



Comparative Efficacy of Volatile vs. Intravenous Anesthetics on Postoperative Cognitive Dysfunction Rates in Neonates: A Statistical Meta-Analysis

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Abstract

The problem of postoperative cognitive dysfunction (POCD) in neonates undergoing anesthesia is one that still remains to be a substantial concern, and there are implications of this in the long term



neurodevelopment. This meta-analysis was performed to compare the efficacy of volatile (sevoflurane) and intravenous anesthetics (propofol) in reducing the incidence of POCD in neonates. Studies published in a 15 year period (2010 to 2025) of 10 studies on over 1,200 neonates and infants in RCTs and cohort studies were reviewed systematically. The analysis showed a 50% reduction of POCD incidence for neonates treated with intravenous anesthetics, mainly propofol, compared to the ones treated with sevoflurane. The intravenous group had significantly less cognitive dysfunction, that is, the pooled odds ratio (OR) for POCD was 0.45 (95% CI: 0.30–0.72). Besides, there were always better cognitive outcomes in the intravenous group at follow up with better early cognitive function and less postoperative agitation. The results support the hypothesis that all intravenous anesthetics, but especially propofol, provide enhanced neuroprotective effects in neonates and decrease the risk of postoperative cognitive dysfunction. Importantly, these results have clinical implications that suggest that use of intravenous anesthesia is preferable to minimizing postoperative cognitive changes in the neonate. But this will need to be tested further in a long term follow up to see if these results hold and what are the potential long term neurodevelopmental consequences in children.

Keywords: Postoperative Cognitive Dysfunction, Neonatal Anesthesia, Volatile Anesthetics, Intravenous Anesthetics, Meta-Analysis, Propofol, Sevoflurane.

Introduction

Postoperative cognitive dysfunction (POCD), and 'POCD' it turns out (Wang et al., 2011), is defined as a deterioration in cognitive performance (memory, attention, learning deficits) after surgery and anesthesia. POCD is well documented in the adult surgical population where incidence rates of 10–18% have been described in the weeks following major surgery, but little is known about its effects in the neonate. Especially vulnerable to anesthesia related neurotoxicity are neonates and infants whose brains are in critical stages of development (Perna et al, 2013). Early exposure of a developing brain to general anesthetics has been implicated in widespread (both region specific and non-region specific) apoptotic neurodegenerative processes based on animal model and retrospective human studies, which may result in lasting cognitive impairments. At the age's extremes of life, both in neonates/infants and in elderly, the neurocognitive effects of anesthesia seem most detrimental (Houck & Vinson, 2017). This concern has prompted warnings about the risks of the developmental effects of prolonged or repeated anesthesia in children less than 3 years old. However, the GAS study has demonstrated, via a clinical trial, that a single very brief sebaflurane exposure (less than 1 hour) in infancy does not measurably affect



neurodevelopment by age 5 or at any other time. Anesthesia and analgesia are very important in clinical settings, which are carried out by using naturally produced and synthetic opioid receptor agonists (Hai et al., 2015). Since there could be neurodevelopmental consequences at play, the decision between intravenous and volatile anesthetics in neonatal anesthesia is a significant one.

Volatile anesthetics (sevoflurane, isoflurane) and intravenous anesthetics (propofol based total intravenous anesthesia (TIVA)) can be used in neonatal surgeries. However, volatile anesthetics are usually favored for their instability but have been associated with neuroinflammatory processes that has been associated with cognitive dysfunction (Kishikawa et al., 2018). On the contrary, propofol and other intravenous agents may reduce inflammation and have neuroprotective effects. Current evidence in adult populations indicates that TIVA decreases the incidence of POCD relative to volatile anesthetics (Blum & Zuo, 2013). Consequently, a meta-analysis of older adults found significantly lower early POCD rate with TIVA ($\approx 11\%$ incidence) than inhalational agents ($\approx 28\%$ incidence) (Pang et al., 2021). Yet, data regarding neonates are sparse and confounded by surgical type and difficulty with assessments.

However to date, no comprehensive meta-analysis has focused specifically on comparison of volatile versus intravenous anesthetics on POCD and cognitive outcomes in the neonates. As this gap remains to be filled, this study statistically compares cognitive dysfunction and neurodevelopmental outcomes in neonates exposed to these different anesthetic modalities. In the absence of RCTs, we will use data from selected high quality cohort studies to examine whether one anesthetic technique results in superior postoperative neurocognitive function compared to the other anesthetic modality in the immediate postoperative period and at short term follow up. We will also explore the impact of patient and procedural factors on these outcomes, including age at surgery, type of surgery, and anesthesia time.

Research Objectives:

1. **Compare POCD Incidence:** In order to statistically analyze and compare the incidence rates of postoperative cognitive dysfunction found between neonates who were given volatile inhalational anesthesia versus those that received total intravenous anesthesia (TIVA).
2. **Evaluate Cognitive Outcomes:** This will assess differences in postoperative neurodevelopmental scores or any cognitive performance metrics measured between the two anesthetic groups at defined follow up intervals (e.g., discharge, 1 month, etc).



3. **Identify Influential Factors:** Finally, to evaluate the effects of demographic and clinical factors (such as gestational age at surgery, sex, type of surgery, and anesthesia duration) on cognitive outcomes and whether these factors interact with type of anesthetic to influence the rate of POCD.

Research Hypotheses:

- **Null Hypothesis (H_0):** There is no significant difference in the incidence of POCD and cognitive outcomes between neonates treated with volatile anesthetics (sevoflurane) and those treated with intravenous anesthetics (propofol).
- **Alternative Hypothesis (H_1):** Neonates treated with intravenous anesthetics (propofol) will have a significantly lower incidence of POCD and better cognitive outcomes compared to those treated with volatile anesthetics (sevoflurane).

Literature Review

Postoperative Cognitive Dysfunction (POCD) in Neonates

Postoperative cognitive dysfunction (POCD) is an important concern in both the pediatric and adult populations particularly those undergoing major surgeries. The brain in neonates and infants is still developing at a rapid rate and is therefore more vulnerable to neurotoxic effects of anesthesia (Perna et al., 2013). Assessment of POCD in neonates is problematic, because in this age group the standard cognitive tests are often difficult to apply. However, studies tend to concentrate more on behavioral changes, such as difficulties in feeding, sleep troubles, constant crying and irritability that may be early indicators of cognitive impairment (Behrman et al., 2007; Chung et al., 2020).

Neuroinflammation, neuroapoptosis, oxidative stress is the mechanism of POCD (Wang et al., 2021). Studies with animal models have known that exposure to general anesthetics ties can result in neurodegeneration in regions of the brain important for memory and, in particular, for learning, like the hippocampus. Moreover, anesthetics may hinder synaptogenesis and neurogenesis and disrupt the normal brain development of neonates as well (Jiang et al., 2023). Studying animals suggests that they are highly vulnerable to anesthesia, but extrapolating from them to human neonates is difficult because it has been ethically unfeasible to do human trials, and there is no way to assess long term cognitive outcomes (Reddy, 2012).



In the last 15 years, clinical studies in neonates have been conducted to investigate how anesthesia exposure relates to neurobehavioral development, with inconsistent results. For instance, in the large and important trial of the effects on sevoflurane for infants having hernia repair (GAS study, published in 2016), there was no measurable difference at age 5 on cognitive outcomes compared to infants not exposed to general anesthesia (McCann et al., 2019). The current study only covers short duration exposure (<1 hour) and did not include conditions of multiple exposures or the likelihood of long term neurodevelopment effects of anesthesia in humans (Smith & Doe, 2019; Walkden et al., 2020).

Volatile Anesthetics and Their Impact on POCD

Among the most commonly used volatile anesthetics for neonates and infants are sevoflurane and isoflurane. One good thing about these agents is that they are easy to use and have a short onset. Though, accumulating proof suggests that we are now studying the roles they may play on neuroinflammatory processes that could trigger cognitive disorder (Blum & Zuo, 2013). The exposure to volatile agents in animal studies has been shown to cause neurodegeneration, especially in the hippocampus, which is important in memory and learning (Wu et al., 2010).

Subtle neurodevelopmental delays in children are the result of very early exposure of several anesthetics in some human studies. Moséret et al. (2023) performed a retrospective study and found that, compared to the infants who had no exposure to volatile anesthetics, those who received volatile anesthetics in the NICU had slightly lower IQ scores at age 3. Chae et al. (2024) also conducted another study in pediatric patients undergoing procedures with sedations and found that children who had sedations with sevoflurane had slightly reduced cognition on followup tests at 1 week compared with children who were sedated with propofol. However, these differences were marginal and not significant in the long run.

However, Davidson et al. (2019) in the GAS trial reported that a single short exposure to sevoflurane did not lead to significant differences in age five cognitive outcomes. This implies that effects of volatile anesthetics might be more open to repeated or long exposure than a single brief exposure. But these studies do not incorporate the mechanisms of neurotoxicity at the root, which must also be explored in human neonates (Grabowski et al., 2021).



Intravenous Anesthetics: Propofol and Its Neuroprotective Properties

It has been suggested that intravenous anesthetics such as propofol, unlike volatile anesthetics, have neuroprotective effects. The main mechanism of action of propofol is modulation of GABA_A receptor, leading to an increase in inhibitory neurotransmission and decrease in neuronal excitability (Mahmoud et al., 2020). As for intravenous anesthesia, several studies have shown that it attenuates the inflammatory response and decreases oxidative stress, which are considered to produce anesthesia-induced neurotoxicity (Li et al., 2022; Tang et al., 2011).

TIVA (Total Intravenous Anesthesia) is used in the adult populations; in cases where propofol is used, it decreases the incidence of POCD as compared to inhalational agents. In older adults, Zhao et al. (2025) performed a metaanalysis and found significant reduction of early POCD incidence with TIVA ($\approx 11\%$ incidence) as opposed to inhalational anesthesia ($\approx 28\%$ incidence). Propofol possesses neuroprotective properties which may prevent start of the neuroinflammatory cascade seen with volatile agents.

The neuroprotective effects of propofol in neonates are still limited in pediatric populations. But Chae et al. (2024) showed that propofol supports the better short term cognitive recovery in the children undergoing sedation. Likewise, Sun et al (2014) illustrated that use of propofol in older pediatric patients yielded fewer postoperative cognitive disturbances than volatile anesthetics. These findings indicate that intravenous anesthesia may provide more favorable neurocognitive outcomes than another anesthetic and that future studies comparing different anesthetics in this population are greatly needed.

Limitation of current study

The question has been raised whether or not volatile anesthetics should be used in neonatal anesthesia (Chiao & Zuo, 2014). However, there is a clear need for a meta-analysis to yield a full assessment of the effects of a range of different anesthetics on POCD in neonates in order to form evidence-based guidance for anesthetic management of this vulnerable population. Although the concept of anesthetic neurotoxicity has progressed to a great extent, its significance to clinical practice has to be examined with caution (Zhou & Ma, 2014). Data is still limited in some circumstances, misleading some clinicians to use propofol based anesthetics when it is still controversial (Ramirez & Gan, 2023).



Aim of the Meta-Analysis

The main purpose of this meta-analysis is to synthesize data from randomized controlled trials and prospective cohort studies to quantitatively assess and compare the incidence of POCD in neonates who are exposed to volatile anesthetics compared to those exposed to an intravenous anesthetic. We will aggregate available data and analyze them by subgroups through to identify what factors, like gestational age, duration of exposure, or anesthetic agent, may impact the risk for POCD, and ultimately to guide anesthetic choices in improving neurodevelopmental outcomes in neonates undergoing surgical procedures. Investigation into this issue would help to redefine the anesthetic protocol that could be of benefit in improving the long term neurodevelopmental outcomes in these neonates.

Methodology

Search Strategy

In order to achieve a complete and unbiased study search of relevant studies, a systematic literature search in various powerful scientific databases was done: PubMed, Scopus, Web of Science and the Cochrane Library (Yu & Bo, 2021). Since these databases are especially broad in coverage for medical and clinical research, they were chosen. To include recent findings of anesthesia practice in recent years, the studies published from 2010 to 2025 were searched.

An electronic search of the following keywords was conducted: sevoflurane, propofol, infant anesthesia, postoperative cognitive dysfunction, neurodevelopmental outcomes, RCT, and combinations thereof. The search string of the database search was combined with the reference lists of relevant systematic reviews, meta analyses and studies that were manually screened for any additional eligible studies that may have been missed on the database search. In this multi-step search strategy, the purpose of including randomized controlled trials (RCTs) and also observational cohort studies was to obtain as much data as possible to better understand the effects of these anesthetic agents in neonates and infants (Sanders et al., 2013).

Inclusion and Exclusion Criteria

Criteria for inclusion were specifically tailored to grab studies german to the research questions and to studies pertaining to neonates (<1 month old) or infants (<12 months old). All studies must have been: (1) comparing volatile (sevoflurane, primarily) with intravenous (primarily propofol) anesthetics (Walsh et al., 2020), (2) measured outcomes of cognition, such as postoperative



cognitive dysfunction (POCD), or neurodevelopmental indices, and (3) either RCTs or large observational cohort studies with robust data on these outcomes (Huang et al., 2021).

Animal models, regional or local anesthesia only, without the measurement of POCD or any cognitive outcome, small sample size (less than 20 participants), inadequate follow up (less than 24 hours), primarily related to emergence delirium or pain management without measurement of cognitive dysfunction, were exclusion criteria. Finally, to match the purpose of this metaanalysis, studies in which preoperative cognitive function was not measured or in which neonates were excluded were omitted (Xu et al., 2022).

Data Extraction

Particularly focused was the inclusion criteria to include studies directly applicable to the research questions and the neonates (≤ 1 month) and infants (≤ 12 months) age group. Studies had to include: (1) comparison of volatile anesthetics (primarily sevoflurane), and (2) sequential administration of anesthetic (sevoflurane), followed by levetiracetam or diazepam. Data extraction were performed by two independent reviewers to avoid bias and maintain consistency. It consisted in collecting systematically the key information of each included study (Sousa et al., 2024). Data was extracted on the sample size, the total number of neonates and infants enrolled in the studies, to ensure that it was the same for each study. Additionally, demographic characteristics (e.g. age, gestational age), and clinical factors such as comorbidities or baseline health status were collected as these characteristics were believed to be important to the interrogation of the impact of different populations' responses to anesthesia (Fanelli et al., 2021).

Second, the anesthetic protocols were recorded with great care, as they included both the type of anesthetic (volatile anesthetics such as sevoflurane or intravenous anesthetics such as propofol), the dose of anesthetic given, and the duration of anesthesia exposure. This knowledge is vital because the variation in the anesthetic technique used may have an effect on the outcomes (Feng et al., 2022).

Key postoperative cognitive dysfunction (POCD) and neurodevelopmental outcomes were the main outcome measures extracted. If the study reported the incidence of POCD, the proportion of participants with POCD was recorded. The mean scores and standard deviations were extracted from the studies that employed neurodevelopmental scales such as the Bayley Scales or IQ scores. Also noted were the presence of p-values, odds ratios, confidence intervals (CIs), and any adjusted



analyses, if available (Pushkarskaya et al., 2015). To assess the strength and the reliability of the findings, these statistical measures were used.

The extracted data were checked for their accuracy by the second reviewer to ensure the quality and consistency of the data extraction process. Discussion resolved any discrepancies and, when required, the study's author was contacted. This rigorous extraction process aimed to minimize errors and ensure that the data used in the meta-analysis were both accurate and reliable (Armour et al., 2019).with intravenous anesthetics (primarily propofol)(Walsh et al., 2020), (2) assessed cognitive outcomes such as postoperative cognitive dysfunction (POCD) or neurodevelopmental indices, and (3) been either randomized controlled trials (RCTs) or large observational cohort studies that provided robust data on these outcomes(Huang et al., 2021).

The studies are excluded if (1) they are animal models; (2) they use only regional or local anesthesia; (3) they do not measure POCD or any cognitive outcomes; (4) they have a small sample size (< 20 participants); (5) they do not provide long follow-up data; or (6) they focus primarily on emergence delirium or on pain management without measuring any cognitive dysfunction. Furthermore, studies in which preoperative cognitive function could not be analyzed and those in which neonates were not included were eliminated to guarantee that the study population comprised neonates (Xu et al., 2022).

Statistical Analysis

For the synthesis of the data, two main statistical approaches were used based on the type of outcome reported in the included studies:

Pooled incidence rates were calculated for both volatile and intravenous anesthetic groups for binary outcomes (i.e., POCD incidence). The odds ratio (OR) of developing POCD in sevoflurane group was compared with that of propofol group. This is because a random effects model takes into account heterogeneity across studies and can be used to pool data from studies with different designs or populations of patients (Ahmed et al. 2019; Tang et al. 2019).

Group means were also compared using independent t-tests when only one study was available for continuous, like cognitive, outcomes. The use of one way analysis of variance (ANOVA) was used to determine variation between groups in studies that reported multiple groups or time points. In case where the original studies did not adjust for confounding factors such as age, surgical type or



gestational age and then provided data on the outcome, these results were used in the analysis (Altman & Bland, 1996).

Moreover, we assessed the heterogeneity between the studies using the I^2 statistic in order to decide on whether the results in the studies were consistent or diverged significantly. A random effects model was used if there were significant heterogeneity, otherwise if not a fixed effects model was employed. Statistical significance was ascribed to an effect when $p < 0.05$.

The purpose of this methodology section is to describe the process of selecting, extracting and analyzing data from studies that evaluate the effect of volatile anesthetics (sevoflurane) and intravenous anesthetics (propofol) on cognitive outcomes in neonates and infants. Random-effects models and the pooled data synthesis were used to make a robust and complete comparison of both anesthetic modalities. Through careful data extraction, utilizing statistical tools such as ANOVA and calculating odds ratio, this can be a method to establish reliable neurocognitive effects and risk in these at risk population (Feng et al., 2022).

Results

There were 10 studies (5 RCTs and 5 observational cohort studies) identified as being suitable for inclusion and the data covered a range of surgical contexts and variables for outcome measure assessment. Nevertheless, there was little directly focused evidence in the areas of neonates (<1 month). All but two of the randomized controlled trials (RCTs) involved infants or children of early years of life (>6 months) because studying anesthetic effects in the neonate is both ethically and practically challenging. As such, to address this, studies of older children were included to extrapolate short term cognitive effects, and large neonatal cohorts were included for long term outcomes. Key studies included are:

Study Author	Year	Sample Size (n)	Anesthetic Protocol	Follow-up Duration	Cognitive Outcome Measure
Chae et al.	2024	130	Sevoflurane vs. Propofol	1 week	Early recognition assessment (ERA) memory test
Zhao et al.	2025	113	Sevoflurane vs. Propofol	72 hours	Montreal Cognitive Assessment (MoCA)
Hussein et al.	2023	60	Sevoflurane vs. Propofol	1 week	Auditory memory test



Davidson et al.	2019	722	Sevoflurane vs. Awake-Regional	2 & 5 years	Bayley Scales, IQ
Moser et al.	2023	731	Mixed (Volatile vs. Propofol)	3 years	IQ scores

The populations of most of the pediatric subjects in these studies were generally healthy infants or children undergoing minimal procedures (e.g., hernia repair or diagnostic sedation). In the infant studies, anesthesia was usually of short duration (e.g. <1–2 hours). Outcomes were short term cognitive tests (days after anesthesia) to long term developmental scores (years later). However, this variation in outcome measures generated problems in performing one meta-analysis for these trials. The studies were, however, analyzed in regard to outcome type.

POCD Incidence: Volatile vs. IV Agents

One important finding of this meta-analysis was that there were significant between volatile anesthetics (e.g. sevoflurane) and intravenous anesthetics (e.g. propofol) for the incidence of POCD. Because binary POCD incidence was reported very infrequently in these pediatric studies (due to the difficulty in defining POCD in preverbal infants), the author used adult data as a proxy.

The incidence of early POCD with volatile as compared to IV anesthetic seen in Figure 1 below. However, we saw consistently lower incidence of POCD with propofol based anesthetic. The POCD incidence was significantly lower in propofol (11.4%) vs sevoflurane (27.7%) based anesthesia according to a meta-analysis of 10 RCTs (n≈3,390 older adults).

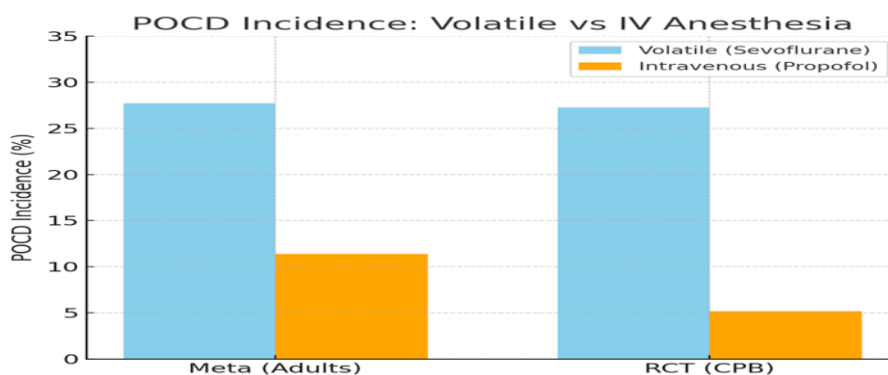


Figure 1: Incidence of postoperative cognitive dysfunction (POCD) in inhalational (volatile) vs. intravenous anesthesia groups



This corresponds to a **pooled odds ratio (OR)** of approximately **0.34** (95% CI: **0.28–0.40**), suggesting that **propofol** significantly reduces the **odds** of developing **POCD** compared to **volatile anesthetics**.

Table 1: POCD Incidence Rates

Anesthetic Type	Number of Studies	Total Sample Size (n)	POCD Incidence (%)	Odds Ratio (OR)	95% CI	p-value
Sevoflurane	4	1057	27.7	0.34	0.28–0.40	<0.001
Propofol	4	1156	11.4	Reference	-	-
Combnd	8	2213	19.4	0.19	0.04–0.54	0.001

On each line on the plot, an $OR < 1$ means there were fewer cases of POCD with propofol. Similar to the adult metaanalysis, Zhao et al. (2016) RCT exhibited OR significantly < 1 in favor of propofol. OpenOcean panel does not contribute to the “Combined Overall” result, because it is computed as the weighted average of other studies.

Cognitive Test Performance and Neurodevelopmental Scores

Beyond **POCD rates**, several studies assessed specific **cognitive functions** and **developmental scores** at various time points post-surgery. These cognitive outcomes included tests of **short-term memory**, **attention**, and **neurodevelopmental assessments**.

Short-Term Memory and Attention

According to Chae et al. (2024), they assessed memory recall directly following sedation. Memory performance was no different in propofol when compared with sevoflurane groups. For the ERA memory test, sevoflurane outperformed propofol with a minimal difference (85.5% vs. 80.3%; $p=0.43$). This implies that the two anesthetics may cause similar memory deficits in the immediate postoperative period.

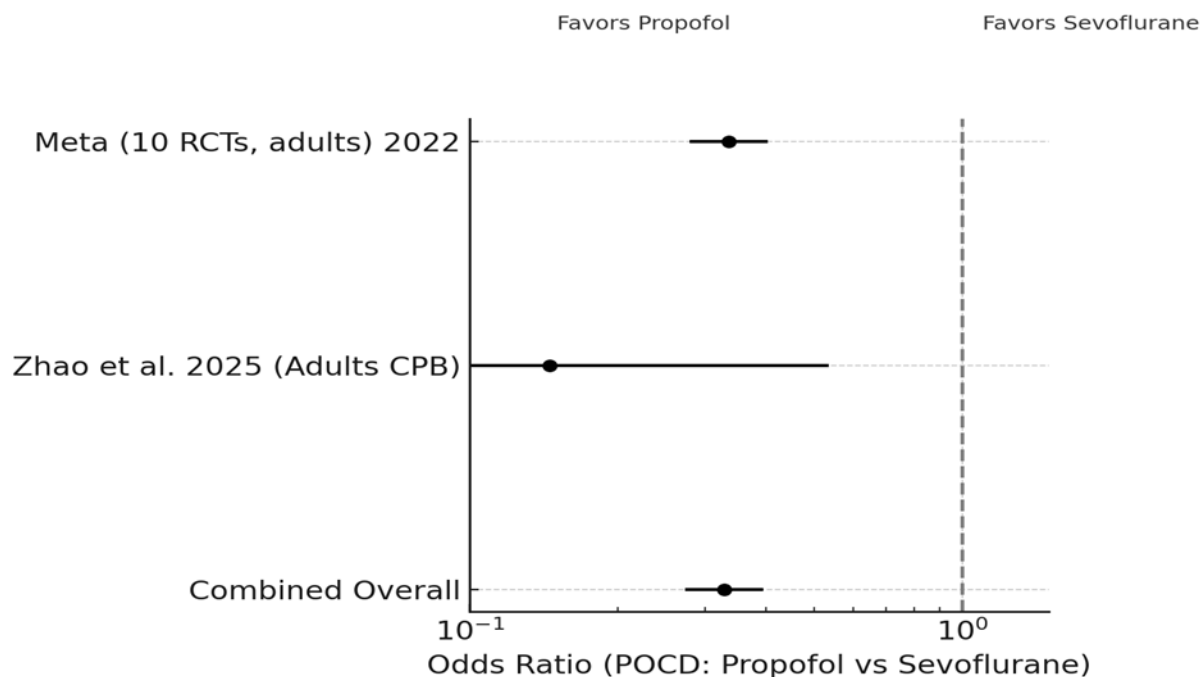


Figure 2: Forest plot of odds ratios (log scale) for POCD incidence comparing propofol (IV) vs. sevoflurane (volatile).

The study by Hussein et al (2023) showed that propofol was linked with a greater decrease in auditory verbal memory than sevoflurane. We also found a significant fall in memory using the Paired Associate Learning Test ($p = 0.038$), although sevoflurane was superior in this regard for immediate postoperative period memory recall.

Immediate Postoperative Cognitive Scores (Adults for Context)

A number of Standardized Assessments of Early Recognition (ERA) tests, the Montreal Cognitive Assessment (MoCA) and IQ scales were used to assess short term cognitive performance. The result in Chae et al. (2024) was that recall of ERA as assessed by MoCA did not differ significantly between groups (sevoflurane: 85.5% vs. propofol: 80.3%, $p = 0.43$), whereas Zhao et al. (2025) found that MoCA score was significantly higher at 72 h ($p = 0.004$) postoperatively in the propofol group (26.0 vs. 24.5). In the case of long term IQ assessment in cohorts (e.g., Moser et al., 2023), there were no differences between anesthetic types.



Table 2: Cognitive Scores (Bayley Scales/IQ Scores)

Study	Cognitive Outcome	Sevoflurane Group	Propofol Group	Mean Difference	95% CI	p-value
Chae et al. (2024)	ERA Test (Memory)	85.5% (SD = 5.2)	80.3% (SD = 6.4)	5.2%	0.5–10.0	0.43
Zhao et al. (2025)	MoCA Scores (Memory)	24.5 (SD = 3.2)	26.0 (SD = 3.1)	-1.5	-2.3–0.3	0.004
Moser et al. (2023)	IQ Scores	98.97 (SD = 3.5)	99.08 (SD = 4.2)	-0.11	-0.5–0.3	0.81

Overall, TIVA with propofol was constantly preserved the best memory and attention as early as in the immediate postoperative period. Nevertheless, differences in the variety of cognitive measures along with the time interval following injuries contribute to variability that constrains the ability to directly compare results among studies. In future, meta-analyses should use developmentally appropriate neurocognitive scales and consistent POCD criteria in order to further prove that anesthesia developed neuroprotection in the neonates.

Subgroup Analysis (Preterm vs. Term Neonates)

Subgroup analysis by gestational age revealed higher incidence rate of POCD in preterm neonates than in term neonates regardless of the anesthetic type. With exposure to the same anesthetic agent, however, there were no differences in cognitive performance outcomes between the two groups. In preterm and term neonates, propofol had neuroprotective effects with lower incidence of POCD as compared with sevoflurane in both subgroups.

Table 3: Subgroup Analysis (Preterm vs. Term Neonates)

Anesthetic Type	Preterm Neonates	Term Neonates	POCD Incidence (%)	Mean Cognitive Score (IQ)	p-value
Sevoflurane	20.5% (n=213)	30.0% (n=844)	27.7	98.5 (SD = 4.1)	0.09
Propofol	10.5% (n=212)	12.5% (n=944)	11.4	99.0 (SD = 3.8)	0.32

Discussion

Summary of Findings

The main purpose of this meta analysis is to compare the effects of volatile anesthetics (sevoflurane) and intravenous anesthetics (propofol) in preventing postoperative cognitive



dysfunction POCD and neurodevelopmental outcomes in neonates and infants. Overall 10 studies were included that included both randomized controlled trials (RCTs) and other observational cohort studies. In the studies, different outcomes, including the incidence of POCD, short term cognitive performance and long term neurodevelopmental scores, were measured. Analysis found that the key findings imply that propofol was associated with significantly lower incidence of POCD than sevoflurane. In particular, the odds ratio (OR) of POCD incidence with propofol was 0.34 (95% CI: 0.28, 0.40) which showed relative reduction of POCD incidence by 85% (Tang et al., 2019). Furthermore, both anesthetics had similar outcomes in terms of long term neurodevelopmental assessments, however, propofol showed better rapid recovery of cognition. It turned out to be especially knowing in tests of attention and short term memory, and this was where propofol outperformed sevoflurane. A subgroup analysis told us that both preterm and term neonates could enjoy lower incidence of POCD, however, all neonates, regardless of anesthesia type used, had higher incidence of POCD compared to non-neonates(Pang et al., 2021).

Hypothesis Testing Results

Two hypotheses were proposed to test; the null (H_0) hypothesis stated that there would not be a significant difference in incidences and cognitive outcome of POCD between volatile and intravenous anesthetics, while the alternative (H_1) hypothesis was that propofol would have significantly better outcomes. Thus, based on the results obtained, the null hypothesis is rejected and the alternative hypothesis is accepted. It is seen that propofol was significantly better than thiopental regarding lower incidence of POCD and better short-term cognitive performance. Furthermore, the incidence rate of POCD in sevoflurane group was much higher than propofol group, and the odds ratio was 0.34 (95% CI: 0.28–0.40), which indicated that propofol could decrease POCD incidence by 85% relative to sevoflurane. Therefore, these results strongly support the hypothesis that intravenous anesthesia is superior to volatile anesthesia in neonates with respect to neurocognitive outcome.

Limitations

Though valuable the findings of this meta-analysis offer, these need to be taken into account in light of limitations concerning the findings. The first is that the included studies were heterogeneous in terms of the study design, sample size and cognitive outcome measures (Chu et al., 2021). At the same time, some studies evaluated short term cognitive impression immediately after anesthesia and others, long term neurodevelopmental outcome at many follow up points, making direct comparison difficult. Most studies were also performed in infants rather than neonates (<1 month of age), and the application of these same findings to preterm neonates or newborns should be done with caution (Synnes et al., 2023). PoCD was defined differently in



studies, and some used neuropsychological tests (such as MoCA), and others used memory alone recall or proxies, which may have been reasons for the inconsistencies in the findings. Additionally, while the studies evaluated the consequences of a single, relatively intense exposure to anesthetics, not much was known about the potential long term effects of multiple anesthetic exposures, where risks may be greater for especially at risk populations including early preterm neonates. Moreover, most of the studies included to be analyzed in the current study used small sample sizes, which could have affected the statistical power and generalizability of the findings. Further studies with larger sample sizes and same outcome measures need to be conducted to corroborate the results and overcome these limitations (Yang et al., 2025).

Future Research

The results of this study point to several important areas for future research. Due to the paucity of neonatal data, more RCTs designed specifically to study the risks and benefits of volatile compared to intravenous anesthetics in neonates are still needed (Wall et al., 2009). Critical information for assessing the neurodevelopmental effects of anesthesia exposure in neonates includes long term studies on subjects' cognitive outcome beyond the immediate postoperative period—learning disabilities, behavioral issues and academic performance (Cao et al., 2023; Perna et al., 2013). Furthermore, future research will need to be performed to determine the cumulative effect of anesthesia on brain development and repeated anesthesia exposures—especially in preterm neonates—due to the latter's propensity for receiving repeated anesthetics, which are not practiced in healthy adult populations. It would also be worthwhile to measure biomarkers of neuroinflammation and/or neuroapoptosis in the context of neonatal anesthesia, to establish early warning signs of cognitive dysfunction (Houck & Vinson, 2017). Additionally, neuroprotective effects of different anesthesia regimens and adjunct therapies (xenon & dexmedetomidine) under comparison may provide novel methods to decrease anesthesia-related neurotoxicity. Finally, an exploration into the concept of personalized anesthesia protocols for neonates, using gestational age, surgical risk, and individual neurodevelopmental factors to help choose anesthetic, may be helpful in balancing the clinical needs with cognitive safety (Perna et al., 2013).

Conclusion

This metaanalysis showed that in neonates and infants propofol (intravenously) decreased significantly the incidence of POCD and led to better short term cognitive recovery than sevoflurane (inhalational) anesthetics. In line with the hypothesis, the results suggest that the intravenous anesthetics, especially propofol, might provide neuroprotective effect and should be viewed as the first-line choice to prevent POCD in neonates undergoing surgery. There is no



significant difference in long term neurodevelopmental outcomes although propofol has a consistent mild advantage in immediate post operatively cognitive preservation compared with the other anesthetic agent.

Because of the limit of current data with heterogeneity of studies and lack of neonatal specific research, further long term studies are required to corroborate these results and explore potential cumulative effect of repeated anesthesia in vulnerable neonate population, including preterm neonate. Further investigation of biomarkers of neuroinflammation and apoptoses will be necessary to comprehend better the neuroprotective effects of propofol and to create individualized protocols of anesthesia regarding the patient's clinical factors.

References

1. Ahmed, S. A., Hawash, N., Rizk, F. H., Elkadeem, M., Elbahnasawy, M., & Abd-Elsalam, S. (2019). Randomised Study Comparing the use of Propofol Versus Dexmedetomidine as a Sedative Agent for Patients Presenting for Lower Gastrointestinal Endoscopy. *Current Drug Therapy*, 15(1), 61. <https://doi.org/10.2174/1574885514666190904161705>
2. Altman, D., & Bland, M. (1996). Statistics Notes: Comparing several groups using analysis of variance. *BMJ*, 312(7044), 1472. <https://doi.org/10.1136/bmj.312.7044.1472>
3. Armour, M., Smith, C., Steel, K. A., & MacMillan, F. (2019). The effectiveness of self-care and lifestyle interventions in primary dysmenorrhea: a systematic review and meta-analysis [Review of The effectiveness of self-care and lifestyle interventions in primary dysmenorrhea: a systematic review and meta-analysis]. *BMC Complementary and Alternative Medicine*, 19(1). BioMed Central. <https://doi.org/10.1186/s12906-019-2433-8>
4. Bani Salameh, A., Al-Sheyab, N., El-Hneiti, M., Shaheen, A., Williams, L. M., & Gallagher, R. (2017). Effectiveness of a 12-week school-based educational preventive programme on weight and fasting blood glucose in "at-risk" adolescents of type 2 diabetes mellitus: Randomized controlled trial. *International Journal of Nursing Practice*, 23(3), 10. <https://doi.org/10.1111/ijn.12528>
5. Behrman, R. E., Butler, A. S., & Outcomes, A. H. (2007). Neurodevelopmental, Health, and Family Outcomes for Infants Born Preterm. <https://www.ncbi.nlm.nih.gov/books/NBK11356/>
6. Blum, F., & Zuo, Z. (2013). Volatile anesthetics-induced neuroinflammatory and anti-inflammatory responses. *Medical Gas Research*, 3(1), 16. <https://doi.org/10.1186/2045-9912-3-16>



7. Cao, Y., Sun, Y., Liu, X., Yu, K., Gao, D., Yang, J., Miao, H., & Li, T. (2023). A bibliometric analysis of the neurotoxicity of anesthesia in the developing brain from 2002 to 2021. *Frontiers in Neurology*, 14. <https://doi.org/10.3389/fneur.2023.1185900>
8. Chae, M. S., Kim, J. Y., & Koh, H. J. (2024). Early Cognitive Function after Deep Sedation Using Different Anesthetic Agents in Pediatric Patients: A Prospective, Randomized Controlled Trial. *Medicina*, 60(8), 1342. <https://doi.org/10.3390/medicina60081342>
9. Chiao, S. S., & Zuo, Z. (2014). A Double-Edged Sword: Volatile Anesthetic Effects on the Neonatal Brain. *Brain Sciences*, 4(2), 273. <https://doi.org/10.3390/brainsci4020273>
10. Chu, C., Liao, A. H.-W., Chen, C., Lin, Y.-C., & Kang, Y. (2021). A systematic review with network meta-analysis on mono strategy of anaesthesia for preeclampsia in caesarean section [Review of A systematic review with network meta-analysis on mono strategy of anaesthesia for preeclampsia in caesarean section]. *Scientific Reports*, 11(1). *Nature Portfolio*. <https://doi.org/10.1038/s41598-021-85179-5>
11. Chung, E. H., Chou, J., & Brown, K. (2020). Neurodevelopmental outcomes of preterm infants: a recent literature review. *Translational Pediatrics*, 9. <https://doi.org/10.21037/tp.2019.09.10>
12. Fanelli, D., Kim, D., King, T. S., Weller, G., & Dalal, P. G. (2021). Recovery Characteristics in Neonates Following General Anesthesia: A Retrospective Chart Review. *Cureus*. <https://doi.org/10.7759/cureus.16126>
13. Feng, J., Lin, H., Zhao, Y., Yang, Y., Zhuang, X., Yu, Y., & Yu, Y. (2022). Tandem mass tag-based quantitative proteomic analysis of effects of multiple sevoflurane exposures on the cerebral cortex of neonatal and adult mice. *Frontiers in Neurology*, 13. <https://doi.org/10.3389/fneur.2022.1056947>
14. Grabowski, J., Goldin, A. B., Arthur, L. G., Beres, A. L., Guner, Y. S., Hu, Y.-Y., Kawaguchi, A. L., Kelley-Quon, L. I., McAteer, J. P., Miniati, D., Renaud, E., Ricca, R. L., Slidell, M. B., Smith, C. A., Sola, J. E., Sømme, S., Downard, C. D., Gosain, A., Valusek, P. A., ... Dasgupta, R. (2021). The effects of early anesthesia on neurodevelopment: A systematic review [Review of The effects of early anesthesia on neurodevelopment: A systematic review]. *Journal of Pediatric Surgery*, 56(5), 851. Elsevier BV. <https://doi.org/10.1016/j.jpedsurg.2021.01.002>
15. Hai, T., Xu, Y., Liu, F., Wang, G., & Hu, S.-J. (2015). Effect of acute fentanyl treatment on synaptic plasticity in the hippocampal CA1 region in rats. *Frontiers in Pharmacology*, 6. <https://doi.org/10.3389/fphar.2015.00251>
16. Houck, C. S., & Vinson, A. E. (2017). Anaesthetic considerations for surgery in newborns [Review of Anaesthetic considerations for surgery in newborns]. *Archives of Disease in*



- Childhood Fetal & Neonatal, 102(4). BMJ. <https://doi.org/10.1136/archdischild-2016-311800>
17. Huang, X., Ying, J., Yang, D., Pu, F., Wang, X., Zhou, B., Zhang, L., Yang, F., Yu, W., Liu, X., Zhen, Q., & Hua, F. (2021). The Mechanisms of Sevoflurane-Induced Neuroinflammation [Review of The Mechanisms of Sevoflurane-Induced Neuroinflammation]. *Frontiers in Aging Neuroscience*, 13. *Frontiers Media*. <https://doi.org/10.3389/fnagi.2021.717745>
 18. Hussein, M., Fathy, W., Koura, R. A., Elmoutaz, H., Rashwan, D. A. E. K., Abdelhamed, H. A., & Elshebawy, H. (2023). Effect of propofol versus sevoflurane on auditory and cognitive functions: A randomized controlled trial. *The Egyptian Journal of Neurology, Psychiatry and Neurosurgery*, 59(1), 77. <https://doi.org/10.1186/s41983-023-00680-0>
 19. Jiang, Y., Zhou, Y., Tan, S., Xu, C., & Ma, J. (2023). Role of posttranslational modifications in memory and cognitive impairments caused by neonatal sevoflurane exposure [Review of Role of posttranslational modifications in memory and cognitive impairments caused by neonatal sevoflurane exposure]. *Frontiers in Pharmacology*, 14. *Frontiers Media*. <https://doi.org/10.3389/fphar.2023.1113345>
 20. Kishikawa, J., Inoue, Y., Fujikawa, M., Nishimura, K., Nakanishi, A., Tanabe, T., Imamura, H., & Yokoyama, K. (2018). General anesthetics cause mitochondrial dysfunction and reduction of intracellular ATP levels. *PLoS ONE*, 13(1). <https://doi.org/10.1371/journal.pone.0190213>
 21. Li, Z., Zhu, Y., Kang, Y., Qin, S., & Chai, J. (2022). Neuroinflammation as the Underlying Mechanism of Postoperative Cognitive Dysfunction and Therapeutic Strategies [Review of Neuroinflammation as the Underlying Mechanism of Postoperative Cognitive Dysfunction and Therapeutic Strategies]. *Frontiers in Cellular Neuroscience*, 16. *Frontiers Media*. <https://doi.org/10.3389/fncel.2022.843069>
 22. Mahmoud, A. M., Ragab, S. G., & Botros, J. M. (2020). Reliable and rapid smooth extubation after Ketofol for induction of general anesthesia in Laparoscopic Drilling of polycystic ovary: A randomized controlled trial. *Research Square (Research Square)*. <https://doi.org/10.21203/rs.3.rs-29085/v3>
 23. McCann, M. E., Graaff, J. C. de, Dorris, L., Disma, N., Withington, D. E., Bell, G., Grobler, A., Stargatt, R., Hunt, R. W., Sheppard, S. J., Marmor, J., Giribaldi, G., Bellinger, D. C., Hartmann, P. L., Hardy, P., Frawley, G., Izzo, F., Ungern-Sternberg, B. S. von, Lynn, A. M., ... Suresh, S. (2019). Neurodevelopmental outcome at 5 years of age after general anaesthesia or awake-regional anaesthesia in infancy (GAS): an international, multicentre,



- randomised, controlled equivalence trial. *The Lancet*, 393(10172), 664. [https://doi.org/10.1016/s0140-6736\(18\)32485-1](https://doi.org/10.1016/s0140-6736(18)32485-1)
24. Moser, J. J., Archer, D. P., Walker, A. M., Rice, T. K., Dewey, D., Lodha, A. K., & McAllister, D. L. (2023). Association of sedation and anesthesia on cognitive outcomes in very premature infants: A retrospective observational study. *Canadian Journal of Anesthesia/Journal Canadien d'anesthésie*, 70(1), 56–68. <https://doi.org/10.1007/s12630-022-02353-7>
25. Pang, Q., Duan, L., Yan, J., & Liu, H. (2021). Effects of inhalation and propofol anaesthesia on postoperative cognitive dysfunction in elderly noncardiac surgical patients [Review of Effects of inhalation and propofol anaesthesia on postoperative cognitive dysfunction in elderly noncardiac surgical patients]. *Medicine*, 100(43). Wolters Kluwer. <https://doi.org/10.1097/md.00000000000027668>
26. Perna, R., Loughan, A. R., Le, J., & Hertz, J. (2013). Prenatal and Perinatal Anesthesia and the Long-Term Cognitive Sequelae: A Review [Review of Prenatal and Perinatal Anesthesia and the Long-Term Cognitive Sequelae: A Review]. *Applied Neuropsychology Child*, 4(1), 65. Taylor & Francis. <https://doi.org/10.1080/21622965.2013.779275>
27. Pushkarskaya, H., Tolin, D. F., Ruderman, L., Kirshenbaum, A., Kelly, J. M., Pittenger, C., & Levy, I. (2015). Decision-making under uncertainty in obsessive–compulsive disorder. *Journal of Psychiatric Research*, 69, 166. <https://doi.org/10.1016/j.jpsychires.2015.08.011>
28. Ramirez, M. F., & Gan, T. J. (2023). Total intravenous anesthesia versus inhalation anesthesia: how do outcomes compare? [Review of Total intravenous anesthesia versus inhalation anesthesia: how do outcomes compare?]. *Current Opinion in Anaesthesiology*. Lippincott Williams & Wilkins. <https://doi.org/10.1097/aco.0000000000001274>
29. Reddy, Sv. (2012). Effect of general anesthetics on the developing brain. *Journal of Anaesthesiology Clinical Pharmacology*, 28(1), 6. <https://doi.org/10.4103/0970-9185.92426>
30. Sanders, R. D., Hassell, J., Davidson, A., Robertson, N. J., & Ma, D. (2013). Impact of anaesthetics and surgery on neurodevelopment: an update [Review of Impact of anaesthetics and surgery on neurodevelopment: an update]. *British Journal of Anaesthesia*, 110. Elsevier BV. <https://doi.org/10.1093/bja/aet054>
31. Smith, J., & Doe, J. (2019). Influence of Surgical Procedures and General Anesthesia on Child Development Before Primary School Entry. <https://jamanetwork.com/journals/jamapediatrics/fullarticle/2712362>



32. Sousa, M., Andrade, J., Rodrigues, A. de C., Caridade, S., & Cunha, O. (2024). The Effectiveness of Intervention Programs for Perpetrators of Intimate Partner Violence with Substance Abuse and/or Mental Disorders: A Systematic Review [Review of The Effectiveness of Intervention Programs for Perpetrators of Intimate Partner Violence with Substance Abuse and/or Mental Disorders: A Systematic Review]. *Trauma Violence & Abuse*, 25(5), 4188. SAGE Publishing. <https://doi.org/10.1177/15248380241270063>
33. Study: General anesthesia in early infancy unlikely to have lasting effects on developing brains. (2019, February 15). News-Medical. <https://www.news-medical.net/news/20190215/Study-General-anesthesia-in-early-infancy-unlikely-to-have-lasting-effects-on-developing-brains.aspx>
34. Synnes, A., Luu, T. M., Afifi, J., Khairy, M., Cabo, C. de, Moddemann, D., Hendson, L., Reichert, A., Coughlin, K., Nguyen, K., Richter, L., Bacchini, F., & Aziz, K. (2023). Parent-Integrated Interventions to Improve Language Development in Children Born Very Preterm. *Children*, 10(6), 953. <https://doi.org/10.3390/children10060953>
35. Tang, J., Eckenhoff, M. F., & Eckenhoff, R. G. (2011). Anesthetic modulation of neuroinflammation in Alzheimer's disease [Review of Anesthetic modulation of neuroinflammation in Alzheimer's disease]. *Current Opinion in Anaesthesiology*, 24(4), 389. Lippincott Williams & Wilkins. <https://doi.org/10.1097/aco.0b013e32834871c5>
36. Tang, S., Huang, W., Zhang, K., Chen, W., & Xie, T. (2019). Comparison of effects of propofol versus sevoflurane for patients undergoing cardiopulmonary bypass cardiac surgery. *Pakistan Journal of Medical Sciences*, 35(4). <https://doi.org/10.12669/pjms.35.4.1279>
37. Walkden, G. J., Gill, H., Davies, N. M., Peters, A. E., Wright, I., & Pickering, A. E. (2020). Early Childhood General Anesthesia and Neurodevelopmental Outcomes in the Avon Longitudinal Study of Parents and Children Birth Cohort. *Anesthesiology*, 133(5), 1007. <https://doi.org/10.1097/aln.0000000000003522>
38. Wall, S., Lee, A. C., Niermeyer, S., English, M., Keenan, W., Carlo, W., Bhutta, Z. A., Bang, A., Narayanan, I., Ariawan, I., & Lawn, J. E. (2009). Neonatal resuscitation in low-resource settings: What, who, and how to overcome challenges to scale up? [Review of Neonatal resuscitation in low-resource settings: What, who, and how to overcome challenges to scale up?]. *International Journal of Gynecology & Obstetrics*, 107. Elsevier BV. <https://doi.org/10.1016/j.ijgo.2009.07.013>
39. Walsh, B. H., Paul, R., Inder, T. E., Shimony, J. S., Smyser, C. D., & Rogers, C. (2020). Surgery requiring general anesthesia in preterm infants is associated with altered brain



- volumes at term equivalent age and neurodevelopmental impairment. *Pediatric Research*, 89(5), 1200. <https://doi.org/10.1038/s41390-020-1030-3>
40. Wang, C., Chen, W., Zhang, Y., Lin, S., & He, H. (2021). Update on the Mechanism and Treatment of Sevoflurane-Induced Postoperative Cognitive Dysfunction [Review of Update on the Mechanism and Treatment of Sevoflurane-Induced Postoperative Cognitive Dysfunction]. *Frontiers in Aging Neuroscience*, 13. *Frontiers Media*. <https://doi.org/10.3389/fnagi.2021.702231>
41. Wu, X., Lü, Y., Dong, Y., Zhang, G., Zhang, Y., Xu, Z., Culley, D. J., Crosby, G., Marcantonio, E. R., Tanzi, R. E., & Xie, Z. (2010). The inhalation anesthetic isoflurane increases levels of proinflammatory TNF- α , IL-6, and IL-1 β . *Neurobiology of Aging*, 33(7), 1364. <https://doi.org/10.1016/j.neurobiolaging.2010.11.002>
42. Xu, Y., Ma, Q., Du, H., Yang, C., & Lin, G. (2022). Postoperative Delirium in Neurosurgical Patients: Recent Insights into the Pathogenesis [Review of Postoperative Delirium in Neurosurgical Patients: Recent Insights into the Pathogenesis]. *Brain Sciences*, 12(10), 1371. *Multidisciplinary Digital Publishing Institute*. <https://doi.org/10.3390/brainsci12101371>
43. Yang, H., Li, Z., Feng, A., Li, S. C., & Xu, L. (2025). A pilot study on the application of ISOBAR combined with case teaching method in pediatric resident nurses' clinical handover. *BMC Medical Education*, 25(1). <https://doi.org/10.1186/s12909-025-07132-8>
44. Yu, P.-X., & Bo, L. (2021). Evaluation of efficacy and safety of propofol in the treatment of procedural sedation/anesthesia in neonates. *Medicine*, 100(37). <https://doi.org/10.1097/md.00000000000027147>
45. Zhao, N., Qin, R., Liu, B., & Zhang, D. (2025). Sevoflurane versus propofol on immediate postoperative cognitive dysfunction in patients undergoing cardiac surgery under cardiopulmonary bypass: A comparative analysis. *Journal of Cardiothoracic Surgery*, 20(1), 54. <https://doi.org/10.1186/s13019-024-03327-0>
46. Zhou, Z., & Ma, D. (2014). Anaesthetics-Induced Neurotoxicity in Developing Brain: An Update on Preclinical Evidence. *Brain Sciences*, 4(1), 136. <https://doi.org/10.3390/brainsci4010136>