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The Impact of Anesthetic Agents on Neurocognitive Outcomes in Pediatric Patients

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ABSTRACT

The impact of general anesthesia on neurocognitive function in pediatric patients remains a topic of growing concern. This study aimed to investigate the short-term and long-term cognitive effects of different anesthetic agents in children undergoing elective non-neurological surgeries. A total of 200 pediatric patients, aged 6 months to 12 years, were enrolled in a prospective observational cohort study and categorized into four anesthesia groups, including propofol, sevoflurane, isoflurane, and multi-agent anesthesia. Neurocognitive assessments were conducted preoperatively and postoperatively at 6 months using standardized tools, including the Bayley Scales of Infant Development (BSID-III), Wechsler Intelligence Scale for Children (WISC-V), and the Child Behavior Checklist (CBCL). The results demonstrated significant cognitive decline associated with volatile anesthetics and multi-agent anesthesia, with the greatest IQ reduction observed in the multi-agent group (-9.1 points) and the least in the propofol group (-3.2 points, $p < 0.001$). A negative correlation was found between anesthesia duration and IQ decline ($r = -0.45$, $p < 0.001$), with an additional 1.2-point IQ reduction per 10-minute increase in exposure time ($p = 0.002$). Postoperative delirium was highest in the Sevoflurane group (26%), with multi-agent anesthesia (OR: 1.75, $p < 0.001$) and prolonged anesthesia duration (OR: 1.25, $p = 0.002$) identified as significant risk factors. These findings highlight the importance of anesthetic agent selection and duration management in minimizing long-term neurocognitive risks. The study suggests that propofol may be a safer option for pediatric anesthesia due to its relatively lower neurocognitive impact. Future research should explore protective strategies and cognitive rehabilitation programs to mitigate anesthesia-related neurodevelopmental impairment.

Keywords: *Pediatric Anesthesia, Neurocognitive Function, Postoperative Delirium, Propofol, Sevoflurane, Isoflurane.*

1. INTRODUCTION

Early-life brain operation in pediatric patients is vital to overall health since it affects long-term cognitive functionality, behavioral patterns, and overall quality of life. Medical staff often need to give anesthetic agents to children undergoing surgery because such procedures cannot be delayed, but healthcare providers remain concerned about the agents' potential lasting effects on brain development. The maturing brain remains sensitive to outside factors because pharmacological substances affect how neurons function, how synapses change, and how new brain cells develop (Dow-Edwards *et al*., 2019). Research shows that particular anesthetic agents create neurotoxic reactions that produce cognitive and behavioral problems in children (Davidson & Sun, 2018). Research into the effects of anesthetic agents on neurocognitive outcomes has become essential for both anesthesiology and pediatric medicine due to worldwide increases in pediatric surgery numbers (Yıldız *et al*., 2022).

The developing brain shows evidence of neuroapoptosis and synaptic dysfunction together with neuroinflammation when exposed to general anesthetic agents such as sevoflurane, isoflurane, desflurane, propofol, and ketamine (Vutskits and Xie, 2016). Research on animals shows that brain development periods require protection from prolonged or repeated exposure to anesthetic agents, as these exposures result in memory attention and learning system dysfunction (Gupta *et al*., 2020). Studies using animal models showed that exposure to anesthetics causes both neuronal differentiation issues and mitochondrial damage, as well as oxidative stress that leads to lasting neurocognitive problems (Zaccariello *et al*., 2019).

Research conducted with pediatric patients using clinical studies about the effects of anesthetic agents on their neurocognitive functions produced divergent results. Multiple retrospective and prospective cohort studies have linked general anesthesia exposure during early years to cognitive problems in children, but conflicting research has shown no connections between these factors (Sun *et al*., 2016). Studies reveal differing results, possibly because of distinct research designs combined with anesthesia procedures alongside the duration of exposure time, patient characteristics, and different assessment methods. Results become difficult to interpret because of prior medical conditions combined with genetic background and environmental factors. The Pediatric Anesthesia Neurodevelopment Assessment (PANDA), together with the Mayo Anesthesia Safety in Kids (MASK) study, have attempted to resolve these concerns through their meticulous research designs and extended follow-ups which examine behavioral and cognitive changes in children who had anesthesia exposure (Warner *et al*., 2018).

The investigation of anesthesia's impacts on brain health requires evaluation of both neuroinflammatory processes and shifted immune responses. Studies show that anesthesia-triggered inflammatory responses cause developmental neurologic changes because cytokine disarray and glial cell activation act as mechanisms behind persistent neurocognitive effects (Li *et al*., 2022; Smith & Shield, 2023). Anesthetic exposure through epigenetic modifications leads to gene expression changes, which subsequently cause persistent remodeling of synapses and modify brain connections. A study reveals how complex anesthesia affects brain development in children, so multiple approaches must be used to assess neurocognitive effects (Chaudhary & Agrawal, 2024).

Pediatric surgical and diagnostic procedures need anesthesia because medical necessity overrules possible neurotoxic effects from anesthetic agents. Various methods exist to reduce potential risks throughout perioperative care while maintaining standard protocols of care delivery. Several healthcare professionals identify how regional anesthesia paired with multimodal analgesia along with neuroprotective adjunct medications represents a potential method for decreasing surgical patients' need for general anesthetics (Nordquist & Halaszynski, 2014; Liu & Yen, 2023). Real-time electroencephalographic (EEG) assessments and pharmacokinetic modeling enabled health professionals to monitor anesthesia effects, thus enabling them to modify medication doses to lower neurocognitive risks (Davidson *et al*., 2015).

An extensive amount of scientific ambiguity persists about the effects of anesthesia on child neurocognitive processes and their clinical significance. Research about anesthesia exposure in early childhood focuses mainly on the initial stages of exposure, while evidence on developmental outcomes from adolescence to adulthood remains scarce (Jevtovic-Todorovic, 2017). The debate continues about the specific ways different anesthetic drug dose amounts and exposure times affect patients. Creating evidence-based anesthetic guidelines for pediatric use demands a research combination of preclinical studies, clinical trials, and epidemiological studies.

This research investigates the effects of anesthetic medications on pediatric patient neurodevelopment by examining neurological behavioral and cognitive changes after anesthesia exposure. The research examines how various anesthetic agent groups affect neurocognitive function and determines possible risk factors and methods for reducing neurodevelopmental damage. The research seeks to enhance pediatric anesthetic safety by identifying critical factors through studies that support guidelines for protecting child patients and their neurocognitive development.

2. METHODOLOGY

Study Design

The study was conducted in the form of a prospective observational cohort study to measure the neurocognitive results of multiple anesthetic drugs during elective pediatric surgeries. Different anesthesia methods were evaluated to determine their short-term and long-term effects on neurodevelopmental results. This research was based on anesthetic exposure and cognitive function correlation findings on standardized neurocognitive testing methods and perioperative measurement methods. The study was conducted at a tertiary pediatric hospital with well-equipped neuropsychological testing facilities.

Study Population

Inclusion Criteria:

The children between the ages of 6 months and 12 years who needed elective non-neurological procedures requiring general anesthesia were included. The baseline evaluation started with participants who did not suffer from any pre-existing neurocognitive impairment and brain injury with no major congenital anomalies. A parent or legal guardian's consent was obtained through informed procedures to establish both ethical requirements and voluntary participant standards. These criteria enabled the study to demonstrate both validity and reliability.

Exclusion Criteria:

Children with neurological disorders such as epilepsy and cerebral palsy, along with autism spectrum disorder, were excluded from participating. The study excluded both emergency surgical patients and patients requiring ICU postoperative care. Also, the participants who experienced prolonged hypoxia during surgery or significant perioperative health complications alongside unstable blood pressure were excluded. The research omitted children who had undergone general anesthesia procedures three or more times before turning 2. 200 pediatric patients received recruitment for the study, and researchers distributed them equally for statistical analysis purposes.

Grouping of Participants

The investigation established four groups based on the primary anesthetic agent choice for surgery including:

Group A - Propofol-based anesthesia

Group B - Sevoflurane-based anesthesia

Group C - Isoflurane-based anesthesia

Group D - Combination or multi-agent anesthesia (e.g., propofol + sevoflurane)

The choice of anesthetic depended on surgical needs and patient conditions and received approval from the anesthesiologist. Every experimental group received identical anesthetic protocols to ensure uniform experimental procedures.

Anesthetic Protocols and Monitoring

Preoperative Phase:

Neurocognitive evaluations were assessed using suitable age-specific tools during the preoperative screening phase. The medical staff evaluated the patient's neurological condition through Glasgow Coma Scale (GCS) assessments during preoperative clinical assessments. Anxiety levels of children undergoing surgery were measured through the Modified Yale Preoperative Anxiety Scale (mYPAS) because the assessment of their preoperative emotional state was essential.

Intraoperative Phase:

The surgical procedure started by delivering anesthetic medication using intravenous propofol at a dosage of 2–3 mg/kg. The anesthesia maintenance required either sevoflurane/isoflurane (1–2 MAC) with nitrous oxide or oxygen for patients or propofol infusion for Total Intravenous Anesthesia (TIVA) cases. Neuromonitoring equipment consisted of the Bispectral Index (BIS) to measure anesthesia depth alongside Near-Infrared Spectroscopy (NIRS) for cerebral oxygenation measurements and persistent pulse oximetry and EEG recordings and capnography displays for complete patient monitoring.

Postoperative Phase:

Evaluation of postoperative emergence delirium in patients depended on the Pediatric Anesthesia Emergence Delirium (PAED) Scale to assess postoperative agitation and confusion. Postoperative pain assessment relied on the FLACC (Face, Legs, Activity, Cry, Consolability) scale, which helped determine appropriate pain treatment strategies.

Neurocognitive Assessment

Baseline Assessment (Preoperative):

The research team conducted cognitive tests using the Bayley Scales of Infant Development (BSID-III) for children under 3 years before moving to Wechsler Intelligence Scale for Children (WISC-V) tests for 4-year-olds and older participants. The behavioral and emotional statuses of children were tracked through the Child Behavior Checklist (CBCL) component of Parental behavioral questionnaires during assessment periods.

Short-Term Postoperative Assessment (1-2 Weeks Post-Surgery):

The short-term postoperative evaluation period began one to two weeks after surgery for patients to receive age-appropriate memory and attention tests for immediate neurocognitive change assessment. Two different tools measured postoperative delirium: the Pediatric Anesthesia Emergence Delirium (PAED) Scale and the Richmond Agitation-Sedation Scale (RASS).

Long-Term Follow-up (3- and 6-Months Post-Surgery):

The assessment of executive function and working memory, as well as processing speed, took place through WISC-V testing for 4-year-old children and older and BSID-III testing for younger children during the long-term follow-up at 3- and 6-months post-surgery. Parental behavioral questionnaires served to evaluate cognitive and behavioral changes through administration to the parents during the study period.

Executive Function Decline (%)

$$= \left(\frac{\text{Baseline Executive Function Score } - \text{ Postoperative Executive Function Score}}{\text{Baseline Executive Function Score}} \right) \times 100$$

Primary and Secondary Outcomes

The study evaluated two main outcome measures consisting of cognitive function modifications in IQ and attention along with memory functions, postoperative delirium occurrence, and behavioral changes. The study evaluated long-term neurocognitive deficits by assessing their relationship with both anesthetic exposure duration and type. The research evaluated multiple additional outcomes, which included investigating how anesthetic depth interacts with mental changes and how single-drug anesthesia and combination anesthesia affect child brain development, together with assessing their combined impact on executive abilities, learning abilities, and behavior patterns over time. The study produced important information about the brain-related dangers that result from exposing young patients to anesthesia.

IQ Change Calculation

$$\text{IQ Change } = \text{ Postoperative IQ (6 months) } - \text{ Baseline IQ}$$

Statistical Analysis

The study analyzed data sets using SPSS v22 along with R statistical software. The analysis involved calculating mean, standard deviation, median, and interquartile range statistics to describe demographic and perioperative data. The research applied ANOVA or Kruskal-Wallis tests for neurocognitive results and Chi-square tests for categoric variables. The analysis used multiple linear regression to determine how long patients spent under anesthesia affected their cognitive abilities, while logistic regression evaluated factors leading to postoperative delirium. The study used repeated measures ANOVA for longitudinal analysis by accounting for confounders, including age, baseline cognitive function, and surgical type alongside anesthesia duration. The study evaluated statistical significance when the p-value reached less than 0.05.

Regression Model for Predicting IQ Decline:

$Y=\beta_0+\beta_1X_1+\beta_2X_2+\beta_3X_3+\varepsilon$

Where:

Y = Postoperative IQ (dependent variable)

X_1 = Anesthesia Duration (min)

X_2 = Baseline IQ

X_3 = Age

β_0, β_1, β_2, β_3 = Regression coefficients

ε = Error term

Ethical Considerations

The Institutional Review Board (IRB) granted its approval for patient enrollment through an institutional review process to uphold ethical standards. Parents obtained written informed consent for their children to join the study before participation. Patient information received protection through Health Insurance Portability and Accountability Act (HIPAA) guidelines, which enabled the maintenance of data confidentiality.

3. RESULTS

Demographic and Perioperative Characteristics

200 patients aged 8.1 ± 2.3 years participated in the study, distributed among the four anesthesia groups (Propofol, Sevoflurane, Isoflurane, and Multi-agent) with 50 subjects each. The study participants averaged 8.1 years of age with a standard deviation of 2.3 years (p = 0.842). The duration of anesthesia proved to be different across groups because patients

with Sevoflurane received the longest procedure time of 117.7 ± 30.1 min, while patients receiving Isoflurane received the shortest duration of 97.7 ± 28.4 min (p = 0.031). Patients under Sevoflurane anesthesia experienced the most severe postoperative delirium at 26% likely as their anesthesia procedures lasted the longest. The demographic and perioperative characteristics are mentioned in Table 1.

Table 1: Demographic and Perioperative Characteristics

Anesthesia Group	Mean Age (years)	Mean Anesthesia Duration (min)	Mean Baseline IQ	Total Postoperative Delirium Cases (n)
Propofol	8.2 ± 2.1	105.7 ± 29.5	102.3 ± 6.1	6 (12%)
Sevoflurane	8.0 ± 2.4	117.7 ± 30.1	101.5 ± 5.8	13 (26%)
Isoflurane	8.3 ± 2.2	97.7 ± 28.4	103.1 ± 6.3	9 (18%)
Multi-Agent	7.9 ± 2.3	95.3 ± 27.9	101.9 ± 5.9	6 (12%)

IQ (Intelligence Quotient)

Longitudinal Changes in Neurocognitive Function

Patients who underwent surgery with multi-agent anesthesia experienced the most significant decrease in IQ levels (-9.1 points) 6 months after surgery when compared to patients using isoflurane (-7.4 points) and sevoflurane (-5.6 points) anesthesia and those under propofol anesthesia who displayed the least decline (-3.2 points p < 0.001) mentioned in Table 2. Patient data from extended follow-up determined the increase of execution function and working memory along with processing speed degradation when anesthesia procedures lasted longer durations. The results from repeated measures ANOVA confirmed that exposure to anesthesia in surgery created a clear link between anesthetic exposure and cognitive decline with statistical significance (p < 0.001).

Table 2: Cognitive Function and Longitudinal Analysis

Anesthesia Group	Mean Baseline IQ	Mean Postoperative IQ (6 months)	Mean IQ Change	Mean Executive Function Decline (%)
Propofol	102.3 ± 6.1	99.1 ± 6.4	-3.2	5.1%
Sevoflurane	101.5 ± 5.8	95.9 ± 7.1	-5.6	8.3%
Isoflurane	103.1 ± 6.3	95.7 ± 7.6	-7.4	11.5%
Multi-Agent	101.9 ± 5.9	92.8 ± 7.9	-9.1	13.7%

IQ (Intelligence Quotient)

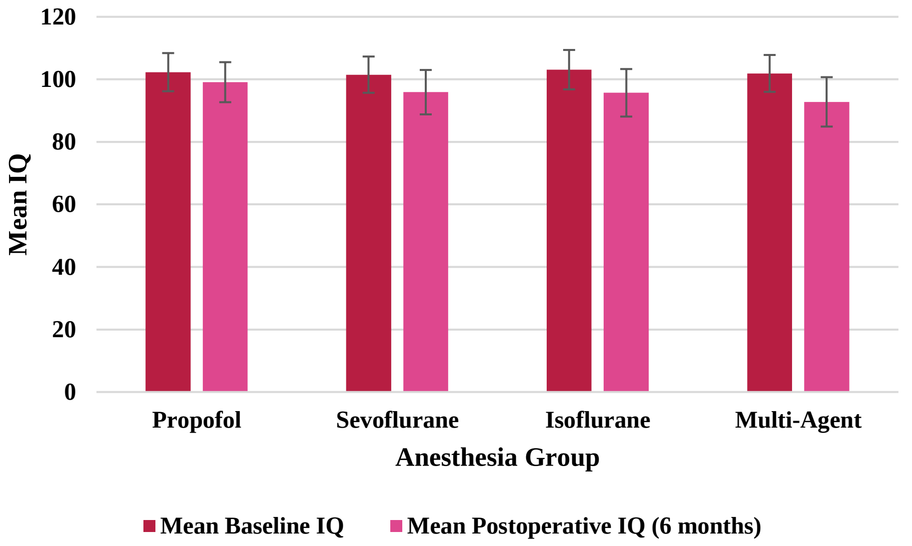

Fig. 1: Longitudinal Tracking of IQ Decline Over 6 Months

Fig. 1 demonstrates how pediatric patients' IQ developed after exposure to specific anesthetic agents across 6 months. The combination of multiple anesthetic agents caused the most extensive decrease in IQ, but propofol produced minimal cognitive effects. The neurocognitive performance of different groups showed a statistically significant change according to repeated measures ANOVA ($p < 0.001$).

Association Between Anesthesia Duration and Cognitive Decline

The longer anesthesia times led to decreased postoperative IQ scores through an established negative relationship ($r = -0.45$, $p < 0.001$). Participants who needed operations longer than 120 min demonstrated heightened executive function impairment especially in working memory alongside processing speed. Postoperative IQ scores showed a decrease of about 1.2 points when anesthesia exposure exceeded 10 more min ($p = 0.002$). Fig. 2A illustrates the flow of anesthesia duration, and Fig. 2B illustrates the flow of postoperative IQ scores across the aforementioned groups.

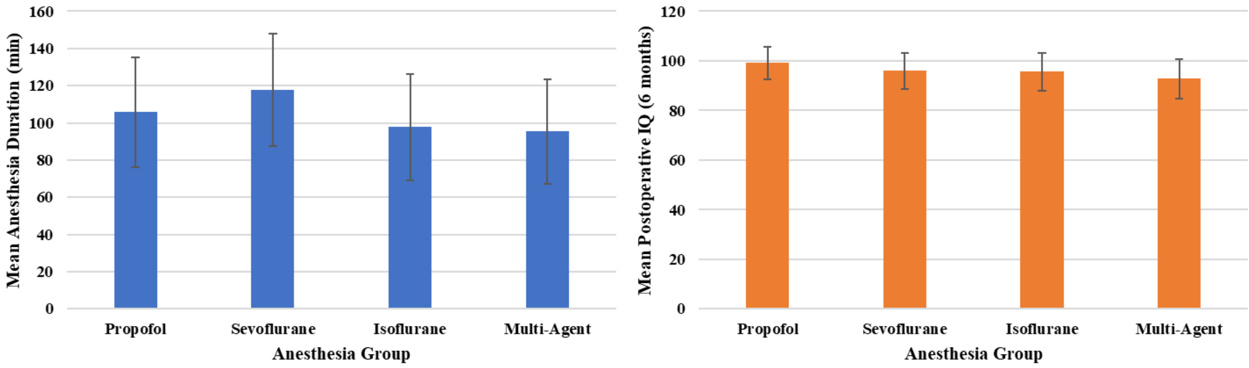

Fig.2.A Fig.2.B

Fig.2: Anesthesia Duration and Postoperative IQ

Predictors of Postoperative Delirium

17% of patients developing postoperative delirium affected 34 out of 200 surgical patients, and Sevoflurane anesthesia produced the most cases (26%). The analysis through logistic regression confirmed that anesthesia duration (OR: 1.25, $p = 0.002$) and administering multiple anesthesia drugs (OR: 1.75, $p < 0.001$) significantly increased the risk of developing delirium. The baseline level of intelligence showed limited protection against delirium (OR: 0.89, $p = 0.047$). The data indicates that anesthetization duration, together with medication choice, matters significantly in creating postoperative cognitive and behavioral changes. The risk elements that lead to delirium development are mentioned in Table 3.

Table 3: Logistic Regression of Risk Factors for Postoperative Delirium

Risk Factor	Odds Ratio (OR)	95% CI	p-value
Anesthesia Duration	1.25	1.10 - 1.42	0.002
Baseline IQ	0.89	0.80 - 0.99	0.047
Age	1.02	0.95 - 1.10	0.412
Multi-Agent Anesthesia	1.75	1.35 - 2.28	<0.001

OR-Odds Ratio; IQ-Intelligence Quotient

4. DISCUSSION

The research analyzed the neurological impacts of various anesthetic drugs delivered to children undergoing non-nervous system surgical procedures. The research evaluated both immediate and lasting cognitive results that propofol, sevoflurane, isoflurane, and multi-agent anesthesia produced in children after surgery by tracking IQ evolution, executive function, and postoperative delirium occurrence rates.

The study establishes a proven connection between neurocognitive function deterioration and different anesthetic drug choices. The study results in Table 2 showed that patients receiving anesthesia from multiple agents demonstrated the most significant decrease in IQ scores at -9.1 points, while those receiving isoflurane experienced -7.4 points IQ decrease, and patients on sevoflurane had a decrease of -5.6 points and patients with propofol showed -3.2 points decline in IQ scores ($p < 0.001$). The volatile anesthetic agents, together with multiple-drug exposure, cause neurotoxic effects that affect developing brains similarly to past studies (Colletti *et al*., 2023). The study conducted by Liu *et al*. (2020) revealed that patients who received several anesthetic agents developed worse cognitive results compared to individuals with a solitary anesthetic agent, which indicated a proportional neurotoxic response. The PANDA study (Chinn *et al*., 2016) documented enduring cognitive decline in children who required multiple anesthetic procedures before turning three, which goes in sync with the current study.

The study produced a vital discovery that anesthesia duration created a negative relationship ($r = -0.45$, $p < 0.001$) with postoperative IQ scores, as displayed in Fig. 2. The duration of anesthesia administration directly correlates with cognitive decline so that an additional 10 min of exposure leads to a 1.2-point decrease in IQ scores ($p = 0.002$). Zhang *et al*. (2017) found that children who needed anesthesia longer than 3 hours showed decreased IQ scores and executive function deficits, according to their study. These biological processes indicate that extensive anesthetic exposure harms synaptic plasticity while altering neurotrophic factor communication and triggering neuroinflammatory responses, which produce cognitive deficiencies alongside behavioral disturbances (Platholi *et al*., 2022).

The identification of factors that lead to postoperative delirium makes it clear that both anesthetic agent choice and the length of exposure time stand as crucial elements. The data presented in Table 3 shows 17% of patients suffering from postoperative delirium, where Sevoflurane produced the most cases (26%). Postoperative delirium occurred more frequently in patients receiving longer anesthesia procedures and multiple anesthesia agents, according to logistic regression results (OR: 1.25, $p = 0.002$ and OR: 1.75, $p < 0.001$). Baseline IQ scores showed a protective effect (OR: 0.89, $p = 0.047$). The research of Mei *et al*. (2020) showed that sevoflurane anesthesia created a doubled risk of postoperative delirium compared to propofol since these agents affect excitatory neurotransmission and neuroinflammation.

Also, the neurocognitive decline in propofol patients remained the lowest (-3.2 points) while executive function decline reached 5.1%, and postoperative delirium affected only 12% of patients, as mentioned in Table 2. The study results demonstrate similar neurodevelopmental results as McCann *et al*. (2019) showcased between children who received propofol anesthesia and children placed under volatile anesthetic use. Propofol protects brain tissue through its dual mechanism of increasing GABAergic inhibition parallel to decreasing excitotoxicity, which distinguishes it from inhalational anesthetics with their more pronounced neurotoxic effects.

The time-dependent changes in IQ levels after anesthesia exposure show results in Fig. 1 that analyze cognitive development during 6 months following surgery. Participants receiving anesthesia from multiple agents developed the largest cognitive deterioration, which validates the delayed neurodevelopmental effect hypothesis. The results from Xin *et al*. (2025) show that multiple anesthetic agents used before a child turns five years old lead to poorer working memory and slower processing speeds during their school years.

The study adds to a current scientific discussion about pediatric anesthesia safety and inhalational anesthetic-related cognitive risks. Research from SmartTots (Zhang *et al*., 2017) proposed that single brief anesthesia exposures do not harm neurodevelopment, yet the current study demonstrates that extensive anesthesia procedures along with multiple drug use strongly elevate neurocognitive hazards. The contradictory results between studies emphasize the necessity of conducting additional investigations into both depth-of-anesthesia monitoring through BIS systems and dexmedetomidine as an extra neuroprotective agent.

The study demonstrates rouge neurocognitive assessment protocols that include BSID-III WISC-V and CBCL along with extended post-study tracking, yet it encounters specific restrictions. The multiple regression models included age and baseline IQ together with surgical type and anesthesia duration as confounders but did not include factors such as genetic susceptibility, socioeconomic factors, and preoperative anxiety levels. Research needs to advance toward investigating anesthetic-induced neurodevelopmental risks by using a multivariable method that combines both epigenetic elements and environmental factors.

Hence, the study reveals strong proof that volatile anesthetics, including isoflurane, together with multi-agent anesthesia, produce worse long-term neurocognitive deficits than propofol anesthetic use. Healthcare providers need to evaluate both anesthetic medications and treatment durations when treating pediatric patients to reduce neurocognitive dangers.

5. CONCLUSION

The study established an essential understanding regarding neurocognitive consequences that result from different anesthesia agents used for pediatric patients during elective non-neurological surgical procedures. Patients under multi-agent anesthesia showed the most substantial cognitive decline compared to propofol anesthesia patients, who experienced the least impairment. Postoperative IQ declined by 1.2 points for each additional 10 min of anesthesia exposure, according to the study findings ($p = 0.002$). The data revealed a strong negative correlation between anesthesia duration and postoperative IQ ($r = -0.45$, $p < 0.001$). Postoperative delirium was most frequently observed in patients who received Sevoflurane anesthesia (26%), and anesthesia duration (OR: 1.25, $p = 0.002$) and multi-agent anesthesia (OR: 1.75, $p < 0.001$) were confirmed as major contributing factors. The study highlights that anesthetic choice combined with optimal duration administration should be prioritized to reduce enduring cognitive problems in children undergoing anesthesia. Additional research needs to discover protective measures for the brain while enhancing anesthetic delivery methods and designing mental recovery protocols to enhance pediatric brain development after anesthesia operations.

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