Neurodevelopmental outcome at 5 years of age after general anaesthesia or awake-regional anaesthesia in infancy (GAS): an international, multicentre, randomised, controlled equivalence trial

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Summary

Background In laboratory animals, exposure to most general anaesthetics leads to neurotoxicity manifested by neuronal cell death and abnormal behaviour and cognition. Some large human cohort studies have shown an association between general anaesthesia at a young age and subsequent neurodevelopmental deficits, but these studies are prone to bias. Others have found no evidence for an association. We aimed to establish whether general anaesthesia in early infancy affects neurodevelopmental outcomes.

Methods In this international, assessor-masked, equivalence, randomised, controlled trial conducted at 28 hospitals in Australia, Italy, the USA, the UK, Canada, the Netherlands, and New Zealand, we recruited infants of less than 60 weeks' postmenstrual age who were born at more than 26 weeks' gestation and were undergoing inguinal herniorrhaphy, without previous exposure to general anaesthesia or risk factors for neurological injury. Patients were randomly assigned (1:1) by use of a web-based randomisation service to receive either awake-regional anaesthetic or sevoflurane-based general anaesthetic. Anaesthetists were aware of group allocation, but individuals administering the neurodevelopmental assessments were not. Parents were informed of their infants group allocation upon request, but were told to mask this information from assessors. The primary outcome measure was full-scale intelligence quotient (FSIQ) on the Wechsler Preschool and Primary Scale of Intelligence, third edition (WPPSI-III), at 5 years of age. The primary analysis was done on a per-protocol basis, adjusted for gestational age at birth and country, with multiple imputation used to account for missing data. An intention-to-treat analysis was also done. A difference in means of 5 points was predefined as the clinical equivalence margin. This completed trial is registered with ANZCTR, number ACTRN12606000441516, and ClinicalTrials.gov, number NCT00756600.

Findings Between Feb 9, 2007, and Jan 31, 2013, 4023 infants were screened and 722 were randomly allocated: 363 (50%) to the awake-regional anaesthesia group and 359 (50%) to the general anaesthesia group. There were 74 protocol violations in the awake-regional anaesthesia group and two in the general anaesthesia group. Primary outcome data for the per-protocol analysis were obtained from 205 children in the awake-regional anaesthesia group and 242 in the general anaesthesia group. The median duration of general anaesthesia was 54 min (IQR 41–70). The mean FSIQ score was 99·08 (SD 18·35) in the awake-regional anaesthesia group and 98·97 (19·66) in the general anaesthesia group, with a difference in means (awake-regional anaesthesia minus general anaesthesia) of 0·23 (95% CI –2·59 to 3·06), providing strong evidence of equivalence. The results of the intention-to-treat analysis were similar to those of the per-protocol analysis.

Interpretation Slightly less than 1 h of general anaesthesia in early infancy does not alter neurodevelopmental outcome at age 5 years compared with awake-regional anaesthesia in a predominantly male study population.

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Research in context

Evidence before this study

We searched MEDLINE and the Cochrane controlled trials register (from their inception to May 20, 2018) for original research and meta-analyses describing the association between anaesthetic exposure during childhood and neurodevelopmental outcome. The search terms used were "anesthesia" AND "child development"; OR "anesthesia" AND "learning disorders". No randomised trials were found, except for the interim analysis of the GAS trial published in 2016, which found equivalence in Bayley-III scores between infants exposed to either regional or general anaesthesia. Most large cohort studies reported an association between surgery before age 4 years and an increased risk for a later diagnosis of behavioural problems or poor academic attainment. In some studies, increased risk was very small, and in others was seen only after multiple exposures. Several, but not all, of the cohort studies found no association with neurocognitive outcome as assessed by formal intelligence quotient (IQ) testing. Weaknesses in these cohort studies included confounding, bias, heterogeneous populations at the time of exposure, and heterogeneous outcome measures, making interpretation and generalisation problematic.

Added value of this study

We report the 5-year neurodevelopmental outcome results for the GAS trial, the first randomised controlled trial designed to assess the effect of general anaesthesia in infancy on neurodevelopmental outcome. We used the most reliable and validated measure of general intellectual ability, the full-scale IQ score on the Wechsler Preschool and Primary Scale of Intelligence, third edition, and found strong evidence for equivalence between awake-regional anaesthesia and slightly less than 1 h of general anaesthesia. No significant differences were seen in a range of other neurocognitive and behavioural measures.

Implications of all the available evidence

This randomised controlled trial provides strong evidence that 1 h of exposure to a general anaesthetic during early infancy does not cause measurable neurocognitive or behavioural deficits at age 5 years. These results are consistent with the MASK and PANDA cohort studies. Nearly half the general anaesthetics in infancy are used for less than 1 h duration, and this study should therefore allay some of the concerns generated by preclinical data and previous cohort studies. This trial does not address the possibility that longer or repeated anaesthesia exposures in early childhood are detrimental. The trial was also conducted in a predominantly male population, and thus further research is needed to answer these questions in female children and those with multiple and prolonged exposures.

Introduction

Concerns about anaesthesia-induced neurotoxicity in the developing brain are ongoing.[1,2] In animal models, exposure to most general anaesthetics at a young age results in a range of morphological changes.[3] These exposed animals, including non-human primates, show neuronal cell death, impaired neurogenesis, glial death, and abnormal axon formation.[4–7] In some animal models, anaesthesia exposure in infancy has also been associated with altered behaviours, including heightened emotional reactivity to threats, and impaired learning and memory formation persisting into early adulthood.[8,9] It is unclear how these findings from animal model translate to humans, whose development is more complex than that of other animals.

Human cohort studies have yielded mixed and conflicting evidence for associations between exposure to anaesthesia in early childhood and various adverse neurodevelopmental outcomes.[10] On the basis of preclinical and clinical findings, the US Food and Drug Administration has mandated warning labels on most general anaesthetics used in children.[11,12] There have also been numerous calls for more definitive research to assess whether anaesthetic exposure in early childhood has a clinically relevant effect on neurodevelopment in humans.[13,14]

Drawing any conclusions about causation from cohort studies is inherently difficult because of probable confounding. Therefore, we did a randomised controlled trial—the neurodevelopmental outcome after general anaesthesia or awake-regional anaesthesia in infancy (GAS) trial—with an equivalence design to show whether an exposure to general anaesthesia in infants causes clinically significant long-term neurodevelopmental changes. We included children undergoing inguinal herniorrhaphy, a surgery for which either a volatile anaesthetic (which has been shown to cause injury and neurobehavioural deficits in animal models) or an awake-regional technique (which does not cause neuronal injury in animal models) can be used.[15] Our hypothesis was that there would be no clinically important differences in neurodevelopmental outcome between general anaesthesia and regional anaesthesia. A finding of equivalence would result in clinicians no longer subjecting children to the various risks of delaying surgery, and anaesthetists not avoiding general anaesthesia by using alternative, and potentially less well established, anaesthetic techniques. As we reported previously,[16] neurodevelopmental outcome at age 2 years (assessed with the Bayley Scales of Infant and Toddler Development III) did not significantly differ between the awake-regional and general anaesthesia groups. Assessment at 2 years was regarded as an interim or secondary outcome because neurodevelopmental delays can be measured more accurately at 5 years of age. Data relating to apnoea in the immediate postoperative period, intraoperative blood pressure, regional anaesthesia, and

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See Online for appendix

surgical outcomes from the GAS trial were also published previously.[17–20] In this Article, we report the primary outcome of the trial, in addition to various secondary outcomes, measured at age 5 years.

Methods

Study design and participants

We did a multicentre, international, parallel-group, randomised, assessor-masked, controlled, equivalence trial comparing neurodevelopmental outcome at age 5 years, in infants randomised to receive awake-regional anaesthesia or general anaesthesia for inguinal herniorrhaphy. The trial was done 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 informed consent was obtained from the infant's parents or guardians. A summary of the protocol is available online.[21]

Infants were included if they were aged 60 weeks' postmenstrual age or less, born at greater than 26 weeks' gestation, and scheduled for inguinal herniorrhaphy. Exclusion criteria were any contraindication for either anaesthetic technique used in the study, a history of congenital heart disease requiring surgery or pharmacotherapy, mechanical ventilation immediately before surgery, known chromosomal abnormalities or other known acquired or congenital abnormalities that might affect neurodevelopment, previous exposure to volatile general anaesthesia or benzodiazepines as a neonate or in the third trimester in utero, any known neurological injury such as cystic periventricular leukomalacia or grade three or four intraventricular haemorrhage, any social or geographical factor that might make follow-up difficult, or having a primary language at home in a region where neurodevelopmental tests were not available in that language. We identified eligible infants from operating room schedules or at preadmission clinics and recruited in the clinic or in the preadmission areas of the operating floor.

Randomisation and masking

Infants were randomly assigned (1:1) to receive either general anaesthesia or awake-regional anaesthesia using a 24-h web-based randomisation service managed by the Data Management and Analysis Centre, Department of Public Health, University of Adelaide, Australia. Randomisation was done in blocks of two or four in a computer-generated random-allocation sequence, with stratification by site and by gestational age at birth (26 weeks to 29 weeks and 6 days, 30 weeks to 36 weeks and 6 days, and 37 weeks or more). The anaesthetist was aware of group allocation, but individuals who administered the neurodevelopmental assessments were not. Parents who asked about their infant's group allocation were informed and told to mask this information from assessors. After assessments were completed, parents and assessors were asked if they were aware of group allocation.

Procedures

The awake-regional group received a spinal, caudal, or combined caudal and spinal anaesthetic, according to institutional preferences. Bupivacaine or levobupivacaine at a dose of 0·75–1 mg/kg was administered for spinal anaesthesia. Caudal anaesthesia was with 0·25% bupivacaine or levobupivacaine up to a total dose of 2·5 mg/kg. In the USA, several patients in whom it was known that the surgery would take longer than 1 h were also administered 3% chloroprocaine via a caudal catheter (loading bolus of 3% chloroprocaine 1 mL/kg over several minutes and then an infusion at 1–2 mL/kg per h). Additional ilioinguinal and field blocks were used according to surgical preference. Oral sucrose was given if the child was unsettled, but no other pharmacological sedation was permitted. Infants who showed agitation that was not resolved by oral sucrose, or in whom the awake-regional anaesthetic was inadequate, were treated with sevoflurane. The administration of sevoflurane, nitrous oxide, or any other general anaesthetic in this group was considered a protocol violation.

The general anaesthesia group received sevoflurane for induction and maintenance in a mix of air and oxygen. The concentration of sevoflurane, choice of airway device, ventilation technique, and use of neuromuscular blocking agents were left to the preference of the anaesthetist. Supplemental opioids and nitrous oxide were not allowed, but caudal, ilioinguinal–iliohypogastric, or field blocks with bupivacaine were permitted to provide postoperative analgesia.

Both groups could also be given oral, rectal, or intravenous paracetamol. Monitoring and recording were identical in both groups, with heart rate, blood pressure, oxygen saturation, and expired sevoflurane concentrations (where applicable) every 5 min. In both groups, intraoperative serum glucose values were measured after induction, and rescue protocols for hypoglycaemia, hypotension, and hypoxaemia were applied as appropriate.

Outcomes

The primary outcome measure was the Wechsler Preschool and Primary Scale of Intelligence, third edition (WPPSI-III) full-scale intelligence quotient (FSIQ) score. Secondary outcome measures were selected NEPSY-II subtests to assess attention and executive function; the Wechsler Individual Achievement Test, second edition (WIAT-II), or the BVN (the Italian equivalent of the WIAT-II); selected subtests of the Children's Memory Scale (CMS); the global executive composite of the Behaviour Rating Inventory of Executive Function, Preschool version (BRIEF-P); the Adaptive Behaviour Assessment System, second edition (ABAS-II); and the Child Behaviour Checklist caregiver questionnaire (CBCL). Neuropsychological assessments were to be done within 4 months of

the child turning 5 years of age. The total assessment time was estimated to take around 3 h to complete, and assessments were done at each site by a child psychologist certified to conduct the tests. Quality control was maintained by a national coordinating psychologist. Participatory tests were administered by the psychologist, and a parent or caregiver completed the informant report questionnaires. Parents were asked if their child had been diagnosed with cerebral palsy, autism spectrum disorder, or attention-deficit hyperactivity disorder (ADHD), or had any other neurodevelopmental issues. They were also asked if the child had received any neurodevelopmental interventions. Hearing or vision problems were also noted. Demographic data, family structure, and medical history since randomisation were recorded, and a brief physical and neurological examination was done for each patient. All these outcome measures were prespecified in the protocol.

All study data were sent to the Murdoch Children's Research Institute in Melbourne, Australia. All data forms were checked by a research assistant not involved in primary data collection or entry. Data on test forms that were not completed according to test manual instructions were rejected.

An independent data safety monitoring committee met around every 6 months during recruitment. Site visits were done by the national coordinating teams for each country annually or biennially, and site visits at the national coordinating sites were done by principal investigators from other nations to check the validity of data. Summary data by allocation were presented to this committee.

Statistical analysis

The study hypothesis was that WPPSI-III FSIQ score at age 5 years is equivalent in infants who have received awake-regional anaesthesia or general anaesthesia for inguinal herniorrhaphy. Because this was an equivalence study, the outcome was analysed on an per-protocol basis to ensure a conservative estimate of the treatment effect in the direction of non-equivalence. Although it is best practice to analyse outcomes on an intention-to-treat basis, there were unavoidable protocol violations in this study (the majority of which were in babies allocated to receive regional anaesthesia who had some exposure to general anaesthesia, particularly if the awake-regional anaesthesia failed). If all infants were analysed on an intention-to-treat basis, this switching from one randomised treatment to the other could dilute the potential effect of general anaesthesia and thus bias the trial towards equivalence.[22]

Equivalence was defined a priori as the 95% CI of the difference in means of the FSIQ lying within –5 and +5 IQ points. Intention-to-treat analyses were also planned. All CIs are two-sided.

The sample size was based on the primary outcome. Assuming an expected difference of 1 standardised score point, a standard deviation of 15, and a 90% chance that a 95% CI will exclude a difference of more than 5 points (the largest difference acceptable to show equivalence), the trial would need 598 infants. The sample size formula used was based on approximations to the normal distribution, and used a two one-sided test procedure. Enrolling roughly 720 participants would allow for 10% loss to follow-up and 10% with a major protocol violation.

We used multiple imputation under a multivariate normal distribution to impute missing outcome data in the primary analysis of all outcomes, with a sensitivity analysis done on only complete cases. Multiple imputations were done with the mi impute mvn statement in Stata (version 14.2). The variables used in the multiple imputation models included baseline, post-randomisation, 2-year cognitive variables, and 5-year outcome variables. A number of prespecified variables were used as possible predictor variables within the imputation approach,

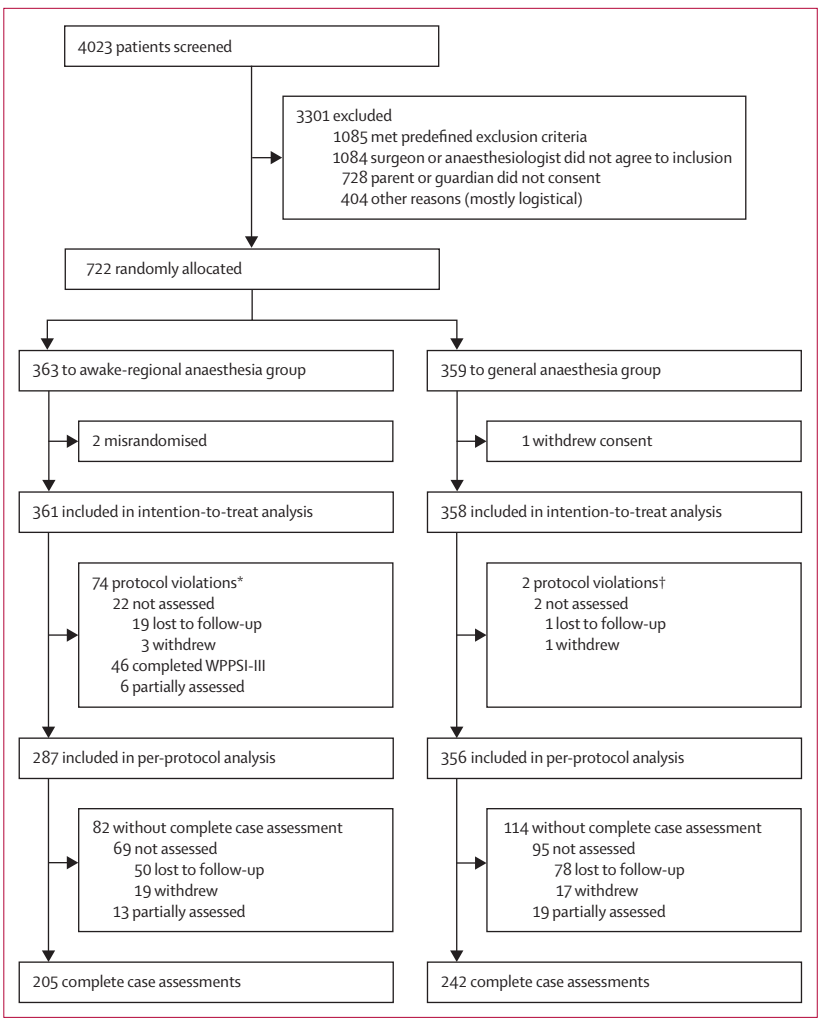

Figure: **Trial profile**
WPPSI=Weschler Preschool and Primary Scale of Intelligence. *Five surgeries cancelled, 69 general anaesthesia required. †Two surgeries cancelled.

including baseline variables (anaesthesia group, country, sex, gestational age at birth, birthweight, antenatal steroids received by mother, mother's education, and maternal age <21 years), variables at surgery (need for fluid bolus for hypotension, duration of surgery, significant postoperative apnoea, and age), variables at age 2 years (composite cognitive, language, motor and social–emotional score on the Bayley Scales of Infant and Toddler Development, third edition; any additional anaesthetic exposures since the inguinal herniorrhaphy; any interventions for neurodevelopmental problems; and any other neurological abnormality), and variables at age 5 years (WPPSI-III FSIQ, any chronic illness, any additional anaesthetic exposures since the inguinal herniorrhaphy, total length of any readmission to hospital, cerebral palsy, any interventions for neurodevelopmental problems, and any other

	Per protocol		Intention to treat	
	Awake-regional anaesthesia (n=287)	General anaesthesia (n=356)	Awake-regional anaesthesia (n=361)	General anaesthesia (n=358)
Baseline demographics				
Sex				
Male	232/287 (81%)	304/356 (85%)	294/360 (82%)	306/358 (85%)
Female	55/287 (19%)	52/356 (15%)	66/360 (18%)	52/358 (15%)
Chronological age at surgery, days	68·9 (30·8), n=287	71·1 (31·7), n=356	70·1 (31·8), n=358	71·0 (31.7), n=357
Postmenstrual age at surgery, days	317·2 (31.9), n=287	319·7 (31.8), n=356	318·3 (32.6), n=357	319·5 (32·0), n=357
Weight of child at surgery, kg	4·2 (1·1), n=287	4·3 (1·1), n=356	4·2 (1·1), n=359	4·3 (1·1), n=357
Pregnancy and birth details				
Postmenstrual age at birth, days	248·2 (28.7), n=287	248·6 (27·2), n=356	248·3 (28.5), n=360	248·6 (27·2), n=358
Prematurity (born at <37 weeks' gestation)	160/287 (56%)	195/356 (55%)	198/361 (55%)	196/358 (55%)
Birthweight, kg	2·3 (0·9), n=287	2·3 (0·9), n=355	2·4 (0·9), n=359	2·3 (0·9), n=357
Z score for birthweight	−0·7 (1·3), n=287	0·7 (1·3), n=355	−0·7 (1·2), n=359	−0·7 (1·3), n=357
Apgar score at 1 min; median (IQR)	9 (7–9), n=237	8·5 (7–9), n=282	9 (7–9), n=292	9 (7–9), n=284
Apgar score at 5 min; median (IQR)	9 (9–10), n=237	9 (9–10), n=282	9 (9–10), n=292	9 (9–10), n=284
One of a multiple pregnancy	52/284 (18%)	61/356 (17%)	62/360 (17%)	62/358 (17%)
Mother received partial course antenatal steroids	16/287 (6%)	19/356 (5%)	20/360 (6%)	19/358 (5%)
Mother received complete course antenatal steroids	95/287 (33%)	98/356 (28%)	114/360 (32%)	98/352 (28%)
Mother diagnosed with chorioamnionitis	10/287 (3%)	12/356 (3%)	11/360 (3%)	12/358 (3%)
Prolonged (>24 h) rupture of the membranes	28/287 (10%)	34/356 (10%)	32/360 (9%)	34/350 (10%)
Mother diagnosed with pre-eclampsia	50/287 (17%)	68/356 (19%)	60/360 (17%)	68/358 (19%)
Sepsis during pregnancy	36/286 (13%)	50/356 (14%)	43/358 (12%)	50/358 (14%)
Mode of delivery of birth				
Cephalic vaginal	135/287 (47%)	157/356 (44%)	169/360 (47%)	157/358 (44%)
Breech vaginal	1/287 (<1%)	6/356 (2%)	3/360 (1%)	6/358 (2%)
Compound vaginal	2/287 (1%)	4/356 (1%)	3/360 (1%)	4/358 (1%)
Caesarean section	149/287 (52%)	189/356 (53%)	185/360 (51%)	191/358 (53%)
Caesarean section and mother went into labour	42/287 (15%)	58/356 (16%)	52/360 (14%)	59/358 (16%)
Mother exposed to nitrous oxide during delivery	48/275 (17%)	62/344 (18%)	61/344 (18%)	62/346 (18%)
Intraventricular haemorrhage	7/286 (2%)	6/356 (2%)	8/359 (2%)	6/358 (2%)
Grade 1	5/286 (2%)	6/356 (2%)	5/359 (1%)	6/358 (2%)
Grade 2	2/286 (1%)	0/356	2/359 (1%)	0/358
Retinopathy of prematurity	17/198 (9%)	16/256 (6%)	20/246 (8%)	16/257 (6%)
Hearing defects detected by perinatal screening	7/253 (3%)	10/356 (3%)	8/316 (3%)	10/325 (3%)
Patent ductus arteriosus diagnosed	23/286 (8%)	21/355 (6%)	27/359 (8%)	21/357 (6%)
Never treated	9/286 (3%)	9/355 (3%)	11/359 (3%)	9/357 (3%)
Treated with NSAIDs	14/286 (5%)	10/355 (3%)	16/359 (4%)	10/357 (3%)

(Table 1 continues on next page)

	Per protocol		Intention to treat	
	Awake-regional anaesthesia (n=287)	General anaesthesia (n=356)	Awake-regional anaesthesia (n=361)	General anaesthesia (n=358)
(Continued from previous page)				
Familial demographics				
Primary language(s) only spoken*	252/287 (88%)	305/356 (86%)	311/360 (86%)	307/358 (86%)
Maternal age at birth >21 years	273/286 (95%)	339/356 (95%)	339/358 (95%)	341/358 (95%)
Family structure two caregivers together (at birth)	261/286 (91%)	324/356 (91%)	328/359 (91%)	326/358 (91%)
Maternal education				
Completed tertiary studies	150/286 (52%)	171/354 (48%)	181/358 (51%)	171/358 (48%)
Continuing tertiary studies	50/286 (17%)	67/354 (19%)	68/358 (19%)	67/358 (19%)
Completed 11 or 12 years of education	62/286 (22%)	83/354 (23%)	77/358 (22%)	87/358 (24%)
Did not complete 11 years of education	25/286 (9%)	33/354 (9%)	32/358 (9%)	34/358 (9%)
Anaesthesia details				
Blood glucose level, mmol/L; median (IQR)	5·4 (4·7–6·1), n=255	5·5 (4·8–6·4), n=314	5·4 (4·7–6·2), n=312	5·5 (4·8–6·4), n=314
Intravenous rescue glucose given	2/282 (1%)	4/356 (1%)	2/350 (1%)	4/356 (1%)
Haemoglobin concentration, g/100 mL	10·3 (2·1), n=250	10·2 (2·0), n=307	10·3 (2·1), n=305	10·2 (2·0), n=307
Need for fluid bolus for hypotension	15/287 (5%)	59/356 (17%)	21/355 (6%)	59/356 (17%)
Vasoactive drugs given (including atropine)	4/287 (1%)	17/356 (5%)	6/355 (2%)	17/356 (5%)
Duration of surgery, min; median (IQR)	26·0 (19·0–35·0), n=286	28·0 (20·0–40·0), n=355	28·0 (20·0–38·0), n=353	28·0 (20·0–40·0), n=355
Duration of sevoflurane exposure, min; median (IQR)	..	54·0 (41·0–70·0), n=356	42·0 (31·0–62·5), n=67†	54·0 (41·0–70·0), n=356
Mean end tidal sevoflurane concentration, %	..	2·6 (0·7), n=356	2·3 (0·8), n=67†	2·6 (0·7), n=356
Total concentration × h of exposure	..	2·6 (1·1), n=356	1·9 (1·0), n=67†	2·6 (1·1), n=356
Any significant apnoea to 12 h post operation‡	6/287 (2%)	15/356 (4%)	10/360 (3%)	15/358 (4%)

Data are n/N (% of non-missing data) or mean (SD), unless otherwise specified. NSAIDs=non-steroidal anti-inflammatory drugs. *The primary language spoken at home is the primary language in each country in which the Bayley was conducted (eg, in Italy, it was done in Italian). †For those cases that received sevoflurane. ‡Significant apnoea defined as a pause in breathing for more than 15 s or more than 10 s if associated with oxygen saturation less than 80% or bradycardia (20% decrease in heart rate).

Table 1: **Baseline demographic data**

neurological abnormality). Since most of these variables also have missingness, they were also imputed where necessary. With many missing observations, these multiple imputation models did not always converge, in which case, to ensure convergence of models, applicable variables were not included. The variables used in the analysis model were always included in the imputation models.

For all continuous outcomes, linear regression was used with the factor variables anaesthesia group (awake-regional anaesthesia and general anaesthesia), with gestational age at birth and country as fixed effects. Adjusted mean differences are presented with 95% CIs.

All binary outcomes were analysed with generalised linear models with binomial link function to enable estimation of risk ratios, adjusting for the same factors as for the linear regression. Risk ratios are presented with 95% CIs.

The following subgroup analyses were prespecified in the statistical analysis plan: country, duration of surgery (≥120 min or <120 min), and age at surgery (>70 days or ≤70 days). A subgroup analysis by ex-term versus ex-preterm (born at <37 weeks' gestation) was also done post hoc. p values for the interactions are shown along with subgroup treatment effect estimates and 95% CIs. All analyses were done in Stata (version 14.2).

The GAS trial is registered in Australia and New Zealand at ANZCTR (number ACTRN12606000441516, first registered Oct 16, 2006); in the USA at ClinicalTrials.gov (number NCT00756600, first registered on Sept 18, 2008); and in the UK at UK Clinical Research Network (number 6635; ISRCTN ID 12437565; MREC number 07/S0709/20). The statistical analysis plan is available at ANZCTR (number ACTRN12606000441516).[23]

Role of the funding source

The funders of this study had no role in study design, data collection, data analysis, data interpretation, writing of the manuscript, or the decision to submit this manuscript for publication. AG had complete access to all the data. All other authors have access to the data on request. All

	Per protocol		Intention to treat	
	Awake-regional anaesthesia group (n=287)	General anaesthesia group (n=356)	Awake-regional anaesthesia group (n=361)	General anaesthesia group (n=358)
Assessment details				
Location of 5-year assessment at hospital	198/216 (92%)	228/257 (89%)	246/268 (92%)	228/257 (89%)
Family demographics at 5 years				
Paid employment is the main family income	201/214 (94%)	237/256 (93%)	243/266 (91%)	237/256 (93%)
Family structure two caregivers living together	194/214 (91%)	223/257 (87%)	230/266 (86%)	223/257 (87%)
Number of children at home				
1	50/214 (23%)	53/257 (21%)	63/266 (24%)	53/257 (21%)
2	95/214 (44%)	133/257 (52%)	120/266 (45%)	133/257 (52%)
3	56/214 (26%)	48/257 (19%)	67/266 (25%)	48/257 (19%)
≥4	13/214 (6%)	23/257 (9%)	16/266 (6%)	23/257 (9%)
Birth order				
1	113/211 (54%)	137/257 (53%)	137/261 (52%)	137/257 (53%)
2	69/211 (33%)	81/257 (32%)	87/261 (33%)	81/257 (32%)
≥3	29/211 (14%)	39/257 (15%)	37/261 (14%)	39/257 (15%)
Age at follow-up assessment	5·2 (0·2), n=217	5·3 (0·3), n=258	5·2 (0·2), n=269	5·3 (0·3), n=258
Events since original anaesthesia				
Any hospitalisation	101/199 (51%)	129/250 (52%)	131/249 (53%)	129/250 (52%)
Number of days hospitalised				
0	105/169 (62%)	127/213 (60%)	125/213 (59%)	127/213 (60%)
1	22/169 (13%)	30/213 (14%)	34/213 (16%)	30/213 (14%)
2	11/169 (7%)	13/213 (6%)	13/213 (6%)	13/213 (6%)
≥3	31/169 (18%)	43/213 (20%)	41/213 (19%)	43/213 (20%)
Any anaesthesia	71/102 (70%)	71/111 (64%)	89/133 (67%)	71/111 (64%)
Number of anaesthetics				
0	104/156 (67%)	132/181 (73%)	131/197 (66%)	134/183 (73%)
1	28/156 (18%)	27/181 (15%)	37/197 (19%)	27/183 (15%)
2	11/156 (7%)	11/181 (6%)	14/197 (7%)	11/183 (6%)
≥3	13/156 (8%)	11/181 (6%)	15/197 (8%)	11/183 (6%)
Any seizures	14/173 (8%)	17/217 (8%)	17/217 (8%)	17/217 (8%)
Events since 2-year assessment				
Child had a head injury that involved loss of consciousness	2/213 (1%)	2/266 (1%)	3/265 (1%)	2/257 (1%)
Child has any chronic illness	38/213 (18%)	43/258 (17%)	48/265 (18%)	43/258 (17%)
Child had any prescribed medication for 2 months or longer	37/214 (17%)	44/257 (17%)	44/266 (17%)	44/257 (17%)
Child has had an intervention for neurodevelopmental issues	49/213 (23%)	60/257 (23%)	64/264 (24%)	60/257 (23%)
Speech therapy	36/217 (17%)	48/259 (19%)	50/269 (19%)	48/259 (19%)
Physiotherapy	11/217 (5%)	17/259 (7%)	12/269 (4%)	17/259 (7%)
Occupational therapy	18/217 (8%)	20/259 (8%)	21/269 (8%)	20/259 (8%)
Psychology	7/217 (3%)	6/259 (2%)	8/269 (3%)	6/259 (2%)
Other interventions	9/217 (4%)	16/259 (6%)	12/269 (4%)	16/259 (6%)
Child attends play group or child care on a regular basis	186/213 (87%)	231/257 (90%)	234/265 (88%)	231/257 (90%)
Physical examination				
Height, cm	110·8 (5·5), n=207	110·8 (5·5), n=237	110·8 (5·4), n=254	110·8 (5·5), n=237
Weight, kg	19·3 (3·3), n=206	19·4 (2·8), n=236	19·4 (3·2), n=253	19·4 (2·8), n=236
Head circumference, cm	51·6 (1·8), n=194	51·2 (2·6), n=224	51·6 (1·8), n=241	51·2 (2·6), n=224
Arm circumference, cm	17·6 (1·9), n=191	17·4 (1·7), n=219	17·6 (1·9), n=233	17·4 (1·7), n=219

Data are n/N (% of non-missing data) or mean (SD).

Table 2: **Demographic data at 5-year assessment**

	Per protocol						Intention to treat					
	Multiple imputation analysis			Complete case analysis			Multiple imputation analysis			Complete case analysis		
	Awake-regional anaesthesia group (n=287)	General anaesthesia group (n=356)	Adjusted mean difference*	Awake-regional anaesthesia group	General anaesthesia group	Adjusted mean difference*	Awake-regional anaesthesia group (n=361)	General anaesthesia group (n=358)	Adjusted mean difference*	Awake-regional anaesthesia group	General anaesthesia group	Adjusted mean difference*
Global function												
WPPSI-III FSIQ composite score	99·1 (18·4)	99·0 (19·7)	0·2 (−2·6 to 3·1)	100·5 (14·3), n=205	100·1 (15·3), n=242	0·6 (−2·1 to 3·3)	98·9 (18·0)	98·8 (19·2)	0·2 (−2·5 to 2·8)	100·4 (14·1), n=251	100·1 (15·3), n=242	0·3 (−2·3 to 2·8)
Verbal and language												
WPPSI-III verbal IQ composite score	100·6 (18·3)	99·7 (20·4)	0·8 (−2·1 to 3·8)	101·8 (14·7), n=206	100·9 (15·4), n=240	0·7 (−2·1 to 3·4)	99·6 (18·6)	99·6 (19·1)	0·0 (−2·6 to 2·7)	101·2 (14·8), n=251	100·9 (15·4), n=240	0·0 (−2·6 to 2·5)
NEPSY-II word generation scaled score	9·1 (4·7)	9·0 (4·8)	0·1 (−0·6 to 0·9)	9·4 (3·4), n=182	9·3 (3·3), n=199	0·1 (−0·6 to 0·8)	9·1 (5·5)	9·1 (4·7)	−0·1 (−0·6 to 0·5)	9·3 (3·5), n=220	9·3 (3·3), n=199	0·1 (−0·6 to 0·7)
NEPSY-II speeded naming combined scaled score	10·6 (19·6)	7·4 (23·9)	3·3 (−1·1 to 7·7)	9·7 (3·0), n=132	9·8 (3·2), n=142	0·0 (−0·7 to 0·8)	8·7 (10·3)	9·2 (15·0)	−0·5 (−4·9 to 3·9)	9·8 (3·0), n=162	9·8 (3·2), n=142	0·1 (−0·6 to 0·8)
Perceptual and visuospatial												
WPPSI-III performance IQ composite score	99·6 (19·3)	100·0 (20·3)	−0·2 (−3·1 to 2·8)	100·7 (15·2), n=206	101·2 (15·9), n=241	0·0 (−2·9 to 2·8)	100·1 (18·2)	99·8 (19·6)	0·4 (−2·3 to 3·1)	101·1 (14·7), n=252	101·2 (15·2), n=241	0·2 (−2·4 to 2·8)
NEPSY-II design copy scaled score	9·4 (23·8)	6·7 (45·1)	3·1 (−2·7 to 8·9)	9·6 (3·4), n=172	9·9 (3·1) n=207	−0·2 (−0·8 to 0·5)	13·7 (44·8)	9·6 (26·1)	3·9 (−2·6 to 10·4)	9·6 (3·3), n=212	9·9 (3·1), n=207	−0·2 (−0·8 to 0·4)
Processing speed												
WPPSI-III processing speed quotient composite score	95·2 (20·8)	94·7 (21·3)	0·8 (−2·5 to 4·0)	95·8 (14·5), n=196	96·3 (15·4), n=220	0·0 (−2·8 to 2·9)	95·8 (20·5)	94·6 (21·1)	1·31 (−1·7 to 4·3)	96·3 (14·4), n=241	96·3 (15·4), n=220	0·3 (−2·4 to 2·9)
Attention and executive function												
NEPSY-II sentence repetition scaled score	6·4 (29·7)	8·3 (24·2)	−1·4 (−5·4 to 2·7)	9·7 (2·9), n=175	9·7 (2·8), n=202	0·0 (−0·6 to 0·6)	13·5 (55·3)	10·8 (23·3)	2·4 (−1·0 to 5·8)	9·7 (3·0), n=214	9·7 (2·8), n=202	−0·1 (−0·6 to 0·5)
NEPSY-II auditory attention combined scaled score	8·7 (4·3)	8·8 (4·6)	−0·1 (−0·8 to 0·6)	9·0 (2·7), n=167	9·3 (3·0), n=183	−0·3 (−0·8 to 0·3)	8·7 (4·2)	8·8 (5·1)	−0·1 (−0·8 to 0·6)	8·9 (3·0), n=207	9·3 (3·0), n=183	−0·3 (−0·8 to 0·3)
NEPSY-II inhibition combined scaled score	7·9 (6·0)	8·4 (5·5)	−0·5 (−1·3 to 0·3)	8·3 (3·1), n=150	8·9 (3·0), n=160	−0·6 (−1·3 to 0·1)	7·8 (7·2)	8·4 (5·1)	−0·6 (−1·5 to 0·4)	8·4 (3·1), n=179	8·9 (3·0), n=160	−0·5 (−1·1 to 0·2)
NEPSY-II statue scaled score	8·6 (33·0)	10·8 (32·1)	−2·6 (−8·9 to 3·8)	8·8 (3·5) n=160	8·6 (3·6). n=182	0·2 (−0·5 to 1·0)	7·1 (19·3)	8·1 (14·0)	−0·9 (−1·7 to −0·2)	8·8 (3·5), n=192	8·6 (3·6), n=182	0·2 (−0·5 to 0·9)
CMS numbers scaled score	8·0 (4·6)	7·8 (4·6)	0·2 (−0·5 to 0·9)	8·3 (3·2), n=194	8·1 (3·4), n=229	0·1 (−0·5 to 0·7)	7·9 (3·9)	7·7 (4·3)	0·1 (−0·5 to 0·8)	8·2 (3·2), n=236	8·1 (3·4), n=229	0·0 (−0·6 to 0·6)
Memory and learning												
NEPSY-II memory for names combined scaled score	8·1 (4·6)	8·0 (4·6)	0·2 (−0·5 to 0·9)	8·1 (3·2), n=180	8·1 (3·2), n=208	0·2 (−0·5 to 0·8)	8·2 (4·4)	8·0 (4·6)	0·2 (−0·5 to 0·9)	8·2 (3·2), n=218	8·1 (3·2), n=208	0·2 (−0·4 to 0·8)
CMS word lists I learning scaled score	8·0 (4·8)	8·3 (4·9)	−0·4 (−1·1 to 0·4)	8·3 (3·4), n=186	8·6 (3·5), n=224	−0·4 (−1·0 to 0·3)	8·1 (4·9)	8·3 (5·3)	−0·3 (−1·0 to 0·5)	8·3 (3·4), n=227	8·6 (3·5), n=224	−0·3 (−1·0 to 0·3)
CMS word lists II delayed scaled score	9·5 (4·0)	9·4 (4·4)	0·1 (−0·5 to 0·8)	9·7 (2·8), n=178	9·6 (2·9), n=209	0·0 (−0·5 to 0·6)	9·5 (3·9)	9·3 (4·7)	0·1 (−0·5 to 0·7)	9·6 (2·9), n=216	9·6 (2·9), n=209	0·0 (−0·6 to 0·5)

(Table 3 continues on next page)

	Per protocol			Intention to treat					
	Multiple imputation analysis			Complete case analysis			Multiple imputation analysis			Complete case analysis		
	Awake-regional anaesthesia group (n=287)	General anaesthesia group (n=356)	Adjusted mean difference*	Awake-regional anaesthesia group	General anaesthesia group	Adjusted mean difference*	Awake-regional anaesthesia group (n=361)	General anaesthesia group (n=358)	Adjusted mean difference*	Awake-regional anaesthesia group	General anaesthesia group	Adjusted mean difference*
(Continued from previous page)												
Social perception												
NEPSY-II affect recognition scaled score	10·1 (28·6)	8·9 (18·1)	1·5 (-1·7 to 4·6)	10·6 (2·8), n=174	10·4 (3·2), n=208	0·3 (-0·4 to 0·9)	11·6 (15·4)	7·4 (74·2)	4·3 (-5·0 to 13·5)	10·6 (2·8), n=215	10·4 (3·2), n=208	0·2 (-0·3 to 0·8)
NEPSY-II theory of mind scaled score	9·3 (4·1)	9·6 (4·6)	-0·3 (-0·9 to 0·4)	9·8 (2·9), n=163	9·8 (3·0), n=178	-0·1 (-0·7 to 0·5)	9·2 (4·6)	9·6 (4·3)	-0·4 (-1·1 to 0·3)	9·7 (3·1), n=197	9·8 (3·1), n=178	-0·2 (-0·8 to 0·4)
Sensorimotor												
NEPSY-II fingertip tapping repetitions combined scaled score	9·5 (5·4)	9·4 (5·2)	0·0 (-0·8 to 0·8)	9·8 (3·4), n=180	9·7 (3·4), n=195	-0·1 (-0·8 to 0·5)	9·6 (4·7)	9·5 (5·3)	0·1 (-0·6 to 0·9)	9·8 (3·4), n=217	9·7 (3·4), n=195	0·0 (-0·6 to 0·6)
NEPSY-II fingertip tapping sequences combined scaled score	7·6 (5·3)	7·1 (6·6)	0·5 (-0·4 to 1·4)	8·1 (3·4), n=173	7·7 (3·6), n=183	0·4 (-0·3 to 1·1)	7·8 (6·2)	7·2 (6·2)	0·6 (-0·4 to 1·6)	8·1 (3·4), n=204	7·7 (3·6), n=183	0·5 (-0·2 to 1·1)
Academic												
WIAT-II word reading composite score	92·1 (20·5) n=220	93·3 (25·9), n=275	-1·0 (-4·5 to 2·5)	92·3 (18·1), n=147	92·8 (21·1), n=167	-1·5 (-4·7 to 1·8)	92·1 (23·7), n=278	93·3 (26·6), n=276	-1·2 (-4·6 to 2·3)	92·8 (18·8), n=175	92·8 (21·1), n=167	-1·3 (-4·4 to 1·8)
WIAT-II spelling composite score	90·2 (16·3), n=220	91·1 (20·6), n=275	-1·2 (-3·6 to 1·2)	90·1 (13·2), n=141	90·8 (16·5), n=152	-1·7 (-4·3 to 0·9)	89·9 (17·8), n=278	91·3 (19·2), n=276	-1·6 (-4·2 to 1·1)	90·6 (13·7), n=166	90·8 (16·5), n=152	-1·5 (-4·0 to 1·0)
WIAT-II numerical operations composite score	98·0 (21·3), n=220	96·1 (26·5), n=275	0·8 (-2·8 to 4·5)	98·8 (16·2), n=146	96·2 (20·8), n=161	0·3 (-3·1 to 3·7)	97·1 (20·8), n=278	96·3 (26·4), n=276	0·5 (-2·9 to 3·9)	98·7 (16·6), n=172	96·2 (20·8), n=161	0·2 (-3·0 to 3·5)

Data are mean (SD). WPPSI-III=Wechsler Preschool and Primary Scale of Intelligence, third edition. FSIQ=full-scale intelligence quotient. IQ=intelligence quotient. CMS=Children's Memory Scale. WIAT-II=Wechsler Individual Achievement Test, second edition. *Awake-regional anaesthesia group minus general anaesthesia group (95% CI), adjusted for gestational age at birth and country.

Table 3: **Primary outcome and results of other individually administered tests**

authors were responsible for the decision to submit this manuscript for publication.

Results

Between Feb 9, 2007, and Jan 31, 2013, 4023 infants were screened for eligibility, and 722 infants were recruited at 28 centres in seven countries (appendix). 363 children were randomly allocated to the awake-regional anaesthesia group and 359 to the general anaesthesia group. After two misrandomisations and one withdrawal of consent by the family (post-randomisation and pre-surgery), 361 children were included in the intention-to-treat analysis for the awake-regional anaesthesia group and 358 children were included for the general anaesthesia group. 76 patients with protocol violations were excluded, leaving 287 patients in the awake-regional anaesthesia and 356 in the general anaesthesia group in the per-protocol analysis (figure). Demographic data at baseline and at the 5-year assessment are shown in table 1 and table 2.

The 5-year follow-up assessments were done between March 13, 2012, and April 27, 2018. 91 families were lost to follow-up in the awake-regional anaesthesia group and 97 in the general anaesthesia group (74% follow-up). Of those who attended for assessment, the WPPSI-III FSIQ was complete for 205 in the awake-regional anaesthesia group and 242 in the general anaesthesia group. Numbers lost to follow-up and numbers of complete case assessments are listed for each site in the appendix.

When multiple imputation was used to account for missing data, WPPSI-III FSIQ means appeared equivalent between the two groups in both the per-protocol analysis (adjusted mean difference for awake-regional anaesthesia minus general anaesthesia 0·23, 95% CI –2·59 to 3·06) and the intention-to-treat analysis (0·16, –2·45 to 2·78; table 3). The adjusted mean differences also suggested equivalence in the complete cases analyses (0·63, –2·09 to 3·35 for per-protocol analysis; and 0·27, –2·27 to 2·80 for intention-to-treat analysis). In all these analyses, the upper and lower bounds of the 95% CIs were well within the prespecified 5-point equivalence margin.

There was also evidence for equivalence of the verbal, performance, and processing speed composite scores of the WPPSI-III, with the 95% CIs for the differences in means within 5 points in all analyses. For all the other individually administered secondary outcomes (table 3) and parent-reported or caregiver-reported outcomes (table 4), none of the 95% CIs for the differences in means were either entirely above or below 0 in any of the analyses (with the exception of NEPSY-II statue scaled score in the multiple-imputation intention-to-treat analysis). Although an equivalence margin was not prespecified for these secondary outcomes, a reasonable assumption of equivalence could be made, as the upper and lower bounds of all 95% CIs were within a third of an SD for all analyses (the equivalence limit prespecified for the primary outcome).

Some of the NEPSY-II subscales had large numbers of missing data and the SDs were very large with the

multiple imputation models due to the low correlations of the variables included in the multiple imputation model with the outcome variable, leading to little information being recovered by the multiple imputations, while additional noise was added.

There was no evidence for any between-group differences in the proportion of children reported by a parent or caregiver to have been diagnosed with a neurodevelopmental disorder, with the 95% CIs of all risk ratios crossing 1 (table 5). However, the low prevalence of these events limits the inferences that can be drawn regarding equivalence.

The subgroup analyses for the primary outcome (appendix) showed that the differences between groups were similar by age at surgery and prematurity. Small sample sizes in some of the countries prevented conclusive interpretation of country differences in the results. Duration of exposure was not analysed because no children had exposures longer than 120 min. The p values for treatment-by-country interaction were 0·0496 (F=1·78) for the complete case analysis and 0·0643 (F=1·69) for the multiple imputation analysis, providing evidence of heterogeneity of the results by country.

The only adverse events during the anaesthesia were related to respiratory complications, as described in full in a previous publication.[17] The frequency of hypotension has also been described elsewhere.[18]

We compared the characteristics of children who attended the 5-year follow-up assessment with the baseline data of the randomised population and the 2-year outcome data (for those who attended the 2-year follow-up). Although there were differences between the characteristics of children who attended the 5-year follow-up and those who did not, there was similar distibution of both scores and lack of attendance between the two anaesthesia groups (appendix). Likewise, there was a similar distribution across groups with respect to unmasking of group allocation for children who attended the 5-year follow-up (appendix).

Discussion

This randomised trial showed strong evidence for equivalence in WPPSI-III FSIQ measured at age 5 years between children who received awake-regional anaesthesia and general anaesthesia for inguinal herniorrhaphy in infancy. In a range of other neuropsychological tests, evidence of equivalence can also be reasonably assumed because the 95% CIs around the differences in means fell within a third of an SD. These results are consistent with the previously reported 2-year outcomes of the GAS trial, assessed with the Bayley Scales of Infant and Toddler Development III.[16]

We assessed the primary outcome at age 5 years because there is robust evidence for the emergence of the unitary construct of general intelligence and for the individual stability of that construct from middle childhood until adulthood. Intelligence quotient (IQ) in children aged

	Per protocol					Intention to treat				
	Multiple imputation analysis			Complete case analysis		Multiple imputation analysis			Complete case analysis	
	Awake-regional anaesthesia group (n=287)	General anaesthesia group (n=356)	Adjusted mean difference*	Awake-regional anaesthesia group	General anaesthesia group	Awake-regional anaesthesia group (n=361)	General anaesthesia group (n=358)	Adjusted mean difference*	Awake-regional anaesthesia group	General anaesthesia group	Adjusted mean difference*
Executive function											
BRIEF-P (global executive composite T score)	49·2 (16·0)	51·9 (17·6)	−2·7 (−5·2 to −0·1)	48·4 (12·5), n=198	51·5 (13·4), n=232	−2·9 (−5·4 to −0·4)	49·6 (15·5)	51·9 (17·5)	−2·4 (−4·8 to 0·1)	48·9 (12·7), n=246	51·5 (13·4), n=232	−2·4 (−4·7 to 0·0)
Adaptive behaviour												
ABAS-II (global adaptive behaviour composite score)	94·4 (20·9)	92·6 (23·3)	2·0 (−1·2 to 5·2)	95·9 (16·3), n=168	94·1 (16·5), n=200	1·5 (−1·7 to 4·8)	94·3 (23·3)	92·5 (23·9)	1·9 (−1·3 to 5·1)	95·5 (16·8), n=205	94·1 (16·5), n=200	1·0 (−2·1 to 4·2)
Maladaptive behaviour												
CBCL (total problems, T score)	45·2 (13·8)	47·1 (16·6)	−2·0 (−4·3 to 0·4)	44·6 (11·7), n=215	46·7 (12·5), n=254	−1·9 (−4·1 to 0·3)	45·7 (15·0)	47·1 (15·6)	−1·4 (−3·6 to 0·8)	45 (12·1), n=265	46·7 (12·5), n=254	−1·5 (−3·6 to 0·6)
CBCL (internalising problems T score)	46·6 (14·4)	48·5 (17·4)	−1·9 (−4·3 to 0·6)	46·1 (12·5), n=215	48·0 (12·5), n=254	−1·8 (−4·1 to 0·4)	46·8 (15·2)	48·5 (16·0)	−1·6 (−3·9 to 0·6)	46·2 (12·5), n=265	48·0 (12·5), n=254	−1·7 (−3·9 to 0·4)
CBCL (externalising problems T score)	44·5 (13·2)	46·1 (15·0)	−1·6 (−3·7 to 0·5)	44·0 (10·7), n=215	45·8 (11·9), n=254	−1·7 (−3·7 to 0·4)	45·1 (13·9)	46·1 (15·0)	−1·1 (−3·1 to 1·0)	44·4 (11·3), n=265	45·8 (11·9), n=254	−1·2 (−3·2 to 0·8)

Data are mean (SD). BRIEF-P=Behaviour Rating Inventory of Executive Function, preschool version. ABAS-II=Adaptive Behaviour Assessment System, second edition. CBCL=Child Behaviour Checklist caregiver questionnaire. *Awake-regional anaesthesia group minus general anaesthesia group (95% CI), adjusted for gestational age at birth and country.

Table 4: **Parent-rated behavioural outcome measures**

	Per protocol			Intention to treat		
	Awake-regional anaesthesia group	General anaesthesia group	Risk ratio (95% CI)	Awake-regional anaesthesia group	General anaesthesia group	Risk ratio (95% CI)
Any developmental issues	25/204 (12%)	21/238 (9%)	1·4 (0·8–2·4)	33/255 (13%)	21/238 (9%)	1·5 (0·9–2·5)
Speech or language issues or interventions	18/214 (8%)	17/257 (7%)	..	24/266 (9%)	17/257 (7%)	..
Psychomotor issues or interventions	8/214 (4%)	6/257 (2%)	..	9/266 (3%)	6/257 (2%)	..
Global developmental delay	2/204 (1%)	0/238	..	4/255 (2%)	0/238	..
Behavioural disorders (ADHD, autism spectrum disorder)	8/211 (4%)	15/251 (6%)	0·7 (0·3–1·7)	13/263 (5%)	15/251 (6%)	0·99 (0·5–2·0)
Diagnosed with ADHD	3/214 (1%)	4/257 (2%)	..	7/266 (3%)	4/257 (2%)	..
Diagnosed with autism spectrum disorder	5/211 (2%)	11/251 (4%)	..	7/263 (3%)	11/251 (4%)	..
Hearing abnormality	8/213 (4%)	11/252 (4%)	0·9 (0·4–2·2)	12/264 (5%)	11/252 (4%)	1·1 (0·5–2·4)
Child has a hearing aid	0/211	3/251 (1%)	..	0/262	3/251 (1%)	..
Visual defect of any type in either eye	21/213 (10%)	31/254 (12%)	0·8 (0·5–1·3)	28/264 (11%)	31/254 (12%)	0·8 (0·5–1·4)
Legally blind (visual acuity <6/60 in both eyes)	0/212	0/254	..	0/263	0/254	..
Cerebral palsy	1/213 (<1%)	3/254 (1%)	0·6 (0·1–5·5)	1/264 (<1%)	3/254 (1%)	0·4 (0·0–3·8)

Frequency data are n/N (% of non-missing data). ADHD=attention-deficit hyperactivity disorder. Risk ratios are presented only for variables prespecified as endpoints in the statistical analysis plan. Risk ratios were adjusted for gestational age at birth and country.

Table 5: **5-year non-psychometric outcome data**

5–6 years is strongly correlated with adult IQ.[24] IQ at age 5 years is also highly predictive of later mathematical ability, and higher IQ in childhood positively predicts a range of benefits in academic, economic, and health outcomes across the lifespan.[25] The WPPSI-III is a well-validated, standardised, and reliable test for assessing IQ in young children.

The WPPSI-III FSIQ was set as the primary outcome because of its strong psychometric properties and predictive potential, and also because of preclinical data;[26] the widespread cortical damage seen in preclinical models would probably result in a global decline in function, and this decline would be best identified by a measure of general intellectual function such as the WPPSI-III.

Secondary outcome measures were selected, on the basis of known vulnerabilities of the developing brain and results of early animal and human studies, to assess a broad range of cognitive domains that could potentially be affected. In choosing the tests, a number of factors were considered: previous studies found deficits in both hippocampal and non-hippocampal memory; deficits that arise from damage to systems that subserve specific skills are spread through various regions of the brain and are particularly susceptible to neurological insult (ie, attention, information processing, and executive function); there is a possibility of a cumulative effect of subtle individual or multiple deficits on skill development such as visuomotor integration, reading, spelling, and arithmetic; and there is previous evidence for social and emotional deficits. Specific individually administered tests and informant report measures were selected from readily available standardised tests that are in common clinical use and have documented reliability and validity statistics for use in this age group.

Several previous cohort studies have sought to identify associations between anaesthesia exposure in early childhood and various neurodevelopmental outcomes. The PANDA study was an ambidirectional cohort study that used a range of neuropsychological tests done at 8–15 years of age to compare neurodevelopmental outcomes between children who had previously undergone inguinal herniorrhaphy under general anaesthesia and their unexposed siblings.[27] The study found no evidence of group differences in IQ scores or scores from various other tests of neurocognitive function and behaviour. Similarly, the MASK cohort study found no evidence for differences in test scores between children that had a single anaesthetic compared with those that had no previous anaesthetics, although children that had multiple anaesthetics did have an increased risk of deficits in processing speed and fine motor outcomes, and parents reported increased problems related to executive function, behaviour, and reading.[28] Other cohort studies have found evidence for an association between anaesthesia exposure and cognitive, memory, listening comprehension, and language deficits.[29–32]

Several other large population-based data-linkage studies have found evidence for an association between anaesthesia in early childhood and a very small decrease in performance in school grades or school readiness tests.[33–36] Cohort studies have yielded mixed evidence for an association between anaesthesia in early childhood and a subsequent diagnosis of ADHD or other learning

disability.[37–44] Although there might be an increased risk of these diagnoses without an increased risk of worse outcomes in neurocognitive testing, other confounding factors are a possible explanation for these observed associations. The GAS trial found no evidence for an increased risk of behavioural disorders such as autism spectrum disorder or ADHD; however, the diagnosis of ADHD and learning disability is typically made in older children, and the low prevalence and consequent low power reduced our ability to draw a definitive conclusion.

In all these cohort studies, any associations found between exposure and poor outcomes could be explained by confounding. For instance, because children receive anaesthesia for surgery or invasive investigations, the condition warranting the procedure might itself be associated with increased risk of adverse neurodevelopmental outcome. Similarly, children with pre-existing but as-yet-undiagnosed behavioural problems might be at greater risk of needing the procedure. Furthermore, perioperative factors other than anaesthesia could also increase the risk of poor neurodevelopmental outcome. In most studies, attempts are made to limit the effects of known confounders through patient selection, matching, and adjustments in the analysis, but the potential influence of confounding can never be eliminated. The GAS trial is, so far, the only randomised trial to assess the effects of anaesthesia on neurodevelopment, and thus provides the strongest human evidence.

Several previous cohort studies have found more evidence for a detrimental effect after multiple exposures compared with a single exposure. In the GAS trial, a substantial number of children had subsequent anaesthetics. The number of children having subsequent anaesthetics was well balanced between groups, and exposure to subsequent anaesthetics is therefore unlikely to have influenced or biased the results of this trial. We also found weak evidence for an interaction between country and treatment. The reason for this is not immediately apparent and, given the marginal level of evidence, this finding should be interpreted with caution.

Despite careful selection of patients, an awake-regional technique is not always adequate for herniorrhaphy. Thus, a substantial number of children in the awake-regional anaesthesia group had some exposure to general anaesthetics. These children were excluded from the per-protocol analysis. The absence of any substantive difference between the per-protocol and intention-to-treat analyses implies that their exclusion did not introduce a bias to the trial. In addition, some children were lost to follow-up. Multiple imputation was used to reduce the effect of these missing data under the missing at random assumption. However, even with multiple imputation, the results could be influenced by the selective follow-up of participants. Children who performed poorly at age 2 years were more likely to be lost to follow-up at age 5 years. The reason for this finding is unclear; however, it is unlikely to lead to a bias as the 2-year outcome was included in the multiple imputations model. Overall, although the loss to follow-up was greater than anticipated in the protocol, the boundaries of the 95% CIs fell within the predefined bounds of equivalence, indicating that the precision of the results was adequate despite this greater-than-expected loss to follow-up.

Given the nature of the interventions, it was impossible to mask the treating surgeons or anaesthetists to group allocation. It was also impractical to completely mask inquisitive parents, as adhesives used to secure the airway usually leave signs of skin irritation in the general anaesthesia group, and there would be a puncture mark in the back from the spinal needle in the regional anaesthesia group. Clinicians making the 5-year assessment were masked successfully in most cases. It is unlikely that unmasking surgeons, anaesthetists, or parents would bias the outcome for the individually administered tests. However, when interpreting parent-reported outcomes, this potential bias should be considered.

There are several considerations to make when assessing the generalisability of the GAS trial. First, the population was predominantly male, which was expected given the surgical pathology selected to create homogeneity within the study sample. Second, the infants were exposed over a narrow period of development (early infancy), this period being chosen as the period of high cerebral vulnerability and because this is when both awake-regional anaesthesia and general anaesthesia are commonly used for herniorrhaphy. When assessing at which age children might be at greatest risk, it is difficult to translate data from other animals to humans.[13,45] In general, because younger animals have been found to be at greater risk, it is expected that human infants and fetuses are most at risk. Some cohort studies have found that children exposed at 2–4 years of age are at greater risk, but this might also be explained by confounding factors, and is less consistent with the preclinical data.[33,34] Third, it could be argued that 5 years of age is too early to detect long-term neurocognitive outcomes because several executive functions and social–emotional skills do not develop until later in life. However, our results of individually administered, standardised tests and parent reports indicate that children who undergo anaesthesia in infancy start school life with no neurodevelopmental risk factors. Exploration of executive function and social–emotional functions later in development could be an area of future study. Fourth, in this trial, children in the general anaesthesia group received only sevoflurane; however, there are several other general anaesthetics that are used for children, such as isoflurane, desflurane, and propofol. No existing preclinical data indicate that any effects seen with sevoflurane would be different to the effects seen with these other agents, and it is therefore reasonable to assume that the GAS trial results would translate to other general anaesthetic agents. Some preclinical data show that the effect might be greater if multiple agents are

given concurrently; therefore, the GAS trial results cannot be generalised to situations in which multiple general anaesthetic agents are given concurrently. Finally, the duration of exposure was on average just under 1 h and less than 2 h for all children. Animal data suggest that longer exposures are more likely to cause neurotoxicity, although there is no clear cutoff for length of exposure that does or does not have an effect. The hour of anaesthesia received by patients in this study was shorter than the exposure used in many of the animal experiments; however, the equivalence of animal exposure time to that in humans is unknown. Furthermore, the median duration of general anaesthesia for children in the 1·5 million procedures in the National Anesthesia Clinical Outcomes Registry (USA) was 57 min, with infants having a median duration of 79 min.[46] Thus, the duration of exposure in the GAS trial is longer than nearly half the anaesthetic exposures among small children.

The number of children potentially affected by national safety warnings, such as those of the US Food and Drug Administration, about the potential neurotoxic of general anaesthesia is substantial. During the first 3 years of life, about 10% of children from developed countries—equating to millions of children per year—receive a general anaesthetic for a variety of surgical, diagnostic, and medical procedures.[27,47] Most of these children are healthy and will be exposed to a single anaesthetic of short or intermediate duration during their childhood.[42] Given the high prevalence of exposure in early childhood, even small effects on brain development due to general anaesthesia could have very large public health consequences. Furthermore, parents and providers could potentially delay necessary procedures in children in an effort to limit exposure at a time of cerebral vulnerability, putting some children at risk for both medical and developmental impairments. The GAS trial, being consistent with data from several previous cohort studies, provides strong evidence that just under 1 h of general anaesthesia in infancy does not cause significant neurocognitive or behavioural deficits.

Contributors

MEM was involved in study design, conception, and conduct, data coordination, data interpretation, and writing and critical revision of the manuscript. JCdG was involved in the coordination and supervision of data collection, data analyses and interpretation, revision of the manuscript, and approval of the final manuscript as submitted. LD contributed to protocol development, data collection, statistical plan, statistical analysis, data interpretation, and writing of the manuscript. ND, DW, and GB were involved in study design and conduct, data acquisition and coordination, data interpretation, and writing of the manuscript. AG contributed to statistical analyses, statistical analysis planning, data interpretation, and revising the manuscript critically. RS, RWH, DCB, NM, and SS were involved in study design, protocol development, data interpretation and writing the manuscript. SJS was involved in study conduct, data acquisition and coordination, revising the manuscript, and submission of paper. JM coordinated study conduct in the USA including data acquisition and follow-up. GG was involved in study conduct, data acquisition, data interpretation, and editing of the paper. PLH was involved in study conduct, data acquisition, assistance with statistical analysis planning, and editing of the manuscript critically. PH was involved in study design, statistical oversight, review of the statistical analysis plan, data interpretation, and editing of the manuscript. GF was involved in study design, data acquisition, and writing of the manuscript. FI, BSvUS, AL, NW, MM, DMP, ARA, PS, and CB were involved in study conduct, data acquisition, and revising the manuscript critically. 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.

Declaration of interests

We declare no competing interests.

Data sharing

The de-identified dataset collected for this analysis of the GAS trial will be available 6 months after publication of this manuscript. The study protocol, analysis plan, and consent forms will also be available. The data can be obtained from the Murdoch Children's Research Institute by emailing andrew.davidson@rch.org.au. Before any data are released, the following are required: a data access agreement must be signed between relevant parties, the GAS Trial Steering Committee must see and approve the analysis plan describing how the data will be analysed, there must be an agreement around appropriate acknowledgment, and any additional costs involved must be covered. Data will only be shared with a recognised research institution which has approved the proposed analysis plan.

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