

Correlation of S100B level and postoperative cognitive dysfunction (POCD) events among patients with ear, nose and throat (ENT) surgeries with controlled hypotension



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ABSTRACT

Introduction: Controlled hypotension is one of the techniques applied to several microscopic ear, nose, and throat (ENT) surgeries. However, this technique has risks and complications, which result in impaired perfusion and oxygenation of organs including the brain that could trigger the postoperative cognitive dysfunction (POCD). Damage that occurs in brain cells can trigger the secretion of biomarker proteins in the blood, one of which is S100B which can indicate nerve damage in the intra and postoperative period. This study aimed to analyze the correlation between S100B protein level and the incidence of POCD in patients who received ENT surgeries with controlled hypotension.

Methods: A cross-sectional study was conducted among patients that underwent elective ENT surgeries at Dr. Soetomo General Academic Hospital, Surabaya, from July to August 2022. Cognitive function was assessed using Mini-mental State Examination (MMSE) at 12 hours before and 2 and 24 hours after surgery. The level of S100B was measured using enzyme-linked immunosorbent assay (ELISA) 12 hours prior surgery and 30 minutes post-surgery.

Results: A total of 31 patients were recruited in the study, including a mean age of 31.7 years. The mean S100B levels in POCD patients pre- and postoperative were 311.97 ng/L, and 415.34 ng/L, respectively. In non-POCD patients, the mean levels of S100B pre and postoperative were 436.90 ng/L, and 444.29 ng/L, respectively. There were 3 (9.7%) patients experienced POCD. Our data suggested there was a significant difference between preoperative and postoperative S100B levels in the groups of patients with POCD (103.37ng/L) and non-POCD (7.38 ng/L) ($p < 0.001$). Patients that experienced POCD had significantly increased S100B compared to those who did not.

Conclusion: There is a correlation between changes of S100B levels and the incidence of POCD in patients undergoing ENT surgeries with controlled hypotension.

Keywords: S100B level, postoperative cognitive dysfunction, controlled hypotension, mini-mental state examination, POCD.
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INTRODUCTION

Controlled hypotension is one of the techniques applied in microscopic ear, nose and throat (ENT) surgeries to minimize the amount of bleeding, increase visualization of the operating field, shorten the duration of the operation, and reduce the risk of complications.¹ It was conducted by lowering systolic blood pressure to the range of 80-90 mmHg with mean arterial pressure (MAP) 50-65 mmHg, or reduce the MAP 20-30% from baseline.² However, the controlled hypotension technique has its own risks or complications that may occur to the patients.³ Low blood pressure could result in impaired organ perfusion

and oxygenation due to decreased blood flow to vital organs such as the heart, brain, kidneys, and splanchnic.² In brain, this condition could trigger postoperative cognitive dysfunction (POCD).⁴

POCD is a functional mental disorder affecting cognitive processes such as verbal memory, visual memory, impaired concentration, attention, and language comprehension. In general, cases of POCD occur in geriatric patient of which 30% of postoperative geriatric patients experience POCD in the first one week.⁵ As many as 30–80% of these POCD events occur in the first week and 10–60% occur 3–6 months after surgery.⁶ The incidence

of POCD in ENT surgeries with controlled hypotension was 13.3% in the first one hour and 6.6% at 24 hours postoperatively.⁷ Mini-Mental State Examination (MMSE) is one of the most common tool used to diagnose the incidence of POCD.⁸

Neuroinflammation, cerebral hypoperfusion, ischemia and apoptosis of brain cells are the pathophysiological mechanisms associated with POCD.⁹ Damage that are occurred in brain cells could trigger the secretion of several biomarker proteins in the blood including S100B, neuron-specific enolase (NSE), glial fibrillary acidic protein (GFAP), and Tau protein.^{10,11} S100B protein is one of

the specific biomarkers that could indicate the occurrence of nerve damages intra and postoperative period.¹² Sensitive and specific biomarkers or predictors are critical to diagnosis dan prognosis of the diseases.¹³⁻¹⁸ In nerve injury, S100B will be secreted from astrocytes, high concentrations of S100B can trigger an inflammatory process in astrocytes and microglia which can ultimately lead to apoptosis and neuronal cell death.¹⁹

Studies on the relationship between S100B levels with the incidence of POCD and controlled hypotension still limited. Therefore, this study aimed to analyze the relationship between S100B protein level and the incidence of POCD in patients who underwent ENT surgeries with controlled hypotension.

METHODS

Study design and sample collection

A cross-sectional study was conducted out among patients that underwent elective ENT surgeries (tympanoplasty, mastoidectomy, septoplasty, rhinoplasty, dan functional endoscopic sinus surgery (FESS)) at Dr. Soetomo General Academic Hospital from July to August 2022. Patients 18–59 years old, underwent elective surgery with general anesthesia, and had physical status with American Society of Anesthesiologists (ASA) I-II were included. Patients with hypertension, psychiatric disorders or Parkinson's disease; used of antidepressant drugs or anticoagulant drugs; history of cerebrovascular disease; preoperative MMSE score 23, severe visual or hearing impairment; unable to read and write; and patients with alcoholism or drug dependence were excluded.

Study variables and data collection

The data used in this study was primary data that included S100B level as independent variable and postoperative cognitive dysfunction event, assessed using MMSE, as dependent variable. MMSE has been used to assess cognitive function frequently including in Dr. Soetomo Hospital.²⁰ Patients who met the inclusion and exclusion criteria were recruited in the study. Cognitive function was assessed using MMSE tool at 12 hours before surgery, 2 and 24

hours after surgery. POCD event was defined if the MMSE score on 2 or 24 hours postoperative decreased 2 points or more compared to the baseline score (preoperative). The level of S100B protein in the blood was measured using enzyme-linked immunosorbent assay (ELISA) using Human S100 Calcium Binding Protein B ELISA kit (BT Lab Bioassay Technology Laboratory, Zhejiang, China) 12 hours prior surgery and 30 minutes post-surgery.

Demographic data such as gender, height, weight, and education attainment were also collected. Duration and type of surgery and duration of anesthesia procedure were also collected. Hemodynamic parameters (systolic blood pressure, diastolic, and mean arterial pressure (MAP), and pulse) were measured every 15 minutes after the patients entered the operating room until the anesthesia process was complete. During the surgeries the MAP was maintained in the range of 60-70 mmHg. Fentanyl 1–2 mcg/kg IV, propofol 1–2 mg/kg IV, rocuronium

0.6–1.2 mg/kg IV were used to induce the anesthesia. During the maintenance phase, isoflurane 1.2–2 vol% FiO₂ 40–50% flow 3–4 lpm, tidal volume 6–8 ml/kg with frequency 12–20 x/min was used with target EtCO₂ 35–40 and SpO₂ >95%.

Statistical analysis

The data were analyzed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). All data on demographic characteristics summarized using descriptive statistics. All measurement data were presented in the form of mean ± standard deviation. In order to assess the association between changes in S100B levels before and after surgery, Mann-Whitney test or Wilcoxon test were used.

RESULTS

A total of 31 patients were enrolled in this study. The demographic characteristics are summarized in Table 1. The mean age was 31.7±11.4 years and more than half patients were male (51.6%). Types of surgery performed include canal wall

Table 1. Demographic characteristics and clinical and MMSE score of patients (n=31).

Characteristics	Frequency (%)
Age (years), mean ± SD	31.7±11.4
Gender	
Female	15 (48.4)
Male	16 (51.6)
Height (cm), mean ± SD	160.7±8.8
Weight (kg), mean ± SD	57.3±11.9
ASA score	
ASA 1	12 (38.7)
ASA 2	19 (61.3)
Education	
Elementary school	2 (6.5)
Junior high school	4 (12.9)
Senior high school	19 (61.3)
Undergraduate	6 (19.4)
Surgery duration (minute), mean ± SD	184.8±49.6
Anesthesia duration (minute), mean ± SD	200±48.8
Surgery type	
Canal wall up and tympanoplasty	10 (32.3)
Canal wall down	7 (22.6)
Functional endoscopic sinus surgery	9 (29)
Septoplasty and turbinoplasty	5 (16.1)
Bleeding amount (ml), mean ± SD	55.9±23.1
MMSE scores	
Preoperative, mean ± SD	28.2±1.4
2 hours postoperative, mean ± SD	27.0±1.8
24 hours postoperative, mean ± SD	27.8±1.8

up (CWU), canal wall down (CWD), septoplasty, turbinoplasty, and FESS with an average length of surgery of 184.8 ± 49.6 average duration of anesthesia 200 ± 48.8 minutes.

MMSE as a diagnostic tool to determine the incidence of POCD was performed 3 times (2 hours postoperative, 2 and 24 hours postoperative). In both POCD and non-POCD groups, the MMSE scores during preoperative (28.2 ± 1.4), 2 hours postoperative (27.0 ± 1.8), and 24 hours postoperative (27.8 ± 1.8) (Table 1). In this study, the POCD event was defined if the MMSE score decreased 2 points from the baseline score. A total of 3 (9.7%) patients experienced POCD in this study.

Inpatients with POCD, the MMSE scores at 2 hours and 24 hours postoperatively were 23.3 ± 1.5 and 23.0 ± 1.7 , respectively (Table 2). Meanwhile, in non-POCD patients, the MMSE scores at 2 hours and 24 hours after surgery were 27.3 ± 1.4 and 28.2 ± 1.4 , respectively. There were significant differences of MMSE scores in POCD patients compared to non-POCD patients at 2 and 25 hours of postoperative ($p < 0.05$) (Table 2).

In the POCD group, the mean level of preoperative S100B was 311.97 ± 136.47 ng/L and postoperative 415.34 ± 131.68 ng/L (Table 3). There was no significant difference of S100B levels between pre- and postoperative ($p = 0.100$). In non-POCD group, the level of S100B preoperative was 436.90 ± 141.03 ng/L and postoperative 444.29 ± 124.65 ng/L. There was also no significant difference of S100B levels between pre- and postoperative ($p = 0.270$) (Table 3).

We then analyzed the difference of delta S100B (DS100B), differences of

S100B levels between postoperative and preoperative, between patients who experienced POCD and non-POCD. In patients with POCD, the delta S100B was 103.37 ± 7.37 ng/L; in the non-POCD patients, the S100B delta was 7.38 ± 39.80 ng/L (Table 3). There was a significant difference of delta S100B between patients who experienced POCD and non-POCD ($p < 0.001$). Patients who experienced POCD had significantly increased S100B compared to those who did not.

The relationship between delta S100B with MMSE score at 2 hours and 24 hours postoperative is depicted in a scatter diagram (Figure 1). There was a significant correlation between delta S100B and MMSE score at 2 hours postoperative ($R = -0.7$ and $p < 0.001$) (Figure 1a). The correlation coefficient value -0.7 indicated that there was a strong relationship between delta S100B with MMSE score at 2 hours postoperative. There was no significant correlation between delta S100B and MMSE 24 hours postoperative ($R = -0.29$ with $p = 0.10$) (Figure 1b).

DISCUSSION

In this study, the lowest MMSE score was at 2 hours postoperatively. This was probably because some patients were still under the effect of sedative drugs. Data analysis performed showed a significant difference between the MMSE score preoperatively with 2 hours postoperatively and 24 hours postoperatively (all with $p < 0.05$). A prospective study found a decrease in the MMSE score when the patient was still in the recovery room then the MMSE score would increase 24 hours postoperatively.⁷

Our study found a significant difference

in MMSE scores between patients with POCD and non-POCD at 2 hours and 24 hours postoperatively ($p = 0.006$) (Table 3). A study on the incidence of POCD in septoplasty surgery with controlled hypotension reported that the incidence of POCD was 6.6% at 24 hours postoperatively.⁷ A prospective study in patients underwent ENT surgery with a target MAP of 55-65 mmHg reported the incidence of POCD was 16.7% in the propofol group and 10% in the desflurane group.⁴

S100B protein in blood serum is one of the specific proteins that can be found in nerve injury.¹⁹ This protein is often used as a biomarker in cognitive disorders such as dementia, Alzheimer's disease or patients with brain trauma. In this study, S100B level was examined as a biomarker of the incidence of POCD in non-geriatric patients receiving controlled hypotension. Our data showed that S100B levels increased at 30 minutes postoperative examination, both in patients with POCD and non-POCD and the difference between preoperative and postoperative levels was not significantly significant. A study on FESS surgery with controlled hypotension reported a significant increase in S100B levels at 60 minutes postoperatively when compared to S100B levels before surgery.²¹

In our study, patients with POCD had a higher S100B level postoperative compared to preoperative (415.34 ng/L vs 311.97 ng/L), but statistically insignificant ($p = 0.10$). The increase in postoperative mean S100B levels may be related to the generation of reactive oxygen species (ROS) in patients receiving general anesthesia using either inhaled gases or intravenous agents. The increase in ROS can trigger astrocyte cells to produce S100B in greater numbers.²²

Our study reported that the delta S100B levels (the changes between postoperative compared to preoperative) in POCD patients had a significantly higher compared to non-POCD patients (103.37

Table 2. Comparison of MMSE scores between POCD and non-POCD patients.

Type of MMSE	POCD		p-value*
	Yes	No	
2 hours postoperative, mean \pm SD	23.3 ± 1.5	27.3 ± 1.4	0.006
24 hours postoperative, mean \pm SD	23.0 ± 1.7	28.2 ± 1.4	0.006

*Analyzed using Mann-Whitney test

Table 3. Comparison of S100B level and delta S100B in POCD and non-POCD groups.

Group	S100B (ng/L)		p-value*	Δ S100B (ng/L)	p-value*
	Preoperative	Postoperative			
POCD	311.97 ± 136.47	415.34 ± 131.68	0.100	103.37 ± 7.37	< 0.001
Non-POCD	436.90 ± 141.03	444.29 ± 124.65	0.270	7.38 ± 39.80	

*Analyzed using Wilcoxon test

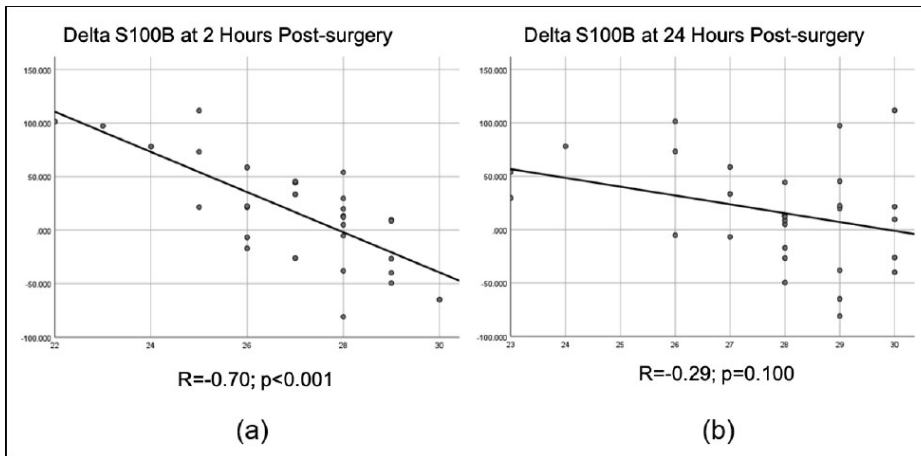


Figure 1. Correlation between delta S100B with (a) MMSE scores at 2 hours postoperative and (b) 24 hours postoperative.

vs. 7.38 $p=0.001$). This result was in line with a previous study in geriatric patients who underwent abdominal, urological, and vascular surgery that found a significant difference between the S100B levels of patients with POCD and non-POCD, even the difference was obtained up to 36 hours postoperative.²³ Neuroinflammation is the main pathogenesis of POCD and inflammation that occurs in brain cells will result in dysfunction to apoptosis of brain cells which lead to the secretion of S100B protein from astrocyte cells in high concentrations.²⁴

CONCLUSIONS

In our study, the incidence of POCD in patients underwent controlled hypotension with a target MAP of 60-70 mmHg was 9.7%. There is a relationship between changes in S100B levels and POCD event in patients undergoing ear and nose surgery who underwent controlled hypotension, that the higher the changes in S100B levels, the likelihood of the occurrence of POCD was greater. However, controlled hypotension with a target MAP of 60-70 mmHg did not significantly change S100B levels.

ETHICAL APPROVAL

Ethical approval was obtained from the Medical Research Ethics Committee of Dr Soetomo General Academic Hospital, Surabaya (Ref. No.0432/KEPK/VI/2022). All patients provided the signed informed consent prior to the study inclusion.

COMPETING INTERESTS

The authors declare no competing interest.

GRANT INFORMATION

None.

AUTHOR CONTRIBUTION

All authors contributed significantly to the research article.

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