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Featured Article

Neurodevelopmental outcomes in infants undergoing general anesthesia

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ABSTRACT

Purpose: Preclinical data strongly suggest that all agents used for general anesthesia (GA) have detrimental effects on the developing brain. However, clinical data are unclear. The purpose of this study was to use a cohort of infants who underwent GA and understand their neurodevelopmental outcomes.
Methods: A cohort of infants who underwent GA was selected between 2010 and 2011, and a control group was created. Data regarding GA, procedures, and outcomes were collected in 2015. The cohort was divided into controls, GA without surgery, GA and surgery once, and multiple general anesthetics. Both univariate and multivariate analysis were performed, and a p value of less than 0.05 was considered significant.
Results: 457 patients, 121 controls, and 336 cases were included. Median follow-up was 5.1 years. While developmental delay and the need for speech therapy were higher with GA, this did not correlate with the duration of GA. Patients having GA for MRI had the poorest outcomes. Multivariate analysis using combined binary outcome measures for psychiatric and neurologic outcomes did not show any significant difference for duration of anesthesia, age at anesthesia, or induction and maintenance agents.
Conclusions: These data suggest that GA during the first year of life may have few significant neurodevelopmental effects compared to controls. Additionally, the duration of GA did not correlate with neurodevelopmental outcomes.
Type of study: Retrospective Case Control Cohort Study.
Level of evidence: 3 b (*according to Oxford Center for EBM Levels of Evidence, March 2009*, http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/).

Estimates suggest that over 5–6 million children undergo procedures that require general anesthesia (GA) in the United States every year, with approximately a million of these being performed in neonates and infants [1]. Until recently, GA in children was considered to be very safe especially with improvements in monitoring and the adoption of standardized techniques. However, preclinical research data from rodents, in the early part of this century, suggested that almost all anesthetic agents were responsible for apoptosis in the developing brain which lead to pervasive neurodevelopmental effects that persisted into adult life [2–7]. Given the sheer volume of GA in children every year, this became a cause for concern and the US Food and Drug Administration (FDA) took notice in 2007, convening a scientific advisory committee which was unable to answer the question in humans because of a paucity of data [1,8].

Epidemiological reports noted a possible association of impaired neurodevelopmental outcomes even after a single anesthetic exposure [9,10]. Other studies suggest that it is the exposure to multiple episodes of GA which lead to developmental issues, while some postulate that there is no association between GA and such outcomes [5,11,12]. Recently, interim analysis of two long-term studies – one a randomized trial comparing regional to general anesthesia (GAS trial) [13], and another looking at sibling pairs (PANDA study) [14] – noted no difference in outcomes using standardized tests after a single exposure to GA. However, despite mixed evidence, a recent consensus statement was released in 2015 endorsed by 19 professional organizations which recommended detailed discussion of the risks of GA with parents in addition to advocating for more research [14,15].

This study proposes to look at a large and varied cohort of patients who underwent GA during infancy and compared them to controls that were matched for gestational age and NICU stays. We hypothesized that neurodevelopmental outcomes would be worse in patients who had multiple and a longer duration of GA based on the experimental evidence-related concerns. We collected granular data on anesthetics used, intra- and post-operative events, as well as the use of narcotics

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and sedatives and had longitudinal follow-up of the cohort that was chosen between 2010 and 11.

1. Methods

1.1. Patient selection and inclusion criteria

Patients were selected from the 2010–2011 time frame using the anesthesia departmental database. Inclusion criteria were age of less than one year at time of GA event and survival after the GA. Patients were included even if no surgical procedure was performed (e.g. MRI). After initial chart review, the patients who had neurologic issues prior to the GA event were excluded, as were the cases who had their first GA after 365 days of life. Those that did not have long-term follow-up and could not be assessed were also excluded. Cardiac surgical cases were not excluded from the cohort as the intent was to bias for any poor outcome from GA, and the analysis would be performed with an without the cardiac cases to allow for any differences to be controlled in uni- and multi-variate analyses. The patient selection is noted in Fig. 1.

1.2. Control group selection

After the GA cohort was created, the NICU database was utilized to select a control group. In addition to being selected from the same time frame as the GA cohort (2010–2011), the controls were matched for gender, race, gestational age and birth weight, and for comorbidities. Patients who subsequently underwent a general anesthesia episode during the first 365 days of life, or did not survive to that time point were excluded. In addition, control group patients were excluded if long-term follow-up information was not available. The initial size of the control cohort was 250, and reduced to 129 after exclusions.

1.3. Anesthesia variables collected

Pre-operative, intraoperative, and post-operative data were collected around the GA episodes. Patients that required pre-operative intubation and ventilation and the use of sedative drugs were recorded. The duration of anesthesia was recorded, as were the induction agent, use of benzodiazepines as a pre-medication, maintenance agent (inhaled or intravenous), use of paralytic agent, use of a reversal agent, extubation after the procedure, intraoperative hypotension or hypoxic events. Post GA events included the use of vasoactive drugs, hypotension, prolonged intubation, narcotic or sedative usage, and neurologic events (e.g. Seizures).

1.4. Neurodevelopmental outcome variables and definitions

A large number of outcomes were used, and the electronic health record (EHR) was searched using advanced search functions for any mention of these variables. The outcomes were divided into neurologic and psychiatric variables. A total of 14 outcome variables were collected as follows: developmental delay (overall, including delayed milestones), verbal or speech delay, gross motor delay, fine motor, global delay, social or behavioral interaction delay, autism spectrum disorder, attention deficit hyperactivity, anxiety, and sleep disturbances. Need for speech therapy (ST), occupational therapy (OT), or physical therapy (PT) was also recorded, and the long-term need for a gastrostomy tube for feeding was included as a delay in initiation of oral feeding. These variables were selected to ensure that the bias would be in overestimation of neurodevelopmental issues rather than underestimation. If any neurologic testing was performed such as EEG, MRI, or formal neurodevelopmental testing the results were recorded as well. While the ideal analysis would have been based on formal testing, or standard assessment by a neurologist or developmental neonatologist, this was rarely performed, and if any mention of the selected variables was in the chart by a pediatrician, it was assumed to be an outcome of interest.

1.5. Creation of sub-cohorts

The overall GA cohort was sub-divided into three main cohorts for the purposes of comparative analysis. In addition to the control group, the cohort included single GA without surgery, single GA surgery, and multiple GA. The purpose of the creation of cohorts was to better understand the effect of GA alone and help to exclude some of the effects of the procedure. The GA without surgery cohort had several different patient types – MRI (cardiac and brain) (40%), cardiac and other vascular interventions (22%), and others (38%)(including bronchoscopy and esophagoscopy).

1.6. Statistical analysis

Data were analyzed in several ways. Descriptive analysis was used to describe the entire cohort of GA and controls and demographics were compared as well as patient factors. Further sub-group analysis and comparative statistics were done using the four groups described above. Univariate analysis was done using student's t test, Fischer's exact test, chi squared analysis, ANOVA, and Mann–Whitney U test where appropriate. Clinically relevant data as well as variables with a univariate p value less than 0.1 were chosen to create multivariate logistic step wise regression models. P values less than 0.05 were considered significant.

2. Results

There were a total of 457 patients that were included in the study after application of the exclusion criteria. Of these, 121 were controls and 336 had exposure to GA. The GA exposure patients were subdivided into GA without surgery, GA with one surgery, and multiple GA groups

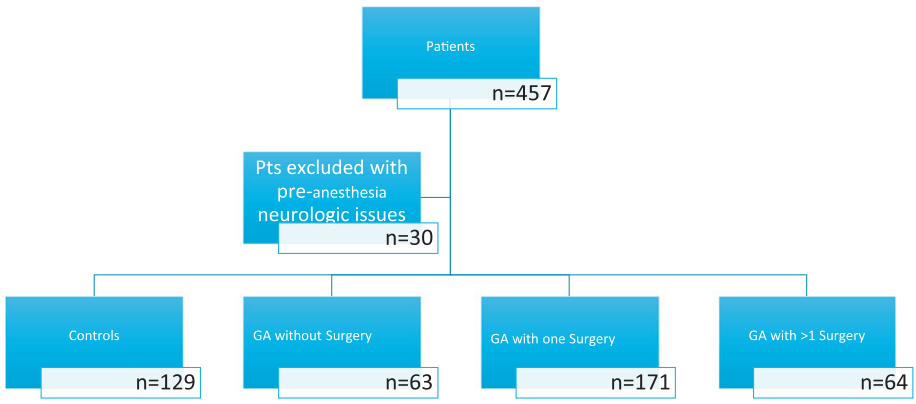

Fig. 1. Flow diagram indicating patients in each group.