

CASE SERIES

TWO CASE REPORTS ON THE EFFECT OF SEVOFLURANE EXPOSURE DURATION ON SERUM LEVELS OF NEURON-SPECIFIC ENOLASE (NSE) AND S100 PROTEIN IN CHILDREN

Demjanski V^{1,2}, Gavrilovska Brzanov A^{1,2}, Mikjunovikj Derebanova Lj^{1,2}, Donev Lj^{1,2}, Kiprijanovska B¹, Soljakova M²

¹University Clinic for Traumatology, Orthopedic Diseases, Anesthesiology, Reanimation and Intensive Care Medicine and Emergency Department, Clinical Center "Mother Theresa", Skopje, Republic of North Macedonia.

²Medical Faculty "Ss. Cyril and Methodius" University, Skopje, Republic of North Macedonia

Abstract

The length of sevoflurane exposure may raise the risk of neuron-specific enolase (NSE) and S100 protein alterations in blood, which might thereafter result in postoperative cognitive dysfunction (POCD). The pathophysiology of POCD caused by the volatile anesthetic sevoflurane has been the subject of extensive research in recent years.

This case study looks at preliminary findings about the effects of different sevoflurane anesthetic exposure durations on the levels of S100 protein and NSE in children's blood. Additionally, it looks into how sevoflurane affects children's early cognitive performance following surgery. To detect neurological effects during general anesthesia and ascertain the length of sevoflurane exposure, we employ the particular markers such as S100 protein and NSE.

In this case study, we present two pediatric patients who underwent general anesthesia with sevoflurane for different durations. The aim was to observe potential postoperative changes in NSE and S100 protein levels, which are biomarkers associated with neuronal injury and cognitive function. After the surgery, we utilize these levels to assess any cognitive problems. The parents or guardians gave their informed consent.

Key Words: *General anesthesia for children; neuron-specific enolase; postoperative cognitive dysfunction in children; S100 protein; sevoflurane*

Introduction

Sevoflurane (1,1,1,3,3,3-hexafluoro-2-[fluoromethoxy]propane ether) is one of the most commonly used volatile anesthetics for both induction and maintenance of general anesthesia, particularly in pediatric patients. Its favorable pharmacokinetics, including rapid onset and offset, minimal airway irritation and hemodynamic stability, make it an ideal choice for children.

However, concerns have emerged regarding its potential neurotoxic effects, particularly in the developing brain. Studies suggest that prolonged or repeated exposure to sevoflurane may contribute to postoperative cognitive dysfunction (POCD), manifesting as impairments in memory, attention and learning (1).

The exact pathophysiological mechanisms underlying sevoflurane-induced cognitive dysfunction remain unclear, but several hypotheses have been proposed. These include neuroinflammation, mitochondrial oxidative stress, disruptions in neurotransmitter signaling, and increased blood-brain barrier permeability. Notably, the role of specific biomarkers such as S100 β and neuron-specific enolase (NSE) has been investigated as potential indicators of neuronal injury. Elevated levels of these biomarkers have been correlated with cognitive impairment, suggesting that they may serve as valuable tools for assessing perioperative neurocognitive changes.

Despite conflicting findings, emerging evidence suggests that young children, whose brains are still developing, may be particularly vulnerable to sevoflurane-induced neurotoxicity. This raises concerns regarding the long-term neurodevelopmental consequences of general anesthesia in pediatric patients, making it crucial to identify risk factors, implement preventive strategies, and establish monitoring protocols for cognitive assessment (2-4).

In this report, we present two pediatric cases in which POCD was observed following sevoflurane anesthesia. We discuss potential contributing factors, the role of neuro-biomarkers, and the importance of early detection and intervention in mitigating the risk of cognitive impairment in young patients.

Case Presentation 1.

The first case we present is a two-year-old patient with 13kg body weight, ASA 1, admitted to the Clinic for Pediatric Surgery for elective surgery with a diagnosis of contracture of digits in the left hand after combustion. The patient was preoperatively prepared with Midazolam syrup (0.5mg/kg), after which he was introduced into general endotracheal anesthesia with Propofol, Fentanyl, Lidocaine and Rocuronium. Intraoperatively, he was administered with Sevoflurane with a MAC of 0.8 for a duration of 80 minutes, and one dose of Paracetamol was also administered. Preoperatively measured values of NSE were 1.96ng/ml and S100 0.134 μ g/L, while one hour postoperatively the values of NSE were 0.156ng/ml and S100 18.28 μ g/L. The following tables present all findings.

Table 1. Intraoperative information about OP and anesthesia.

Variables		Short duration	Long duration
Duration of surgical intervention			70 min.
Duration of exposure to sevoflurane			80 min.
ANESTHESIA		Medication	mg/kg
Premedication		Sir. Midazolam	0.5mg/kg
Induction:	Hypnotic	Propofol	4.5mg/kg
	Relaxing agent	Rocuronium	0.4mg/kg

	Opioid analgesic	Fentanyl	0.004mg/kg
Anesthesia maintenance		Sevoflurane	MAC 0.8
Additional therapy		Paracetamol	15mg/kg
		Lidocaine 1%	0.5mg/kg

Table 2. Perioperative monitoring.

Variables	Before induction	10 min. after induction	30 min. after induction
BP (mmHg)	110/53	117/60	118/65
Pulse/min	116	112	111
SpO ₂ %	99	99	99
EtCO ₂	49	42	41

Table 3. Laboratory values of examined biomarkers.

Variables	Preoperatively	After 1 hour
S100	0.134	0.156
NSE	1.96	18.28

Table 4. Postoperative pain and anxiety.

Variables	PACU	After 1 hour
VAS	6	5
Anxious scale	2 – medium anxious	3 - calm
RASS - scale	3 – sedated easily agitated	3 - sedated easily agitated

Case Presentation 2.

The second case was a twelve-year-old 56kg body weight patient, ASA 1, admitted to the Clinic of Pediatric Surgery for elective surgery with a diagnosis of pyogenic granuloma on the hand. The patient was preoperatively prepared with Midazolam syrup (0.5mg/kg), after which he was introduced into general endotracheal anesthesia with Propofol, Fentanyl and Lidocaine. Intraoperatively, he was administered Sevoflurane with a MAC of 0.8 for 12 minutes. Preoperatively measured values were NSE 20.29ng/ml, and S100 0.064µg/L, while one hour postoperatively the NSE values were 19.89ng/ml and S100 0.100µg/L. All findings are presented in the following tables.

Table 5. Intraoperative information about OP and anesthesia.

Variables	Short duration	Long duration
Duration of surgical intervention	10 min.	
Duration of exposure to sevoflurane	12 min.	
ANESTHESIA	Medication	mg/kg

Premedication		Sir. Midazolam	0.5 mg/kg
Induction:	Hypnotic	Propofol	4.5mg/kg
	Opioid analgesic	Fentanyl	0.004mg/kg
Anesthesia maintenance		Sevoflurane	MAC 0.8
Additional therapy		Lidocaine 1%	1mg/kg

Table 6. Perioperative monitoring.

Variables	Before induction	10 min. after induction	30 min. after induction
BP (mmHg)	120/80	110/65	
Pulse/min	80	66	
SpO2 %	99	100	
EtCO2	34	34	

Table 7. Laboratory values of examined biomarkers.

Variables	Preoperatively	After 1 hour
S100	0.064	0.100
NSE	20.29	19.89

Table 8. Postoperative pain and anxiety.

Variables	PACU	After 1 hour
VAS	4	3
Anxious scale	3 - calm	3 - calm
RASS - scale	2- sedated not agitated	0 - calm

Discussion

Anesthetic agents, including sevoflurane, are widely recognized for their neuroprotective properties, primarily through their ability to reduce cerebral metabolic demand and oxygen consumption. This effect helps maintain the balance between brain energy supply and demand, thereby increasing neuronal tolerance to hypoxic and ischemic injury. However, emerging evidence suggests that certain anesthetics, particularly volatile agents such as sevoflurane, may also exert neurotoxic effects, especially with prolonged exposure. This paradoxical effect has been linked to neuroinflammation, oxidative stress, and alterations in neurotransmitter function, ultimately leading to neuronal damage and cognitive dysfunction (5,6). In our presented cases, the potential for sevoflurane-induced neurotoxicity was evaluated using two well-established biomarkers of neuronal injury: neuron-specific enolase (NSE) and S100 protein. Both biomarkers serve as indicators of blood-brain barrier integrity and neuronal distress. NSE, an enzyme found in neurons and neuroendocrine cells, is widely used as a marker of neuronal damage. S100 protein, primarily found in astrocytes and Schwann cells, plays a role in calcium homeostasis, inflammatory regulation and cellular proliferation. Under normal physiological

conditions, both biomarkers are present in the serum at very low levels. However, disruption of the blood-brain barrier due to ischemic, traumatic, or toxic insults can result in their elevated serum concentrations.

The findings from the two cases provide valuable insight into the potential impact of sevoflurane exposure on neurological integrity. In the first case, the patient was exposed to sevoflurane for 80 minutes, resulting in a significant postoperative increase in NSE levels. However, S100 protein levels remained unchanged. The selective increase in NSE suggests a primary neuronal injury rather than a widespread disruption of the blood-brain barrier. The lack of S100 elevation could indicate that astrocytic and glial responses were either delayed or less pronounced in this scenario. The second patient was exposed to sevoflurane for only 12 minutes, with no significant increase in NSE or S100 levels. This suggests that brief exposure to sevoflurane may not lead to measurable neuronal or astrocytic damage, reinforcing the hypothesis that anesthetic duration plays a critical role in neurotoxicity. Several factors could explain the observed discrepancy between NSE and S100 levels in Case 1: **Selective neuronal vulnerability:** Neurons may be more susceptible to direct anesthetic-induced injury than astrocytes, leading to an increase in NSE without a concurrent rise in S100; **Delayed astrocytic response:** S100 protein release may occur later in the neuroinflammatory cascade, potentially manifesting at later time points beyond the immediate postoperative period; **Different pathways of cellular injury:** NSE elevation may result from direct neuronal stress, while S100 release typically occurs in conditions involving more extensive blood-brain barrier disruption (7).

These findings underscore the potential risks of prolonged sevoflurane administration, particularly in pediatric patients with developing brains. Several studies have suggested that repeated or prolonged exposure to volatile anesthetics may contribute to postoperative cognitive dysfunction (POCD), neuroinflammation and long-term neurodevelopmental deficits. This is particularly concerning in children, as their immature blood-brain barrier and ongoing synaptic development may render them more vulnerable to anesthetic-induced toxicity (8).

Given the lack of definitive evidence regarding the long-term impact of anesthetic-induced biomarker changes, further studies are warranted to: Investigate the time course of NSE and S100 changes postoperatively to determine whether delayed elevations occur. Assess additional biomarkers such as glial fibrillary acidic protein (GFAP) and tau protein for a more comprehensive evaluation of neuronal injury. Explore potential neuroprotective strategies, including pharmacological interventions and anesthetic technique modifications, to minimize neurotoxicity in pediatric populations (8).

Those cases highlight the differential effects of sevoflurane exposure duration on neuronal injury biomarkers, with a significant increase in NSE following prolonged exposure but no changes in S100 levels. These findings suggest that sevoflurane-induced neurotoxicity may primarily affect neurons rather than astrocytes in the early postoperative period. While brief exposure appears to be well tolerated, prolonged administration may contribute to neuronal stress, warranting further research into protective strategies and long-term neurocognitive outcomes.

Conclusion

This article discusses the pathophysiology and etiology of postoperative cognitive dysfunction (POCD) following general anesthesia, as well as the timely identification and assessment of individuals with this critical clinical condition. This study shows that postoperative levels of biomarkers of cerebral damage and postoperative agitation are significantly influenced by the length of sevoflurane exposure.

References:

1. Silva FP, Schmidt AP, Valentin LS, et al. S100B protein and neuron-specific enolase as predictors of cognitive dysfunction after coronary artery bypass graft surgery: A prospective observational study. *Eur J Anaesthesiol*. 2016 Sep;33(9):681-9. doi: 10.1097/EJA.0000000000000450. PMID: 27433840.
2. Wu X, Shan C, Peng B, Shi X, Zhang F, Cao J. Comparison of desflurane and sevoflurane on postoperative recovery quality after tonsillectomy and adenoidectomy in children. *Exp Ther Med*. 2019 Jun;17(6):4561-4567. doi: 10.3892/etm.2019.7467. Epub 2019 Apr 4. PMID: 31086588; PMCID: PMC6488999.
3. Zhu X, Yao Y, Guo M, Li J, Yang P, Xu H, Lin D. Sevoflurane increases intracellular calcium to induce mitochondrial injury and neuroapoptosis. *Toxicol Lett*. 2021 Jan 1; 336:11-20. doi: 10.1016/j.toxlet.2020.11.002. Epub 2020 Nov 7. PMID: 33171207.
4. McCarthy RA, Warrington EK. *Cognitive neuropsychology: a clinical introduction*. 7th ed. Elsevier Science; 1990. 428.
5. Yuan SM. S100 and S100 β : biomarkers of cerebral damage in cardiac surgery with or without the use of cardiopulmonary bypass. *Rev Bras Cir Cardiovasc*. 2014 Oct-Dec;29(4):630-41. doi: 10.5935/1678-9741.20140084. PMID: 25714218; PMCID: PMC4408827.
6. Geyer C, Ulrich A, Gräfe G, Stach B, Till H. Diagnostic value of S100B and neuron-specific enolase in mild pediatric traumatic brain injury. *J Neurosurg Pediatr*. 2009 Oct;4(4):339-44. doi: 10.3171/2009.5.PEDS08481. PMID: 19795965.
7. Isgro MA, Bottoni P, Scatena R. Neuron-Specific Enolase as a Biomarker: Biochemical and Clinical Aspects. *Adv Exp Med Biol*. 2015; 867:125-43. doi: 10.1007/978-94-017-7215-0_9. PMID: 26530364.
8. Aun CST, McBride C, Lee A, et al. Short-Term Changes in Postoperative Cognitive Function in Children Aged 5 to 12 Years Undergoing General Anesthesia: A Cohort Study. *Medicine (Baltimore)*. 2016 Apr;95(14):e3250. doi: 10.1097/MD.00000000000003250. PMID: 27057869; PMCID: PMC4998785.
9. Qiao, Y., Feng, H., Zhao, T. et al. Postoperative cognitive dysfunction after inhalational anesthesia in elderly patients undergoing major surgery: the influence of anesthetic technique, cerebral injury and systemic inflammation. *BMC Anesthesiol* 15, 154 (2015). <https://doi.org/10.1186/s12871-015-0130-9>.

