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S100B AS A SEROLOGIC MARKER FOR COGNITIVE DYSFUNCTION FOLLOWING OPEN-HEART SURGERY

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ABSTRACT

Objective: Postoperative cognitive dysfunction (POCD) can feature a wide spectrum of clinical symptoms, from asymptomatic to debilitating dementia, that lead to increased dependence, lower quality of life, morbidity, and mortality. Protein S100B is a direct marker for neuronal cell damage. We aimed to evaluate S100B as a biomarker for predicting POCD following open-heart surgery.

Methods: This was an observational-analytic study to assess changes of the S100B level following open-heart surgery in Cipto Mangunkusumo Hospital, Jakarta. All subjects underwent cognitive function evaluations that consisted of six psychometric tests on the day prior to surgery and five days after surgery. Cognitive dysfunction was determined if there was a>20% cognitive score drop from baseline values in at least two tests. Blood samples for S100B were obtained (1) before the induction of anesthesia and (2) six hours after surgery. Samples were analyzed using enzyme-linked immunosorbent assay for S100B. All data were analyzed using SPSS 20.

Results: Among the 55 subjects analyzed, 31 (56.4%) were found to have a decline in cognitive function. There were no differences in baseline characteristics, comorbidities, and perioperative data. Oxygen contents also did not show significant differences at any time. The S100B levels in all subjects increased. This increase was>1.5x higher in subjects with POCD compared to those without POCD (2.15[0.22–60.03] vs. 1.33[0.15–19.77] ng/ml, p = 0.16). However, this difference was not statistically significant.

Conclusion: This study showed that serum S100B is higher in POCD patients and has the potential to be a biomarker for predicting POCD after open-heart surgery.

Keywords: Cardiac surgery, POCD, S100B

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INTRODUCTION

Postoperative cognitive dysfunction (POCD) can feature a wide spectrum of clinical symptoms, from asymptomatic to debilitating dementia. Patients with POCD have increasing dependence, lower quality of life, and a higher rate of morbidity and mortality [1–3]. Globally, POCD prevalence can be as high as 40%, with that number rising to up to 50% following open-heart surgery. A 2017 study in our hospital showed that the prevalence of POCD following open-heart surgery was 40.7% [4].

The pathophysiology of POCD remains unclear. Many hypotheses have linked cerebral neuronal cell damage to cellular hypoxia and neuroinflammation during surgery [5]. Cardiopulmonary bypass (CPB) in open-heart surgery also triggers a cascade of inflammatory events and their consequences. This process is inevitable as synthetic CPB material comes into contact with human cells [6]. Hemodynamic management during CPB may also contribute to oxygen delivery to tissues. As yet, there is no method for assessing the efficacy of oxygen delivery and uptake in tissue. The inadequacy of oxygen delivery and uptake in brain tissues may trigger neuronal brain damage.

There are several biomarkers associated with neuronal cell damage. These include neuron-specific enolase, glial fibrillary acidic protein, protein Tau, metalloproteinase, microtubule-associated protein 2, and protein S100B [5]. Protein S100B is a direct marker for neuronal cell damage. We aim to evaluate the value of S100B as a biomarker for predicting POCD following open-heart surgery.

MATERIALS AND METHODS

This is an observational-analytic study to assess changes in S100B level following open-heart surgery and to analyze the effect of oxygen content during and after surgery. Sampling was conducted using nonprobability sampling in Cipto Mangunkusumo Hospital, Jakarta. Using the rule of thumb, we obtained a sample size of 60 subjects. As five subjects were dropped from the study, 55 were included in the analysis.

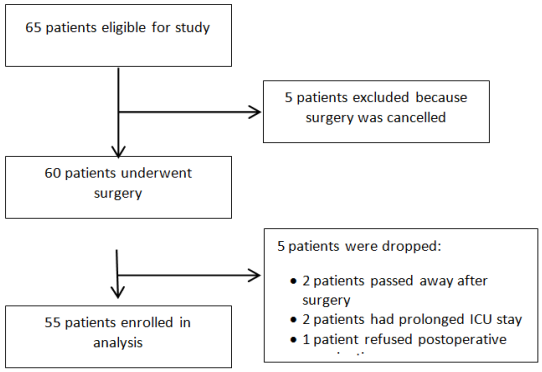

Fig. 1: Subject recruitment diagram

One day prior to surgery, all subjects underwent cognitive function evaluation using the immediate and delayed Rey auditory verbal learning test, the trail making test A and B, and the digit span forward and backward test. All of these tools have been validated in the Department of Psychiatry at Cipto Mangunkusumo Hospital. These tests were repeated five days after surgery. Cognitive dysfunction was determined if there was a>20% cognitive score drop from baseline values in at least two tests.

On the day of surgery, a central venous catheter (CVC) and arterial line were inserted before anesthetic induction. Blood samples for S100B were obtained from the CVC, while blood gas was obtained from the arterial line. Blood samples collected for S100B were centrifuged at 3000 rpm for 5 min and stored in a refrigerator at-80 °C. Samples were then analyzed for S100B using enzyme-linked immunosorbent assay.

Anesthesia for all subjects was conducted in accordance to hospital protocol. Arterial blood gas analysis was done (1) 10 min after CPB began, (2) 10 min after CPB was stopped, (3) 6 h after surgery, and (4) 24 h after surgery. The next S100B test was done at 6 h after surgery in the intensive care unit. All data were analyzed using SPSS 20. Statistical differences were considered meaningful if p-value<0.05.

RESULTS

Of the 55 subjects included in this study, 31 (56.4%) suffered POCD. There were no differences in baseline characteristics, comorbidities, CPB, and aortic cross-clamp time among any of the subjects. Oxygen content before, during, and after surgery also did not show significant differences.

The S100B levels in all subjects were increased after surgery compared to before surgery. This increase was found to be>1.5x higher in subjects who had POCD compared to those who did not have POCD. Statistically, however, this difference was not significant.

In all subjects, an analysis was done to determine oxygen content, expressed in PaO_2, Hb, and SaO_2. There was no difference between oxygen content during and after surgery, except for in Hb levels at 24 h after surgery.

Table 1: Baseline characteristics

Profile	POCD		p-value
	Yes (n=31)	No (n=24)	
Age (years)	55.4±11.7	50.9±13.6	0.20
Gender (%)			
Male	64.5	66.7	0.87
Female	35.5	33.3	
Body weight (kg)	61.2±12.6	66.4±12.0	0.12
Body height (cm)	158.6±9.5	161.6±7.1	0.20
BMI (kg/m^2)	24.2±4.0	25.4±4.3	0.29
Comorbidity (%)			
Hypertension	58.1	62.5	0.74
Diabetes mellitus	38.7	33.3	0.68
Chronic kidney disease	12.9	20.8	0.43
Cerebrovascular disease	3.2	4.2	0.85
Surgery (%)			
CABG	54.8	58.3	0.80
Valve	32.3	41.7	0.47
CABG+Valve	4 12.9	-	0.07
CPB duration (mins)	127 (60–400)	116 (74–186)	0.36
Cross clamp duration (mins)	90 (40–308)	93 (41–131)	0.73

Note: Data expressed in mean (±standard deviation) or median (minimum-maximum). Abbreviation: POCD, postoperative cognitive dysfunction; BMI, body mass index; CABG, coronary artery bypass graft.

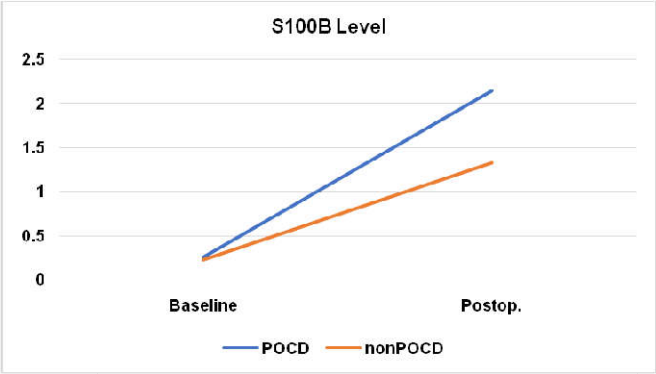

Fig. 2: The change of S100B level from the baseline value

Table 2: Changes in S100B level after surgery

S100B level (pg/ml)	POCD		p-value
	Yes (n = 31)	No (n = 24)	
Baseline	0.26 (0.08–20.58)	0.23 (0.08–0.49)	0.19
After surgery	2.15 (0.22–60.03)	1.33 (0.15–19.77)	0.16

Note: Data expressed in median (minimum-maximum). Abbreviation: POCD, postoperative cognitive dysfunction.

Table 3: Variable changes during and after surgery

Variables	POCD		p-value
	Yes (n = 31)	No (n = 24)	
PaO_2 (mmHg)			
Basal	155 [84–430]	222 [71–437]	0.09
During CPB	286.6±44.3	271.7±53.0	0.26
Post-CPB	262.4±101.0	251.7±106.4	0.70
6 hr post-op	143 [90–301]	157 [72–237]	0.36
24 hr post-op	129 [82–284]	134 [84–255]	0.98
Hb (g/dL)			
Basal	12.7±1.7	12.8±1.8	0.83
During CPB	8.4±1.6	8.8±1.3	0.38
Post-CPB	9.5±1.7	10.1±1.2	0.14
6 hr post-op	9.4±1.3	10.0±1.2	0.08
24 hr post-op	9.6 [7.3–12.3]	10.2 [6.4–12.1]	0.03*
SaO_2 (%)			
Basal	99 [95–100]	99 [93–100]	0.36
During CPB	99 [94–100]	99 [99–100]	0.51
Post-CPB	99 [91–100]	99 [94–100]	0.96
6 hr post-op	99 [95–100]	99 [94–100]	0.33
24 hr post-op	99 [96–100]	99 [96–100]	0.18
CaO_2 ml O_2/dL			
Basal	17.6±2.2	17.9±2.6	0.63
During CPB	12.2±2.2	12.6±1.8	0.38
Post-CPB	13.5±2.1	14.3±1.8	0.15
6 hr postop	13.1±1.7	13.9±1.7	0.10
24 hr postop	13.4±1.5	14.0±1.6	0.16
$ScvO_2$, %			
Basal	83.2±6.9	80.4±4.7	0.10
During CPB	85.2±6.7	83.5±7.1	0.34
Post-CPB	85.0±5.9	84.6±5.4	0.80
6 hr postop	76.0±7.5	75.2±5.6	0.66
24 hr postop	76.2±5.7	76.9±6.2	0.64

Note: Data expressed in mean (±standard deviation) or median (minimum-maximum). Abbreviation: POCD, postoperative cognitive dysfunction; CPB, cardiopulmonary bypass.

DISCUSSION

Incidence of POCD in this study was higher than in our previous study (56.4% vs. 40.7%) [4]. The oxygenation statuses in this study were maintained well during and after surgery, both in subjects with and without POCD. It is, therefore difficult to argue that neuronal damage that contributes to POCD stems from oxygenation changes. During open-heart surgery, especially during CPB, oxygenation is carefully controlled by the perfusionist. As the lung is bypassed, even on patients with preoperative lung damage, oxygenation can be well maintained. The only period where preoperative lung dysfunction may affect the oxygenation status is the period right before CPB starts. However, in this study, all subjects displayed good oxygenation status. The effect of anesthesia on the oxygenation status was also minimal, as the baseline blood gas values were obtained before the patients underwent anesthesia.

The oxygenation sufficiency in the blood does not directly reflect brain oxygenation sufficiency. The amount of oxygen extraction in this study was not evaluated. However, from our $ScvO_2$ data, we can infer that there was no imbalance between oxygen supply and demand [7, 8]. A drop in postoperative $ScvO_2$ value was observed, but there were no differences between subjects with and without POCD.

The hemoglobin level may also influence the oxygen content. There were no differences in the hemoglobin levels between subjects with and without POCD, except at 24 h after surgery (table 3). At this time, hemoglobin levels were found to be lower in subjects with POCD compared to subjects without POCD. However, this difference was subtle and not clinically significant.

This study suggests that neuronal damage is one of the causes of POCD, as the level of S100B, a neuronal damage marker, increased after surgery. S100B is known to have a damage-associated molecular pattern, which is released by a damaged cell or activated by stress. This protein also plays a role in inflammation [9]. In the literature, the normal S100B value is unclear, but the cut-off limit is 0.10 µg/l [10]. As a prognostic factor, changes in concentration or trends are more valuable than the absolute value [10].

The levels of basal S100B in all subjects had a wide range, but they were not different between subjects with and without POCD. After surgery, there was a wide range of S100B levels in subjects with POCD. The median value of S100B in subjects with POCD was 1.5x higher than in subjects without POCD. Even though this difference is not statistically significant, further investigation should be made on the effect of neuronal damage in POCD. Neuroinflammation during open-heart surgery is almost always linked to CPB. The use of synthetic cannulas, hemodilution, and microemboli during CPB are among the factors estimated to play a role in brain inflammation and brain oxygenation disturbance.

In our study, we found that there was no difference in the duration of CPB between subjects who experienced POCD and those who did not. The finding is also true for comorbidities, gender, and age of subjects. This finding is similar to that of a previous study in our hospital in 2017. Several theories have explained that the inflammation is due to surgical trauma [6]. However, this study showed that there is no meaningful difference between different surgeries in POCD and non-POCD subjects. As the anesthesia regimen was similar for all subjects, anesthesia may only affect brain perfusion indirectly, through hemodynamic changes. The limitation of this study is the lack of analysis of subjects' hemodynamics. Variation of hemodynamics (e. g., blood pressure fluctuations) has the potential to compromise organ perfusion, including in the brain. Further studies should consider cerebral oxygenation monitoring and correlation analysis between hemodynamic fluctuations, cerebral perfusion, and POCD incidence.

The statistical difference in this study is not meaningful, probably due to the small number of samples. The limitation of this study was that the evaluation of S100B after surgery was only assessed once at 6 h post-surgery. Further studies should aim to assess S100B levels

at 24 h post-surgery, as this may better reflect the peak level. In traumatic brain injury cases, the serum S100B levels peaked in the first 24 h following trauma and decreased after [9–11].

CONCLUSION

In conclusion, this study showed that the S100B serum levels were higher in POCD patients. Therefore, the S100B level has the potential to be a biomarker for predicting POCD after open-heart surgery.

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Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

All authors have none to declare.

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