short overall treatment time and decreased heart dose, are now reflected with modern whole-breast irradiation. The 10-year results of UK and Canadian trials comparing 5 weeks versus 3 weeks of whole-breast irradiation show that local control is equivalent but side-effects are reduced with the 3-week treatment.[7,8] The UK Fast Forward study[9] is going further and investigating just five treatments for whole-breast irradiation over 1 week. Moreover, recent advantages in cardiac-sparing whole-breast irradiation techniques have reduced the heart dose substantially.[10]

So how does Strnad and colleagues' trial[1] fit with the future for breast radiotherapy? We know that breast cancer represents a spectrum of different diseases, with variation in prognosis, and that radiotherapy is no longer a one-size-fits-all strategy but ranges from highly complex treatments to the breast and regional lymph nodes, to complete avoidance of any radiation. It is likely that APBI will have a place within this array of treatments. The challenge will be to select the most appropriate treatment for the individual patient and to personalise radiotherapy based on tumour biology.[11]

*C E Coles, J R Yarnold
Oncology Centre, Cambridge University NHS Foundation Trust, Cambridge CB2 0QQ, UK (CEC); and Institute of Cancer Research and Royal Marsden Hospital NHS Foundation Trust, London, UK (JRY)
charlotte.coles@addenbrookes.nhs.uk

We declare no competing interests.

1 Strnad V, Ott OJ, Hildebrandt G, et al, on behalf of the Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. *Lancet* 2015; published online Oct 20. http://dx.doi.org/10.1016/S0140-6736(15)00471-7.
2 Marta GN, Macedo CR, Carvalho H de A, Hanna SA, da Silva JL, Riera R. Accelerated partial irradiation for breast cancer: systematic review and meta-analysis of 8653 women in eight randomized trials. *Radiother Oncol* 2015; **114:** 42–49.
3 Haviland JS, Bliss JM, Bentzen SM, Cuzick J. In regard to Vaidya et al. *Int J Radiat Oncol Biol Phys* 2015; **92:** 954–55.
4 Olivotto IA, Whelan TJ, Parpia S, et al. Interim cosmetic and toxicity results from RAPID: a randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. *J Clin Oncol* 2013; **31:** 4038–45.
5 Yarnold J, Bentzen SM, Coles C, Haviland J. Hypofractionated whole-breast radiotherapy for women with early breast cancer: myths and realities. *Int J Radiat Oncol Biol Phys* 2011; **79:** 1–9.
6 Coles C, Yarnold J, for the IMPORT Trials Management Group. The IMPORT trials are launched (September 2006). *Clin Oncol (R Coll Radiol)* 2006; **18:** 587–90.
7 Haviland JS, Owen JR, Dewar JA, et al, on behalf of the START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* 2013; **14:** 1086–94.
8 Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010; **362:** 513–20.
9 Coles CE, Brunt AM, Wheatley D, Mukesh MB, Yarnold JR. Breast radiotherapy: less is more? *Clin Oncol (R Coll Radiol)* 2013; **25:** 127–34.
10 Taylor CW, Kirby AM. Cardiac side-effects from breast cancer radiotherapy. *Clin Oncol (R Coll Radiol)* 2015; published online June 28. DOI:10.1016/j.clon.2015.06.007.
11 Bellon JR. Personalized radiation oncology for breast cancer: the new frontier. *J Clin Oncol* 2015; **33:** 1998–2000.

Anaesthetics, infants, and neurodevelopment: case closed?

Godong/BSIP/Science Photo Library

Published Online October 25, 2015 http://dx.doi.org/10.1016/S0140-6736(15)00669-8

See Articles page 239

Exposure of young animals, including non-human primates, to all anaesthetic and many sedative agents used in current clinical practice consistently produces neural injury.[1,2] Findings of initial studies showed accelerated apoptosis, and later investigations have suggested several other potential mechanisms of injury. This injury is associated with later impairment of learning and memory.[3] If these findings are also relevant to children, there might be profound consequences for anaesthetic care.[4] However, up to now, all evidence in humans has been provided by observational studies, which have inherent limitations, especially the potential confounding effects of the conditions that necessitate exposure to anaesthesia.[5,6] In *The Lancet*, Andrew Davidson and colleagues[7] present preliminary results of the General Anaesthesia compared to Spinal anaesthesia (GAS) study, the first randomised clinical trial to address the question of whether exposure of young children to anaesthesia is associated with adverse neurodevelopmental outcomes.

Both general and regional anaesthesia techniques are used in many paediatric centres for infants undergoing inguinal herniorrhaphy. Davidson and colleagues' multicentre multinational study[7] was designed as an equivalence trial comparing infants undergoing hernia repair. 722 infants were randomly assigned to receive either general anaesthesia (n=359) with sevoflurane, which is a single agent implicated as neurotoxic in animal studies, or awake-regional anaesthesia (n=363) with caudal or spinal blockade, for the same procedure. The primary outcome of the trial is neurodevelopmental outcome at age 5 years. Major experimental advantages to the design included the use of a single anaesthetic agent without adjuvants to provide general

anaesthesia, and assessing one surgical procedure. In this planned interim analysis of neurodevelopmental outcomes at 2 years, the researchers noted equivalence between the two groups in composite cognitive score on the Bayley Scales of infant and toddler development (difference in means between the groups 0·169, 95% CI −2·30 to 2·64, where a difference in means of 5 points was defined as the clinical equivalence margin). Although there were some instances of crossover between groups and loss to follow-up, this finding was quite robust in several sensitivity analyses, and, in view of the confidence intervals, there is little doubt that even a much larger study would have concluded equivalence for this secondary outcome. The trial itself is very well designed and reported, and the researchers should be congratulated for overcoming the large logistical challenges that were likely to be involved. Thanks should also be given to the parents who were willing to participate.

Davidson and colleagues' findings[7] are largely consistent with existing literature. Data from animal studies suggest that a dose–response relationship between anaesthetic duration and injury exists, and studies typically use durations of exposure greater than the mean duration of general anaesthesia in this study (54 min). This is especially true for studies looking at behavioural endpoints (by contrast with histological injury). Some data also suggest that combinations of agents produce additional effects. Thus, the fact that one rather brief exposure of infants to a single agent did not produce adverse neurodevelopmental effects is consistent with most preclinical findings.

The scientific literature regarding use of anaesthesia in children is restricted to observational studies in which heterogeneity poses interpretive challenges, and that have many limitations.[6] Nonetheless, the interim results of the GAS study[7] are in agreement with most previous findings, with some caveats. The most important is that outcomes assessed in previous studies were measured at later ages, and might not be presaged by the Bayley scores at age 2—ie, consequences of any injury might not yet be detectable. Even so, most epidemiological studies have found no association between single exposures of children to anaesthetics and adverse outcomes, as defined by broad domains amenable to epidemiological methods, including intelligence quotient, learning disabilities, and group-administered achievement tests.[8,9] By contrast, every observational study that has examined multiple exposures to anaesthesia finds associations, which might imply a so-called multiple-hit mechanism, could reflect a dose–response relationship, or simply be the result of confounding.

Thus, interim results of the GAS trial[7] are consistent with the idea that one brief exposure of infants to general anaesthesia is unlikely to be associated with adverse neurodevelopmental outcomes, which is welcome news for parents and professionals. However, the case is not yet closed in practice. The applicability of any particular clinical trial to other settings depends on what factors might moderate any effects, such as sex (most GAS participants were male) and the use of combinations of agents for many procedures,[10] such as midazolam, propofol, sevoflurane, or nitrous oxide, all of which are implicated in toxic effects. The potential contribution of surgical trauma (eg, inflammatory responses) also cannot be excluded, such that the type of surgical procedure might also be relevant. Additionally, results of recent observational studies have shown associations between even single exposures and differences in some specific cognitive domains which require specialised testing to assess and which cannot be evaluated at age 2.[11–14] Finally, as a practical matter, it is not possible to know whether one exposure to anaesthesia, which might not have consequences, will eventually become an element of several exposures to anaesthesia, which might.

To establish causal relationships between exposures and outcomes in biology is a complex process that requires the proper interpretation and synthesis of several lines of evidence. Definitive studies that produce the answer are rare, partly because the answer often depends on many factors. Observational studies have clear limitations but are important in establishing causal links—eg, between smoking and cancer. Although no randomised trials have assessed the causal relationship between smoking and cancer, the relationship is beyond dispute when all the evidence is considered. Randomised trials can provide important evidence, but have their own limitations. For example, if multiple exposures are necessary for injury, it will be very difficult to design a randomised trial to evaluate such a hypothesis. Additionally,

exposure to anaesthesia at a young age after the index surgery (which occurred in roughly 15% of children in the GAS study[7]) biases towards equivalence. Nonetheless, as the first (and for the near future, only) randomised trial in this area, the GAS study will probably be regarded as a landmark, and future reports of the primary outcome at 5 years of follow-up from this trial are eagerly awaited.

David O Warner, Randall P Flick
Department of Anesthesiology, Mayo Clinic, Rochester, MN 55905, USA (DOW); and Departments of Anesthesiology and Pediatrics and Adolescent Medicine, Mayo Clinic, Rochester, MN, USA (RPF)
warner.david@mayo.edu

We declare no competing interests.

1 Jevtovic-Todorovic V, Hartman RE, Izumi Y, et al. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. *J Neurosci* 2003; **23:** 876–82.
2 Sanders RD, Hassell J, Davidson AJ, Robertson NJ, Ma D. Impact of anaesthetics and surgery on neurodevelopment: an update. *Br J Anaesth* 2013; **110** (suppl 1)**:** i53–i72.
3 Paule MG, Li M, Allen RR, et al. Ketamine anesthesia during the first week of life can cause long-lasting cognitive deficits in rhesus monkeys. *Neurotoxicol Teratol* 2011; **33:** 220–30.
4 Rappaport BA, Suresh S, Hertz S, Evers AS, Orser BA. Anesthetic neurotoxicity: clinical implications of animal models. *N Engl J Med* 2015; **372:** 796–97.
5 Wang X, Xu Z, Miao CH. Current clinical evidence on the effect of general anesthesia on neurodevelopment in children: an updated systematic review with meta-regression. *PLoS One* 2014; **9**: e85760.
6 Flick RP, Warner DO. A users' guide to interpreting observational studies of pediatric anesthetic neurotoxicity: the lessons of Sir Bradford Hill. *Anesthesiology* 2012; **117:** 459–62.
7 Davidson AJ, Disma N, de Graaff JC, et al, for the GAS consortium. Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. *Lancet* 2015; published online Oct 25. http://dx.doi.org/10.1016/S0140-6736(15)00608-X.
8 Lei SY, Hache M, Loepke AW. Clinical research into anesthetic neurotoxicity: does anesthesia cause neurological abnormalities in humans? *J Neurosurg Anesthesiol* 2014; **26:** 349–57.
9 Hansen TG. Anesthesia-related neurotoxicity and the developing animal brain is not a significant problem in children. *Paediatr Anaesth* 2015; **25:** 65–72.
10 Lee BH, Hazarika OD, Quitoriano GR, et al. Effect of combining anesthetics in neonates on long-term cognitive function. *Int J Dev Neurosci* 2014; **37:** 87–93.
11 Ing C, DiMaggio C, Whitehouse A, et al. Long-term differences in language and cognitive function after childhood exposure to anesthesia. *Pediatrics* 2012; **130:** e476–85.
12 Stratmann G, Lee J, Sall JW, et al. Effect of general anesthesia in infancy on long-term recognition memory in humans and rats. *Neuropsychopharmacology* 2014; **38:** 2275–87.
13 Ing CH, DiMaggio CJ, Malacova E, et al. Comparative analysis of outcome measures used in examining neurodevelopmental effects of early childhood anesthesia exposure. *Anesthesiology* 2014; **120:** 1319–32.
14 Backeljauw B, Holland SK, Altaye M, Loepke AW. Cognition and brain structure following early childhood surgery with anesthesia. *Pediatrics* 2015; **136:** e1–12.

Trends in cause-specific mortality in Chinese provinces


Lhaba Cering/Xinhua Press/Corbis

Published **Online** October 26, 2015 http://dx.doi.org/10.1016/S0140-6736(15)00553-X

See **Articles** page 251

China's extraordinary economic development has brought with it huge improvements in public health. Children born in China today are expected to live almost a decade longer on average than are individuals born in 1990.[1] The country now has more people aged 65 years and older than any other country in the world, placing enormous pressures on its health-care infrastructure.[2] As average incomes have increased, lifestyles have changed, and access to health care has improved, the country has experienced a rapid transition away from infectious diseases and towards non-communicable diseases as causes of mortality. As a consequence, China now faces very different public health challenges to those of 25 years ago. Economic development, accompanied by rural-to-urban migration on an unprecedented scale,[3] has also resulted in substantial social and environmental problems, including a rapid rise in health inequalities[4] and air pollution levels far in excess of recommended limits.[5]

In *The Lancet*, Maigeng Zhou and colleagues[6] report trends in cause-specific mortality across provinces in China between 1990 and 2013. The investigators collected the available routine data for each province and did analyses based on well-established methods developed for the Global Burden of Disease Study 2013.[1] Their study investigated how patterns in 240 causes of deaths have changed during the period, and examined differences in mortality in each of China's 33 province-level administrative units, including Hong Kong and Macau.

The results of the study[6] show the huge progress that has been made throughout China. In 1990, lower respiratory infections and preterm birth complications were the leading causes of years of life lost (YLLs) in most provinces. By 2013, the national average age-standardised death rate had fallen by almost a third, and life expectancy had improved throughout the country. Substantial shifts have occurred in the major causes of mortality during that period, including reductions that in some cases exceed 90%, such as in age-standardised death rates for infectious diseases, especially improvements in deaths from diarrhoeal disease and lower respiratory infections. In 2013, the leading causes of YLLs were stroke (also the most common cause in 27 provinces[7]), ischaemic heart disease (which is increasing in men but not in women, possibly because of high smoking prevalence in men),

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

*Andrew J Davidson, Nicola Disma, Jurgen C de Graaff, Davinia E Withington, Liam Dorris, Graham Bell, Robyn Stargatt, David C Bellinger, Tibor Schuster, Sarah J Arnup, Pollyanna Hardy, Rodney W Hunt, Michael J Takagi, Gaia Giribaldi, Penelope L Hartmann, Ida Salvo, Neil S Morton, Britta S von Ungern Sternberg, Bruno Guido Locatelli, Niall Wilton, Anne Lynn, Joss J Thomas, David Polaner, Oliver Bagshaw, Peter Szmuk, Anthony R Absalom, Geoff Frawley, Charles Berde, Gillian D Ormond, Jacki Marmor, Mary Ellen McCann, for the GAS consortium**

Summary

Background Preclinical data suggest that general anaesthetics affect brain development. There is mixed evidence from cohort studies that young children exposed to anaesthesia can have an increased risk of poor neurodevelopmental outcome. We aimed to establish whether general anaesthesia in infancy has any effect on neurodevelopmental outcome. Here we report the secondary outcome of neurodevelopmental outcome at 2 years of age in the General Anaesthesia compared to Spinal anaesthesia (GAS) trial.

Methods In this international assessor-masked randomised controlled equivalence trial, we recruited infants younger than 60 weeks postmenstrual age, born at greater than 26 weeks' gestation, and who had inguinal herniorrhaphy, from 28 hospitals in Australia, Italy, the USA, the UK, Canada, the Netherlands, and New Zealand. Infants were randomly assigned (1:1) to receive either awake-regional anaesthesia or sevoflurane-based general anaesthesia. Web-based randomisation was done in blocks of two or four and stratified by site and gestational age at birth. Infants were excluded if they had existing risk factors for neurological injury. The primary outcome of the trial will be the Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III) Full Scale Intelligence Quotient score at age 5 years. The secondary outcome, reported here, is the composite cognitive score of the Bayley Scales of Infant and Toddler Development III, assessed at 2 years. 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. This trial is registered with ANZCTR, number ACTRN12606000441516 and ClinicalTrials.gov, number NCT00756600.

Findings Between Feb 9, 2007, and Jan 31, 2013, 363 infants were randomly assigned to receive awake-regional anaesthesia and 359 to general anaesthesia. Outcome data were available for 238 children in the awake-regional group and 294 in the general anaesthesia group. In the as-per-protocol analysis, the cognitive composite score (mean [SD]) was 98·6 (14·2) in the awake-regional group and 98·2 (14·7) in the general anaesthesia group. There was equivalence in mean between groups (awake-regional minus general anaesthesia 0·169, 95% CI −2·30 to 2·64). The median duration of anaesthesia in the general anaesthesia group was 54 min.

Interpretation For this secondary outcome, we found no evidence that just less than 1 h of sevoflurane anaesthesia in infancy increases the risk of adverse neurodevelopmental outcome at 2 years of age compared with awake-regional anaesthesia.

Funding Australia National Health and Medical Research Council (NHMRC), Health Technologies Assessment-National Institute for Health Research UK, National Institutes of Health, Food and Drug Administration, Australian and New Zealand College of Anaesthetists, Murdoch Childrens Research Institute, Canadian Institute of Health Research, Canadian Anesthesiologists' Society, Pfizer Canada, Italian Ministry of Heath, Fonds NutsOhra, and UK Clinical Research Network (UKCRN).

Lancet 2016; 387: 239–50

Published **Online** October 25, 2015 http://dx.doi.org/10.1016/S0140-6736(15)00608-X

This online publication has been corrected. The corrected version first appeared at thelancet.com on Jan 14, 2016

See **Comment** page 202

*See appendix for a full list of study investigators

Anaesthesia and Pain Management Research Group, Murdoch Childrens Research Institute, Melbourne, VIC, Australia (A J Davidson MD, M J Takagi PhD, P L Hartmann BPsych, G Frawley MBBS, G D Ormond MSc)**; Melbourne Children's Trials Centre, Murdoch Childrens Research Institute, Melbourne, VIC, Australia** (A J Davidson)**; Department of Anaesthesia and Pain Management, The Royal Children's Hospital, Melbourne, VIC, Australia** (A J Davidson, G Frawley)**; Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia** (A J Davidson, R W Hunt PhD)**; Department of Anesthesia, Istituto Giannina Gaslini, Genoa, Italy** (N Disma MD, G Giribaldi MD)**; Department of Anaesthesia, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, Netherlands** (J C de Graaff PhD)**; Department of Anesthesia, Montreal Children's Hospital, Montreal, Canada** (D E Withington BM)**; Department of Anesthesia, McGill University, Montreal, Canada** (D E Withington)**; Paediatric Neurosciences Research Group, Fraser of Allander Unit** (L Dorris DClinPsy)**, Department of Anaesthesia** (G Bell MBChB, N S Morton MD)**, Royal Hospital for Children,**

Introduction

Substantial preclinical evidence exists that describes how general anaesthesia drugs change brain development in young animals.[1] These changes include accelerated apoptosis and other effects such as changes to dendritic morphology.[2–5] Findings have also shown that exposure to general anaesthesia in young animals is associated with long-term cognitive and behavioural changes.[3,6,7] These effects have been described in various species including non-human primates.[7–10] The changes are seen with several different general anaesthesia drugs, are greater with longer exposure, and are less severe in older animals.[2,8] The clinical relevance of these findings is unknown and much debated.[11–14]

In human beings, there is conflicting evidence for an association between exposure to anaesthesia in early childhood and adverse long-term neurodevelopmental outcome; however, confounding restricts any assumption of causality.[15–30] Young children who receive anaesthesia are inevitably having surgery or an investigative procedure.

Glasgow; Mental Health and Wellbeing, University of Glasgow, Glasgow, UK (L Dorris); School of Psychological Science, La Trobe University, Victoria, VIC, Australia (R Stargatt PhD); Child Neuropsychology, Murdoch Childrens Research Institute, Melbourne, VIC, Australia (R Stargatt, M J Takagi); Department of Neurology (D C Bellinger PhD, J Marmor MEd), Department of Psychiatry (D C Bellinger), Boston Children's Hospital, Harvard Medical School, Boston, MA, USA; Department of Environmental Health, Harvard T H Chan School of Public Health, Boston, MA, USA (D C Bellinger); Clinical Epidemiology and Biostatistics Unit (T Schuster PhD, S J Arnup MBiostat), Neonatal Research Group (R W Hunt), Murdoch Childrens Research Institute, Melbourne, VIC, Australia; National Perinatal Epidemiology Unit, Clinical Trials Unit, University of Oxford, Oxford, UK (P Hardy MSc); Department of Neonatal Medicine, The Royal Children's Hospital, Melbourne, Australia (R W Hunt); Department of Anesthesiology and Pediatric Intensive Care, Ospedale Pediatrico 'Vittore Buzzi', Milan, Italy (I Salvo MD); University of Glasgow, Glasgow, UK (N S Morton); School of Medicine and Pharmacology, University of Western Australia, Perth, WA, Australia (Prof B S von Ungern Sternberg PhD); Department of Anaesthesia and Pain Management, Princess Margaret Hospital for Children, Perth, WA, Australia (Prof B S von Ungern Sternberg); Department of Anesthesia, Ospedale Papa Giovanni XXIII, Bergamo, Italy (B G Locatelli MD); Department of Paediatric Anaesthesia and Operating Rooms, Starship Children's Hospital, Auckland District Health Board, Auckland, New Zealand (N Wilton MBBS); Department of Anesthesiology, University of Washington, Seattle, WA, USA (A Lynn MD); Department of Anesthesia, University of Minnesota, Minneapolis, MN, USA (J J Thomas MD); Department of Anesthesiology, Children's Hospital Colorado and University of Colorado School of Medicine, Aurora, CO, USA

Research in context

Evidence before this study

We searched MEDLINE and Cochrane controlled trial register (last search done on Sept 18, 2015) for original research and meta-analyses describing the association between anaesthesia exposure in early life and neurodevelopmental outcome. We used combinations of the search terms "anesthesia", and "child development", or "learning disorders". The search found no randomised trials but several cohort studies. Several reviews have concluded that there is an association between anaesthesia in childhood and neurodevelopmental outcome. Findings of two meta-analyses have shown an association between anaesthesia in children and a range of neurodevelopmental outcomes. 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 reviews conclude that causation cannot be established or excluded.

Added value of this study

We report results from the first randomised controlled trial assessing the effect of general anaesthesia in infancy on neurodevelopmental outcome. We used the best measure of neurodevelopment available to assess 2-year-old children, and noted strong evidence for equivalence between the use of awake-regional anaesthesia and just less than 1 h of general anaesthesia. However, it should be noted that this was an analysis of a secondary outcome with the primary outcome planned at 5 years of age, and in view of the limited sensitivity of developmental assessment at 2 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 substantially to the weight that should be given to the results compared with the mixed results found in previous cohort studies. However, reassessment at an older age is necessary before definitive conclusions can be drawn. The trial does not rule out the possibility that longer or many exposures to anaesthesia in early childhood can cause neurodevelopmental changes. Further research is needed to address these questions.

Added risk of poor neurodevelopmental outcome might be due to the underlying pathology, comorbidity, or other perioperative 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]

In view of the many potential confounding factors, a randomised trial is the best study design to establish whether anaesthesia exposure in early childhood causes long-term neurodevelopmental changes. Fortuitously there are two established anaesthetic techniques for inguinal herniorrhaphy in infancy; awake-regional and sevoflurane-based general anaesthesia. Therefore, we undertook a randomised controlled trial comparing neurodevelopmental outcome in children who were randomly assigned to receive either awake-regional or sevoflurane-based general anaesthesia for inguinal herniorrhaphy in early infancy: the General Anaesthesia compared to Spinal anaesthesia (GAS) trial. The primary outcome for the trial will be the Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III) Full Scale Intelligence Quotient score at age 5 years. As a secondary outcome, we also planned a priori to assess neurodevelopmental outcome at age 2 years. In this paper we report all secondary outcomes at 2 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

In this observer-blind, international, multisite, randomised, controlled, equivalence trial, we assessed awake-regional anaesthesia versus general anaesthesia in infants undergoing 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 ethics committee approval was obtained at each site and written consent obtained from the child's parents or guardians. A summary of the protocol is available online.

Participants

Eligibility criteria included infants up to 60 weeks postmenstrual age (ie, gestational age at birth plus chronological 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 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 (eg, 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. We identified eligible infants 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 h web-based randomisation service was managed by the Data Management and Analysis Centre, Department of Public Health, University of Adelaide, Australia. Participants were randomly assigned (1:1) to receive either general anaesthesia or awake-regional anaesthesia. Randomisation was done in blocks of two or four and stratified by site and gestational age at birth: 26–29 weeks and 6 days, 30–36 weeks and 6 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 who did the assessment were masked to group allocation. Once their assessment was completed they were asked to indicate if they were aware of group allocation.

Procedures

The awake-regional group received either an awake-spinal anaesthetic, an awake-caudal anaesthetic, or a combined spinal-caudal anaesthetic according to institutional

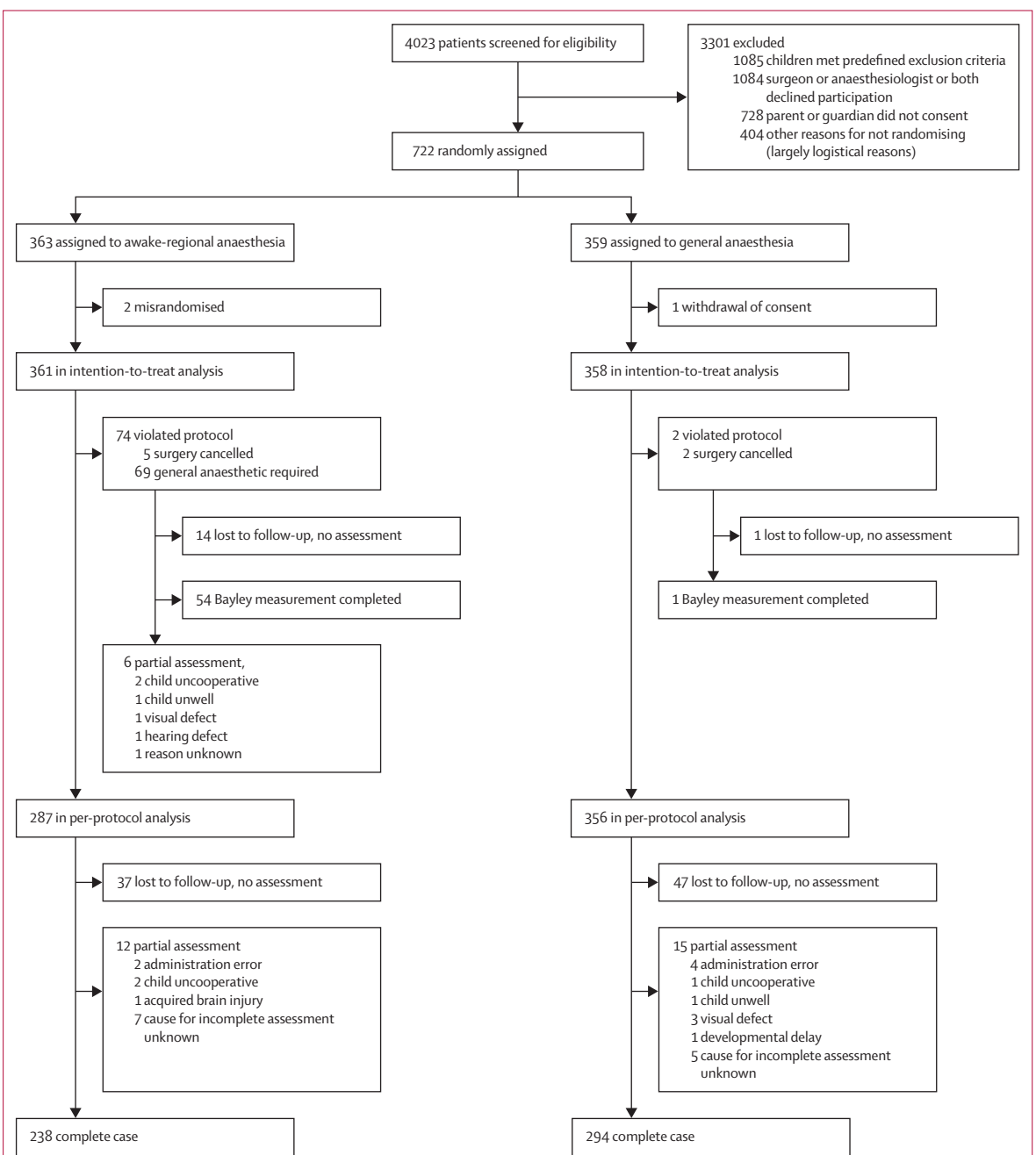

Figure: **Trial profile**

(Prof D Polaner MD); **Department of Anaesthesia, Birmingham Children's Hospital, Birmingham, UK** (O Bagshaw FRCA); **Department of Anesthesiology, Children's Medical Centre Dallas, Dallas, TX, USA** (P Szmuk MD); **Department of Anaesthesiology, University Medical Centre Groningen, Groningen University, Groningen, Netherlands** (Prof A R Absalom MBChB); **and Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA** (Prof C Berde MD, M E McCann MD)

Correspondence to:
Dr Andrew J Davidson, Anaesthesia and Pain Management Research Group, Murdoch Childrens Research Institute, The Royal Children's Hospital, Flemington Road, Parkville, Victoria 3052, Australia
andrew.davidson@rch.org.au

See **Online** for appendix

For the **protocol** see http://www.thelancet.com/protocol-reviews/09PRT-9078

protocols. Spinal anaesthesia was done with 0·2 mL/kg 0·5% isobaric bupivacaine with a minimum volume of 0·5 mL. Because isobaric bupivacaine was unavailable at some sites, other agents were used (in the USA, 0·13 mL/kg of hyperbaric 0·75% bupivacaine, and in the UK 0·2 mL/kg 0·5% levobupivacaine). Caudal anaesthesia was done with up to a total dose of 2·5 mg/kg of 0·25% bupivacaine. In the UK, 0·25% levobupivacaine was used. In the USA, if surgery was likely to take longer than 1 h, some patients were given a loading dose of 3% chloroprocaine (1 mL/kg in divided doses of no more than 0·25 mL/kg per 15 s) via a caudal cannula and then an infusion of 1–2 mL/kg per h. Ilioinguinal and field blocks could also be done. The total dose of bupivacaine did not exceed 2·5 mg/kg. In the awake-regional group, oral sucrose was used to settle the child if needed and all other forms of sedation avoided. If the awake-regional anaesthesia was ineffective then a general anaesthesia was done with sevoflurane, and if the child became unsettled intraoperatively, sevoflurane was given to supplement the awake-regional anaesthesia. Both were regarded as protocol violations.

The general anaesthesia group received sevoflurane for induction and maintenance in a mix of air and oxygen. 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 or field block with bupivacaine could be done in both groups to provide postoperative analgesia. Oral or intravenous acetaminophen could also be given. Heart

	RA group as per protocol (N=287)	GA group as per protocol (N=356)	RA group intention to treat (N=361)	GA group intention to treat (N=358)
Baseline demographics				
Sex, 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)
Postmenstrual 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				
Postmenstrual 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%)
Birthweight (kg)	2·3 (0·9)	2·3 (0·9)	2·4 (0·9)	2·3 (0·9)
Z score for birthweight	–0·68 (1·3)	–0·69 (1·3)	–0·66 (1·2)	–0·69 (1·3)
Apgar score at 1 min	9 (7–9)	8·5 (7–9)	9 (7–9)	9 (7–9)
Apgar score at 5 min	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 h)	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%)
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%)

(Table 1 continues on next page)

rate, blood pressure, oxygen saturation, and (where applicable) expired sevoflurane concentrations were recorded every 5 min.

Serum glucose was measured after anaesthetic induction. There were rescue protocols for hypoglycaemia, hypotension, and hypoxaemia. If the blood pressure fell more than 20% below baseline, an intravenous bolus fluid was given plus vasoactive drugs if deemed necessary. Hypoglycaemia (blood sugar <3·0 mmol/L) was treated with a bolus of 5 mL/kg of 10% dextrose. Oxygen by face mask in the awake-regional arm and an increased FiO_2 in the general anaesthesia group was used at the discretion of the anaesthetist to maintain arterial oxygen saturation higher than 95%.

Assessments were undertaken within 2 months either side of 2 years of age (corrected for prematurity). The assessment took about 2 h 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 Behaviour 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. We also recorded demographic data, family history, and medical history, and did a brief physical and neurological examination. The physical examination included anthropometric measurements such as length, weight, and arm and head circumference. The neurological examination included cranial nerve examination, posture assessment, and the muscle strength, tone, and reflexes of the arms and legs.

All study data were sent to the Murdoch Children's 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 every 6 months 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 prespecified to be the composite cognitive score of the Bayley-III. The hypothesis (as stated in the protocol)

	RA group as per protocol (N=287)	GA group as per protocol (N=356)	RA group intention to treat (N=361)	GA group intention to treat (N=358)
(Continued from previous page)				
Familial demographics				
Primary language(s) only spoken*	252 (88%)	305 (86%)	311 (86%)	307 (86%)
Maternal age at birth >21 years	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				
Blood glucose concentration (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 intravenously	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%)
Duration of surgery (min)	26·0 (19·0–35·0)	28·0 (20·0–40·0)	28·0 (20·0–38·0)	28·0 (20·0–40·0)
Duration of sevoflurane exposure (min)	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 per h	NA	2·6 (1·1)	1·9 (1·0)†	2·6 (1·1)
Any significant apnoea to 12 h postoperatively‡	6 (2%)	15 (4%)	10 (3%)	15 (4%)

Data are n (% of non-missing data) or mean (SD), median (IQR) unless otherwise stated. RA=awake-regional anaesthesia. GA=general anaesthesia. IVH=intraventricular haemorrhage. PDA=patent ductus arteriosus. *The primary language spoken at home is the primary language in each country that the Bayley was done (eg, Italian in Italy). †For those cases that received sevoflurane. ‡Significant apnoea defined as a pause in breathing for >15 s or >10 s if associated with oxygen saturation <80% or bradycardia (20% decrease in heart rate).

Table 1: **Baseline demographics**

	RA group as per protocol (N=287)	GA group as per protocol (N=356)	RA group intention to treat (N=361)	GA group intention to treat (N=358)
Assessment details				
Location of 2-year assessment at hospital	204 (96%)	240 (94%)	250 (95%)	241 (94%)
Family demographics at 2 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 inguinal herniorrhaphy 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%)
CNS	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 or 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 2 months or longer	43 (17%)	50 (16%)	93 (17%)	59 (19%)
Child had febrile seizures after the hernia repair	8 (3%)	9 (3%)	10 (3%)	9 (3%)
Child had other seizures after 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%)

(Table 2 continues on next page)

was that the composite cognitive score of the Bayley-III measured at 2 years of age in infants who are anaesthetised for inguinal herniorraphy is equivalent when using general anaesthesia compared with awake-regional anaesthesia. 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 an SD of 15 in the reference population. The subscales (eg, fine motor scale) are reported as scaled scores, with a mean of 10 and an 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 prespecified secondary outcome

Because this is an equivalence study, the outcome was analysed on an as-per-protocol 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 minus five and plus five points. Intention-to-treat 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 5-year follow-up WPPSI-III Full Scale Intelligence Quotient score. Assuming an expected difference of one standardised score point and a 90% chance that a 95% CI will exclude a difference of more than five points (the largest difference acceptable to show equivalence), the trial would need 598 infants. Enrolling roughly 720 participants would allow for 10% loss to follow-up and 10% with a major protocol violation.

We used multiple imputation with chained equations to impute missing outcome data in the analysis of all outcomes.[36] The following prespecified variables were used as predictor variables within the imputation approach: anaesthesia group, country, sex, gestational age at birth, standardised *Z* score for birthweight, mother received antenatal steroids, mother diagnosed with chorioamnionitis, intraventricular haemorrhage, maternal age, maternal education, rescue glucose given intravenously, need for fluid bolus for hypotension, vasoactive drugs given for hypotension, duration of surgery, dose of sevoflurane (concentration multiplied by h), significant postoperative apnoea, corrected age at assessment, any more anaesthetic exposures since the inguinal herniorraphy, any malformations, any chronic illness, any prescribed medication for 2 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 CIs based on inverse probability of censoring weighting were reported.[37]

Risk ratios with 95% CIs were reported for the proportion of individuals that fell below one and two SDs of the composite cognitive score. Risk ratios were generated using generalised linear models for a binomial distributed response variable using a log link (binomial log-linear regression). These analyses were not prespecified in the study protocol (post-hoc analyses). All analyses were done in Stata (version 13).

This trial is registered with ANZCTR, number ACTRN12606000441516, ClinicalTrials.gov, number NCT00756600, and the UK Clinical Research Network (UKCRN), number 12437565.

Role of the funding source

The funders 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, GDO, and Suzette Sheppard were responsible for submitting the manuscript. AJD made the final decision to submit the paper for publication.

Results

Between Feb 9, 2007, and Jan 31, 2013, we recruited 722 infants from 28 hospitals in Australia, the USA, the UK, Italy, the Netherlands, Canada, and New Zealand (appendix p4). There were two misrandomisations and one withdrawal of consent leaving 361 in the intention-to-treat analysis in the awake-regional anaesthesia group and 358 in the general anaesthesia group (figure). Table 1 summarises demographic data for each group at baseline and table 2 summarises demographic data at 2 years. There were 74 protocol violations in the awake-regional anaesthesia group (five due to surgery being cancelled and 69 received some sevoflurane or other general anaesthesia) and two violations in the general anaesthesia group (surgery cancelled).

Follow-up was from March 5, 2009, to March 6, 2015. 47 families were lost to follow-up in the general anaesthesia group and 52 in the awake-regional anaesthesia group. 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 awake-regional arm). Of those that attended for assessment, the cognitive scale of the Bayley-III was completed by 292 in the awake-regional group and 295 in the general anaesthesia group (figure). Very few children were unable to complete the Bayley-III due to developmental delay or other recognised reason for cognitive impairment. In 97% of cases the psychologist and paediatrician were unaware of group allocation at the time of assessment (appendix p5).

Table 3 shows the Bayley-III cognitive, language, motor, social-emotional, and adaptive behaviour scores, and the MacArthur-Bates data for each group. For the cognitive composite score, we noted evidence for equivalence in means between the awake-regional anaesthesia and general anaesthesia groups in both the as-per-protocol and the intention-to-treat analyses using multiple imputation to account for missing outcome data (awake-regional minus general anaesthesia: 0·169, 95% CI –2·30 to 2·64 for the as-per-protocol analysis and 0·256, –2·06 to 2·57 for the intention-to-treat analysis). These results were consistent with the findings of the complete case analyses (awake-regional minus general anaesthesia 0·458, 95% CI –2·02 to 2·94 for the as-per-protocol analysis and 0·430, –1·90 to 2·76 for the intention-to-treat analysis). There was also evidence for equivalence between groups in the composite motor scores, composite language scores, and the composite adaptive behaviour scores (table 4). The results were consistent in both as-per-protocol and intention-to-treat 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 as per protocol and intention to treat) and upper 95% confidence interval limits exceeding the prespecified 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 appendix shows results of the inverse probability weighting and worst case imputation scenarios for missing data (appendix pp 5–6). 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 showed consistent robustness of the study findings with regard to data missingness.

	RA group as per protocol (N=287)	GA group as per protocol (N=356)	RA group intention to treat (N=361)	GA group intention to treat (N=358)
(Continued from previous page)				
Occupational therapy	9 (4%)	12 (4%)	12 (4%)	12 (4%)
Psychology	1 (<1%)	6 (2%)	1 (<1%)	6 (2%)
Developmental medicine or early intervention	8 (3%)	7 (2%)	9 (3%)	7 (2%)
Child attends play group or 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. RA=awake-regional anaesthesia. GA=general anaesthesia.

Table 2: **2-year descriptive statistics demographic data**

	RA group as per protocol	GA group as per protocol	RA group intention to treat	GA group intention to treat
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 are n, mean (SD). RA=awake-regional anaesthesia. GA=general anaesthesia.

Table 3: **Descriptive statistics Bayley-III and MacArthur-Bates scores by group**

Overall, only a few children had a diagnosis of cerebral palsy, hearing or visual impairment, or specific behavioural diagnoses such as autism spectrum disorder (table 5). The event rate was too low for any meaningful comparative analysis. There was no evidence for a difference between groups in the proportion of children one or two SDs below the age mean on the cognitive composite score (appendix pp 6–7).

Details of adverse events during and immediately after anaesthesia have been reported previously.[32]

Discussion

We noted strong evidence for equivalence between awake-regional anaesthesia and general anaesthesia in infancy in terms of neurodevelopmental outcome at 2 years of age. Equivalence was shown in many domains of neurodevelopmental assessment and the 95% CIs fell within a third of an SD, well inside our predefined boundaries of clinical equivalence.

There are no previous randomised trials assessing the effect of anaesthesia in infancy on long-term neurodevelopmental outcomes. 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 could also be explained by the confounding effects of surgery, pathology, or comorbidity. 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 because of a reliance on outcome measures, such as school grade, which might not detect subtle effects, or because their broad inclusion criteria include children exposed to anaesthesia at an older age when the risk might be less. The heterogeneity of the cohort studies also makes it difficult to analyse the effects of duration of exposure, type of anaesthetic drugs used, or doses or combination of drugs used. The above limitations inherently limit the capacity for cohort studies to establish the link between exposure to anaesthesia and neurodevelopmental outcome. These limitations highlight the importance of methodologically robust and adequately powered trials such as this one.[31]

	Difference in RA–GA*	Difference in SE	95% CI for difference in RA–GA
Cognitive composite score			
APP multiple imputation	0·169	1·26	−2·30 to 2·64
APP complete case	0·458	1·26	−2·02 to 2·94
ITT multiple imputation	0·256	1·18	−2·06 to 2·57
ITT complete case	0·430	1·19	−1·90 to 2·76
Language composite score			
APP multiple imputation	1·146	1·39	−1·59 to 3·88
APP complete case	0·628	1·37	−2·07 to 3·32
ITT multiple imputation	1·454	1·32	−1·14 to 4·05
ITT complete case	0·942	1·30	−1·61 to 3·49
Motor composite score			
APP multiple imputation	0·598	1·20	−1·77 to 2·97
APP complete case	0·410	1·19	−1·92 to 2·74
ITT multiple imputation	0·143	1·13	−1·08 to 3·37
ITT complete case	1·031	1·14	−1·20 to 3·26
Social-emotional composite score			
APP multiple imputation	1·005	2·09	−3·12 to 5·13
APP complete case	2·012	1·70	−1·32 to 5·35
ITT multiple imputation	1·183	2·03	−2·82 to 5·19
ITT complete case	2·015	1·62	−1·17 to 5·20
Adaptive behaviour composite score			
APP multiple imputation	−0·893	1·34	−3·52 to 1·73
APP complete case	−1·223	1·33	−3·83 to 1·38
ITT multiple imputation	−0·502	1·28	−3·03 to 2·02
ITT complete case	−0·830	1·28	−3·34 to 1·68
MacArthur-Bates percentile score			
APP multiple imputation	−1·811	3·06	−7·85 to 4·23
APP complete case	−2·359	2·71	−7·69 to 2·98
ITT multiple imputation	−0·544	2·87	−6·20 to 5·11
ITT complete case	−1·113	2·57	−6·17 to 3·94

RA=awake-regional anaesthesia. GA=general anaesthesia. APP=as per protocol. ITT=intention to treat. *Adjusted for gestational age at birth.

Table 4: **Between-group comparisons in Bayley-III and MacArthur-Bates scores**

	RA group as per protocol (N=287)	GA group as per protocol (N=356)	RA group intention to treat (N=361)	GA group intention to treat (N=358)
Child has a hearing defect				
Conductive	9 (3%)	6 (2%)	9 (2%)	6 (2%)
Sensorineural	0	3 (1%)	1 (<1%)	3 (1%)
Hearing aid	1 (<1%)	3 (1%)	2 (1%)	3 (1%)
Legally blind (<6/60 in both eyes)	1 (<1%)	0	1 (<1%)	0
Cerebral palsy	1 (<1%)	4 (1%)	1 (0%)	4 (1%)
Autism spectrum disorder	2 (1%)	0	2 (1%)	0

Data are n (% of non-missing data). RA=awake-regional anaesthesia. GA=general anaesthesia.

Table 5: **2-year non-psychometric outcome data**

In this analysis we chose the cognitive scale of the Bayley-III as the main outcome of interest. Changes recorded in preclinical studies tend to be diffusely distributed over several brain regions. Such diffuse changes are most likely to have an effect on general cognition.

The results of two recent studies have shown that whereas children exposed to anaesthesia had similar school grades, those exposed had an increased risk of not sitting the tests.[26,28] This finding raises the possibility that a subpopulation of exposed children might have significant neurodevelopmental delay. To investigate this possibility, we compared the proportion of children in each group that scored two SDs below the age mean on the composite cognitive score. We noted no difference; however, in view of the limited power of this analysis, equivalence cannot be assumed. We have also reported the number of children with the diagnosis of autism spectrum disorder, cerebral palsy, and visual or hearing defects. This trial was not powered to detect differences in these diagnoses or events, and as expected we noted a low event rate in both groups. At 2 years of age it is difficult to accurately diagnose the presence of disorders such as autism spectrum disorder, or to accurately assess vision and hearing, and some children could still have undiagnosed neurological or neurobehavioural disorders.

Data from most preclinical studies suggest that prolonged exposure to general anaesthesia is necessary before injury is seen (usually at 2 or 3 h).[8] However, changes have been noted with 1 h of exposure.[38] In this trial, the median sevoflurane exposure was 54 min in the general anaesthesia group and hence the results are consistent with most preclinical data. The trial is an important adjunct to these data because translating doses and exposures from animals to human beings is uncertain, and shorter duration of exposure could still have clinically relevant effects that cannot be detected in animal models.

In human cohorts, some researchers have found an association with a single short exposure,[17,24] whereas others have only found an association after longer or several exposures.[22] There was no increase in learning disabilities in infants and toddlers exposed to 2 h or less of general anaesthesia in one study;[22] anaesthetic exposure was less than 90 min in 365 (61%) of 593 exposed patients. This finding highlights that most anaesthetics in young children are of fairly brief duration. An internal audit of anaesthetic duration in infants at Boston Children's Hospital showed that 53% of anaesthetics done in babies younger than 12 months of age were less than 2 h in duration. Thus, with regards to duration of exposure, our results are probably relevant to roughly half the anaesthetics given to infants.

The finding of equivalence after short exposure does not rule out the possibility that longer exposure to anaesthetics might have an effect on neurodevelopment. Further trials are needed before any assumptions can be made about the effect of prolonged anaesthesia exposure in infancy. Results of some studies have also shown a stronger association between several anaesthesia

exposures and adverse outcome than with a single exposure.[20,30] This situation might be the result of a greater effect of confounding; inevitably, children who undergo many procedures are more likely to have chronic disease. Our trial cannot address the possible increased toxic effects with multiple exposures.

Our trial has several limitations. Awake-regional anaesthesia inevitably has a failure rate. As this was an equivalence trial, we took the as-per-protocol analysis to be the most conservative analysis, assuming that treatment failure would bias toward no difference. In view of the possibly contentious nature of this assumption, we planned a priori to undertake a secondary intention-to-treat analysis. We noted no measureable differences between the as-per-protocol and intention-to-treat 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 awake-regional anaesthesia failure, led to an appreciable amount of missing data; however, both the multiple imputation analysis and the inverse probability weighting showed consistent robustness of the findings.

Another limitation is that although the Bayley-III is a well validated assessment method of current development, early neurobehavioural assessment of children is not a perfect predictor of long-term outcome because of the substantial variability in developmental timing in young children. Although Bayley-III has a stronger correlation with intelligence quotient at age 5 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 needed at a later date to identify mild or circumscribed deficits in cognitive functions such as executive skills and memory.[39,40] Therefore, it is important that the children be reassessed later in their development to confirm the results and to more thoroughly assess multiple domains of cognition. Children in this trial are undergoing assessment at 5 years of age and the results should be known after 2018.

It is important to note that this study reports the results of a secondary outcome. This analysis of the secondary outcome was prespecified 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 because of the recognition that there was growing concern over the issue of neurotoxicity and existing evidence to guide practice was inherently limited, and although the 2-year assessment was not definitive, it would still provide higher quality evidence than that which existed up to now. The 2-year assessment was also planned because of concerns over the feasibility of maintaining the cohort for the longer-term follow-up.

In this study, more than 80% of participants were male. It is well recognised that sex can have an effect on recovery from brain injury. The effect is variable and depends on the nature of the injury and outcome measured, although generally greater effects are recorded in males and indeed the neurotoxic effect of anaesthesia on rodents has been shown to be greater in males.[41] Thus, the finding of equivalence in our trial with a preponderance of males makes it unlikely that equivalence would not also be shown in females.

In this trial, sevoflurane was used without other general anaesthetics. We chose a sevoflurane-only anaesthetic because this reflects common practice for anaesthesia for inguinal herniorrhaphy, and the preclinical effects of sevoflurane have been clearly described. Some preclinical data have suggested that combinations of general anaesthetics might be more injurious, and thus our trial cannot shed light on the possibility that an effect might be seen if other agents are added.[3] Finally, the MacArthur-Bates score is dependent on parental report and hence might be open to bias. Additionally, the standardisation data are of varying degrees of validation across different languages.

In conclusion, this trial found strong evidence that exposure of just less than 1 h to a sevoflurane general anaesthesia in infancy does not increase the risk of adverse neurodevelopmental outcome at 2 years of age. Although not definitive, this is the strongest clinical evidence to date that sevoflurane general anaesthesia in infancy does not result in substantial neurotoxicity.

Contributors

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 report 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 report critically. JCdG was involved in the coordination and supervision of data collection, data analysis and interpretation, contribution to the statistical analysis plan, revised the report, and approved the final report as submitted. DEW was involved in study design and conduct, data acquisition and coordination, data interpretation, and revising the report critically. LD contributed to protocol development, data collection, statistical plan, statistical analysis, data interpretation, and writing of the report. GB was involved in study conduct, data coordination, and writing and reviewing the report. RS was the lead neuropsychologist and, along with DCB and RWH, was involved in study design, concept, conduct, data interpretation, and critically revising the report. TS and SJA were involved in interim analyses, contribution to the statistical analysis plan, data interpretation, and revising the report critically. PH was involved in study design, study conduct, interim analyses, contribution to the statistical analysis plan, data interpretation, and editing of the report. MJT contributed to the statistical analysis, data interpretation, and preparation of the report. GG and PLH were involved in study conduct, data acquisition, data interpretation, and revising the report critically. IS, BSvUS, BGL, NW, AL, JJT, DP, OB, PS, ARA, and JM were involved in study conduct, data acquisition, and coordination and revising the report critically. NSM and MEM were involved in study design, concept, and conduct, data coordination, data interpretation, writing the report, and revising it critically. GF and CB were involved in study design and concept, study conduct, data acquisition, contribution to data interpretation, and revising the report critically. GDO was involved in study conduct, data acquisition and coordination, contribution to the statistical analysis plan, and revising the report.

Declaration of interests
The views expressed in this publication are those of the author(s) and not necessarily those of the MRC, NHS, NIHR or the Department of Health UK. We declare no competing interests. The full list of members of the GAS consortium, the Trial Steering Committee and Data Safety Monitoring Committee are listed in the appendix (pp 1–3).

Acknowledgments
All hospitals and centres were generously supported by departmental funding. In addition to this funding, specific grants received for this study are as follows: Australia: The Australian National Health & Medical Research Council (Project Grants #1002906 and 491226); Australian and New Zealand College of Anaesthetists (Project Grant #11/021 and 07/012); Murdoch Childrens Research Institute; Victorian Government's Operational Infrastructure Support Program. US: National Institute of Health (Project Grant # NIH 1-R01 hD06 1136-01A1); Food and Drug Administration (Project Grant #FDA-SOL-08-SAFEKIDS-Clin 002-Project 2). Italy: Italian Ministry of Heath, Young Researchers Grant (Project Grant #167/GR-2009-1476067). Netherlands: Fonds NutsOhra grant #1305-144 and Vrienden WKZ 16.13.038. Canada: Canadian Institute of Health Research (Project Grant #MCT-98031), Canadian Anesthesiologists' Society, Pfizer Canada Inc. UK: Health Technologies Assessment–National Institute for Health Research UK (Project Grant # 07/01/05). We are also grateful to the following individuals who contributed to the running of the study: Mark Fagjman (Department of Anaesthesia, Monash Medical Centre, Melbourne, VIC, Australia); Daniela Tronconi (Department of Anesthesia, Istituto Giannina Gaslini, Genoa, Italy); David C van der Zee (Department of Pediatric Surgery, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Netherlands); Jan Hulscher (Department of Surgery, University Medical Center Groningen, Groningen University, Groningen, Netherlands); Michael Rivkin (Department of Neurology, Children's Hospital Boston, Boston, MA, USA); Michelle Sadler-Greever (University of Washington, Seattle Children's Hospital, Department of Anesthesia and Pain Medicine, Seattle, WA, USA); Debra Faulk (Children's Hospital Colorado and University of Colorado School of Medicine, Department of Anesthesiology, Colorado, CO, USA); Greta Wilkening (Neurosciences Institute, Children's Hospital Colorado, CO, USA); Edward Goldson (Department of Pediatrics, Division of Developmental-Behavioral Pediatrics, Children's Hospital Colorado, Colorado, USA). Danai Udomtecha and Sarah Titler (The University of Iowa Hospital, Department of Anesthesia, Iowa, IA, USA); Roxana Ploski and Alan Farrow-Gilespie (Children's Medical Centre Dallas, Department of Anesthesiology, University of Texas Southwestern Medical Center, Dallas and Children's Medical Center at Dallas and Outcome Research Consortium, Dallas, TX, USA); Timothy Cooper (Division of Developmental Medicine and the Center for Child Development, Monroe Carell Jr Children's Hospital at Vanderbilt, Nashville, TN, USA); Elizabeth Card (Perioperative Clinical Research Institute, Vanderbilt University Medical Center, Nashville, TN, USA); Wendy Boardman (Dartmouth-Hitchcock Medical Center, Department of Anesthesiology, NH, USA); Theodora K Goebel (Department of Anesthesiology and Critical Care Children's Hospital of Philadelphia, Philadelphia, PA, USA).

References

1 Jevtovic-Todorovic V, Absalom AR, Blomgren K, et al. Anaesthetic neurotoxicity and neuroplasticity: an expert group report and statement based on the BJA Salzburg Seminar. *Br J Anaesth* 2013; **111:** 143–51.
2 Briner A, Nikonenko I, De Roo M, Dayer A, Muller D, Vutskits L. Developmental stage-dependent persistent impact of propofol anesthesia on dendritic spines in the rat medial prefrontal cortex. *Anesthesiology* 2011; **115:** 282–93.
3 Jevtovic-Todorovic V, Hartman RE, Izumi Y, et al. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. *J Neurosci* 2003; **23:** 876–82.
4 Sanchez V, Feinstein SD, Lunardi N, et al. General anesthesia causes long-term impairment of mitochondrial morphogenesis and synaptic transmission in developing rat brain. *Anesthesiology* 2011; **115:** 992–1002.
5 Istaphanous GK, Ward CG, Nan X, et al. Characterization and quantification of isoflurane-induced developmental apoptotic cell death in mouse cerebral cortex. *Anesth Analg* 2013; **116:** 845–54.
6 Paule MG, Li M, Allen RR, et al. Ketamine anesthesia during the first week of life can cause long-lasting cognitive deficits in rhesus monkeys. *Neurotoxicol Teratol* 2011; **33:** 220–30.
7 Raper J, Alvarado MC, Murphy KL, Baxter MG. Multiple anesthetic exposure in infant monkeys alters emotional reactivity to an acute stressor. *Anesthesiology* 2015; published online Sept 2. DOI:10.1097/ALN.0000000000000851
8 Slikker W Jr, Zou X, Hotchkiss CE, et al. Ketamine-induced neuronal cell death in the perinatal rhesus monkey. *Toxicol Sci* 2007; **98:** 145–58.
9 Brambrink AM, Back SA, Riddle A, et al. Isoflurane-induced apoptosis of oligodendrocytes in the neonatal primate brain. *Ann Neurol* 2012; **72:** 525–35.
10 Brambrink AM, Evers AS, Avidan MS, et al. Isoflurane-induced neuroapoptosis in the neonatal rhesus macaque brain. *Anesthesiology* 2010; **112:** 834–41.
11 Hansen TG. Anesthesia-related neurotoxicity and the developing animal brain is not a significant problem in children. *Paediatr Anaesth* 2015; **25:** 65–72.
12 Psaty BM, Platt R, Altman RB. Neurotoxicity of generic anesthesia agents in infants and children: an orphan research question in search of a sponsor. *JAMA* 2015; **313:** 1515–16.
13 Rappaport BA, Suresh S, Hertz S, Evers AS, Orser BA. Anesthetic neurotoxicity—clinical implications of animal models. *N Engl J Med* 2015; **372:** 796–97.
14 Crosby G, Davis PJ. General anesthesia in infancy is associated with learning disabilities-or not. *Anesth Analg* 2013; **117:** 1270–72.
15 Davidson AJ. Anesthesia and neurotoxicity to the developing brain: the clinical relevance. *Paediatr Anaesth* 2011; **21:** 716–21.
16 DiMaggio C, Sun LS, Ing C, Li G. Pediatric anesthesia and neurodevelopmental impairments: a Bayesian meta-analysis. *J Neurosurg Anesthesiol* 2012; **24:** 376–81.
17 Ing C, DiMaggio C, Whitehouse A, et al. Long-term differences in language and cognitive function after childhood exposure to anesthesia. *Pediatrics* 2012; **130:** e476–85.
18 Ing CH, DiMaggio CJ, Malacova E, et al. Comparative analysis of outcome measures used in examining neurodevelopmental effects of early childhood anesthesia exposure. *Anesthesiology* 2014; **120:** 1319–32.
19 Lei SY, Hache M, Loepke AW. Clinical research into anesthetic neurotoxicity: does anesthesia cause neurological abnormalities in humans? *J Neurosurg Anesthesiol* 2014; **26:** 349–57.
20 Flick RP, Katusic SK, Colligan RC, et al. Cognitive and behavioral outcomes after early exposure to anesthesia and surgery. *Pediatrics* 2011; **128:** e1053–61.
21 Sprung J, Flick RP, Katusic SK, et al. Attention-deficit/hyperactivity disorder after early exposure to procedures requiring general anesthesia. *Mayo Clin Proc* 2012; **87:** 120–29.
22 Wilder RT, Flick RP, Sprung J, et al. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. *Anesthesiology* 2009; **110:** 796–804.
23 DiMaggio C, Sun LS, Li G. Early childhood exposure to anesthesia and risk of developmental and behavioral disorders in a sibling birth cohort. *Anesth Analg* 2011; **113:** 1143–51.
24 DiMaggio C, Sun LS, Kakavouli A, Byrne MW, Li G. A retrospective cohort study of the association of anesthesia and hernia repair surgery with behavioral and developmental disorders in young children. *J Neurosurg Anesthesiol* 2009; **21:** 286–91.
25 Bartels M, Althoff RR, Boomsma DI. Anesthesia and cognitive performance in children: no evidence for a causal relationship. *Twin Res Hum Genet* 2009; **12:** 246–53.
26 Hansen TG, Pedersen JK, Henneberg SW, et al. Academic performance in adolescence after inguinal hernia repair in infancy: a nationwide cohort study. *Anesthesiology* 2011; **114:** 1076–85.
27 Hansen TG, Pedersen JK, Henneberg SW, Morton NS, Christensen K. Educational outcome in adolescence following pyloric stenosis repair before 3 months of age: a nationwide cohort study. *Paediatr Anaesth* 2013; **23:** 883–90.
28 Block RI, Thomas JJ, Bayman EO, Choi JY, Kimble KK, Todd MM. Are anesthesia and surgery during infancy associated with altered academic performance during childhood? *Anesthesiology* 2012; **117:** 494–503.
29 Bong CL, Allen JC, Kim JT. The effects of exposure to general anesthesia in infancy on academic performance at age 12. *Anesth Analg* 2013; **117:** 1419–28.

30 Wang X, Xu Z, Miao CH. Current clinical evidence on the effect of general anesthesia on neurodevelopment in children: an updated systematic review with meta-regression. *PLoS One* 2014; **9:** e85760.

31 Davidson AJ, Becke K, de Graaff J, et al. Anesthesia and the developing brain: a way forward for clinical research. *Paediatr Anaesth* 2015; **25:** 447–52.

32 Davidson AJ, Morton NS, Arnup SJ, et al, and the General Anesthesia compared to Spinal anesthesia (GAS) Consortium. Apnea after Awake Regional and General Anesthesia in Infants: The General Anesthesia Compared to Spinal Anesthesia Study-Comparing Apnea and Neurodevelopmental Outcomes, A Randomized Controlled Trial. *Anesthesiology* 2015; **123:** 38–54.

33 Frawley G, Bell G, Disma N, et al, and the General Anesthesia compared to Spinal anesthesia (GAS) Consortium. Predictors of Failure of Awake Regional Anesthesia for Neonatal Hernia Repair: Data from the General Anesthesia Compared to Spinal Anesthesia Study-Comparing Apnea and Neurodevelopmental Outcomes. *Anesthesiology* 2015; **123:** 55–65.

34 Bayley N. Bayley scales of infant and toddler development. 3rd ed. San Antonio: Harcourt Assessment Inc, 2006.

35 Fenson L, Marchman VA, Thal DJ, Dale PS, Reznic JS, Bates E. MacArthur-Bates Communicative Development Inventories: User's Guide and Technical Manual 2nd edn. Baltimore Brookes Publishing, 2007.

36 van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res* 2007; **16:** 219–42.

37 Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. *Stat Methods Med Res* 2013; **22:** 278–95.

38 Johnson SA, Young C, Olney JW. Isoflurane-induced neuroapoptosis in the developing brain of nonhypoglycemic mice. *J Neurosurg Anesthesiol* 2008; **20:** 21–28.

39 Harris SR, Langkamp DL. Predictive value of the Bayley mental scale in the early detection of cognitive delays in high-risk infants. *J Perinatol* 1994; **14:** 275–79.

40 Bode MM, D'Eugenio DB, Mettelman BB, Gross SJ. Predictive validity of the Bayley, Third Edition at 2 years for intelligence quotient at 4 years in preterm infants. *J Dev Behav Pediatr* 2014; **35**: 570–75.

41 Lee BH, Chan JT, Kraeva E, Peterson K, Sall JW. Isoflurane exposure in newborn rats induces long-term cognitive dysfunction in males but not females. *Neuropharmacology* 2014; **83:** 9–17.