Is a short anesthetic exposure in children safe? Time will tell: a focused commentary of the GAS and PANDA trials

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Abstract: Early life exposure to general anesthesia in preclinical studies has consistently led to permanent cognitive deficits later in life. However, the extent to which this finding is translatable to humans is the subject of much debate as the results from clinical studies have been mixed. Recently two well-designed clinical trials have attempted to add clarity to our murky understanding. The General Anesthesia compared to Spinal anesthesia (GAS) trial, was an international, prospective, randomized, multicenter, equivalence trial comparing infants undergoing herniorrhaphy receiving general anesthesia *vs.* neuraxial anesthesia. The results released are from a pre-determined secondary outcome of a behavioral/developmental assessment of 2 years old that found equivalence between the two groups. The Pediatric Anesthesia NeuroDevelopment Assessment (PANDA) trial was an ambi-directional cohort trial, comparing patients receiving general anesthesia for hernia repair before 3 years old *vs.* sibling-matched controls. The neuropsychological battery performed showed no difference between siblings. Taken together, there is cautious optimism that short anesthesia exposure may not lead to significant cognitive decline in humans, but one should also consider that the GAS trial has yet to release the primary endpoint, IQ testing at age 5, and the PANDA trial may not represent the general population given the high socioeconomic status and high control IQ scores. Furthermore, as seen in preclinical studies, the cognitive deficit might not be significant until later in life, and longer exposures to anesthesia may have a more deleterious effect on cognitive function. While these new studies greatly increase our understanding in humans, there are many more questions that need to be addressed.

Keywords: Early anesthesia; pediatric anesthesia; neurotoxicity; cognitive impairment; RCT

Submitted Jul 28, 2016. Accepted for publication Aug 14, 2016.
doi: 10.21037/atm.2016.10.43
View this article at: http://dx.doi.org/10.21037/atm.2016.10.43

Whether general anesthesia early in life leads to poorer neurocognitive outcomes has been widely debated, with human and animal studies showing mixed results (1-4). It is a difficult problem to systematically address in humans due to the inherent confounds of surgical intervention and/or disease state that is generally comorbid with anesthesia exposure. Furthermore, while rodent and non-human primate studies consistently exhibit a neurotoxic effect of anesthesia on a cellular level immediately after exposure, the mechanism of injury and lasting effects on behavior and cognition are less clear (5-7). Two studies in the field recently reported outcomes of clinical trials aimed at determining whether general anesthesia leads to decreased cognitive function in exposed subjects compared to controls (8,9). In the first study, Davidson and colleagues report the secondary outcome of the General Anesthesia compared to Spinal anesthesia (GAS) trial, showing no difference in neurodevelopmental outcomes at 2 years of age between infants who had inguinal hernia repair under either general or neuraxial anesthesia. In the second study, Sun and colleagues present the primary and secondary outcomes for the Pediatric Anesthesia NeuroDevelopment Assessment (PANDA) trial, reporting no significant differences in cognitive function or behavior between subjects who underwent inguinal hernia repair with an inhaled anesthetic and their non-exposed siblings. While the GAS and PANDA studies make important advances in our understanding of anesthetic safety, there are still many questions that remain to be answered.

An early description of cognitive dysfunction following

anesthesia in young animals ignited the field in 2003. Infant rats were given an anesthetic of isoflurane, nitrous oxide and midazolam and were subsequently found to have significant neuronal cell death and lasting memory impairment (10). Since then there have been many animal studies demonstrating this effect in different species (5,11), with different anesthetic agents (12-15), and affecting different domains of cognition (16-18). Early studies focused on anesthesia-induced apoptosis (10,19), however the developing brain possesses neurons in excess and normal apoptosis is present during development (20,21). It was subsequently shown that anesthesia induced apoptosis was not sufficient to cause the cognitive deficit (6). Anesthesia exposure at later ages in development results in a less significant insult, underscoring a time-sensitive period of vulnerability and further complicating our understanding of the mechanism of injury (14,22). Similarly, the duration of anesthesia is a critical determinant of the extent of the deficit, with shorter, lower concentrations leading to less or undetectable insults (18,23,24).

A number of retrospective observational human studies have been done, with varied results. These include several large epidemiological studies. The Western Australian Pregnancy Cohort, initially established in the 1980s to study the effects of ultrasound in pregnancy, was used to compare subjects who had received anesthetics before age 3 with control subjects. Outcomes were measured by neuropsychological tests administered at age 10, academic achievement, and billing codes indicating International Classification of Disease, 9th Edition, Clinical Modification (ICD-9) diagnoses at subsequent clinical visits (25,26). The authors found a strong association between early anesthesia and language and cognition deficits on the neuropsychological tests and corresponding ICD-9 codes, but no significant correlation with achievement tests. This study was limited due to lack of details about the anesthetic exposure. In another cohort study, Danish subjects who had undergone pyloroplasty before 3 months of age were compared in terms of standardized test performance and teacher evaluations to age matched peers and were found not to be significantly different after adjusting for known confounders (sex, birth weight, parental age and parental education) (27). A Netherlands Twin study using a national twin registry showed an association with lower scores and cognitive assessments for twin pairs in which one or both received anesthesia before age 3 compared to control pairs (28). However, no difference was detected within twin pairs in which only one twin was exposed, leading the authors to conclude that the anesthesia by itself was not a causal factor of the learning problems detected later in life. In the United States, a retrospective cohort study in Minnesota showed a significant effect of multiple but not a single anesthetic exposure before 4 years specifically in language and cognitive domains, but not in emotional or behavioral realms (29,30). The New York Medicaid database was also used to study this phenomenon and found an increase in risk of behavior and developmental diagnoses with hernia surgery before age 3 compared to age matched controls (31) siblings (32). Most recently, a retrospective cohort study from Canada stratified risk for cognitive/behavior deficits based on age at which patients received anesthesia (33). The outcome measure of this study was the Early Development Instrument (EDI), completed by teachers of kindergarten students. Interestingly, they found an association with deficits in children who received anesthesia from ages 2–4, but not 0–2. An earlier ambi-directional cohort trial found a difference in recognition memory using a similar task both in rodents and human children. Children anesthetized for greater than 120 minutes before age 2 were found to have a deficit compared with age matched controls (18). Each study design has its own limitations and the key confounding variables remain difficult to control for.

In light of the above studies providing some evidence of a correlation between anesthesia exposure and altered cognitive function in humans, both the GAS and PANDA trials were conceived to fill the need for larger prospective trials. The GAS trial is a multi-center, international, randomized controlled equivalence trial. Study subjects that met inclusion parameters for the GAS trial were randomly assigned to receive either awake-regional anesthesia (n=238) (spinal, caudal, or combined spinal-caudal) or sevoflurane general anesthesia (n=294) (with optional regional supplementation; caudal, ilioinguinal-iliohypogastric or field block) during herniorrhaphy. Exclusion criteria included a contraindication to either anesthetic technique, congenital heart disease, mechanical ventilation immediately prior to surgery, congenital abnormalities which are known to affect cognition, chromosomal abnormalities, previous volatile anesthesia exposure, benzodiazepine exposure as infant or in-utero, intraventricular hemorrhage (greater than grade 2), neurologic injury which would impair cognitive function, and social issues which would prevent follow up. Premature birth was not excluded and both groups had approximately 55% births before 37 weeks gestation, 3% had hearing deficits in both groups, and 7% and 6% of regional

and general anesthesia respectively had intraventricular hemorrhage (grade 1 or 2). The vast majority of the subjects were male (81% regional, 85% general). The average age at the time of anesthesia was 68.9 days (regional), and 71.1 days (general). The average sevoflurane exposure time was 54 min.

The primary endpoint will be the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III) to be assessed when subjects reach 5 years of age. The current reported results are a secondary endpoint in which the Bailey Scales of Infant and Toddler Development III (Bailey-III) were used to assess development and cognitive performance at 2 years of age. The composite scores of the Bailey-III consist of cognitive, language, motor, adaptive behavior, and social-emotional scales. The overall composite scores between the regional and general anesthesia groups were statistically equivalent. A subgroup analysis also revealed no difference between all the Bailey-III subsets except the social-emotional scales. The authors conclude that this provides strong evidence that early life general anesthesia with sevoflurane for less than 1 hour has no effect on neurocognitive function in 2 years old.

The PANDA trial was a prospective sibling matched cohort study. It enrolled 105 sibling pairs, one of which underwent herniorrhaphy at less than 36 months of age during which an inhaled general anesthetic was administered. A comprehensive battery of neuropsychological assessments was applied to subjects and siblings ages 8–15 years old. In addition to a Full Scale IQ score (WASI), the battery included many other domains including memory, motor speed and processing, visuospatial reasoning, language, attention, executive function and behavior. A panel of experts created the specific battery prior to enrollment. Inclusion criteria was ASA status 1 or 2, age 36 weeks or older at birth, biologically related sibling within 3 years of age with no anesthesia exposure prior to 36 months and 36 weeks or older at birth. Like the GAS trial, the vast majority (90%) of the test subjects were male, while the sibling controls were 56% male. The duration of anesthesia exposure was 84 minutes on average. Demographically, subjects were overwhelmingly white (86%), of middle to upper middle socioeconomic status with self-reported parental income from $80,000 to greater than $100,000 in 58% of subjects and 84–87% owning their own home. They were also well educated (40% maternal, 32% paternal possessing post graduate degrees).

WASI IQ test was the primary outcome, which showed no significant difference between subjects and matched sibling controls in either the Full Scale score or the subcategories of verbal and performance. There was also no significant difference between the secondary outcomes of memory, attention, visuospatial function, executive function, language, motor and processing speed or behavioral domains. There were significant differences in internalizing behavior of exposed siblings compared to controls after controlling for sex, but with the limited number of exposed girls, the authors were unable to further study any sex differences. The authors conclude that a single early anesthetic administered to otherwise healthy children under age 3 does not result in cognitive deficits.

In considering both of these studies, interpretation should include a few points. For the GAS trial, the primary results have yet to be reported and the results recently published of the Bayley-III should be viewed with the understanding that the test was designed for identification of patients at risk of developmental delay so that early intervention could be initiated (34). Previous epidemiologic studies on early anesthesia have not revealed a clear correlation with global developmental delay on the same magnitude as autism or cerebral palsy so it is not surprising that regional and general anesthesia were equivalent for these outcomes. In addition to the limited sensitivity of this test, the short duration of anesthesia may cause an overall subtle phenotype that falls below the detection threshold or there may be no deficit at all. Because cognitive deficits may worsen with age [seen in preclinical studies (7,14,35-37)], any neurocognitive problem may only be recognized in older children capable of more complex neuropsychological analysis. We are still awaiting the primary endpoint from this study, the WPPSI-III intelligence quotient scores of subjects at 5 years of age. The prospective randomized control design of the trial is powerful, however, the time from randomization to testing many years later is a limitation given the long delay before complex neuropsychological testing is possible and the likelihood of a slowly developing deficit that could remain undetectable even at age 5.

In the PANDA trial, the cohort studied is significantly different from the general population, being mostly white, highly educated and of advanced socioeconomic status (SES). A number of recent preclinical studies suggest that an adverse or enriched environment after anesthesia exposure may have a critical influence on cognitive outcome (16,38). An enriched environment, which includes social housing, exercise, and a complex home cage, rescues the behavioral deficit exhibited by anesthesia-exposed

rats, while an adverse environment may aggravate the detrimental effects of exposure (16,39). It is difficult to translate the environment experienced by rodents to human subjects, however, it is likely that the group's SES and education is a correlate of environmental enrichment, evidenced by the high average IQ in subjects and controls reported in the PANDA study (95% confidence interval: 108–113 for both subject and controls). There is a large body of evidence from the behavioral sciences showing the complex relationship between parental SES and child IQ scores (40-42). Another consideration is that 23 out of 105 sibling controls had anesthesia after age 3 and were not excluded from the analysis. This may be significant if these control subjects decreased the averages of the control group, making it harder to detect a difference between the groups. An important feature of this study design is that it recruited a well matched treatment and control group who could be tested in the future in different domains such as recognition memory which has been shown to be sensitive to early anesthesia (18).

One potential protective factor in both the GAS and PANDA trials is the length of anesthetic exposure. The average sevoflurane exposure was 54 and 84 min respectively. Rodent studies show little to no deficit at short durations of anesthesia (35,43) and previous human studies generally identify a deficit only after longer exposures (greater than 2 hours) which is consistent with rodent data (18,30,43).

The sex of the subjects studied was overwhelmingly male, with 80% in GAS and 90.5% in PANDA trial. This is not a recruitment oversight but represents a disproportionate burden of surgical need as the most common surgeries in infants are mostly or exclusively male: inguinal herniorrhaphy, hypospadias, circumcision, and pyloromyotomy. There is pre-clinical data that suggests that males may be more vulnerable to the effects of early anesthesia, so this experimental design would be more likely than a sex-matched cohort to show an anesthetic effect (44). If these results are replicated it provides some reassurance that short anesthetic exposure in males may not be as concerning as has been imagined.

In conclusion, both GAS and PANDA are well-designed clinical trials with encouraging results suggesting that there is no significant neurocognitive deficit for short anesthetic exposure early in life. There are several major considerations to keep in mind however, not least is the GAS trial results are only secondary endpoints and the primary endpoint data has yet to be published. In the PANDA trial, the high SES and advanced education of the household yields a higher IQ than the general population. This may change the threshold of vulnerability or be a source of environmental enrichment which allows the subjects to compensate for the insult. Additionally, both trials had mean anesthetic durations of less than 2 hours which likely leads to a less severe (possibly undetectable) cognitive insult and neither study specifically assessed recognition memory, which was previously reported to be impaired after a 2-hour exposure early in life (18) (PANDA trial assessed face-recognition however, this can be performed solely on the basis of global familiarity decreasing its sensitivity for recognition memory). Given a lack of data regarding longer duration exposures and no defined critical age at exposure, the most prudent clinical plan may be to delay elective surgeries as long as possible and to minimize anesthetic duration for non-essential surgeries. These well-designed studies represent an important advance in the field and provide some reassurance regarding brief exposures, but many questions surrounding early anesthesia and cognition remain unanswered.

Acknowledgements

Funding: This work was supported by the National Institutes of Health (NIH) (R01GM112831).

Footnote

Provenance: This is a Guest Perspective commissioned by Guest Editor Zhongcong Xie, MD, PhD (Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Charlestown, MA, USA).
Conflicts of Interest: The authors have no conflicts of interest to declare.

Comment on: Davidson AJ, Disma N, de Graaff JC, *et al.* Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. Lancet 2016;387:239-50.
Sun LS, Li G, Miller TL, *et al.* Association Between a Single General Anesthesia Exposure Before Age 36 Months and Neurocognitive Outcomes in Later Childhood. JAMA 2016;315:2312-20.

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Cite this article as: Chinn GA, Sasaki Russell JM, Sall JW. Is a short anesthetic exposure in children safe? Time will tell: a focused commentary of the GAS and PANDA trials. Ann Transl Med 2016;4(20):408. doi: 10.21037/atm.2016.10.43

