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Neurodevelopmental outcome at two years of age after general and awake-regional anaesthesia in infancy: a randomised controlled trial

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Authors' contributions:

AJD was involved in study design and concept, conduct, data coordination, contribution to the statistical analysis plan, data interpretation, writing and coordinating drafts of the manuscript and revising it critically and approving the version to be published. ND was involved in study design and conduct, data acquisition and coordination, data interpretation and revising the manuscript critically. JCdeG was involved in the coordination and supervision of data collection, data analyses and interpretation, contribution to the statistical analysis plan, revised the manuscript and approved the final manuscript as submitted. DEW was involved in study design and conduct, data acquisition and coordination, data interpretation and revising the manuscript critically. LD contributed to protocol development, data collection, statistical plan, statistical analysis, data interpretation and writing of the manuscript. GB was involved in study conduct, data coordination and writing and reviewing the manuscript. RS was the lead neuropsychologist and along with DCB and RWH was involved in study design, concept, conduct, data interpretation and critically revising the manuscript. TS and SJA were involved in interim analyses, contribution to the statistical analysis plan, data interpretation, and revising the manuscript critically. PH was involved in study design, study conduct, interim analyses, contribution to the statistical analysis plan, data interpretation and editing of the manuscript. MJT contributed to the statistical analysis, data interpretation, and manuscript preparation. GG and PLH were involved in study conduct, data acquisition, data interpretation and revising the manuscript critically. IS, BSvonUS, BGL, NW, AL, JTT, DP, OB, PS, ARA and JM were involved in study conduct, data acquisition and coordination and revising the manuscript critically. NSM and MEMcC was involved in study design, concept and conduct, data coordination, data interpretation, writing the manuscript and revising it critically. GF and CB was involved in study design and concept, study conduct, data acquisition, contribution to data interpretation and revising the manuscript critically. GDO was involved in study conduct, data acquisition and coordination, contribution to the statistical analysis plan and revising the manuscript.

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Summary

Background—There is pre-clinical evidence that general anaesthetics affect brain development. There is mixed evidence from cohort studies that young children exposed to anaesthesia may have an increased risk of poorer neurodevelopmental outcome. This trial aims to determine if GA in infancy has any impact on neurodevelopmental outcome. The primary outcome for the trial is neurodevelopmental outcome at 5 years of age. The secondary outcome is neurodevelopmental outcome at two years of age and is reported here.

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Methods—We performed an international assessor-masked randomised controlled equivalence trial in infants less than 60 weeks post-menstrual age, born at greater than 26 weeks gestational age having inguinal herniorrhaphy. Infants were excluded if they had existing risk factors for neurologic injury. Infants were randomly assigned to awake-regional (RA) or sevoflurane-based general anaesthesia (GA). Web-based randomisation was performed in blocks of two or four and stratified by site and gestational age at birth. The outcome for analysis was the composite cognitive score of the Bayley Scales of Infant and Toddler Development, Third Edition. The analysis was as-per-protocol adjusted for gestational age at birth. A difference in means of five points (1/3 SD) was predefined as the clinical equivalence margin. The trial was registered at ANZCTR, ACTRN12606000441516 and ClinicalTrials.gov, NCT00756600.

Findings—Between February 2007, and January 2013, 363 infants were randomised to RA and 359 to GA. Outcome data were available for 238 in the RA and 294 in the GA arms. The median duration of anaesthesia in the GA arm was 54 minutes. For the cognitive composite score there was equivalence in means between arms (RA-GA: +0·169, 95% CI −2·30 to +2·64).

Interpretation—For this secondary outcome we found no evidence that just under an hour of sevoflurane anaesthesia in infancy increases the risk of adverse neurodevelopmental outcome at two years of age compared to RA.

Introduction

There is considerable preclinical evidence describing how GA agents alter brain development in young animals.[1] This includes accelerated apoptosis and a variety of other changes including changes to dendritic morphology.[2–5] There is also evidence that exposure to GA in young animals is associated with long term cognitive and behavioural changes.[3, 6, 7] These effects have been described in a variety of species including non-human primates.[7–10] The changes are seen with several different GA agents, are greater with longer exposure and less severe in older animals.[2, 8] The clinical significance of these findings is unknown and hotly debated.[11–14]

In humans there is conflicting evidence for an association between exposure to anaesthesia in early childhood and adverse long term neurodevelopmental outcome; however confounding limits any assumption of causality.[15–30] Young children that receive anaesthesia are inevitably having surgery or an investigative procedure. Added risk of poor neurodevelopmental outcome may be due to the underlying pathology, co-morbidity or other peri-operative risk factors.

These results have prompted recommendations to consider delaying surgery in infancy and there have been several calls for more research to address this important issue.[12, 13, 31] Given the large number of potential confounding factors, a randomised trial is the best study design to determine if anaesthesia exposure in early childhood causes long term neurodevelopmental changes. Fortuitously there are two established anaesthetic techniques for inguinal herniorrhaphy in infancy; RA and sevoflurane based GA. We therefore undertook a randomised controlled trial comparing neurodevelopmental outcome in children who were randomly assigned to receive RA or sevoflurane based GA for inguinal herniorrhaphy in early infancy: the General Anaesthesia compared to Spinal anaesthesia

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(GAS) trial. The aim of the trial is to determine if GA does not increase the risk of adverse neurodevelopmental outcome. The primary outcome for the overall trial will be the Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III) Full Scale Intelligence Quotient score at five years of age. As a secondary outcome we also planned *a priori* to assess neurodevelopmental outcome at 2 years of age. In this paper we report all secondary outcomes at two years of age. Data from the trial relating to post- anaesthesia apnoea and success of regional block have been published elsewhere.[32, 33]

Methods

Study design

The GAS trial is a prospective, observer blind, international multi-site, randomised, controlled, equivalence trial examining RA versus GA in infants undergoing inguinal herniorrhaphy. The trial was performed at 28 hospitals in Australia, Italy, The USA, The UK, Canada, The Netherlands and New Zealand. Institutional Review Board or Human Research Ethics Committee approval was obtained at each site and written consent obtained from the child's parents or guardians. The protocol has been previously published at http://www.thelancet.com/protocol-reviews/09PRT-9078

Participants

Eligibility criteria included infants up to 60 weeks' postmenstrual age scheduled for unilateral or bilateral inguinal herniorraphy born at greater than 26 weeks gestation. Exclusion criteria included any contraindication for either anaesthetic technique, a history of congenital heart disease requiring surgery or pharmacotherapy, mechanical ventilation immediately prior to surgery, known chromosomal abnormalities or other known acquired or congenital abnormalities which might affect neurodevelopment, previous exposure to volatile GA or benzodiazepines as a neonate or in the third trimester *in utero*, any known neurologic injury such as cystic peri-ventricular leukomalacia or grade three or four intra-ventricular haemorrhage (IVH), any social or geographic factor that may make follow up difficult (such as planned house move, homelessness, no telephone communication available), or having a primary language at home in a region where neurodevelopmental tests are not available in that language. Eligible infants were identified from operating room schedules or at pre-admission clinics and recruited in the clinic or in the preadmission areas of the operating floor.

Randomisation and Masking

A 24-hour web-based randomisation service was managed by The Data Management & Analysis Centre, Department of Public Health, University of Adelaide, South Australia. Participants were randomised with a 1:1 allocation ratio to either GA or RA. Randomisation was performed in blocks of two or four and stratified by site and gestational age at birth: 26 to 29 weeks and six days, 30 to 36 weeks and six days and 37 weeks or more. The anaesthetist was aware of group allocation. Parents were not informed of the group allocation but were told if they asked. The psychologists and paediatricians performing the assessment were masked to group allocation. Once their assessment was completed they were asked to indicate if they were aware of group allocation.

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Procedures

The RA group received either an awake-spinal anaesthetic, an awake-caudal anaesthetic, or a combined spinal-caudal anaesthetic according to institutional protocols. Spinal anaesthesia was performed with 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 US, 0·13ml/kg of hyperbaric 0·75% bupivacaine and in the UK 0·2 ml/kg 0·5% levobupivacaine). Caudal anaesthesia was performed with up to a total dose of 2·5 $mg.kg^{-1}$ of 0·25% bupivacaine. In the UK 0·25% levobupivacaine was used. In the US if surgery was likely to take greater than one hour, 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. Ilioinguinal and field blocks could also be done. The total dose of bupivacaine did not exceed 2·5 mg/kg. In the RA group oral sucrose was used to settle the child if required and all other forms of sedation avoided. If the RA was ineffective then a GA was performed with sevoflurane, and if the child became unsettled intra-operatively sevoflurane was administered to supplement the RA. Both were regarded as protocol violations.

The GA group received sevoflurane for induction and maintenance in an air/oxygen mix. The concentration of sevoflurane was left to the discretion of the anaesthetist, as was choice of airway device, ventilation technique and use of any neuromuscular blocking agents. No opioid or nitrous oxide was allowed. A caudal, ilioinguinal-iliohypogastric and/or field block with bupivacaine could be performed in both groups to provide post-operative analgesia. Oral or intra venous acetaminophen could also be given. Heart rate, blood pressure, oxygen saturation and (where applicable) expired sevoflurane concentrations were recorded every five minutes.

Serum glucose was measured after anesthetic induction. There were rescue protocols for hypoglycaemia, hypotension and hypoxemia. If the blood pressure fell >20% below baseline an intravenous bolus fluid was administered and vasoactive drugs given if deemed necessary. Hypoglycaemia (blood sugar <3·0mmol/L) was treated with a bolus of 5ml/kg of 10% dextrose. Oxygen by face mask in the RA arm and an increased FiO_2 in the GA arm was used at the discretion of the anaesthetist to maintain arterial oxygen saturation > 95%.

Two Year Assessments

Assessments were performed within two months either side of two years of age (corrected for prematurity). The assessment took approximately two hours to complete. A trained psychologist administered the Bayley-III. [34] The Bayley-III has cognitive, language and motor scales. The cognitive scale includes tasks assessing attention, memory, sensorimotor development, exploration, concept formation, and simple problem solving. The language scale assesses expressive and receptive skills, and the motor scale assesses fine and gross motor skills. Parents completed the Bayley-III Social-Emotional and Adaptive Behavior Questionnaires and the MacArthur-Bates Communicative Development Inventory: Words and Sentences (MacArthur-Bates).[35] The MacArthur-Bates is a parent informant measure that assesses expressive language in children aged 16–30 months of age. Demographic data, family history, and medical history were also noted, and a brief physical and neurological

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examination was performed. The physical examination included anthropometric measurements such as length, weight, arm and head circumference. The neurologic examination included cranial nerve examination, posture assessment and the muscle strength, tone and reflexes of the upper and lower extremities.

All study data were sent to the Murdoch Childrens Research Institute in Melbourne, Australia. All forms were checked for data quality by trained research assistants and double checked by a research assistant who was not involved in the primary data collection or entry. An independent data safety monitoring committee met at six monthly intervals during recruitment. Summary data by allocation were presented to the committee. There were no formal interim analyses of neurodevelopmental outcome.

Statistical Analysis

The main outcome for the analysis at 2 years of age was pre-specified to be the composite cognitive score of the Bayley-III. The hypothesis (as stated in the protocol) was that the composite cognitive score of the Bayley-III measured at two years of age in infants who are anaesthetised for inguinal herniorraphy is equivalent when using GA compared with RA. The components of the Bayley-III are reported as scaled scores and as composite scores. The five composite scores (Cognitive, Language, Motor, Adaptive Behaviour, and Social-Emotional Scales) are standardised to have a mean of 100 and a SD of 15 in the reference population. The sub-scales (e.g., fine motor scale) are reported as scaled scores, with a mean of 10 and a SD of 3. The other secondary outcomes for this analysis are the language, motor, social-emotional, and adaptive behaviour scores from the Bayley-III and the age-adjusted Vocabulary Production Score from the MacArthur-Bates. Published normative scores were used at all sites with forms and instructions translated locally. Diagnosis of cerebral palsy was another pre-specified secondary outcome

Since this is an equivalence study, the outcome was analysed on an APP basis to ensure a conservative estimate in the direction of non-equivalence. Equivalence was defined *a-priori* if the 95% confidence interval of the difference in means lies within -five and +five points. ITT analyses were also planned. Analyses were adjusted for categories of gestational age at birth (182–209 days; 210–258 days; ≥259 days)

The sample size was based on the primary outcome for the GAS trial; the five year follow up WPPSI-III Full Scale IQ score. Assuming an expected difference of one standardised score point, and a 90% chance that a 95% confidence interval will exclude a difference of more than five points (the largest difference acceptable to demonstrate equivalence), the trial would need 598 infants in total. Enrolling approximately 720 participants would allow for 10% loss to follow-up and 10% with a major protocol violation.

Multiple imputation using chained equations was used to impute missing outcome data in the analysis of all outcomes.[36] The following pre-specified variables were used as predictor variables within the imputation approach: anaesthesia group, country, gender, gestational age at birth, standardized z-score for birth weight, mother received antenatal steroids, mother diagnosed with chorioamnionitis, IVH, maternal age, maternal education, rescue glucose given intra-venously, need for fluid bolus for hypotension, vasoactive drugs given for

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hypotension, duration of surgery, dose of sevoflurane (concentration x hours), significant post-operative apnoea, corrected age at assessment, any more anaesthetic exposures since the inguinal herniorraphy, any malformations, any chronic illness, any prescribed medication for two months or longer, total length of any readmission to hospital, any interventions for neurodevelopmental problems, diagnosis of cerebral palsy, any other neurological abnormality.

For the purpose of sensitivity analysis, effect estimates were computed using best and worst case imputation scenarios. Furthermore, effect estimates and confidence intervals based on inverse probability of censoring weighting were reported.[37]

Risk ratios with 95% confidence intervals were reported for the proportion of individuals that fall below one and two SDs of the composite cognitive score. Risk ratios were generated using generalized linear models for a binomial distributed response variable employing a log link (binomial log-linear regression). These analyses were not pre-specified in the study protocol (*post hoc* analyses). All analyses were carried out in Stata 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

The GAS trial is registered in Australia and New Zealand at ANZCTR: ID# ACTRN12606000441516 first registered on 16th October 2006; in the United States (US) at ClinicalTrials.gov: ID#: NCT00756600 first registered on 18th September 2008; and in the United Kingdom (UK) at UK Clinical Research Network (UKCRN) ID#: 6635 (ISRCTN ID#: 12437565; MREC No: 07/S0709/20).

Role of the Funding Source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had access to the data, and AJD, GO and Suzette Sheppard were responsible for submitting the manuscript. AJD made the final decision to submit the paper for publication.

Results

Seven hundred twenty-two infants were recruited into the trial between February 9, 2007, and January 31, 2013 from 28 centres in Australia, the US, the UK, Italy, the Netherlands, Canada and New Zealand (appendix). There were two mis-randomisations and one withdrawal of consent leaving 361 in the ITT analysis in the RA arm and 358 in the GA arm. Table 1 summarises demographic data for each arm at baseline and table 2 summarises demographic data at two years. There were 74 protocol violations in the RA arm (five due to surgery being cancelled and 69 receiving some sevoflurane or other GA) and two violations in the GA arm (surgery cancelled).

Follow up was from March 5, 2009 to March 6, 2015. Forty-seven families were lost to follow up in the GA arm and 52 in the RA arm. Of those lost to follow up some reason for non-attendance was gained in 19 and in only one case was non-attendance due to developmental delay (this child was in the RA arm). Of those that attended for assessment, the cognitive scale of the Bayley-III was completed by 292 in the RA arm and 295 in the GA

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arm (Figure 1). Very few children were unable to complete the Bayley-III due to developmental delay or other recognised reasons for cognitive impairment. In 97% of cases the psychologist and paediatrician were unaware of group allocation at the time of assessment. (appendix)

The Bayley-III Cognitive, Language, Motor, Social-Emotional and Adaptive Behaviour scores, and the MacArthur-Bates data are summarised for each group in table 3.

For the Cognitive Composite score there was evidence for equivalence in means between RA and GA arms in both the APP and the ITT analyses using multiple imputation to account for missing outcome data (RA-GA: +0·169, 95% CI −2·30 to +2·64; and RA-GA: +0·256, 95% CI −2·06 to +2·57 for APP and ITT respectively). These results were consistent with the findings of the complete case analyses (RA-GA: +0·458, 95% CI −2·02 to +2·94; and RA-GA: +0·430, 95% CI −1·90 to +2·76, for APP and ITT respectively). There was also evidence for equivalence between arms in the Composite Motor scores, Composite Language scores and the Composite Adaptive Behavior scores (Table 4). The results were consistent in both APP and ITT analyses, and when using complete case and multiple imputation. With mean differences of one and two score points (multiple imputation and complete case analysis for APP/ITT) and upper 95% confidence interval limits exceeding the pre-specified five point equivalence margin, evidence for equivalence with regard to the Social-Emotional Composite scale of the Bayley-III was not compelling. There was no evidence for a difference between groups in MacArthur-Bates scores (Table 4).

The results of the inverse probability weighting and worst case imputation scenarios for missing data are presented in the appendix. The worst case scenario results represent theoretical boundaries to what extent the actual effect estimates could have been affected by selective dropout. However, both multiple imputation analysis as well as inverse probability weighting demonstrated consistent robustness of the study findings with regard to data missingness.

Overall a low number of children had a diagnosis of cerebral palsy, hearing or visual impairment or specific behavioural diagnoses such as autistic spectrum disorder (ASD) (table 5). The event rate was too low for any meaningful comparative analysis. There was no evidence for a difference between arms in the proportion of children one or two SDs below the age mean on the cognitive composite score (appendix).

Details of adverse events during and immediately after anaesthesia have been reported in the earlier publication.[32]

Research in context

Evidence before this study

Medline and Cochrane controlled trial register were searched (search last done 18th September 2015) for original research and meta-analyses describing the association between anaesthesia exposure in early life and neurodevelopmental outcome. Combinations of search terms “anesthesia”, and “child development”, or “learning disorders” were used. The search

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revealed no randomised trials but several cohort studies. There have been numerous reviews that have concluded that there is an association between anaesthesia in childhood and neurodevelopmental outcome.[19, 31] There have been two meta-analyses that have found evidence for an association between anaesthesia in children and a range of neurodevelopmental outcomes.[16, 30] All reviews and meta-analyses acknowledge the weaknesses of the cohort studies; including strong likelihood of confounding, bias, heterogeneous populations at times of exposure, and heterogeneous outcome measures, some of which are poorly defined or insensitive. All conclude that causation cannot be established or excluded.

Added value of this study

We report a secondary outcome from the first randomised controlled trial assessing the impact of general anaesthesia in infancy on neurodevelopmental outcome. Using the best measure of neurodevelopment available for assessing a two year old child, strong evidence for equivalence between awake-regional and just under an hour of general anaesthesia was found. However it should be noted that this was an analysis of a secondary outcome with the primary outcome planned at five years of age, and given the limited sensitivity of developmental assessment at two years of age, this trial does not provide the definitive answer.

Implications of all the available evidence

Although there are some limitations that should be noted when interpreting the trial, the randomised prospective design adds significantly to the weight that should be given to the results compared to the mixed results found in previous cohort studies. It should however be emphasised that reassessment at an older age is necessary before definitive conclusions can be drawn. The trial does not rule out the possibility that longer, or multiple exposures to anaesthesia in early childhood may cause neurodevelopmental changes. Further research is needed to address these questions.

Discussion

In this trial we found strong evidence for equivalence between RA and GA in infancy in terms of neurodevelopmental outcome at two years of age. Equivalence was demonstrated in multiple domains of neurodevelopmental assessment and the 95% confidence intervals fell within a third of a SD; well inside our pre-defined boundaries of clinical equivalence.

There are no previous randomised trials examining the effect of anaesthesia in infancy on long term neurodevelopmental outcomes (see research in context panel). Previous cohort studies have found mixed results.[19] Some studies have found an association between exposure to anaesthesia in early childhood and increased risk of poor neurodevelopmental outcome.[16–18, 20–24, 28] Although this association fits with preclinical animal data, it may also be explained by the confounding effects of surgery, pathology or co-morbidity. Conversely some cohort studies have found no evidence for an association.[25–27] These studies have limited ability to rule out a link between anaesthesia and neurodevelopmental outcome due to a reliance on outcome measures, such as school grade, which may not detect

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subtle effects, or their broad inclusion criteria include children exposed to anaesthesia at an older age where the risk may be less. The heterogeneity of the cohort studies also make it difficult to analyse the effects of duration of exposure, type of anaesthetic drugs used, doses or combination of drugs used. The above limitations inherently limit the capacity for cohort studies to determine the link between exposure to anaesthesia and neurodevelopmental outcome. These limitations highlight the importance of methodologically robust and adequately powered trials such as this trial.[31]

In this analysis we chose the cognitive scale of the Bayley-III as the main outcome of interest. Changes seen in preclinical studies tend to be diffusely distributed over several brain regions. Such diffuse changes are most likely to have an impact on general cognition. Of note, there was also no evidence for a difference in any of the other Bayley-III domains.

Two recent studies have found that while children exposed to anaesthesia had similar school grades, those exposed had an increased risk of not sitting the tests.[26, 28] This raises the possibility that a sub-population of exposed children may have significant neurodevelopmental delay. To investigate this possibility we compared the proportion of children in each arm that scored two standard deviations below the age mean on the composite cognitive score. There was no evidence for a difference; however given the limited power of this analysis, equivalence cannot be assumed. We have also reported the number of children with the diagnosis of ASD, cerebral palsy and visual or hearing defects. This trial was not powered to detect differences in these diagnoses or events, and as expected we found a low event rate in both arms. It should also be noted that at two years of age it is difficult to accurately diagnose the presence of disorders such as ASD, or to accurate assess vision and hearing, and it is possible some children may still have undiagnosed neurologic or neurobehavioural disorders.

Most pre-clinical studies suggest that prolonged exposure to GA is required before injury is seen, usually at least two to three hours.[8] However changes have been seen with one hour of exposure.[38] In this trial the median sevoflurane exposure was 54 minutes in the GA arm and hence the results are consistent with the majority of pre-clinical data. The trial is an important adjunct to these data as translating doses and exposures from animal to humans is uncertain, and it is possible that shorter duration of exposure may still have clinically relevant effects that cannot be detected in animal models.

In human cohorts some studies have found an association with a single short exposure. [17, 39] Others studies have only found an association after longer or multiple exposures.[22] This study that found there was no increase in learning disabilities in infants and toddlers exposed to two or less hours of GA.[22] This study revealed that anaesthetic exposure was less than 90 minutes in 61% of the exposed patients and less than two hours in 85% of the exposed patients highlighting that the vast majority of anaesthetics in young children are of fairly brief duration. An internal audit of anaesthetic duration in infants at Boston Children’s Hospital revealed that 53% of anaesthetics done in babies less than12 months of age were less than two hours duration. Thus, as far as duration of exposure, it is likely our results are pertinent to approximately half the anaesthetics delivered to infants.

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The finding of equivalence after short exposure does not rule out the possibility that longer exposure to anaesthetics may have an effect on neurodevelopment. Further trials are required before any assumptions can be made about the impact of prolonged anaesthesia exposure in infancy.

Some studies have also found a stronger association between multiple anaesthesia exposures and adverse outcome than with single exposure.[20, 30] It is possible this reflects a greater effect of confounding; inevitably children having multiple procedures are more likely to have significant conditions or chronic disease. Our trial cannot address the possible increased toxicity with multiple exposures.

There are a number of limitations to our trial. RA inevitably has a failure rate. As this was an equivalence trial we took the APP analysis to be the most conservative analysis – assuming that treatment failure would bias toward no difference. Given the possibly contentious nature of this assumption, we planned *a priori* to perform a secondary ITT analysis. There were no measureable differences between APP and ITT analyses, implying no bias was introduced by treatment failure. In this study there was a loss to follow up of almost 14%. This, along with RA failure lead to an appreciable amount of missing data, however both the multiple imputation analysis and the inverse probability weighting demonstrated consistent robustness of the findings.

Another limitation is that while the Bayley-IIII is a well validated assessment tool of current development, early neurobehavioural assessment of children is not a perfect predictor of long term outcome due to the considerable variability in developmental timing in young children. Whilst the Bayley-III has been shown to have a stronger correlation with IQ at age five years than earlier versions of the test, it was not designed to assess a broad range of cognitive functions. Cognitive skills emerge and differentiate over childhood and a more detailed neuropsychological assessment is required at a later date to identify mild or circumscribed deficits in cognitive functions as executive skills and memory.[4041] It is thus important that the children be reassessed later in their development to confirm the results and to more thoroughly examine multiple domains of cognition. Children in this trial are undergoing assessment at five years of age and the results should be known after 2018.

It is important to note that this manuscript reports the results of a secondary outcome. The primary outcome is planned at 5 years, for the reason mentioned above. This analysis of the secondary outcome was pre-specified in the study protocol, however the study was not specifically powered for the secondary outcome and thus it should be interpreted with caution and not regarded as definitive. The analysis of the secondary outcome was planned due to the recognition that there was growing concern over the issue of neurotoxicity and existing evidence to guide practice was inherently limited, and while the two year assessment was not definitive, it would still provide higher quality evidence than that which existed to date. The two year assessment was also planned due to concerns over the feasibility of maintaining the cohort for the longer term follow-up.

In this study over 80% of participants were male. It is well recognised that gender can have an impact on recovery from brain injury. The effect is variable and depends on the nature of

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the injury and outcome measured, though generally greater effects are seen in males and indeed the neurotoxic effect of anaesthesia on rodents has been shown to be greater in males.[42] Thus the finding of equivalence in our trial with a preponderance of males makes it unlikely that equivalence would not also be demonstrated in females.

In this trial sevoflurane was used without other general anaesthetics. We chose a sevoflurane only anaesthetic as this reflects common practice for anaesthesia for inguinal herniorrhaphy, and the preclinical effects of sevoflurane have been clearly described. There are some preclinical studies that suggest combinations of general anaesthetics may be more injurious and thus our trial cannot shed light on the possibility that an effect may be seen if other agents are added. [3]

Lastly it should also be noted that the MacArthur-Bates is dependent on parental report and hence may be open to bias. In addition the standardisation data is of varying degrees of validation across different languages.

In conclusion, this trial found strong evidence that exposure of just under an hour to a sevoflurane GA in infancy does not increase the risk of adverse neurodevelopmental outcome at two years of age. While not definitive, this is the strongest clinical evidence to date that just under an hour of sevoflurane GA in infancy does not result in significant neurotoxicity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

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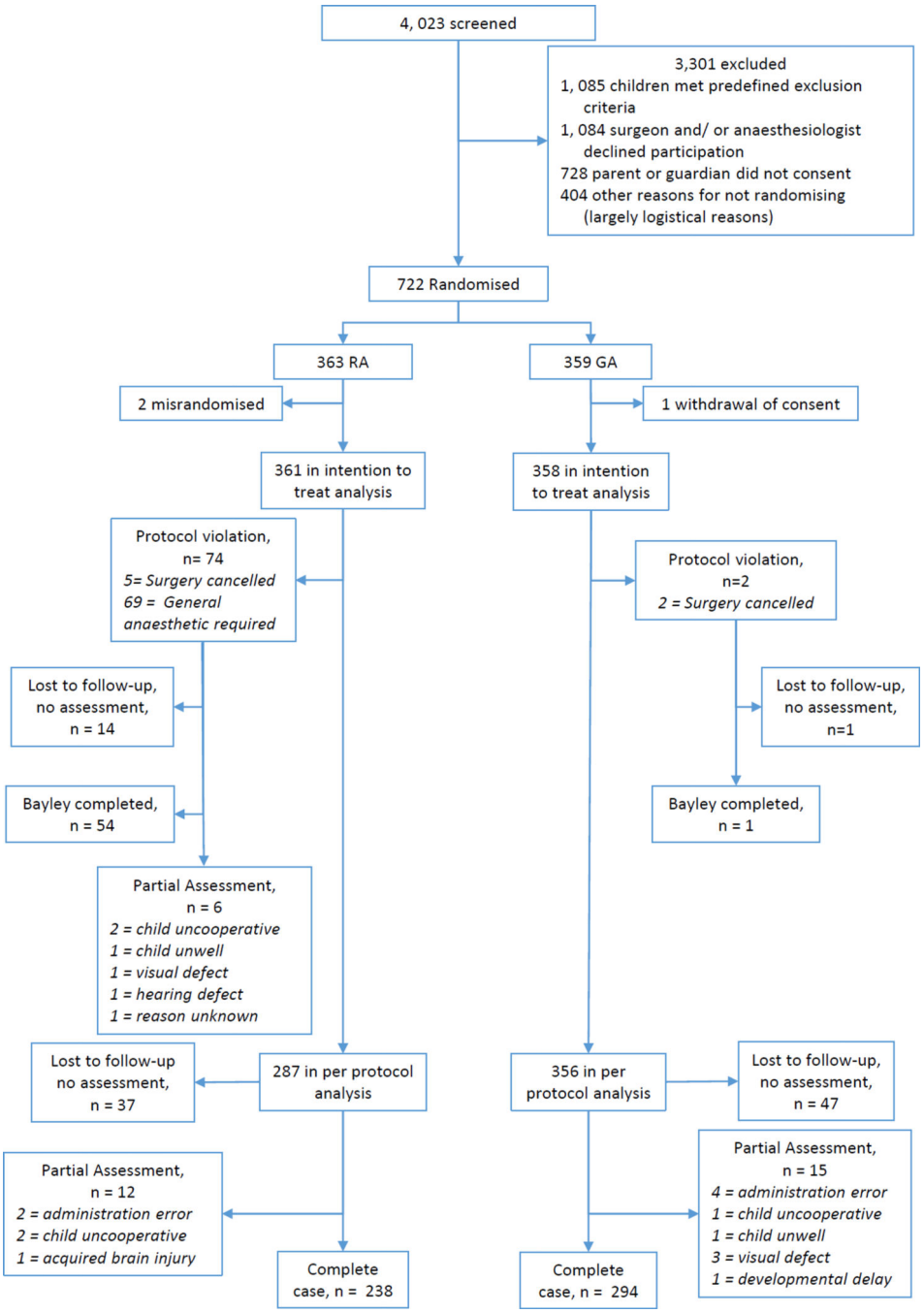

Figure 1.
Trial profile

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Table 1

Descriptive statistics of birth, pregnancy and peri-anaesthesia data

	RA Arm APP (N=287)	GA Arm APP (N=356)	RA Arm ITT (N=361)	GA Arm ITT (N=358)
Baseline demographics				
Gender, Male	232 (81%)	304 (85%)	294 (82%)	306 (86%)
Chronological age at surgery (days)	68·9 (31)	71·1 (32)	70·1 (32)	71·0 (32)
Post menstrual age at surgery (days)	317·2 (32)	319·7 (32)	318·3 (33)	319·5 (32)
Weight of child at surgery (kg)	4·2 (1·1)	4·3 (1·1)	4·2 (1·1)	4·3 (1·1)
Pregnancy and birth details				
Mean (SD) Post menstrual age at birth (days)	248·2 (29)	248·6 (27)	248.3 (29)	248.6 (27)
Prematurity (Born < 37 weeks gestation)	160 (56%)	195 (55%)	198 (55%)	196 (55%)
Birth Weight (kg)	2·3 (0·9)	2·3 (0·9)	2·4 (0·9)	2·3 (0·9)
Z score for birth weight	−0.68 (1·3)	0.69 (1·3)	−0.66 (1·2)	−0.69 (1·3)
Median (IQR) Apgar score at 1 minute	9 (7–9)	8·5 (7–9)	9 (7–9)	9 (7–9)
Median (IQR) Apgar score at 5 minutes	9 (9–10)	9 (9–10)	9 (9–10)	9 (9–10)
One of a multiple pregnancy	52 (18%)	61 (17%)	62 (17%)	62 (17%)
Mother received partial course antenatal steroids	16 (6%)	19 (5%)	20 (6%)	19 (5%)
Mother received complete course antenatal steroids	95 (33%)	98 (28%)	114 (32%)	98 (28%)
Mother diagnosed with chorioamnionitis	10 (4%)	12 (3%)	11 (3%)	12 (3%)
Prolonged rupture of the membranes (>24 hours)	28 (10%)	34 (10%)	32 (9%)	34 (10%)
Mother diagnosed with pre-eclampsia	50 (17%)	68 (19%)	60 (17%)	68 (19%)
Sepsis during pregnancy	36 (13%)	50 (14%)	43 (12%)	50 (14%)
Mode of delivery of birth				
Cephalic vaginal	135 (47%)	157 (44%)	169 (47%)	157 (44%)
Breech vaginal	1 (<1%)	6 (2%)	3 (1%)	6 (2%)
Compound vaginal	2 (1%)	4 (1%)	3 (1%)	4 (1%)
Caesarean section	149 (52%)	189 (53%)	185 (51%)	191 (53%)

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	RA Arm APP (N=287)	GA Arm APP (N=356)	RA Arm ITT (N=361)	GA Arm ITT (N=358)
Caesarean section and mother went into labour	42 (15%)	58 (16%)	52 (14%)	59 (16%)
Mother exposed to nitrous oxide during delivery	48 (18%)	62 (18%)	61 (18%)	62 (18%)
IVH	7 (2%)	6 (2%)	8 (2%)	6 (2%)
IVH Grade 1	5 (2%)	6 (2%)	5 (2%)	6 (2%)
IVH Grade 2	2 (1%)	0	2 (1%)	0
Retinopathy of prematurity	17 (9%)	16 (6%)	30 (8%)	16 (6%)
Hearing defects detected by perinatal screening	7 (3%)	10 (3%)	8 (3%)	10 (3%)
PDA diagnosed	23 (8%)	21 (6%)	27 (8%)	21 (6%)
PDA never treated	9 (3%)	9 (3%)	11 (3%)	9 (3%)
PDA treated with non-steroidal anti-inflammatory drugs	14 (5%)	10 (3%)	16 (4%)	10 (3%)
Familial Demographics:				
Primary language(s) only spoken *	252 (88%)	305 (86%)	311 (86%)	307 (86%)
Maternal Age at Birth >21	273 (96%)	339 (95%)	339 (95%)	341 (95%)
Family structure two caregivers together, at Birth	261 (91%)	324 (91%)	328 (91%)	326 (91%)
Maternal education				
Completed tertiary studies	150 (52%)	171 (48%)	181 (51%)	171 (48%)
Continuing tertiary studies	50 (17%)	67 (19%)	68 (19%)	67 (19%)
Completed year 11 or 12	62 (22%)	83 (23%)	77 (22%)	84 (24%)
Did not complete year 11	25 (9%)	33 (9%)	32 (9%)	34 (10%)
Anaesthesia Details:				
Median (IQR)Blood glucose level (mmol/L)	5·4 (4·7–6·1)	5·5 (4·8–6·4)	5·4 (4·7–6·2)	5·5 (4·8–6·4)
Rescue glucose given IV	2 (1%)	4 (1%)	2 (1%)	4 (1%)
Haemoglobin (g/100 ml)	10·3 (2·1)	10·2 (2·0)	10·3 (2·1)	10·2 (2·0)
Need for fluid bolus for hypotension	15 (5%)	59 (17%)	21 (6%)	59 (17%)
Vasoactive drugs given (including atropine)	4 (1%)	17 (5%)	6 (2%)	17 (5%)

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	RA Arm APP (N=287)	GA Arm APP (N=356)	RA Arm ITT (N=361)	GA Arm ITT (N=358)
Median (IQR)Duration of surgery (mins)	26·0 (19·0–35·0)	28·0 (20·0–40·0)	28·0 (20·0–38·0)	28·0 (20·0–40·0)
Median (IQR) Duration of sevoflurane exposure (mins)	NA	54.0 (41.0–70.0)	42.0 (31.0–62.5) **	54.0 (41.0–70.0)
End tidal sevoflurane concentration (%)	NA	2·6 (0·7)	2·3 (0·8) **	2·6 (0·7)
Total concentration x hours per	NA	2·6 (1·1)	1·9 (1·0) **	2·6 (1·1)
Any significant apnoea to 12hrs postop ***	6 (2%)	15 (4%)	10 (3%)	15 (4%)

Data are n(% of non-missing data) or Mean (SD), unless otherwise stated. APP= As Per Protocol; GA= General Anaesthesia; ITT= Intention to treat; IV= Intra-venously; IVH= Intra ventricular haemorrhage; IQR= Interquartile Range; PDA = Patent ductus arteriosus; RA= Awake Regional Anaesthesia.

* The primary language spoken at home, is the primary language in each country that the Bayley was conducted e.g in Italy it was conducted in Italian

** For those cases that received sevoflurane

*** significant apnoea defined as a pause in breathing for more than 15 seconds or more than 10 seconds if associated with oxygen saturation less than 80% or bradycardia (20% decrease in heart rate)

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Table 2

2 year descriptive statistics demographic data

	RA Arm APP (N=287)	GA Arm APP (N=356)	RA Arm ITT (N=361)	GA Arm ITT (N=358)
Assessment details				
Location of two year assessment at hospital	204 (96%)	240 (94%)	250 (95%)	241 (94%)
Family demographics at two years				
Paid employment is main family income	222 (90%)	267 (88%)	274 (90%)	268 (88%)
Family structure, two caregivers living together	226 (91%)	274 (90%)	277 (90%)	275 (90%)
Number of children at home				
1	88 (36%)	118 (39%)	115 (37%)	118 (39%)
2	109 (44%)	120 (40%)	131 (43%)	121 (40%)
3	37 (15%)	43 (14%)	45 (14%)	43 (14%)
>3	14 (6%)	22 (7%)	17 (6%)	22 (7%)
Birth order				
1	123 (50%)	161 (53%)	154 (50%)	161 (53%)
2	87 (35%)	90 (30%)	107 (35%)	91 (30%)
>2	37 (15%)	52 (17%)	46 (15%)	52 (17%)
Corrected age at assessment (weeks)	108·9 (13·0)	108 (9·8)	108·7 (12·5)	108 (9·8)
Events since original anaesthesia				
Number of hospitalisations since inguinal herniorrhaphy operation				
0	172 (69%)	206 (68%)	210 (68%)	207 (68%)
1	51 (20%)	64 (21%)	69 (22%)	64 (21%)
2	14 (6%)	18 (6%)	16 (5%)	18 (6%)
>2	6 (2%)	8 (3%)	8 (3%)	8 (3%)
Number of anaesthetics since				

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	RA Arm APP (N=287)	GA Arm APP (N=356)	RA Arm ITT (N=361)	GA Arm ITT (N=358)
inguinal hemiorrhaphy operation				
1	34 (14%)	36 (12%)	42 (14%)	36 (12%)
2	5 (2%)	6 (2%)	6 (2%)	6 (2%)
>2	4 (2%)	4 (1%)	4 (1%)	4 (1%)
Child had a head injury that involved the loss of consciousness	7 (3%)	4 (1%)	7 (2%)	4 (1%)
Child has an acquired brain Injury	1 (0%)	1 (0%)	1 (0%)	1 (0%)
Child has any malformations				
Cardiac	0	4 (1%)	0	4 (1%)
Central Nervous System	3 (1%)	1 (<1%)	3 (1%)	1 (<1%)
Genitourinary	6 (2%)	4 (1%)	8 (3%)	4 (1%)
Genetic condition	1 (<1%)	0	1 (<1%)	0
Respiratory	0	1 (<1%)	0	1 (<1%)
Skeletal	4 (2%)	11 (4%)	4 (1%)	11 (4%)
Cleft lip/palate	1 (<1%)	0	1 (<1%)	0
Craniofacial	2 (1%)	0	2 (1%)	0
Child has any chronic illness	42 (17%)	43 (14%)	50 (16%)	43 (14%)
Child had any prescribed medication for two months or longer	43 (17%)	50 (16%)	93 (17%)	59 (19%)
Child had febrile seizures following the hernia repair	8 (3%)	9 (3%)	10 (3%)	9 (3%)
Child had other seizures following the hernia repair	1 (<1%)	4 (1%)	1 (<1%)	4 (1%)
The child has had an intervention for neurodevelopmental issues since the inguinal herniorrhaphy operation	46 (19%)	55 (18%)	54 (18%)	55 (18%)
Speech Therapy	22 (9%)	27 (9%)	28 (9%)	27 (9%)
Physiotherapy	22 (9%)	27 (9%)	26 (8%)	27 (9%)
Occupational Therapy	9 (4%)	12 (4%)	12 (4%)	12 (4%)

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	RA Arm APP (N=287)	GA Arm APP (N=356)	RA Arm ITT (N=361)	GA Arm ITT (N=358)
Psychology	1(<1%)	6 (2%)	1 (<1%)	6 (2%)
Developmental medicine/early intervention	8 (3%)	7 (2%)	9 (3%)	7 (2%)
Child attends play group/child Care on a regular basis	147 (60%)	177 (58%)	186 (61%)	178 (58%)
Physical examination				
Height (cm)	86·6 (5·5)	86·9 (4·9)	86·4 (5·2)	86·9 (4·9)
Weight (kg)	12·6 (2·0)	12·6 (1·9)	12·6 (2·0)	12·6 (1·9)
Head circumference (cm)	49·1 (2·1)	48·8 (2·2)	49·0 (2·0)	48·8 (2·2)
Arm circumference (cm)	16·4 (2·0)	16·1 (1·8)	16·4 (2·0)	16·1 (1·8)

Data are n(% of non-missing data) or Mean (SD), unless otherwise stated. APP= As Per Protocol; GA=General Anaesthesia; ITT= Intention to treat; RA= Awake Regional Anaesthesia.

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Table 3

Descriptive statistics Bayley-III and Macarthur-Bates Scores by group

	RA Arm APP	GA Arm APP	RA Arm ITT	GA Arm ITT
Cognitive				
Cognitive, Scaled Score	238, 9·7 (2·8)	294, 9·6 (2·9)	292, 9·7 (2·8)	295, 9·6 (2·9)
Cognitive, Composite Score	238, 98·6 (14·2)	294, 98·2 (14·7)	292, 98·6 (14·2)	295, 98·2 (14·6)
Language				
Receptive Language, Scaled Score	236, 8·7 (2·9)	285, 8·6 (2·9)	287, 8·8 (2·9)	286, 8·6 (2·9)
Expressive Language Scaled Score	235, 9·3 (2·9)	290, 9·3 (3·0)	287, 9·4 (2·9)	291, 9·3 (3·0)
Language, Composite Score	235, 94·6 (15·4)	285, 94·0 (15·6)	286, 94·9 (15·5)	286, 94·0 (15·6)
Motor				
Fine Motor, Scaled Score	234, 10·5 (2·7)	287, 10·4 (2·7)	287, 10·6 (2·8)	288, 10·4 (2·7)
Gross Motor, Scaled Score	234, 8·8 (2·4)	279, 8·7 (2·6)	285, 8·9 (2·5)	280, 8·7 (2·6)
Motor, Composite Score	232, 98·3 (13·2)	274, 97·9 (13·4)	283, 98·9 (13·5)	275, 97·8 (13·4)
Social Emotional				
Social Emotional, Scaled Score	218, 9·5 (3·8)	267, 9·1 (3·7)	267, 9·5 (3·8)	268, 9·1 (3·7)
Social Emotional, Composite Score	218, 97·4 (19·0)	267, 95·4 (18·3)	267, 97·4 (19·2)	268, 95·4 (18·3)
Adaptive Behaviour				
Communication Scaled Score	233, 9·7 (2·9)	291, 9·6 (2·9)	288, 9·8 (2·9)	292, 9·6 (2·9)
Community Use Scaled Score	233, 9·8 (2·8)	291, 9·9 (2·7)	288, 9·9 (2·8)	292, 9·8 (2·7)
Functional Pre-Academics Scaled Score	233, 9·0 (3·0)	291, 9·2 (2·9)	288, 9·1 (3·0)	292, 9·2 (2·9)
Home Living Scaled Score	233, 9·9 (2·8)	291, 10·1 (2·7)	288, 9·9 (2·9)	292, 10·1 (2·7)
Health and Safety Scaled Score	233, 9·0 (2·8)	291, 9·3 (2·7)	288, 9·0 (2·9)	292, 9·3 (2·7)
Leisure Scaled Score	233, 9·4 (3·0)	291, 9·9 (2·8)	288, 9·5 (3·1)	292, 9·9 (2·8)
Self-Care Scaled Score	233, 6·8 (2·6)	291, 6·6 (2·5)	288, 6·8 (2·6)	292, 6·6 (2·5)
Self-Direction Scaled Score	233, 9·7 (3·2)	291, 10·0 (3·2)	288, 9·8 (3·2)	292, 10·0 (3·2)
Social Scaled Score	233, 9·3 (2·9)	291, 9·5 (2·8)	288, 9·4 (2·9)	292, 9·5 (2·8)
Motor Scaled Score	233, 9·8 (3·2)	291, 10·0 (2·9)	288, 9·9 (3·3)	292, 10·0 (2·9)
Adaptive Behaviour Composite Score	233, 93·1 (15·6)	291, 94·3 (14·7)	288, 93·4 (16·1)	292, 94·3 (14·7)
MacArthur Bates Percentile Score	195, 32·4 (27·9)	247, 34·7 (28·7)	240, 33·6 (28·0)	247, 34·7 (28·7)

Data as n, mean (SD). APP= As Per Protocol; GA= General Anaesthesia; ITT= Intention to treat; RA= Awake-Regional Anaesthesia.

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Table 4

Between group comparisons in Bayley-III and MacArthur-Bates scores

Scale		*A: RA - GA	SEA	95% CI forA: RA - GA	
Cognitive Composite score	APP multiple imputation	0·169	1·26	−2·30	2·64
	APP complete case	0·458	1·26	−2·02	2·94
	ITT multiple imputation	0·256	1·18	−2·06	2·58
	ITT complete case	0·430	1·19	−1·90	2·76
Language composite score	APP multiple imputation	1·146	1·39	−1·59	3·88
	APP complete case	0·628	1·37	−2·07	3·32
	ITT multiple imputation	1·454	1·32	−1·14	4·05
	ITT complete case	0·942	1·30	−1·61	3·49
Motor composite score	APP multiple imputation	0·598	1·20	−1·77	2·97
	APP complete case	0·410	1·19	−1·92	2·74
	ITT multiple imputation	0·143	1·13	−1·08	3·37
	ITT complete case	1·031	1·14	−1·20	3·26
Social emotional composite score	APP multiple imputation	1·005	2·09	−3·12	5·13
	APP complete case	2·012	1·70	−1·32	5·35
	ITT multiple imputation	1·183	2·03	−2·82	5·19
	ITT complete case	2·015	1·62	−1·17	5·20
Adaptive behaviour composite score	APP multiple imputation	−0·893	1·34	−3·52	1·73
	APP complete case	−1·223	1·33	−3·83	1.38
	ITT multiple imputation	−0·502	1·28	−3·03	2·02
	ITT complete case	−0·830	1·28	−3·34	1·68
MacArthur Bates Percentile Score	APP multiple imputation	−1·811	3·06	−7·85	4·23
	APP complete case	−2·359	2·71	−7·69	2·98
	ITT multiple imputation	−0·544	2·87	−6·20	5·11
	ITT complete case	−1·113	2·57	−6·17	3·94

*Adjusted for gestational age at birth. APP= As Per Protocol; GA= General Anaesthesia; ITT= Intention to treat; RA= Awake Regional Anaesthesia.

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Table 5

2 year non-psychometric outcome data

	RA Arm APP (N=287)	GA Arm APP (N=356)	RA Arm ITT (N=361)	GA Arm ITT (N=358)
Child has a hearing Defect				
Conductive	9 (3%)	6 (2%)	9 (2%)	6 (2%)
Sensorineural	0	3 (1%)	1 (<1%)	3 (1%)
Child has a hearing aid	1 (8%)	3 (25%)	2 (15%)	3 (23%)
Child is legally blind (<6/60 in both eyes)	1 (2%)	0	1 (2%)	0
Child has Cerebral Palsy	1 (<1%)	4 (1%)	1 (0%)	4 (1%)
The child has Autism Spectrum Disorder	2 (1%)	0	2 (1%)	0

Data are n (% of non-missing data), unless otherwise stated. APP= As Per Protocol; GA= General Anaesthesia; ITT= Intention to treat; RA= Regional Anaesthesia.

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