



Research Paper

Exposure to general anesthesia before 4 years of age did not affect growth and development: A nationwide retrospective cohort study using an early childhood health screening database

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ABSTRACT

Introduction: There is little evidence that anesthetics are associated with neurotoxicity in children. In this study, we used a nationwide database to evaluate the association between general anesthesia and attention deficit/hyperactivity disorder (ADHD) in pediatric patients.

Methods: We retrospectively analyzed data from the National Health Insurance Service-infant medical checkup cohort database. We included all pediatric patients born in 2008 and 2009 and classified them into two groups according to their history of exposure to general anesthesia. Group G included pediatric patients who had been exposed to general anesthesia at least once before 4 years of age. Group O included a 1:4 matched cohort based on birth weight, sex, and income decile. The primary outcome was the prevalence of ADHD. Secondary outcomes included head circumference, height, weight, visual and auditory development.

Results: Among 17,451 participants, 315 (1.8%) underwent general anesthesia before 4 years of age. After propensity score matching, 1259 participants were selected in group O, with no significant differences between the groups in terms of birth weight, sex, income decile, and prematurity. Among all 1574 participants, 17 (1.08%) were diagnosed with ADHD, without a significant difference between the two groups ($P = 0.33$). There was also no significant difference in head circumference, height, weight, auditory and visual development ($P = 0.43, 0.45, 0.49, 0.32, 0.13$, respectively).

Conclusion: Children who underwent surgery requiring general anesthesia before 4 years of age did not have an increased risk of ADHD or developmental disorders. Future studies should assess the association between duration of surgery and occurrence of ADHD.

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1. Introduction

In the last two decades, warnings have been issued on the neurotoxicity of anesthetics in young animals, having detrimental effects on the nervous system and neurodevelopment [1]. One of the major neurodevelopmental processes is myelination, which starts at the end of the second trimester of pregnancy and continues throughout childhood. Most of the commonly used anesthetics and sedative agents target the γ -aminobutyric acid or N-

methyl-D-aspartate receptors, which play an important role in neurodevelopment.

In 2017, the United States Food and Drug Administration issued a warning that repeated or lengthy use of general anesthetics and sedative drugs during surgeries or procedures in children younger than 3 years may negatively affect the development of children's brains [2]. However, this warning was based on little evidence in humans and should be supported by large high-quality human studies.

It has been reported that multiple anesthesia exposures were associated with later development of attention deficit/hyperactivity disorder (ADHD) [3]. ADHD can affect a wide range of psychological domains, such as cognition, interpersonal, school, and family functioning, which might not only increase the familial but also the social financial burden [3]. However, a retrospective

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matched-cohort study in Taiwan found that exposure to general anesthesia before 3 years of age was not associated with ADHD [4].

The diversity in the reported outcomes and the generally small differences seen in human studies are not inconsistent with the preclinical data given the predominantly short exposures and the ranges of populations and outcomes assessed [5].

In this study, we used a nationwide database to evaluate the association between general anesthesia and ADHD in pediatric patients who underwent health care checkups. The primary outcome was the development of ADHD before school age and the secondary outcomes were the head circumference, height, weight, auditory and visual development.

2. Patients and methods

2.1. Ethical considerations

The study was reviewed and approved by the institutional review board (IRB No 2018-09-006) and the need to obtain informed consent was waived because we used de-identified administrative data.

2.2. Study data

In Korea, all newborn babies have an opportunity to undergo infant medical checkup without charge. The medical checkup service includes seven checkups between the ages of 4 and 71 months (1st at 4–6; 2nd at 9–12; 3rd at 18–24; 4th at 30–36; 5th at 42–48; 6th at 54–60; and 7th at 66–71 months). The National Health Insurance Service (NHIS) collects these data as an NHIS-infant medical checkup cohort database [6]. The database includes infants who underwent at least one of the first or second medical checkup, and 5% of the sample is extracted for each birth year between 2008 and 2012. The collected data include social and economic variables (including age, location, type of subscription, income rank, disability, death, etc.), medical resource utilization status (consultations and medical checkups), and clinic status (status, facility, equipment, and personnel data of the clinics by type, establishment, and location [city and state]).

2.3. Participants

We included all pediatric patients born in 2008 and 2009 who underwent medical checkups. The exclusion criteria were as follows: (1) patients who did not undergo the seventh medical checkup; (2) patients who underwent major surgery, including percutaneous coronary angioplasty and resection, stent implantation, coronary artery bypass surgery, cardiac catheterization, artificial pacemaker implantation, basal brain surgery, or congenital heart deformity surgery; and (3) patients diagnosed with neoplasms; endocrine, mental, and behavioral disorders; congenital malformations, deformations, and chromosomal abnormalities; or nervous system diseases (ICD-10 code C, E, F, G, and Q).

The patients were classified into two groups according to the history of exposure to general anesthesia. Group G included pediatric patients who had been exposed to general anesthesia at least once before 4 years of age. Group O included a control matched cohort; each pediatric patient was matched to four pediatric participants based on the birth weight, sex, and income decile.

2.4. Outcomes and definitions

The characteristics of participants included sex, birth weight, income decile, and prematurity. The diagnosis of prematurity was based on diagnoses with ICD-10 code "P."

The primary outcome was the prevalence of ADHD, which was diagnosed based on the ICD-10 code "F90." The secondary outcomes included the head circumference, height, weight, visual, and auditory development, which were collected during the seventh health checkup. In addition, we evaluated these outcomes according to the number of exposures to general anesthesia. Patients who underwent general anesthesia only once were classified as group G1, whereas those who underwent general anesthesia at least twice were classified as group G2.

2.5. Statistical analysis

To improve the study efficiency and precision, propensity score matching was performed using the caliper matching method to match patients from the two groups in a 1:4 ratio. The propensity score was calculated by logistic regression analysis using sex, birth age, and income decile as covariates in order to examine the effect of general anesthesia on the prevalence of ADHD.

Prior to propensity score matching, patients' characteristics were summarized using descriptive statistics. For continuous variables, data are presented as mean (standard deviation) and groups were compared using the Mann-Whitney *U* test. Descriptive variables were analyzed using chi-square or Fisher's exact test, as appropriate. Post-matching continuous variables are presented as mean [standard deviation] and compared using the Wilcoxon signed rank test. Categorical variables are presented as absolute numbers (percentage) and statistical differences between the groups were analyzed using the McNemar test. All statistical tests were two-sided with a significance level of 0.05. SAS version 9.3 (SAS Institute, Cary, NC) was used for analysis.

3. Results

We identified 17,485 pediatric participants who were born in 2008 and 2009 with available data from the seventh medical health checkup. Of these, 34 who had missing data were excluded. Among the 17,451 participants, 315 (1.8%) had a history of exposure to general anesthesia (Fig. 1). After performing 1:4 matching, 1259 patients were selected for group O, with no significant differences between groups G and O in terms of birth weight, sex, and income decile (Table 1).

Among all 1574 participants, 17 (1.08%) were diagnosed with ADHD, with no significant difference between the two groups ($P = 0.33$). The prevalence of ADHD was 1.59% in group G and 1.03% in group O before matching (Table 2). After matching, the prevalence of ADHD in group O was 0.95%, and there was still no significant difference compared to group G ($P = 0.33$). There was also no significant difference in the head circumference, height, weight, or auditory and visual development (requiring further thorough checkup) between the two groups, both pre- and post-matching ($P = 0.43, 0.45, 0.49, 0.32, \text{ and } 0.13$, respectively).

When the outcomes were compared according to the number of exposures to general anesthesia, there was a significant difference between the groups regarding birth weight, sex, height, and visual development (Table 3). However, the prevalence of ADHD was not significantly different among the groups ($P = 0.59$).

4. Discussion

In this study, we evaluated the association between general anesthesia and the development of ADHD in pediatric patients based on a nationwide database. Our results indicated that exposure to general anesthesia before the age of 4 years was not associated with an increased risk of ADHD before school age. Moreover, it was not associated with differences in head circumference,

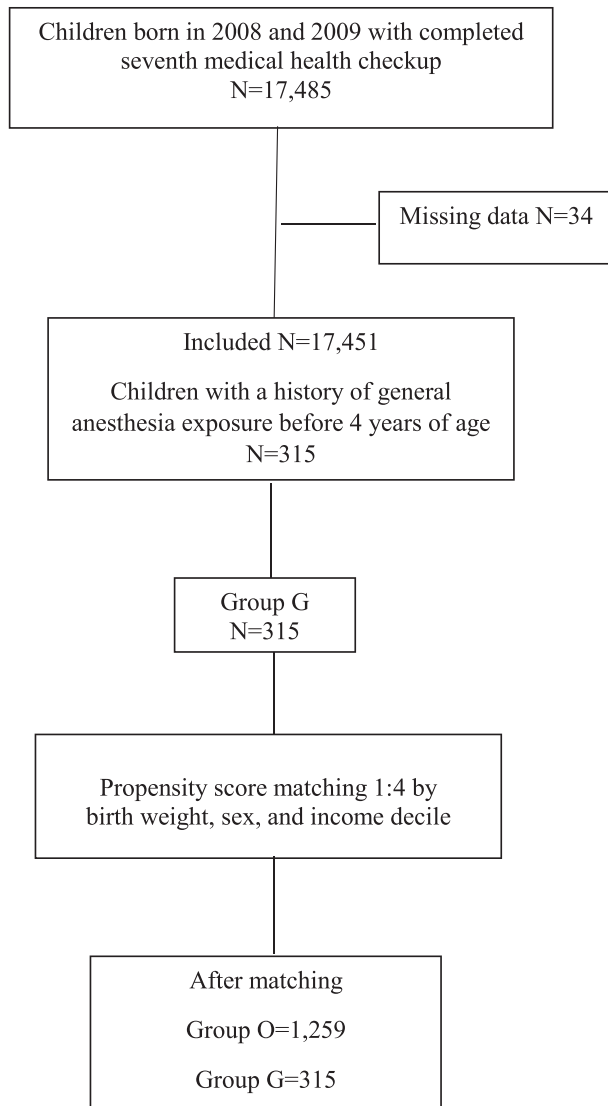


Fig. 1. Study flow diagram.

height, weight, auditory, or visual development. In addition, the number of exposures to general anesthesia did not affect the prevalence of ADHD in children who were exposed to general anesthesia in early childhood.

ADHD is a heterogeneous disorder with childhood onset characterized by hyperactivity, symptoms of inattention, and impulsivity, a clinical presentation consistent with a neuropsychological disorder. Its prevalence has been reported to range from 2.2% to 17.8% worldwide, with great variations among different studies [7]. However, in our study, we found that the prevalence of ADHD in Korea was 1.59% in group G and 1.03% in group O before matching.

The association between general anesthetics and development of ADHD is thought to be underlain by molecular mechanisms and neuronal network dysfunction [8]. The anesthetics might influence the neural circuits in the prefrontal cortex and basal ganglia via dopaminergic, glutaminergic, and neurotrophic factor-mediated mechanisms [8]. However, clinical studies on the association between exposure to anesthetic agents in early childhood and the occurrence of ADHD have demonstrated diverse results. Sprung et al. found that children repeatedly exposed to general anesthesia before 2 years of age were at an increased risk of development of ADHD [3]. Likewise, a recent nationwide retrospective study using the Taiwan NHI program concluded that children with multiple or longer (more than 3 h) general anesthesia exposures before 3 years of age had an increased likelihood of a later ADHD diagnosis [9]. In contrast, Ko et al. found no association between general anesthesia and development of ADHD, similar to our findings [4]. Furthermore, we found no evidence of an association between the number of exposures to general anesthesia and ADHD diagnosis.

These discrepancies might be due to the variety of specific assessment tools used in different studies to evaluate different criteria within development, cognition, intelligence, academic achievement, and neuropsychological diagnosis. As brain development in young children is dynamic and ongoing, associations in other domains might have been missed [10]. Physical growth can be assessed by changes in weight, height, and head circumference. These can be readily plotted over time to determine disparities between normality and those indicating disease onset or other effects compromising growth. Cerebral immaturity and plasticity influence the sensitivity to drugs, pain responses, and behavior, and increases the potential harm from apoptosis with anesthesia [11].

Table 1
Patients' characteristics before and after propensity score matching.

	Group O (n = 17,136)	Group G (n = 315)	P-value	Matched group O (n = 1259)	Matched group G (n = 315)	P-value
Birth weight (kg)	3.19 [0.5]	3.08 [0.5]	<0.0001	3.09 [0.5]	3.08 [0.5]	0.47
Income decile	6.64 [2.9]	6.69 [2.9]	0.44	6.71 [2.83]	6.71 [2.8]	0.47
Sex (male/female)	8682/8454	205/110	<0.0001	812/447	205/110	0.85
Prematurity	358	13	0.045	49	12	0.68

Data are presented as mean [standard deviation] or numbers.

Table 2
Outcome data before and after propensity score matching.

	Group O (n = 17,136)	Group G (n = 315)	P-value	Matched group O (n = 1259)	Matched group G (n = 315)	P-value
Head circumference (cm)	51.1 [1.5]	51.2 [1.4]	0.27	51.2 [1.4]	51.2 [1.4]	0.43
Height (cm)	114.0 [4.5]	113.8 [4.5]	0.34	113.9 [4.4]	113.9 [4.53]	0.45
Weight (kg)	21 [3.3]	20.9 [3.0]	0.4	21.1 [3.6]	20.9 [3.12]	0.49
Auditory development (need thorough checkup)	214	6	0.305	15	6	0.32
Visual development (need thorough checkup)	353	12	0.033	29	12	0.13
ADHD	176	5	0.33	12	5	0.33

Data are presented as mean [standard deviation] or numbers. ADHD, attention deficit/hyperactivity disorder.

Table 3
Outcome data according to the number of exposures to general anesthesia.

	Group O (n = 17,136)	Group G1 (n = 265)	Group G2 (n = 50)	P-value
Birth weight (kg)	3.2 [0.5]	3.1 [0.5]	2.9 [0.6]	<0.0001
Income decile	6.64 [2.9]	6.69 [2.8]	6.7 [3.1]	0.89
Sex (male/female)	8682/8454	179/86	26/24	<0.0001
Head circumference (cm)	51.12 [1.47]	51.26 [1.42]	50.85 [1.29]	0.09
Height (cm)	114 [4.5]	114.14 [4.5]	112.4 [3.9]	0.021
Weight (kg)	21.02 [3.3]	21.04 [3.08]	20.06 [3.1]	0.079
Auditory development (need thorough checkup)	214	4	2	0.21
Visual development (need thorough checkup)	358	8	4	0.0078
ADHD	176	4	1	0.59

Data are presented as mean [standard deviation] or numbers. ADHD, attention deficit/hyperactivity disorder.

According to SmartTots, more than 1 million children 4 years of age or younger undergo surgical procedures requiring anesthesia each year in the United States alone [12]. Each year, more infants and toddlers receive anesthesia and/or sedation for surgery, procedures, and imaging studies. Based on previous research, a concern has been raised of the possibility of injury to the developing brain by the exposure to anesthetic drugs. However, considering the great number of children exposed to surgery and anesthesia each year worldwide, the effect size of potential neurotoxicity is most likely to be minimal, as the clinical presentation or potential phenotype has not yet been defined [10]. Therefore, the reduced power because of a small sample size and effect size is a major problem in the research of anesthesia-related neurotoxicity.

A major strength of our study is that it was based on a large and representative nationwide database that is used as a reliable research tool for identifying trends and demographics. A large-scale database can offer a vast amount of information, which can help to improve the quality of medical care. Administrative claim databases are more useful for the evaluation of long-term complications, and patients can often be tracked within the time period of the databases for assessment of specific events. We excluded pediatric patients who underwent major surgery as well as those diagnosed with neoplasms, endocrine, mental and behavioral disorders, congenital malformations, deformations, and chromosomal abnormalities, and nervous system diseases, to rule out the possibility of the disease itself having a greater effect than that of the anesthesia. In addition, we used demographic data, including head circumference, height, and weight, that have not been included in other claim database research.

Nonetheless, our study has some limitations. First, as all cohort studies, our study has the inherent limitation of possibly including confounding factors, as it is known to be difficult to eliminate confounding factors. It remains controversial which outcomes that affect neurologic or behavior domains should be assessed and at which ages. Second, we could not assess the association between duration of surgery and occurrence of ADHD. Thus, our results cannot represent the outcomes of exposure to long-lasting surgery. Third, claims data can contain coding errors, leading to some unclear results. It was not possible to determine whether maternal factors and Apgar score at birth can be related to ADHD development.

In summary, our retrospective analysis of children exposed to general anesthesia before 4 years of age found no association with increased risk of ADHD or developmental disorders.

Ethical approval

The study was reviewed and approved by the institutional review board (IRB No 2018-09-006).

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Author contribution

Eun-Jin Ahn contributed to data collection, data analysis, data interpretation, and writing of the manuscript. Si Ra Bang contributed to the literature review, figure preparation, study design, data collection, analysis, interpretation, and writing of the manuscript.

Guarantor

Si Ra Bang.

Research registration number

Not applicable.

Consent

The study was reviewed and approved by the institutional review board (IRB No 2018-09-006) and the need to obtain informed consent was waived because we used de-identified administrative data.

Conflict of interest statement

No conflict of interest.

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This study used NHIS-NSC data (NHIS-2018-2-293) made by National Health Insurance Service (NHIS). The authors declare no conflict of interest with the NHIS.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijso.2020.07.001>.

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