistical Analysis:

Analysis populations

The primary analysis is reported as intention to treat (ITT) excluding participants who withdrew consent or were randomized after surgery. 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.

Data analysis

For occurrence of moderate and any hypotension, a comparison between GA and RA groups is presented as a relative risk (RR) estimated using the generalised estimating equation (GEE) approach, assuming binomially distributed outcome data, and applying a log link function and robust standard errors in Stata 13 (Stata Corp LP., USA). A fixed effect was fitted for each group and gestational age (treated as a continuous outcome) and an exchangeable correlation was assumed between observations within the same site. It is noted in the results where the GEE approach did not converge, and an alternative, more conservative method was applied.

For average MAP, a comparison between GA and RA groups is presented as a difference in means as estimated from a 3-level random intercept model, where site is the top level, individual is the second level and observation within individual is the third level, using xtmixed with maximum likelihood estimation in Stata 13 (Stata Corp LP., USA). A random intercept is fit to each randomization site and individual, and a fixed effect is fit for each group and gestational age. The residual errors within each individual were assumed to have an autoregressive structure of order 4, to account for the expected autocorrelation between successive blood pressure measurements. An order of 4 was chosen by performing a likelihood ratio test between models fit with successive orders of autogression for observations in the anesthesia time period, and selecting the highest order where $p<0.05$. All estimates are presented with 95% confidence intervals (CIs) and two-sided p-values   As a further secondary analysis we aimed to identify

risk factors for prolonged hypotension (3 or more consecutive epochs <35 mm Hg).   Prolonged

hypotension was chosen instead of any hypotension because the outcomes are likely to be more

severe.   . The following risk factors for prolonged hypotension (3 or more consecutive epochs

<35 mm Hg) were identified a-priori: chronological age, gender, weight at time of surgery,

postmenstrual age at time of surgery, gestational age at birth, preoperative fasting time,

preincisional times, intraoperative temperature (mean and minimum values) and duration of

surgery. These risk factors were chosen by previous research and consensus by and clinical

expertise of the authors.

To assess the strength of association of each risk factor with prolonged hypotension we present

estimates from: a tri-variable model as described in Data Analysis, including allocated study

group and gestational age in addition to the risk factor of interest; and a full multivariable model

containing all risk factors of interest. Prior to constructing the full multivariable model we

assessed the set of risk factors for multicollinearity by visual inspection of twoway scatterplots

and by calculating the variance inflation factors. We determined that only one factor in the

following sets of factors could be estimated in the full model: mean intraoperative temperature

and minimum intraoperative temperature; and weight at surgery, PMA at surgery and

chronological age at surgery. We selected the factor with the strongest tri-variable association for

the full model.

Sample size considerations

The sample size for the GAS study was based on the 5 year neurodevelopmental outcome.(13)

In line with CONSORT recommendations, post-hoc power calculations were not done and

instead results are presented with confidence intervals, which capture the uncertainty in our

findings that reflect the sample size.

For our sample size of 709, the observed reduction in moderate hypotension from 49% to 16% in

the GA and RA arms respectively can be estimated with a 95% confidence interval of 2.4 to 4.1

for relative risk, using an unadjusted two-sample χ^2 proportions test. The confidence intervals

presented in the Results differ because our analysis accounts for the randomization stratification

factors, and non-independence between observations taken within the same site.

Results:

722 infants were recruited into the trial (see figure 1). For the ITT analysis 355 were in the RA

arm and 356 in the GA arm (figure 1). Baseline, demographic, anesthetic and surgical data are

summarized in table 1. There were 394 premature infants and 325 term infants. In the RA arm 70

patients had a protocol violation involving exposure to sevoflurane or sedation; 10 patients were

converted to GA with no block attempted, 23 had a partially successful RA but required sedation after incision and 37 had a regional block attempted but were converted to GA before incision. Thus for the APP analysis 286 were in the RA arm and 356 in the GA arm. There was no hypoglycemia noted in any of the infants. There were no infants with patent ductus arteriosus or other conditions known to alter blood pressure at the time of surgery. Most of the GA group also received concurrent caudal blocks for intra and postoperative analgesia. The mean end-expiratory sevoflurane concentration measured in the GA group was 2.6 (0.7) %.

MAP was not measured in 14% of epochs in the RA group and 15% in the GA group. The missing data occurred mostly at the beginning and end of cases. MAP was missing for 32% of the first three epochs after the start of anesthesia in both the GA and RA groups, while in the last epoch 33% of GA and 23% of RA cases were missing MAP. Furthermore, in 71% of GA cases the first MAP measurement was taken in the 10 minutes after the start of anesthesia, compared to 51% of RA cases. The initial baseline MAP for the GA group was 59 mm Hg and 62 mm Hg for the RA group by ITT and 61 mm Hg for the RA group by APP.

The relative risk of general anesthesia compared with regional anesthesia predicting any measured hypotension<35 mm Hg from the start of anesthesia to leaving the operating room was 2.8 (CI 2.0, 4.1, p value <0.001) by ITT analysis and 4.5 (CI 2.7,7.4, p value <0.001) by APP (Table 4). The percentages of infants in the GA group who exhibited any epochs of any and moderate hypotension were 87% and 49% respectively. In the RA group the percentages of

infants exhibiting any epochs of any and moderate epochs of hypotension were 41% and 16 % by

ITT and 34% and 9% by APP, respectively (Table 2). In the GA group, 15% (54 infants)

experienced 5-9 epochs and 8% (28 infants) experienced 10 or more epochs of moderate

hypotension with three infants experiencing 15 or more epochs. In the RA group on APP

analysis, 8% (22 infants) experienced 1-4 epochs and 2% (5 infants) experienced 5-9 epochs of

moderate hypotension. These epochs could be consecutive or nonconsecutive.   In the GA group,

18% (63 infants) had prolonged hypotension (3 or more consecutive measurements<35 mm Hg)

and in the RA group, 3% (11 infants) by ITT and 0% (1 infant) by APP had prolonged

hypotension.

There was strong evidence that the mean MAP for the GA group was 10 mm Hg below the mean

MAP for the RA group in each time period (preincision, surgical time, anesthesia time) and type

of analysis (ITT, APP)(Table 3). There was strong evidence for increased risk of any

hypotension during the anesthesia time period in the GA group in both the ITT population (RR =

2.1, 95% CI:1.8 – 2.4 , p <0.001), and the APP population (RR = 2.5, 95% CI:2.1 - 3.0, p

<0.001), and similarly for moderate hypotension (ITT, RR = 4.8, 95% CI:2.0 - 4.1, p <0.001 ;

APP, RR = 4.5, 95% CI:2.7 - 7.4, p <0.001) (table 4).

In a multivariable prediction model (N=609, 69 events with complete data) the risk of prolonged

hypotension was significantly associated with assignment to the GA group (GA RR = 4.63, 95%

CI:2.23 - 9.66, p <0.001), lower weight at time of surgery (per kg RR =0.56 , 95% CI :0.47 -

0.67, p <0.001) and minimum intraoperative temperature (per deg C RR =0.78 , 95% CI:0.65 -

0.95, p =0.011). There was no evidence for an association between fasting time, surgical time,

and gender (table 5). We note that mean intraoperative temperature and minimum intraoperative

temperature; and weight at time of surgery, PMA and chronological age at surgery, were highly

associated with each other. As a result, the full model can only estimate the association between

one of these factors with prolonged hypotension. The alternative factors provided almost the

same strength of association with prolonged hypotension. Each factor may be independently

important, but the sample size was too small to estimate these associations reliably.

Interventions for hypotension occurred more commonly in the GA group compared with the RA

group (19.2% vs 7.3% by ITT and 19.2% vs 6.6% by APP).   The most common intervention

was a fluid bolus, which accounted for 75% or more of the interventions (table 6). The relative

risk for GA compared to RA predicting an intervention for hypotension were 2.8 (95% CI:1.7 -

4.4) by ITT and 2.8 (95% CI:1.7 - 4.9) by APP.

Discussion:

In this analysis we found more frequent hypotension in the GA group compared with the RA group. The GA group was more likely to demonstrate any and moderate hypotension for both single measurements and 3 or more consecutive measurements.

There are many different working definitions of hypotension for awake premature and term infants but the acceptable lower limits of blood pressures in neonates and young infants undergoing general anesthesia have not been established.(14,15) Normative data from preterm and term infants reveal a steady increase in blood pressure over the first month of life.(12,16-18) In term infants, the systolic blood pressure at birth averages 62 mm Hg but by one month of age it is >80 mm Hg, representing an increase of almost 30% .(17) The slope for the rise in blood pressure for preterm infants is similar.(18) The rise in calculated MAP over the first month of life is approximately 15% from a mean calculated MAP of 52 mm Hg on day 1 to 61 mm Hg on day 30.(16,17)   It is also important to note that the blood pressures of infants born prematurely are higher than those of term infants at 41 weeks post menstrual age.{Tan, 1988 #182} The

reasons for this are unclear but may have to do with the inflammatory stress that premature infants endure while developing. These expected blood pressure differences between term and expremature infants highlight the importance of obtaining accurate baseline blood pressures in all infants and neonates before anesthesia.

It is generally believed that maintaining blood pressure within the limits of cerebral autoregulation is optimal for cerebral protection. Several studies have shown that the lower limit of cerebral autoregulation for some infants is indeed fairly close to the definition of MAP hypotension using the infant's age in postmenstrual weeks, although there is also evidence that some premature infants are able to demonstrate cerebral autoregulation at a MAP level considerably lower than their gestational age in weeks.(19,20) A retrospective analysis of infants less than 6 months of age undergoing sevoflurane anesthesia found that the lower limit of autoregulation was 45 mm Hg but cerebral oxygenation did not decrease until the MAP was less than 35 mm Hg.(10)

Although it is known that hypotension can lead to decreased cerebral perfusion and thus to hypoxic ischemic injury to the brain, there are many unknowns to consider in infants undergoing general anesthesia.   First the duration of hypotension that puts infants at risk is unknown. In a small case series of infants less than 3 months of age undergoing general anesthesia between 120 and 180 minutes who did show evidence of perioperative hypoxic ischemic injury, 5 of the 6

patients had a mean intraoperative MAP of less than 35 mm Hg for the entire procedure.(21)   It

is important to note as previously published, no neurocognitive differences were found in the 2

year interim neurocognitive evaluations between the GA and RA group even though the lowest

mean single systolic blood pressures noted in the GA group were below the American Heart

Association guidelines for hypotension in neonates at 55 mm Hg.(22,23)   Also, studies have

shown that a MAP below 35 mm Hg can lead to decreased cerebral perfusion and cerebral

oximetry values but there has been no established link between these factors intraoperatively and

later neurocognitive outcomes.{Rhondali, 2013 #2695}{Rhondali, 2015 #2693}   Risk factors

for poor neurocognitive outcomes including hypotension and duration of hypotension will be

analyzed when the final 5 year neurocognitive outcome assessments are completed.

Other risk factors that were associated with moderate prolonged hypotension were weight at the

time of surgery and minimal temperature recorded during the procedure but these effects sizes

were small. Weight was a stronger predictor of moderate hypotension than chronological age,

postmenstrual age or gestational age at birth. Speculatively, weight might be a proxy for overall

health as well as age.

Criteria for either the timing or type of intervention for hypotension in young infants have not yet

been developed. In our study, a fluid bolus was administered in approximately 75% of

hypotensive episodes; vasoactive agents were the sole therapy in approximately 15% of

interventions in the GA group and 21% in the RA group.

Study Limitations:

There are several limitations to this study that warrant discussion. The blood pressure values were missing in 14% of our study data, most commonly at the very beginning or end of the case. However, sensitivity analysis of these missing values to include additional hypotensive measurements for the missing values did not alter the direction of the values. The initial measured blood pressures in the RA group occurred later than the initial blood pressure measurements in the GA group, which might have introduced a bias.

Another limitation is that location (calf vs arm) and sizes were not standardized as part of the protocol. Pediatric anesthesiologists conventionally use the rule of 2/3rds; the cuff width should be 2/3 the length of the underlying bone of the limb measured. However, this is not the most accurate method of sizing blood pressure cuffs. Measuring the limb circumference at midpoint and choosing a blood pressure cuff width that is 40% of this circumference is more accurate.(24,25) This may have introduced some nonsystematic bias into the data since the participants are likely to follow the same rule in all patients. The cuff position among patients in the RA group was predominantly the lower limbs. We chose not to adjust for limb placement because there is very little difference in limb blood pressure measurements in infants. However, leg blood pressures are usually slightly lower than arm blood pressures so any bias in our measurements would result in underestimates of the true blood pressure in the regional group.

There also was no standardization of the noninvasive blood pressure monitoring systems across the sites however both these factors should have been accounted for by randomization.

Another limitation is that the definitions of hypotension in infants undergoing general anesthesia are not really developed. The blood pressures we considered to indicate hypotension may in fact have been adequate blood pressures for some or all of the infants who exhibited them. In addition, the risks of hypotension to neurodevelopment are presumably duration dependent and "at risk" duration is not known. We arbitrarily chose 3 or more consecutive epochs of moderate hypotension to be important.

In conclusion, a substantial percentage of our patients had calculated mean arterial blood pressures less than 35 mm Hg at some point during their anesthetic and the incidence was much higher for those who received sevoflurane anesthesia. The importance and consequences, particularly on neurodevelopment, of transient intraoperative hypotension during anesthesia in infancy are unknown. The potential for interplay between hypotension and the putative direct effects of general anesthetics on neurodevelopment are especially intriguing. Further consideration and investigation of this issue is warranted.

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References

1. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, Gawande AA. An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet 2008;372:139-44.
2. Tzong KY, Han S, Roh A, Ing C. Epidemiology of pediatric surgical admissions in US children: data from the HCUP kids inpatient database. J Neurosurg Anesthesiol 2012;24:391-5.
3. Wilder RT, Flick RP, Sprung J, Katusic SK, Barbaresi WJ, Mickelson C, Gleich SJ, Schroeder DR, Weaver AL, Warner DO. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. Anesthesiology 2009;110:796-804.
4. DiMaggio C, Sun LS, Li G. Early childhood exposure to anesthesia and risk of developmental and behavioral disorders in a sibling birth cohort. Anesth Analg 2011;113:1143-51.
5. Ing C, Dimaggio C, Whitehouse A, Hegarty MK, Brady J, von Ungern-Sternberg BS, Davidson A, Wood AJ, Li G, Sun LS. Long-term Differences in Language and Cognitive Function After Childhood Exposure to Anesthesia. Pediatrics 2012.
6. Jevtovic-Todorovic V, Hartman RE, Izumi Y, Benshoff ND, Dikranian K, Zorumski CF, Olney JW, Wozniak DF. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci 2003;23:876-82.
7. Stratmann G, Sall JW, May LD, Bell JS, Magnusson KR, Rau V, Visrodia KH, Alvi RS, Ku B, Lee MT, Dai R. Isoflurane differentially affects neurogenesis and long-term neurocognitive function in 60-day-old and 7-day-old rats. Anesthesiology 2009;110:834-48.
8. Yon JH, Daniel-Johnson J, Carter LB, Jevtovic-Todorovic V. Anesthesia induces neuronal cell death in the developing rat brain via the intrinsic and extrinsic apoptotic pathways. Neuroscience 2005;135:815-27.
9. Englehart MS, Allison CE, Tieu BH, Kiraly LN, Underwood SA, Muller PJ, Differding JA, Sawai RS, Karahan A, Schreiber MA. Ketamine-based total intravenous anesthesia versus isoflurane anesthesia in a swine model of hemorrhagic shock. The Journal of trauma 2008;65:901-8; discussion 8-9.

10.   Rhondali O, Pouyau A, Mahr A, Juhel S, De Queiroz M, Rhzioual-Berrada K, Mathews S, Chassard D. Sevoflurane anesthesia and brain perfusion. Paediatr Anaesth 2015;25:180-5.

11.   Crapanzano MS, Strong WB, Newman IR, Hixon RL, Casal D, Linder CW. Calf blood pressure: clinical implications and correlations with arm blood pressure in infants and young children. Pediatrics 1996;97:220-4.

12.   Park MK, Lee DH. Normative arm and calf blood pressure values in the newborn. Pediatrics 1989;83:240-3.

13.   Davidson AJ, Morton NS, Arnup SJ, de Graaff JC, Disma N, Withington DE, Frawley G, Hunt RW, Hardy P, Khotcholava M, von Ungern Sternberg BS, Wilton N, Tuo P, Salvo I, Ormond G, Stargatt R, Locatelli BG, McCann ME, General Anesthesia compared to Spinal anesthesia C. Apnea after Awake Regional and General Anesthesia in Infants: The General Anesthesia Compared to Spinal Anesthesia Study--Comparing Apnea and Neurodevelopmental Outcomes, a Randomized Controlled Trial. Anesthesiology 2015;123:38-54.

14.   Brady KM, Mytar JO, Lee JK, Cameron DE, Vricella LA, Thompson WR, Hogue CW, Easley RB. Monitoring cerebral blood flow pressure autoregulation in pediatric patients during cardiac surgery. Stroke 2010;41:1957-62.

15.   Nafiu OO, Voepel-Lewis T, Morris M, Chimbira WT, Malviya S, Reynolds PI, Tremper KK. How do pediatric anesthesiologists define intraoperative hypotension? Paediatr Anaesth 2009;19:1048-53.

16.   Tan KL. Blood pressure in full-term healthy neonates. Clin Pediatr (Phila) 1987;26:21-4.

17.   Report of the Second Task Force on Blood Pressure Control in Children--1987. Task Force on Blood Pressure Control in Children. National Heart, Lung, and Blood Institute, Bethesda, Maryland. Pediatrics 1987;79:1-25.

18.   Tan KL. Blood pressure in very low birth weight infants in the first 70 days of life. J Pediatr 1988;112:266-70.

19.   Tyszczuk L, Meek J, Elwell C, Wyatt JS. Cerebral blood flow is independent of mean arterial blood pressure in preterm infants undergoing intensive care. Pediatrics 1998;102:337-41.

20.   Munro MJ, Walker AM, Barfield CP. Hypotensive extremely low birth weight infants have reduced cerebral blood flow. Pediatrics 2004;114:1591-6.

21.   McCann ME, Schouten AN, Dobija N, Munoz C, Stephenson L, Poussaint TY, Kalkman CJ, Hickey PR, de Vries LS, Tasker RC. Infantile postoperative encephalopathy: perioperative factors as a cause for concern. Pediatrics 2014;133:e751-7.

22.   Davidson AJ, Disma N, de Graaff JC, Withington DE, Dorris L, Bell G, Stargatt R, Bellinger DC, Schuster T, Arnup SJ, Hardy P, Hunt RW, Takagi MJ, Giribaldi G, Hartmann PL, Salvo I, Morton NS, von Ungern Sternberg BS, Locatelli BG, Wilton N, Lynn A, Thomas JJ, Polaner D, Bagshaw O, Szmuk P, Absalom AR, Frawley G, Berde C, Ormond GD, Marmor J, McCann ME, consortium GAS. Neurodevelopmental

outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. Lancet 2015.

23. Kleinman ME, Chameides L, Schexnayder SM, Samson RA, Hazinski MF, Atkins DL, Berg MD, de Caen AR, Fink EL, Freid EB, Hickey RW, Marino BS, Nadkarni VM, Proctor LT, Qureshi FA, Sartorelli K, Topjian A, van der Jagt EW, Zaritsky AL, American Heart A. Pediatric advanced life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Pediatrics 2010;126:e1361-99.

24. Devinck A, Keukelier H, De Savoye I, Desmet L, Smets K. Neonatal blood pressure monitoring: visual assessment is an unreliable method for selecting cuff sizes. Acta Paediatr 2013;102:961-4.

25. Clark JA, Lieh-Lai MW, Sarnaik A, Mattoo TK. Discrepancies between direct and indirect blood pressure measurements using various recommendations for arm cuff selection. Pediatrics 2002;110:920-3.

Table 1. 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 (81.7%)	306 (85.5%)	231 (80.8%)
Gestational age at birth (days)	248.3 (28.5)	248.6 (27.2)	248.2 (28.7)
Chronological age at surgery (days)*	70.1 (31.8)	71.0 (31.7)	68.9 (30.9)
Post menstrual age at surgery (days)*	318.3 (32.6)	319.5 (32)	317.1 (32.0)
Birth weight (kg)	2.4 (0.9)	2.3 (0.9)	2.3 (0.9)
Weight at time of surgery (kg)*	4.2 (1.1)	4.3 (1.1)	4.2 91.1)
Median Apgar at 1 minute	9 (7-9)	9 (7-9)	9 (7-9)
Median Apgar at 5 minutes	9 (9-10)	9 (9-10)	9 (9-10)
Ever ventilated with a tracheal tube	47 (13.1%)	45 (12.6%)	37 (12.9%)
Ever required supplemental oxygen	95 (26.4%)	81 (22.6%)	76 (26.6%)
Supplemental oxygen immediately prior to surgery*	6 (1.7%)	6 (1.7%)	4 (1.4%)
Electronic monitoring for apnea in previous 24 hr	17 (4.7%)	17 (4.8%)	13 (4.6%)
Observed apnea previous 24 hrs *	6 (1.7%)	8 (2.2%)	6 (2.1%)
Fasting time (mins)*	368.2 (146.4)	367.3 (155.1)	370.7 (152.6)
Pre-operative intravenous fluid*	46 (12.8%)	45 (12.6%)	36 (12.6%)
Hemoglobin (g.100ml)*	10.3 (2.1)	10.2 (2.0)	10.3 (2.0)
Baseline oxygen saturation	99 (98-100)	99 (98-100)	99 (98-100)
Baseline heart rate	152.4 (19.7)	149.9 (16.3)	153.4 (19.9)
*Surgical details**			
Bilateral hernia exploration/repair	162 (45.9%)	161 (45.4%)	127 (44.4%)
Surgery time: from knife to skin to last stitch (mins)	28.0 (20-38)	28 (20-40)	26.0 (19-35)
*Anesthesia details**			
Anesthesia time: from start skin prep for regional or induction of GA, to out of operating theatre (mins)	51.0 (40-69)	66 (51.5-84.5)	46.5 (39-61)
Suxamethonium	0	1 (0.3%)	0
Non depolarising	20 (5.5%)	125 (34.9%)	0

neuromuscular blocker			
Spinal without caudal*	222 (64%)	0	193 (67%)
Caudal without spinal*	7 (2%)	332 (93.3%)	4 (1%)
Caudal plus spinal*	117 (34%)	0	89 (31%)
Ilioinguinal block	3 (0.8%)	16 (4.5%)	2 (0.7%)
Field block	51 (14.4%)	40 (11.2%)	36 (12.6%)
Laryngeal mask airway used	7 (2.0%)	60 (16.9%)	0
Tracheal tube used	40 (11.3%)	281 (79.4%)	0
Minimum systolic blood pressure (mmHg)	70·7 (15·3)	54·8 (11·7)	73·2 (14·3)

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 before the start of surgery whether the blocks were effective or not. GA as per protocol data are not presented as only two children in the GA arm had surgery cancelled, so the data is very similar to the intention to treat data.   ECG= electrocardiogram; GA= general anesthesia; IQR=interquartile range; RA=regional anesthesia.

Table 2.

	Intention to Treat				
Outcome by frequency and by time period	**GA (355)**	**RA (354)**	**As per Protocol-RA (286)**	**RA to Supplemental GA/Sedation (23)**	**RA to Full GA (37)**
Number of Epochs of Hypotension <35 mm Hg					
Any Epoch < 35 mm Hg	**49% (175)**	**16%(56)**	**9% (27)**	**22% (5)**	**51% (19)**
0	51% (180)	84% (298)	91% (259)	78% (18)	49% (18)
1-4	26% (93)	11% (39)	8% (22)	17% (4)	30% (11)
5-9	15% (54)	3% (12)	2% (5)	4% (1)	11% (4)
10-15	7% (25)	1% (3)	0% (0)	0% (0)	5% (2)
15-19	1% (3)	0% (1)	0% (0)	0% (0)	3% (1)
20 or >	0% (0)	0% (1)	0% (0)	0% (0)	3% (1)
Number of Epochs of Hypotension <45 mm Hg					
Any Epoch < 45 mm Hg	**87% (309)**	**41%(145)**	**34% (98)**	**52% (12)**	**76% (28)**
0	13% (46)	59% (209)	66% (188)	48% (11)	24% (9)
1-4	20% (72)	22% (79)	23% (65)	17% (4)	24% (9)
5-9	36% (128)	14% (49)	10% (29)	26% (6)	32% (12)
10-14	23% (82)	4% (13)	1% (4)	9% (2)	14% (5)
15-19	6% (20)	1% (2)	0% (0)	0% (0)	0% (0)
20 or >	2% (7)	1% (2)	0% (0)	0% (0)	5% (2)

Table 2. Outcomes: Frequency of Hypotensive Events during Anesthesia Time and Blood Pressure Estimates by Time Period.   Outcome measures are reported in percentage of total patients from each treatment group who exhibited outcome and comparison between RA and GA groups are presented as relative risk (RR) with 95% confidence interval (CI) and p-value. RA number for ITT is 354 rather than 361 because of missing outcome data; there were 5 cancelled surgeries and 1 withdrawal of consent and 1 RA case where no outcome data was collected. GA

number for ITT is 355 rather than 358 because there were 2 cancelled surgeries and 1 GA case

with missing hemodynamic data. [a] Estimate not adjusted for gestational age.

Table 3.

Estimates of MAP and HR					
Time Period	GA Mean (SD)	RA Mean (SD)	As per Protocol-RA Mean (SD) (286)	Estimate Difference GA-RA (ITT)	95% CI
Preincision MAP	43.7 (10.5)	55.8 (13.7)	58.2 (13.1)	-12.9	[-14.5, -11.3]*
Preincision HR	144.6 (15.2)	159.3 (21.8)	160.6 (22.1)	-15.4	[-17.6, -13.2]*
Surgical MAP	40.9 (9.3)	52.1 (11.6)	54.2 (10.5)	-12.2	[-13.6, -10.8]*
Surgical HR	138.3 (14.7)	146.8 (19.0)	147.3 (19.2)	-8.9	[-11.1, -6.7]*
Anesthesia MAP	42.4 (10.2	53.0 (12.2)	55.2 (11.3)	-11.3	[-12.7, -10.0]*
Anesthesia HR	141.9 (16.3)	150.9 (20.8)	151.6 (21.1)	-10.3	[-12.2, -8.3]*

Table 3. Time period data presented as mean and standard deviation in mm Hg ; ITT=intention to treat, APP= as per protocol,MAP=mean arterial pressure, GA= general anesthesia, RA=regional anesthesia, SD=standard deviation. CI = Confidence Interval. *P value <0.001 Values are unadjusted for gestational age at birth.

Table 4. Relative Risks for Hypotension-related outcomes General Anesthesia compared with

Regional Anesthesia

			Intention to Treat		As Per Protocol	
		Outcome	Relative Risk (95% CI)	*P* value	Relative Risk (95% CI)	*P* value
Anesthesia Time	AnyHypotension	MAP<45 mm Hg (single epoch) [a]	2.1 [1.8,2.4]	<0.001	2.5 [2.1, 3.0]	<0.001
		MAP<45 mm Hg (triple epoch)	3.5 [2.7,4.4]	<0.001	6.8 [4.5, 10.1]	<0.001
	Moderate Hypotension	MAP<35 mm Hg (single epoch)	2.8 [2.0, 4.1]	<0.001	4.5 [2.7, 7.4]	<0.001
		MAP<35 mm Hg (triple epoch)	5.1 [2.7,10.1]	<0.001	44.7 [6.9,290.1]	<0.001
		Any Intervention for Blood Pressure[b]	2.8 [1.7,4.4]	<0.001	2.8 [1.7, 4.9]	<0.001
Preincision Time	AnyHypotension	MAP<45 mm Hg (single epoch)	2.8 [2.1, 3.6]	<0.001	3.6 [2.4, 5.3]	<0.001
		MAP<45 mm	12.3	<0.001	NA	

		Hg (triple epoch)	[4.8,31.4]			
	Moderate Hypotension	MAP<35 mm Hg (single epoch)	3.4 [2.3, 5.0]	<0.001	5.5 [3.1,9.9]	<0.001
		MAP<35 mm Hg (triple epoch)	NA		NA	
Surgical Time	Any Hypotension	MAP<45 mm Hg (single epoch)[a]	2.1 [1.8, 2.5]	<0.001	2.6 [2.2,3.1]	<0.001
		MAP<45 mm Hg (triple epoch)	3.0 [2.3, 4.1]	<0.001	6.6 [4.4, 9.8]	<0.001
	Moderate Hypotension	MAP<35 mm Hg	3.2 [2.2, 4.7]	<0.001	5.6 [3.5, 8.9]	<0.001
		MAP<35 mm Hg (triple epoch)	5.2 [2.4, 11.1]	<0.001	NA	

Estimates of difference between groups presented as relative risk and 95% confidence intervals (95% CI). [a] Estimate not adjusted for gestational age. [b] Estimate obtained from generalised linear model using a log-link assuming outcome data follows a binomial distribution and robust standard errors allowing for observations within sites to be clustered.

Table 5. Relative risk of 3 consecutive epochs of MAP <35 mm trivariable and multivariable

model during anesthesia time (time in the room).

Predictor	Relative risk tri*	95% CI	P value	Relative risk multi N=609	95% CI	P value
General Anesthesia vs Regional Anesthesia[a]	5.62	2.60,12.1	<0.001	4.64	2.23,9.66	<0.001
Gestational birth age (days)[a]	0.94	.90,0.98	0.009	1.01	0.97,1.06	0.533
Weight at surgery (kg)	0.60	0.49,0.72	<0.001	0.56	0.47,0.67	<0.001

Log Fasting time (1-2.7, 2.7-7.4, 7.4-20 hrs)	0.95	0.65,1.40	0.808	0.94	0.67,1.32	0.711
Log Surgery time (1-2.7, 2.7-7.4, 7.4-20 hrs)	1.27	0.78,2.07	0.331	1.43	0.87,2.36	0.161
Sex male vs female	1.05	0.59,1.85	0.873	0.96	0.56,1.63	0.870
Chronologic Age at surgery (weeks)[b]	0.92	0.86,0.97	0.003	-	-	-
PMA at surgery (weeks)[b]	0.92	0.86,0.97	0.003	-	-	-
Mean Temperature (degrees Celsius)[c]	0.73	0.51,1.03	0.073	-	-	-
Minimum Temperature (degrees Celsius)	0.74	0.60,0.90	0.003	0.78	0.65,0.95	0.011

Estimates of difference between groups presented as relative risk and 95% confidence intervals (95% CI). Relative risk tri is the ratio of risk for factor of interest plus randomized anesthetic group and gestational age, and includes all non-missing observations. Relative risk multi is the ratio of risk found in a multivariable model. [a] Bivariable model containing group and gestational age as predictors [b] Factors were strongly associated with weight at surgery and therefore not included in full model. [c] Factor was strongly associated with mean temperature and therefore not included in full model. PMA means post menstrual age.

Table 6. Interventions for Hypotension

Intervention	GA	RA (ITT)	RA (APP)
Bolus only	14.4% (51)	5.6% (20)	5.2% (15)
Vasoactive only	2.8% (10)	1.4% (5)	1.4% (4)
Both	2.0% (7)	0.3% (1)	0 (0)
Total	19.2% (68)	7.3% (26)	6.6% (19)

Data presented as percentage of group that was treated. Parentheses represent actual number of patients treated. ITT=intention to treat, APP= as per protocol. GA=general anesthesia, RA=regional anesthesia.