A Multi-site Randomized Controlled Trial Comparing Regional and General Anesthesia for Effects on Neurodevelopmental Outcome and Apnea in Infants

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Experimental Design and Methods:

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 Plan:

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, 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 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]