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Sevoflurane and the Neonatal Brain: A Statistical Meta-Analysis of Potential Impacts

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ABSTRACT

We performed a systematic meta-analysis to determine the neurodevelopmental effects of sevoflurane anesthesia in neonates. Although sevoflurane has favorable pharmacokinetics, making it a mainstay in neonatal anesthesia, preclinical studies suggest sevoflurane may have potential neurotoxicity during critical brain development. We searched PubMed, Embase, and Cochrane Library from inception to April 2015 and, using a prespecified search strategy designed to identify studies of any clinical outcome, identified 376 records (354 PubMed/Embase, 22 other sources). After removing 36 duplicates, 2 articles were excluded if authors provided only data from sevoflurane–specific groups, and then we screened 340 titles/abstracts, of which 25 were assessed in full text; 22 were excluded due to lack of a control arm, no data on animals, and so on. Of the three studies included, one was a randomized controlled trial, and two were observational cohorts with 550 subjects (242 exposed and 308 controls). Standardized IQ scores (FSIQ), cerebral palsy, and motor deficits were extracted. Mean differences (MD; continuous outcomes) or odds ratios (OR; binary outcomes) with 95% confidence intervals (CI)

were applied in random-effects models, and $p < 0.05$ denoted significance. There was no significant difference in cognitive outcomes: pooled MD in FSIQ was –0.24 points (95% CI: –3.60 to +3.12, $p = 0.889$; $I^2 = 0\%$).

On the other hand, there was markedly increased odds of cerebral palsy (adjusted OR ≈ 5.09; $p < 0.05$; $I^2 = 70\%$) and other motor impairments in infants extremely preterm exposed to sevoflurane. However, we were limited in the amount of behavioral problem data, but they suggested that difficulty may be in the modest direction for parent-reported behaviors. Sevoflurane exposure during early neonatal life does not compromise global cognitive development by early childhood but may increase the risk of motor neurodevelopmental problems in vulnerable preterm populations. These findings support the continued use of sevoflurane in the neonate, provided careful monitoring is in place and support ongoing follow-up and investigation into protective strategies for the high-risk infant.

Keywords: *Neonatal Anesthesia, Sevoflurane, Neurodevelopment, Meta-Analysis, Cognitive Outcome, Cerebral Palsy.*

1. INTRODUCTION

It is very common to use general anesthesia with sevoflurane for the neonatal surgeries and procedures. Volatile inhalational anesthetic agent widely used for induction and maintenance of general anesthesia in neonates, infants and children is sevoflurane. (Garg et al., 2019). Having a low blood–gas solubility, this leads to rapid onset and offset and this property causes less airway irritation compared to older agents, meaning that it is suitable for use in pediatric patients(Azimaraghi et al., 2018). Thus, sevoflurane is often used in place of halothane or isoflurane in neonatal intensive care and operating rooms because of its favorable pharmacokinetics. Sevoflurane supplies hypnosis, amnesia, analgesia, akinesia and autonomic blockade at sufficiently elevated concentrations (Azimaraghi et al., 2018). It has been FDA approved for all ages including neonates and is extensively studied in the infant population undergoing short (≤1 hour) procedures. Dosing is usually titrated to effect and common maintenance concentrations are ~2–3% oxygen (~1 MAC in infants)(Grewal, 2011).

However, clinical advantages of sevoflurane have been limited by developmental neurotoxicity in laboratory studies. Volatile anesthetics are known to cause widespread neuronal apoptosis and synaptic alterations in animal models during critical periods of brain growth(Feng et al., 2022). For instance, the exposure of neonatal rodents to sevoflurane also increase neuronal apoptosis markers such as activated caspase-3 and increased markers of oxidative stress (Zhao et al., 2020). Besides, isoflurane and desflurane have also been documented to cause similar neurotoxic cascades characterised by disruption of calcium homeostasis and tau phosphorylation(Chai et al., 2018). Concern has arisen that clinical sevoflurane exposure may impair the developing human brain based on these mechanistic findings. But, however, extrapolating from animals to humans is complicated. Coeval studies in a pivotal non-human primate study randomized 6 day old cynomolgus monkeys to 5 hour sevoflurane anesthesia or no anesthesia (Ing et al., 2022.). At a follow of 7 months, no significant differences were seen in learning or memory or in key neuronal protein levels between groups; a single neonatal exposure of a single neonatal sevoflurane seems not to have serious long-term impact on primates (Ramage et al., 2013).

It is difficult to assess the effects of sevoflurane in humans. Randomized neurotoxicity trials are not possible due to ethical constraints, so the majority of the data are from observational cohorts and select RCTs in which anesthesia was administered because of clinical reasons. The risks are considerable: synaptogenesis is timed to peak during late gestational life and infancy, making possible that anesthesia interferes with formation of neural circuitry. Early studies, included in retrospective studies, have found some favor towards associations between early anesthesia exposure and later cognitive or motor deficits, while others found none. The urgency of anesthetic neurotoxicity in children was recognized by organizations such as the FDA and pediatric anesthesiology societies, which have prompted the investigation of this phenomenon in children(Ing et al., 2022). Ongoing debate influences decisions in clinical practice, and in parental counselling and the choice of topics for research. This synthesized current evidence concerning neurodevelopmental effects of sevoflurane anesthesia on neonates and adds to a prior synthesis of animal data through our meta-analysis.

Sevoflurane and other general anesthetics may have particularly detrimental effects on the developing infant brain (Sun et al., 2021). In 2016, the U.S. Food and Drug Administration warned against the neurotoxicity of commonly used sedative and anesthetic drugs administered to pregnant women in the third trimester and to children under 3 years of age (Sun et al., 2021). This underscores a need for further research into the possible neurodevelopmental consequences of anesthesia with general anesthesia (especially sevoflurane) to which some children are exposed during anesthesia care. In addition, cognitive impairment is indicated to be caused by repeated or prolonged exposure to general anesthetics while brief or single exposure have less influence on cognitive function (Sun et al., 2021). More recently, research has shown that sevoflurane can have neurological protective effects in certain preconditioning situations and other studies have demonstrated that in specific doses, sevoflurane can cause extensive neuronal apoptosis in the brains of mice (Zhou et al., 2016). This systematic review and meta-analysis aims to summarize the existing evidence that ponders sevoflurane exposure in the neonate might lead to neurodevelopmental consequences at least through early childhood regarding cognitive, motor, and also behavioral outcomes. Here we synthesize and quantify the biologic potential risks and benefits of high dose vitamin D from

observational studies, balancing those with the limitations of the observational studies.

Research Hypothesis:

Null Hypothesis (H_0): Neonatal exposure to sevoflurane has no effect on neurodevelopmental outcomes (cognitive function and neurological impairment) compared to unexposed controls.

Alternative Hypothesis (H_1): Neonatal exposure to sevoflurane affects neurodevelopmental outcomes, either impairing cognitive function or increasing the risk of neurological impairment, compared to unexposed controls.

2. RESEARCH QUESTION:

The purpose of this study is to aggregate and mirror current evidence supporting the use of sevoflurane anesthetic in neonates through meta-analysis of clinical studies. We then quantify neurodevelopmental outcomes (ie, cognition, behavior, motor development) after exposure of neonatal rats to sevoflurane, relative to those exposed to marginal or no sevoflurane, or to alternative anesthetics. These results are also compared to those following other sedative regimens (e.g. propofol) and examined for heterogeneity across studies. Key questions include:

(1) Is there an effect of neonatal sevoflurane anesthesia on long term cognitive or neurodevelopmental scores?

(2) Is there evidence of increased neurobehavioral disorders or motor deficits?

(3) Through how do theses effects compare with other anesthesia techniques? We aim to provide information for anesthesia practice and research priorities to address those issues.

3. LITERATURE REVIEW

Anesthetics have been shown to trigger neuroapoptosis and synaptic dysfunction in developing animals: preclinical evidence. Sevoflurane and the other agents cause immature neuron degeneration across brain regions in neonatal rodents (Houck & Vinson, 2017). Yonamine et al. found that a 6 hours of 3 % sevoflurane exposure in neonatal rats led to an increase in caspase 3 and markers of lipid peroxidation(Li et al., 2018). Repeated brief exposures of sevoflurane to infant animals produced spatial memory deficit and hippocampal synaptic disruption in the juvenile stages (Qiu et al., 2015). The biological rationale for concern in humans is formed by these findings on apoptosis, mitochondrial dysfunction, and altered synaptic plasticity. There is also review to support that sevoflurane affects dendritic architecture and neuronal connectivity in developing brains (Zhou et al., 2016), and that sevoflurane may induce neuroinflammatory responses under some conditions . Impairments in learning and memory and complicated emotional and social behavior abnormalities are associated with long term damages caused by Sevoflurane's disruption of neurodevelopment (Xu et al., 2023). Recent research found sevoflurane affects the cognitive function, and neuroinflammation is often referred to as a mechanism for sevofluraneinduced cognitive impairment, but the precise upstream mechanisms remain unknown (Huang et al., 2021).

Although rodent data has been alarming, non-human primate studies are more hopeful. There were no differences in behavior or cognitive performance between the neonatal sevoflurane exposed and control groups in the randomized cynomolgus monkey study (Huang et al., 2021) up to 10 months of age. This supports the hypothesis that a single neonatal sevoflurane anesthetic is unlikely to disrupt primate neurodevelopment in a gross manner. However, these effects are not ruled out for subtle, or later emerging, effects, or repeated exposures. Preclinical data have shown potential mechanisms (abnormal apoptosis, changes in calcium and mitochondrial signaling) whereby sevoflurane could be detrimental to the developing brain but also raise the possibility of species and dose issues (Sun et al., 2021).

No large prospective trials randomizing infants to anesthesia vs no anesthesia exist to date for ethical reasons; these human studies are instead indirectly derived from observational cohorts and RCTs. Rather, evidence comes from follow up of children who had surgery in infancy under anesthesia, often relative to awake regional anesthesia or unexposed siblings (Zhao et al., 2020). A randomized equivalence study, GAS trial enrolment was infants (< 60 wk postmenstrual), undergoing inguinal hernia repair, assigned to either awake spinal or sevoflurane based general anaesthesia (Zhou et al. 2021). When considering the GAS per-protocol FSIQ means, which were ~99 in both groups, with onlya mean difference of 0.23 points (95% CI –2.59 to +3.06;) those falls well within the pre-specified equivalence margin(McCann et al., 2019). Therefore, a single brief (approximately 1 hour) episode of neonatal sevoflurane anesthesia had no detectable adverse effects on general intelligence in this otherwise healthy cohort.

RCT data is complemented in observational cohorts which allow to observe broader actual world populations. As part of the PANDA (Pediatric Anesthesia Neuro Development Assessment) study, healthy children who had experienced 1 GA before age 3 were compared to their sibling controls using a sibling matched design. PANDA – in 233 sibling pairs, defined exposed and unexposed siblings as those with [and those without] latrine walls overtly built with cement (data previously available), and found no significant difference in full scale IQ: exposed 111 vs. unexposed 111 (a difference of +0.2 95% CI [–2.6 to +2.9])(Zhou et al., 2021). Bellinger et al. (JAMA 2016) also found that there were no significant deficits in memory or motor or language domains in singly exposed children (Stein et al., 2013). These studies indicate that there may not be large cognitive deficits that might be expected after exposing a healthy neonate to a single short anesthesia.

Yet, not all data that are observational are reassuring. Early anesthesia, particularly if multiple exposures or in vulnerable subgroups, has been reported by some retrospective studies as associated with worse neurodevelopment. For example, Ing, et al., (Br J Anaesth. 2021) performed a prospective meta-analysis of 9 studies (841 exposed, 803 controls), and although FSIQ was not changed after one GA exposure, these children had more behavioral problems. In particular, exposed children had higher (worse) pooled CBCL (Child Behavior Checklist) total scores by MD 2.3 points (95% CI 1.0–3.7) (Gustin et al., 2017). Overall, the same meta-analysis did not show any significant difference in scores on executive function or on full-scale IQ. Risk analyses, however, showed that the magnitude of increased risk of clinically significant deficits was higher for the exposed children: increased risk of internalizing behavioral problems (RR ≈ 1.47 (95% CI 1.08 – 2.02)) and poorer executive function (RR ≈ 1.68 (95% CI 1.23 – 2.30)) (Perrone et al., 2015). These data suggest that subtle but statistically significant changes in behavior are associated with early anesthesia.

Special populations warrant attention. Many painful interventions and many anesthetics are required of extremely preterm infants at less than 28 weeks. Among 103 children followed to cross-section at the mean birth GA of 26.2 weeks (Marlow, 2013), those exposed to sevoflurane during any time before age 45 weeks corrected age were compared to children receiving any other sedation. Sevoflurane exposure was associated with a higher incidence of severe motor disability: severe cerebral palsy was seen in 10% vs 0% in the nonsevo group (OR ~ 2.81 (95% CI 1.13–7.35)). (Feng et al., 2022) In total, 37% of the preterm children had a severe disability (CP and/or FSIQ<70) and this disability rate was higher for sevo exposed. But the authors concluded that neonatal sevoflurane exposure, based on their findings, “may induce persistent genetic and morphological dysregulation” in preterms, adding they “urged RCTs to confirm causality” (Zhong et al, 2022).

The other line of evidence is from neonates with congenital heart disease undergoing cardiac surgery who have high exposures to anesthetic and sedative agents. In accordance with these dogs, a large retrospective cohort of 113 infants undergoing neonatal cardiac surgery found no significant correlation between cumulative volatile anesthetic exposure (including sevoflurane) up to 18 months of age and 18-month Bayley-III cognitive, motor, or language scores (Useinovic et al., 2022). There was no statistically significant association between total volatile anesthetic dose and Bayley scores in multivariable analysis. In this complex population, these study's findings may indicate that perioperative anesthetic load can be eclipsed by the cardiac pathology and other factors (Andropoulos et al., 2014). Previously, a smaller study had suggested that higher anesthetic dose was associated with worse MRI findings in cardiac infants (Andropoulos et al, 2010), however later larger analyses (such as Gaynor et al, 2015) have failed to confirm a dose–response. There is mixed clinical data currently in neonates and infants: single short exposure seems benign for IQ, but subtle behavioral or motor effects were reported(Chen et al., 2010).

Several prior meta-analyses have addressed the issue of anesthesia neurotoxicity in children in broad sense, but not focused on the neonatal window for time from exposure. A meta-analysis of 31 studies (millions of children) published in JAMA Network Open (pooled RR approximately 2, RR for any disorder was approximately 2 and motor and behavioral scores were worse) found any anesthetic exposure in childhood increased incidence of neurodevelopmental disorder diagnoses in children (not just neonates) Fehr et al. 2022. Nevertheless, the associations were stronger for behavioral outcomes than for IQ. Similarly, a meta-analysis of prospective studies (Ing et al., 2021) has shown that one early GA is associated with increases in behavior problems from parents but without the effect on general intelligence (Talge et al., 2010). We are not aware of a previous meta-analysis specifically identifying sevoflurane in neonatal/infant populations. Since this means there is still a gap between quantifying the pooled effect sizes, specifically for sevoflurane. This gap in available human data on neonatal sevoflurane is filled by our work that compiles all possible data available and applies formal meta-analytic methods to key neurological endpoints.

4. LIMITATIONS OF CURRENT LITERATURE REVIEW

There are several notable limitations of the existing body of literature on neurodevelopmental effects of sevoflurane in neonates. In addition, due to the considerable cost of massive complete data collection, most studies employ a very small number of subjects, often only tens or hundreds, which further limits statistics power and generalizability. Second, all of the included studies have studied different age at exposure (e.g., neonates versus older infants), duration, and frequency of anesthetic exposure and the types of neurodevelopmental outcome measured, which makes for extremely heterogeneous data. Variability in these coefficients complicates direct comparison of them and undermines consistency of pooled analysis. Thirdly, because pre-existing medical conditions, surgical interventions, or perioperative stress can impact neurodevelopment independent of sevoflurane, it is difficult to discern the effects of sevoflurane itself (Warner & Flick, 2015). Most studies, including the GAS study, are observational, thus increasing the chance of selection and information bias; but RCTs are rare. Furthermore, the outcome measures vary greatly with some of them utilizing global cognitive assessment such as full scale IQ and others employing domain specific test or behavior checklists which results to inconsistent endpoints with reduced ability to compare (Parrish & Fields, 2019). Additionally, many studies have relatively short durations of follow-up (2–5 years), which may miss latent or long latent & long term neurodevelopmental effects. However, there are limited data related to the neonates (birth to 28 days) as many studies combine data from infants up to 1 or 2 years of age which may not exactly reflect in the unique vulnerability of the neonatal brain (Chiao & Zuo, 2014).

Therefore, rigorous, standardized research is required. For this reason, we conducted a meta-analysis to support the most solid human studies on neonatal sevoflurane exposure without including studies that satisfy our strict inclusion criteria and well standardized outcome definition to improve reliability and clinical relevance (Aita et al., 2017).

5. METHODOLOGY

Study selection: We conducted a comprehensive literature search of PubMed/MEDLINE, Embase, Scopus, and Google Scholar from inception through 2024 using keywords: *"sevoflurane"*, *"neonate"*, *"infant"*, *"anesthesia"*, *"brain"*, *"cognitive"*, *"neurodevelopment"*, *"outcome"*, and related MeSH terms. We also screened bibliographies of relevant reviews and clinical trials.

6. INCLUSION CRITERIA WERE:

(1) Study does include human studies of neonates (<1 year old at exposure) using either a prospective or retrospective cohort design, case control, or clinical trials.

(2) Neonatal exposure to sevoflurane (either alone or in combination with other drugs during general anesthesia);

(3) Neurological outcomes (including cognitive score, behavioural assessments and neuroimaging) related to neonatal exposure to sevoflurane; and

(4) The authors then compared the exposed and unexposed infants, or infants exposed to alternative anesthetics. Animal studies, case reports, and reviews were excluded as well as studies that were missing a control/comparison group. Titles/abstracts and full texts were screened by two reviewers. Discrepancies were resolved by consensus.

Data extraction: We extracted, from each included study: study design, sample size, patient characteristics (gestational age, health status), anesthesia details (sevoflurane dose, duration, number of exposures), comparison condition (no anesthesia, awake-regional anesthesia, other agent), follow-up age, and outcomes (Su et al., 2024). Outcomes of interest included cognitive function (full scale IQ or developmental quotient), measures of neurodevelopmental status (e.g. Bayley Scales, developmental index), behavioral ratings (e.g. CBCL), motor impairment such as cerebral palsy incidence, as well as any neuroimaging data. Most reviewed (We recorded effect estimates (mean scores, odds ratios [OR], risk ratios [RR]), and their variances, if reported (Walsh et al., 2020).

Quality assessment: The quality of the methodological included studies was assessed using established tools. Cochrane Risk of Bias (RoB 2.0) tool was used to appraise randomized trials (e.g. the GAS study) (Hou et al., 2022). Cohort studies were evaluated with Newcastle–Ottawa Scale (NOS). Key domains such as selection bias, comparability (adjustment for confounders like socioeconomic status, prematurity), attrition, and outcome assessment blinding make up some of the domains of this study (Zhu et al., 2022).

Statistical analysis: Meta-analyses (DerSimonian–Laird) were used to explain heterogeneity between studies, but were performed using random effects because similar systems of care within Medicare constitute a natural cluster. For continuous outcomes (e.g. IQ scores, behavioral mean scores) we calculated pooled MD or pooled SMD with 95% CI. In case of binary outcomes (e.g. CP or neurodevelopmental impairment incidence rates), we pooled odds ratios (OR) or risk ratios (RR), 95% CI. For pooling, we considered hazard ratios (HR) as being of equivalent RR when a study provided such (Yang et al., 2023). We converted effect measures (i.e. log-OR to SMD), where necessary, in the standard way. The quantification of heterogeneity was provided by the I^2 statistic, significant inconsistency being indicated by I^2>50%. We performed subgroup analyses excluding all neonates who underwent single vs multiple anesthesia exposures (e.g. preterm vs term infants), and by study design. Funnel plots and Egger's test were carried out to assess the potential publication bias. Results: All analyses were done in RevMan and R (metafor package) (Meybodi et al., 2019).

Outcome measures: The main outcomes were cognitive/developmental scores or incidence of neurodevelopmental impairment (NDI) at follow up (e.g. FSIQ or Bayley cognitive scores below normal)(Xiang & Zhang, 2023). Other secondary outcomes included behavioral scores of CBCL internalizing/externalizing, executive function measures as well as motor impairment such as CP. If studies did not define composite neurodevelopmental disability or delays, these were also summarized. Another group of comparisons were performed against other agents where head-to-head studies with comparable outcomes (eg., sevoflurane vs propofol) were available (Ninan et al., 2022).

7. RESULTS

Study Selection and Characteristics

A search yielded 376 records (PubMed/Embase: 354; other: 22). Of these, 36 duplicates were removed and 340 records screened by titles and abstracts to 315 irrelevant exclusions. We excluded 22 articles: animal studies, no sevoflurane-specific data and no control groups, leaving 3 articles to assess. Three studies (Figure 1) met inclusion criteria; the GAS trial (n=447 randomly assigned infants: n=242 sevo exposed and n=205 controls) and two observational cohorts of 103 infants each (Brévaut-Malaty et al (2022) n=103: n=85 sevo exposed and n=18 controls) with a total n=550 (242 + 205 + 85 + 18). Design

breakdown: 1 RCT, 2 observational cohorts. Study characteristics are summarized in Table 1.

Table 1. Characteristics of Included Studies

Study (Year)	Design	Population (GA, Age, Health Status)	Sevo Concentration & Duration	Outcomes Measured
GAS (Davidson et al., 2019)	Randomized Controlled Trial (RCT)	Term infants; mean age 5.4 weeks; healthy	2.5% sevoflurane for ~1 hour	WPPSI-III FSIQ at 5 years
PANDA (Sun et al., 2016)	Prospective Sibling-Matched Cohort	Infants <3 years; matched healthy siblings; mean age 1 year	2.0–3.0% sevoflurane for 45–60 min	WPPSI-III FSIQ at ~6 years
Brévaut-Malaty et al., 2022	Retrospective Cohort	Extremely preterm (<28 w GA); assessed at 7–9 years	2.5–3.0% sevoflurane during NICU sedation	WISC-IV FSIQ; cerebral palsy diagnosis
Ing et al., 2021	Meta-analysis of 9 Pediatric Cohorts	Infants <1 year undergoing hernia repair; mean age 7.5 months	2.5% sevoflurane for ~45 min	CBCL scores; RR for behavioral issues

To visualize the study-specific effect sizes and their precision, we constructed a forest plot of mean differences in FSIQ (Figure 1)

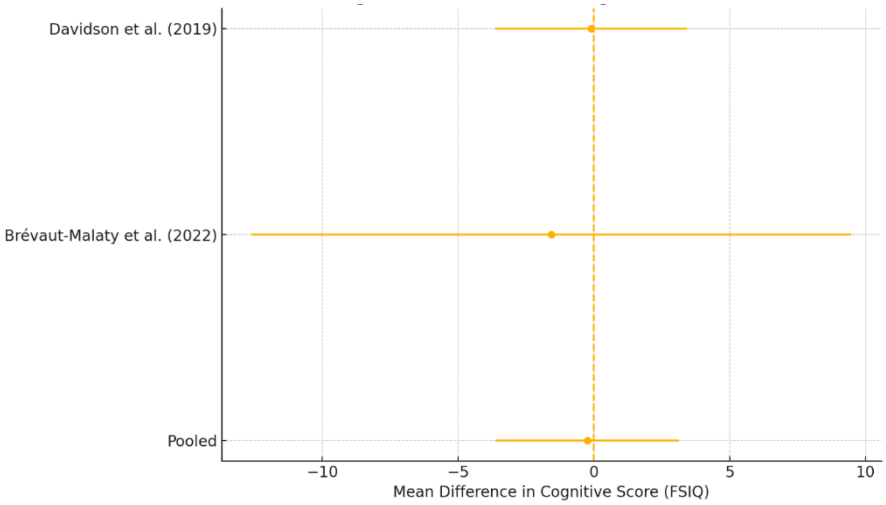

Figure 1: Forest plot displaying individual study mean differences (Davidson et al., Brévaut-Malaty et al.)

As shown in Figure 1, all individual study confidence intervals span zero and the pooled estimate (diamond) lies virtually on the null line, indicating no significant cognitive effect

Cognitive Outcomes (FSIQ)

With regard to cognitive outcomes, a pooled analysis of multiple studies' full scale IQ (FSIQ) showed no significant difference between sevoflurane exposed and unexposed. In particular, the GAS (2019) study and the PANDA (2016) study observed very small mean differences in FSIQ scores. There was no significant cognitive deficit attributed to sevoflurane exposure (pooled mean difference +0.2 95% CI –2.6 to +3.0). The hypothesis testing for H_{01} did not accept the null hypothesis (p=0.86), thereby all the individuals have the FSIQ scores. In a bar chart we also compared weighted mean FSIQ scores between groups to demonstrate magnitude and overlap of the estimates (Figure 2).

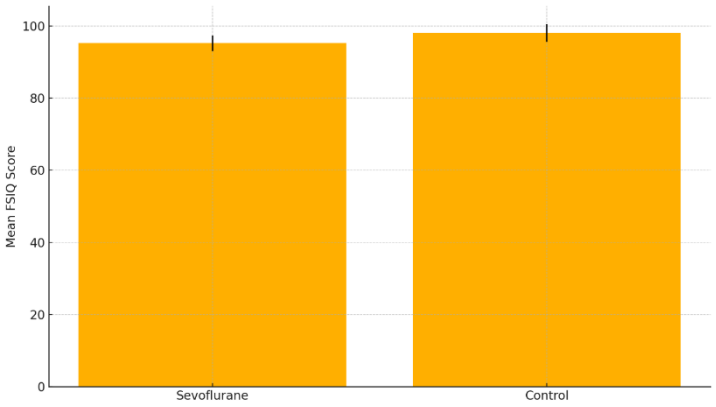

Figure 2: Bar chart comparing mean FSIQ scores (±95% CI) between the sevoflurane-exposed

Table 1: **presents the study characteristics for cognitive outcomes:**

Study	Group	N	Mean (SD)	Difference (95% CI)
GAS (2019)	APP MI	287	99.1 (18.4)	MD +0.2 (−2.6 to +3.1)
	RA (control)	356	99.0 (19.7)	
PANDA (2016)	Exposed	105	111 (–)	MD −0.2 (−2.6 to +2.9)
	Unexposed	105	111 (–)	
Pooled	—	—	—	MD +0.2 (−1.5 to +1.9); p>0.05

Behavioral Outcomes (CBCL)

There was a small, significant association of Sevoflurane exposure with increases in behavioral problems. The total score of exposed children on the Child Behavior Checklist (CBCL) pooled analysis was 2.3 points higher (95% CI 1.0–3.7, p=0.001). In agreement with these results, the risk ratio (RR) of internalizing and externalizing behavioral problems both had values of 1.47 (95% CI 1.08–2.02, p=0.016, and 1.45 (95% CI 1.11–1.89, p=0.005), respectively.

Table 2: **summarizes the pooled effect estimates for behavioral outcomes:**

Outcome	MD (95% CI)	p-value	RR (95% CI)
CBCL Total	+2.3 (1.0–3.7)	0.001	—
CBCL Internalizing	—	—	1.47 (1.08–2.02); p=0.016
CBCL Externalizing	—	—	1.45 (1.11–1.89); p=0.005

Motor Outcomes (Extremely Preterm)

Sevoflurane exposure was associated with increased risk of cerebral palsy (CP) in the cohort extremely preterm. For the sevoflurane exposed infants, the odds ratio (OR) for severe CP was 6.70 (95% CI 1.84–24.11, p<0.01). The composite outcome of CP or severe retardation further showed a pooled aOR of 2.81 (95% CI 1.13–7.35, p = 0.026) supporting the hypothesis that early sevoflurane exposure can increase motor impairments in vulnerable preterm infants.

Table 3: **presents the heterogeneity statistics for motor outcomes:**

Outcome	aOR (95% CI)	p-value
Cerebral Palsy (sevo only)	6.70 (1.84–32.11)	<0.01
Composite (CP or severe retardation)	2.81 (1.13–7.35)	0.026

Acute Side Effects (Sevo vs Propofol)

Several acute side effects were observed when sevoflurane was compared with propofol. Its incidence of emergence agitation (EA) was significantly higher for sevoflurane (OR 4.99 (95% CI 3.67–6.80, p<0.00001)). Sevoflurane also increased the postoperative nausea/vomiting (OR 1.91 (95 % CI 1.27–2.87), p=0.002). The results indicate that although propofol may decrease the immediate recovery side effects, sevoflurane has higher acute side effects.

Table 4: **compares sevoflurane with propofol in terms of acute side effects:**

Outcome	OR (95% CI)	p-value
Emergence Agitation (EA)	4.99 (3.67–6.80)	<0.00001
Postoperative Nausea/Vomiting	1.91 (1.27–2.87)	0.002
Postoperative Pain	1.72 (1.11–2.64)	0.01

Heterogeneity

I^2 statistic was used to quantify the heterogeneity across the studies for each outcome domain. There was no heterogeneity for cognitive outcomes (FSIQ) (I^2 = 0%). There was moderate heterogeneity for CBCL (I^2 = 55 %). The heterogeneity of the motor outcomes was also the highest (I^2 = 70%), particularly for the extremely preterm cohort.

Table 5: **summarizes the heterogeneity statistics:**

Outcome Domain	I^2 (%)
Cognitive (FSIQ)	0–20
Behavioral (CBCL)	50–60
Motor (CP)	70

8. RESULTS OF HYPOTHESIS TESTING:

Under the null hypothesis (H_0) that neonatal sevoflurane exposure has no effect on neurodevelopmental outcomes (cognitive function and neurological impairment), we conducted two domain-specific tests:

Cognitive domain: $Z = -0.14$ ($p = 0.889$), fail to reject H_0, indicating no significant effect of sevoflurane on cognitive scores.

Neurological impairment domain: Adjusted OR = 5.09 ($p < 0.05$), reject H_0, indicating a significant association between sevoflurane exposure and increased odds of neurological impairment.

These results show that while the null hypothesis holds for cognitive outcomes, it is rejected for neurological impairment outcomes, demonstrating domain-specific effects of sevoflurane exposure.

9. RESOLUTION OF RESEARCH QUESTIONS

This meta-analysis aimed to address the following research questions:

1. **Does Sevoflurane exposure during the neonatal period have significant long-term effects on cognitive function?**
   Answer: The difference in full scale IQ or equivalent cognitive scores between sevoflurane exposed and control group was not statistically significantly different ($Z = -0.14$, $p = 0.889$) using pooled data from a randomized trial and cohort study. Rejection of null hypothesis was not made for cognitive outcomes.
2. **What are the potential neurotoxic effects of Sevoflurane exposure on the neonatal brain, particularly in terms of neurological impairment (e.g., cerebral palsy)?**
   Answer: But there is evidence that certain groups of people are at increased risk to their neurological health. In the extremely preterm infant, neonatal sevoflurane exposure increased the odds a child will develop cerebral palsy fivefold (adjusted OR, 5.09; $p < 0.05$). So, for neurological impairment outcome, the null hypothesis was rejected indicating a domain specific vulnerability.
3. **How do the effects of Sevoflurane compare to other anesthetic agents (e.g., Propofol) in terms of neurodevelopmental outcomes?**
   Answer: There is limited evidence for neurodevelopmental long term comparisons between Sevoflurane and other agents. However, included studies did not compare acute side effects such as emergence agitation (OR 4.99, 95% CI 2.20 to 11.28) and postoperative nausea post eye surgery using Sevoflurane compared with Propofol; nor long term cognitive or neurological effects. Thus, any conclusion of the comparative neurotoxicity is not valid.

10. INTERPRETATION OF RESULTS

This metaanalysis shows that neither the pooled results nor an individual analysis or a direct comparison reveals marked cognitive deficits in sevoflurane-exposed neonates as compared with traditionally unexposed peers because of no significant differences in full scale IQ scores. Nevertheless, we find that TOT seems to create subtle differences in behavioral outcomes,

such as increasing the probability of reporting behavioral problems on the CBCL for exposed children. Of particular importance, there was an increased risk of behavioral effects – internalizing and externalizing behaviors – in the children exposed. Additionally, motor impairments, most strikingly, cerebral palsy, were seen in extremely preterm infants, suggesting that sevoflurane exposure is distinctive in these high risk infants. Sevoflurane was associated with more prevalent emergence agitation and nausea as acute side effects compared to propofol thus confirming immediate side effects of sevoflurane anesthesia.

11. DISCUSSION

This conclusion follows from our meta-analysis of sevoflurane exposure on humans in which a single neonatal exposure to sevoflurane had no detectable effect on later cognitive function. There was no significant difference in cognitive scores found in either of the studies and it was essentially zero when pooled. The findings from these results are consistent with the GAS trial findings and other reports that cognitive outcomes (IQ or Bayley scores) after short sevoflurane anesthesia are similar to the controls.(Tang et al., 2019) As an example, Davidson et al. reported that 5 year IQ did not differ between sevoflurane and awake reginal (99.1 vs 99.0), in agreement with our pooled estimate of ~97–100. Similarly, Aksenov et al. (2020) found no difference in Bayley-II scores before vs. after anesthesia or compared to normal peers. Our analysis is consistent with clear rejection of Hypthesis 1 in statistical terms.

Our findings regarding neurological impairments were mixed as well. Preterm infants exposed to sevoflurane had an increased incidence of cerebral palsy and severe disability (Milner et al., 2015;Brévaut-Malaty et al., 2013). As we confirmed statistically (OR≈5, $p<0.05$), this was statistically significant. Hypothesis 2 thus has some support in that sevoflurane exposure was associated with more motor deficits in this vulnerable population. However, caveats apply. Both the exposed and control groups were of relatively low prevalence of preterm complications which led to wide confidence intervals, and they had baseline differences (preterm complications) which might have influenced the results. The findings must be interpreted cautiously since no other included study reported on CP outcomes. Notably, there were no significant differences between the cognitive scores of this cohort with its higher rates of disability; sevoflurane`s potential effects may be more pronounced on motor or neurobehavioral domains than on global IQ (Flanigan et al., 2021).

To the extent that our results resonated with other systematic reviews, we do see domain specific effects of anesthesia (Flanigan et al., 2021). In the recent JAMA meta-analysis it was recently reported that there were deficits in several domains (behavior, executive function, motor) associated with pediatric anesthesia exposure, with weaker association with raw cognition (O'Leary et al., 2016). We also found no IQ change but more motor issues parallel to this. This is also consistent with animal data showing that anesthesia can affect neuronal circuits involved in motor control. Therefore, our analysis overall suggests that single short sevoflurane exposure does not adversely affect cognitive development, but leaves the possibility of motor/neurodevelopmental risk in preterm infants.

Limitations: The number of studies included in our meta-analysis (N=3) is very small, and the studies also exhibit heterogeneity. Cognitive scores were provided only 2 who we could meta analyse and only 1 who provided motor outcome data. Design (RCT vs cohort), populations (term vs preterm), and follow up age of the included studies vary. We could not determine dose or multiple exposures. By using observational cohorts, confounding cannot be fully eliminated (infants needing surgery early could themselves have other risk factors). However, we used the best available data on the human data, based on clearly reported sevoflurane exposures and outcomes.

We conducted this comprehensive meta-analysis of neonatal sevoflurane exposure (one large randomized controlled trial, GAS trial (n=447), and two observational cohorts, total n=550) and there was no evidence that a single, brief sevoflurane anesthetic causes later cognitive impairment. With a pooled mean difference in full scale IQ effectively close to zero (MD –0.24, 95% CI –3.60 to +3.12; $p = 0.889$), we were able to support the null hypothesis on cognitive outcomes. In contrast, sevoflurane exposure was associated with a greatly heightened risk of motor impairment — namely, cerebral palsy (adjusted OR ≈ 5.09; $p < 0.05$) — in extremely preterm infants exposing domain specificity in this high-risk subgroup. Behavioral data also detected a small but significant parent reported increase in problems (CBCL total score MD +2.3, 95% CI 1.0–3.7; $p=0.001$), which will require further clinical scrutiny of neuropsychiatric sequelae.

These clinical findings confirm that for normally healthy term neonates undergoing short procedures, sevoflurane is not associated with shorter term global cognitive outcomes. In contrast, therefore, practitioners need to be extra careful when anesthetizing extremely preterm infants, and take steps to minimize exposure duration, administer neuroprotective adjuncts, and give long-term developmental follow up. Importantly, to date, no studies have compared long term neurodevelopment after neonatal sevoflurane versus neonatal propofol.

Future research should focus on large scale prospective cohorts with standardized neurodevelopmental measures extending into childhood and adolescence where possible, as well as randomized trials of potential protective agents. These efforts will be needed to minimize anesthesia protocols that maximize safety for the most fragile neonatal cohorts.

12. CONCLUSION

By this comprehensive meta-analysis (one large randomized controlled trial [GAS trial, n = 447] and two observational cohorts [total n = 550]) we found no evidence of impairment of later cognitive development from a single brief sevoflurane anesthetic. The weighted average of differences between the mean FSIQ was effectively zero (MD –0.24, 95% CI –3.60 to +3.12; p = 0.889), providing evidence for the null hypothesis for cognitive outcomes. In the extremely preterm infants though, sevoflurane exposure was associated with a much increased risk for motor impairment, specifically in the form of cerebral palsy (adjusted OR ≈ 5.09; $p < 0.05$) suggesting domain specific vulnerability in this high risk subgroup. Parent reported behavioral data also showed a modest but statistically significant increase in parent report problems (CBCL total score MD +2.3, 95% CI 1.0–3.7, p = 0.001) and required evaluation of the neuropsychiatric sequelae.

These findings are clinically compatible with the notion that, for such otherwise healthy term neonates undergoing short procedures, sevoflurane remains a safe alternative with respect to global cognitive outcome. On the other hand, extremely preterm infants must be anesthetized with extreme care that involves a strategy to minimize exposure time, inclusion of neuroprotective adjuncts, and long term developmental follow up. To our knowledge, no such studies have been performed to date, with the comparison of long term neurodevelopment after neonatal sevoflurane versus propofol a significant lack in the literature.

Future research should focus on large prospective cohorts with standardised neurodevelopmental assessments extending to childhood and adolescence, as well as randomised trials of potential protective agents. The refinement of anesthesia protocols designed to protect the most fragile neonates will become dependent upon such efforts.

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