Role of S100B, sTNFR-1, lactate, ScvO2, and SctO2 measured by NIRS as predictor of neurological deficit in pediatric congenital heart surgery

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Abstract

***Background*: Process related to systemic inflammatory response syndrome (SIRS) in congenital heart disease (CHD) surgery using cardiopulmonary bypass (CPB) machine often causes post-operative complications. This process begins with mitochondrial dysfunction in SIRS, initiated by the release of inflammatory mediators such as tumor necrosis factor receptor-α (TNF-α) and soluble tumor necrosis factor receptor-1 (sTNFR-1). Neurological injury following pediatric congenital heart surgery remains common. Studies related to brain-derived protein (S100B) biomarker for cerebral hypoxia caused by microcirculation and mitochondrial dysfunction as a consequence of SIRS in CPB or pediatric CHD surgery have yet to be conducted. Observation to identify cerebral hypoxia is necessary due to the fact that early stages of cerebral hypoxia are often asymptomatic. Near-infrared spectroscopy (NIRS) is a tool used for observing oxygen delivery to the brain by measuring cerebral oxygen saturation (SctO2). In Indonesia, NIRS remains uncommon and no study has been conducted to date.**

***Objectives*: To evaluate the role of S100B, sTNFR-1, lactate, and superior vena cava and cerebral saturations as predictors of neurological injury in CHD patients undergoing corrective surgeries, as measured using NIRS during and after surgical procedure.**

***Methods*: This was a prospective cohort study. Inclusion criteria were pediatric patients with CHD aged 1 month to 6 years old undergoing corrective surgery. Exclusion criteria were patients with Down syndrome, single coronary artery, and not consented to participate in the study. For analysis, subjects were divided into 2 groups: (1) those with neurological deficits and (2) those without neurological deficits. All subjects were observed closely in intensive care unit (ICU) until they were discharged. Blood examinations were performed 3 times: before surgery, after CPB, and 4 hours after CPB.**

***Results*: Fifty-one patients were observed from March to October 2015. Significant differences were observed in the value of S100B, STNFR-1, lactate, and area under the curve (20% AUC) baseline for cerebral saturation between both groups, as measured using NIRS. Those parameters could be used as predictors of post-CPB neurological deficit incidence in children with CHD.**

***Summary*: In CHD patients undergoing corrective surgery, S100B value, sTNFR-1, lactate, and 20% AUC baseline for cerebral saturation could be used as predictors of neurological deficit following corrective surgery.**

Key words: S100B, sTNFR-1, lactate, ScvO2, congenital heart surgery, CPB, NIRS.

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Introduction

Congenital heart disease (CHD) is the most common congenital disease, contributing up to 30% of total congenital disease cases. In Indonesia, 45,000 babies were born with CHD, with 25% of them needing surgical intervention in their first year of life. Data from the Cardiac Service Center of Cipto Mangunkusumo National General Hospital in 2009-2010 showed 11% mortality in 37 babies aged less than 24 months old undergoing surgical correction for tetralogy of Fallot (ToF). (1,2)

Systemic inflammatory response syndrome (SIRS) in CHD surgery with cardiopulmonary bypass machine (CPB) often causes post-operative complications. (3-5) Mitochondrial dysfunction in SIRS starts with the release of inflammatory mediators, such as Tumor Necrosis Factor α (TNF-α), which binds to TNF receptor on the cell surface, releasing soluble TNF receptor (sTNFR-1 and sTNFR-2). (6-8) Neurological injury (shock, ischemic lesions, and encephalopathies) after pediatric heart surgery remains common. Prospective studies showed cognitive and motor impairment, as well as cerebral palsy. (9-11) SIRS affecting the brain correlated with the degree of hypoxia in the brain. (12,13)

Studies on brain-derived protein (S100B) measurements have been conducted in neonatal patients with hypoxia-ischemia, children with head injury, post-cardiopulmonary resuscitation, and septic shock. Those studies reported good prognostic value towards the reduction of neurological symptoms and death. Data from previous study showed an increase in S100B during brain cells injury. A study on S100B as a biomarker for cerebral hypoxia caused by microcirculation and mitochondrial dysfunction as a consequence of SIRS has yet to be conducted in pediatric CHD surgery with CPB. Measurements of cerebral hypoxia is necessary since it is often asymptomatic at early stage. Near-infrared spectroscopy (NIRS) could study the oxygen perfusion in the brain by measuring cerebral oxygen saturation (SctO2), which is safe for pediatric population due to its noninvasive and non-ionizing radiation properties. NIRS is rarely utilized in Indonesia and no study has been conducted as of yet. (14-16)

Methods

This was a prospective cohort study conducted to investigate the association between S100B, sTNFR-1, lactate concentration, central vein saturation (ScvO2), and cerebral oxygen saturation and the incidence of neurological deficits in CHD patients following surgery with CPB. A prediction model for neurologic deficiency was developed with multivariate analysis.

The study was conducted at the Cardiac Service Center of Cipto Mangunkusumo National General Hospital and Jakarta Heart Hospital. Blood samples were analyzed at the Immunoendocrinology Integrated Laboratory of Faculty of Medicine, Universitas Indonesia. The accessible population consists of pediatric patients undergoing corrective surgery at the Cardiac Service Center of Cipto Mangunkusumo National General Hospital during the study period.

We analyzed the effect of hypoxia in CHD patients undergoing cardiac surgery using cardiopulmonary bypass on several parameters, including S100B, sTNFR-1, lactate, and ScvO2 concentration in the blood. The first blood sample was taken prior to surgery from the central vein catheter during anesthesia. The second blood sample was taken immediately following off bypass (in operating room). The third blood sample was taken 4 hours after off bypass (in the ICU). In addition to blood examinations, all patients were monitored using NIRS to measure their cerebral oxygenation (SctO2).

Descriptive data were presented in the forms of texts, tables, and graphs; the data were reported as mean with standard deviation (SD) when the distribution was normal, otherwise as median with a range of minimum and maximum interquartile (IQ). Confidence interval was presented for all data, if appropriate. Comparison of both groups (CHD patients undergoing corrective surgery with and without complication) was based on the subjects' characteristics. Independent T-test was used for normally distributed numerical (continuous) data, and Mann-Whitney was used for non-normally distributed data. Chi-square was used for categorical data to compare the proportion of the subjects' characteristics between groups. Study effectiveness was measured using delta mean difference between observation of treatment groups and ANOVA was performed if several assumptions were fulfilled. The assumptions were delta distribution following normal distribution and delta covariant matrix were homogenous between groups. If the assumptions were not fulfilled, Mann-Whitney test was used instead.

Results

Samples were taken from March to September 2015. The study was conducted in the operating room and the ICU of Cardiac Service Center of Cipto Mangunkusumo National General Hospital and Jakarta Heart Hospital. Subjects were recruited consecutively (using non-probability consecutive sampling methods) based on inclusion and exclusion criteria. The total number of subjects studied until September 30, 2015, were 51 patients

(**Table 1**).
In this study, subjects were followed-up after surgery, since they were transferred to ICU until they were discharged from the hospital. During the observation phase, 11 patients developed neurological deficits. The manifestations of neurological deficit varied from being irritable to death (**Table 2**).
For analysis, subjects were grouped based on the presence of neurological deficit after surgery, and parameters were compared between both groups. Serum S100B level and cerebral oxygen concentration at the end of CPB were regarded as parameters of cerebral hypoxia, serum sTNFR-1 level was regarded as mitochondrial dysfunction parameter, lactate was regarded as microcirculation dysfunction parameter, while ScvO2 was regarded as systemic hypoxia parameter (**Figure 1**).
In the group with neurological deficit, the median value of S100B, sTNF-1, lactate, ScvO2 and 20% area under the curve (AUC) baseline for cerebral saturation were 355.72 pg/ml, 4144.24 pg/ml, 3.20 mmol/l, 71.00%, and 2827 min%, respectively. In the group without neurological deficit, the median value of S100B, sTNF-1, lactate, ScvO2, and 20% AUC baseline for cerebral saturation were 150.06 pg/ml, 2409.27 pg/ml, 1.90 mmol/l, 79.60%, and 794.5 min%, respectively. This study showed statistically significant differences in the value of S100B, STNFR-1, lactate, and 20% AUC baseline for cerebral oxygen saturation between both groups (**Table 3**).
Survival function as a predictor of neurological deficit was then calculated using the parameters showing statistical significance.
The survival function was calculated using the following formula:

$$S(t) = [S_{0(t)}]^{\exp(1.51 * S100B + 2.51 * sTNF + 1.09 * Lactate + 1.57 * AUC\ 20\% + 0.03 * duration\ of\ CPB)}$$

Where: S=survival, t=time, exp=exponential.

In order to obtain prediction models for neurological deficits in the surgical correction of congenital heart disease, bivariate analysis was performed to show the relationship between variables studied with the incidence of neurological deficits. The cut-off points of S100B, lactate, STNFR-1, ScvO2, 20% AUC, and the duration of CPB associated with neurological deficits were calculated using receiver operating characteristic (ROC) analysis.
Based on the performed analysis and considering the specificity and likelihood ratio (LR)+, the cut-off value determined for S100B level, sTNFR-1, lactate, ScvO2, and 20% AUC were ≥333.8 pg/ml, ≥3178.8 pg/ml, ≥2.6 mmol/l, <75.5%, and was ≥1227 min%, respectively (**Table 4**).
After determining the cut-off points, co-linearity between variables that would proceed into modeling was tested. Co-linearity was observed between both NIRS variables; thus, 20% AUC was selected over 25% AUC due to the fact that the first variable was considered as an earlier alarm for a disturbance on cerebral oxygenation. Cox's proportional hazards regression models was performed as the final step. Through these measures, prediction models for neurological deficits in CHD correction surgery were finally obtained. Because NIRS is not widely available and limited only in certain hospitals, we created 2 prediction models: one with NIRS and another one without NIRS (**Table 5**).
Using the aforementioned model with NIRS as the predictor variable, the cut-off score used as a predictor of neurological deficit incidence in CHD surgery was 1596 (**Table 6**).

Discussion

This study was conducted on children to investigate the association between S100B level following corrective procedure using cardiopulmonary bypass technique with the incidence of neurological deficit following the surgery. All patients were observed before and during surgery in the ICU until they were transferred to the ward. Observations were made on the clinical conditions, laboratory results, and other studied parameters.
The comparison of S100B concentrations in both groups (with and without neurological deficit) was analyzed. A study by Abu-Sultaneh et al on neonates undergoing corrective surgery for CPB found that the mean concentration of S100B was elevated during CPB. Pre-surgical concentration was 55+38 pg/ml, which was elevated to 610+38 pg/ml at the end of CPB. (14)
Comparison of sTNFR-1 level between groups was measured using ligand pairs TNF-α (TNF-1), known to have better prognostic value than TNF-α. The inflammatory effect of TNF-α occurs following binding to two receptors on the cell's surface which are sTNF-1 (sTNFR-1) and sTNF-2 (sTNFR-2). As a response, soluble TNF receptors (sTNFR-1 and sTNFR-2) will be released from the cells. sTNFR will bind to TNF-α and competes on the cell's surface receptors. This result is in accordance with that of Shabaan Ali et al, (15) which concluded that the increasing concentration of S100B after surgery was due to proinflammatory cytokine activation, which was also increased after surgery.
Comparison of lactate concentration between both

groups was performed by measuring lactate concentration in patients undergoing open-heart surgery. It was aimed to observe the presence of tissue perfusion disorder caused by cardiopulmonary bypass machines. Hyperlactatemia presenting after heart surgery originated from the decreased blood flow caused by either low stroke volume or low blood flow during cardiopulmonary bypass procedure. Therefore, increasing lactate can be reduced by improving blood flow.

Comparison of ScvO2 concentration between both groups was performed to describe the mixed venous saturation from the surface of the upper body, lower body, and coronary sinus. The blood was taken from the pulmonary artery catheter. This method is rarely used in children; thus, a central vein catheter was used instead. However, the perfusion of organs in the lower body will be less than the brain during shock, leading to a decrease in the saturation of inferior vena cava.

SctO2 concentration between groups was compared using NIRS. NIRS is a diagnostic tool used to monitor the distribution of oxygen to the brain by measuring cerebral oxygen saturation. This technology is safe, especially for pediatric patients, due to its non-invasive and non-ionizing radiation properties. NIRS is rarely utilized in Indonesia and literatures discussing the utilization of NIRS in Indonesia remains limited to date. A study performed by Abu-Sultaneh et al in neonatal patients undergoing CHD surgical correction found SctO2 concentration ranged from <50, arterial-cerebral saturation difference (da-SctO2) >50 and AUC<50. These values were observed to be increased in CHD patients with below-threshold cerebral saturation in the middle of surgical correction with lung-heart bypass machine. (14)

Conclusion

In CHD patients undergoing surgical correction, CPB, S100B, sTNFR-1, lactate, and AUC 20% baseline of cerebral saturation can be used as predictors of neurological deficit incidence after the surgery.

Table 1. Variables of patient

Variables	All patients (n=51)	Neurological deficit (-) (n=40)	Neurological deficit (+) (n=11)
Gender, n - Male - Female	 24 27	 18 22	 6 5
Age (month), median (range)	22 (3.00-76.00)	34 (4.00-76.00)	14 (3.00-73.00)
Weight (kg), median (range)	9 (3.40-21.00)	10.15 (3.40-18.00)	8.00 (3.50-21.00)
Height (cm), median (range)	77 (50.00-121.00)	84.50 (50.00-118.00)	70.00 (50.00-121.00)
Nutrition status (weight/height), n - Normal - Mild malnutrition - Moderate malnutrition - Severe malnutrition	 19 19 6 7	 14 16 4 6	 5 3 2 1
Cyanotic CHD, n	31	21	10
Aristotle basic score, mean (SD)	7.03 (1.74)	6.71 (1.63)	8.20 (1.71)
Duration of surgery (minutes), median (range)	190 (95-420)	180 (95-310)	225 (155-420)
Duration of CPB (minutes), mean (SD)	81.18 (36.98)	75.40 (33.66)	102.55 (42.17)
Core temp (°C), median (range)	32.00 (30.00-35.00)	32.30 (30.50-35.00)	31.90 (30.00-35.00)
Duration of ICU (days), median (range)	3.00 (1.00-19.00)	2.00 (2.00-10.00)	4.00 (1.00-19.00)
Duration of intubation (hours), median (range)	26.00 (4.00-244.00)	21.00 (7.00-198.00)	98.00 (4.00-244.00)
AUC 20% baseline 24h (minute%), median (range)	804.00 (3.00-15545.00)	794.5 (10.00-5395)	2827.00 (3.00-15545)
AUC 25% baseline 24h (minute%), median (range)	655.00 (0-13064)	484.5 (4.00-2785)	2132.00 (0.00-13064)

Legend: CHD=congenital heart disease; CPB=cardiopulmonary bypass; ICU=intensive care unit; AUC=area under the curve.

Table 2. Types of neurological deficit

Neurological deficit	N
LMN type of paraplegia	1
Decreased level of consciusness	1
Behaviour disorder (irritable)	2
Ischemic infark	2
Mortality	5
Total	11

Legend: LMN=lower motor neuron.

Table 3. Comparison of S100B, sTNFR-1, lactate, and ScvO2 in 3 sampling times

	Neurological deficit	Pre-surgery Median (range)	Off CPB Median (range)	4h after off CPB Median (range)
S100B	Yes	13.37 (2.89-351.39)	355.72 (50.32-1230.61)	148.90 (24.48-1032.47)
	No	8.57 (1.58-166.30)	150.66 (3.08-748.82)	16.87 (2.41-229.16)
	p	0.043	0.007	0.000
sTNFR-1	Yes	728.5 (538.1-1288.5)	4144.2 (1688.3-7879.3)	2765.3 (908.9-7633.8)
	No	670.5 (314.5-1703.5)	2409.2 (931.3-6802.6)	1176.4 (666.4-2201.8)
	p	0.196	0.001	0.000
Lactate	Yes	1.2 (0.4-6.5)	3.2 (1.1-9.4)	3.3 (1.4-8.9)
	No	1.3 (0.5-5.4)	1.9 (0.6-4.0)	1.6 (0.6-3.9)
	p	0.215	0.019	0.002
ScvO2	Yes	81.5 (59.4-84.9)	71.0 (28.2-87)	71.7 (33.9-86.8)
	No	80.5 (42.8-95.1)	79.6 (52-94.4)	77.95 (59-89)
	p	0.606	0.070	0.090

Legend: S100B=brain-derived protein; sTNFR-1=soluble tumor necrosis factor receptor-1; ScvO2=central vein saturation; CPB=cardiopulmonary bypass.

Table 4. Relationship between predictor variables with neurological deficit incidence

Predictor variables	Neurological deficit, n (%)		HR (CI 95%)	p
	Yes	No		
S100B - ≥333.8 - <333.8	 7 (63,64) 4 (36,36)	 7 (17.5) 33 (82.50)	6.372 (1.854-21.903)	0.003
sTNF-1 - ≥3178.81 - <3178.81	 9 (81.82) 2 (18.18)	 8 (20.0) 32 (80.0)	8.647 (1.210-61.76)	0.032
Laktat - ≥2.6 - <2.6	 7 (63.64) 4 (36.36)	 8 (20.0) 32 (80.0)	4.909 (1.432-16.827)	0.011
AUC 20% - ≥1227 - <1227	 9 (81.82) 2 (18.18)	 11 (27.50) 29 (72.50)	8.745 (1.884-40.605)	0.006
AUC 25% - ≥971 - <971	 8 (72.73) 3 (27.27)	 10 (25.0) 30 (75.0)	5.941 (1.571-22.452)	0.009
Duration of surgery (minute)	254.73 (SD 23.50)	189.53 (SD 8.27)	6.285 (1.356-29.131)	0.002
Duration of CPB (minute)	102.54 (SD 12.72)	75.3 (SD 5.32)	2.529 (0.671-9.543)	0.003

Legend: S100B=brain-derived protein; sTNF-1=soluble tumor necrosis factor-1; AUC=area under the curve; CPB=cardiopulmonary bypass; HR=hazard ratio; CI=confidence interval; SD=standard deviation.

Table 5. Prediction model using NIRS as predictor variable

Variables	Coefficient	SE	z	p	CI 95%	Score
S100B≥333.8	1.51	0.73	2.08	0.037	0.08-2.93	13
sTNF≥3178.81	2.51	1.00	2.15	0.032	0.19-4.12	14
AUC 20% 24h baseline ≥1227	1.57	0.96	1.62	0.105	-0.33-3.47	11
Lactate	1.09	0.71	1.53	0.125	-0.30-2.48	10
Duration of CPB (minute)	0.03	0.01	2.79	0.005	0.01-0.05	18

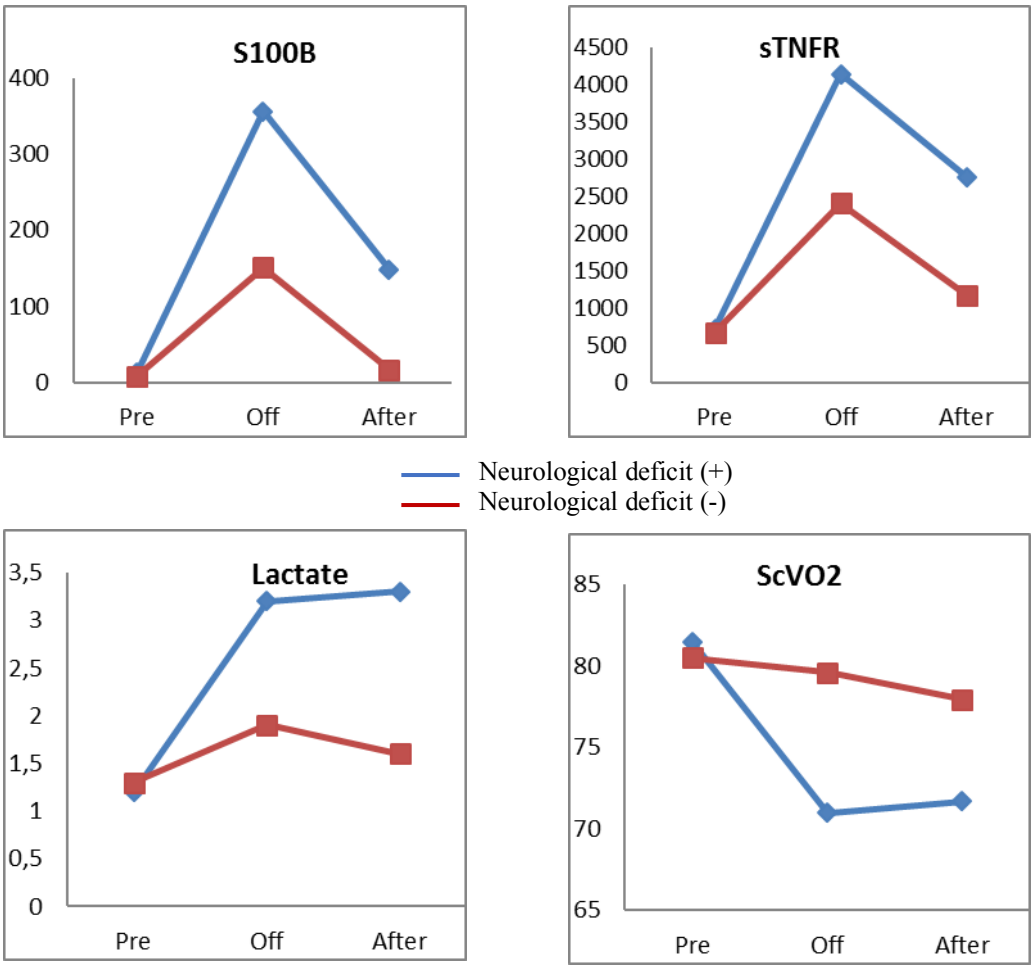
Legend: NIRS=near infrared spectroscopy; S100B=brain-derived protein; sTNF=soluble tumor necrosis factor; AUC=area under the curve; CPB=cardiopulmonary bypass; SE=standard error; CI=confidence interval.

Table 6. Cut-off point prediction model using NIRS as predictor variable

Score	Neurological deficit (+) n=11	Neurological deficit (-) n=40	Total n=51	p
<1596	4	28	32	0.041
>1596	7	12	19	

Legend: NIRS=near infrared spectroscopy.

Figure 1. Graphics showing comparison of serum level of S100B, sTNFR, lactate, and ScvO2 between groups with neurological deficit and without neurological deficit



Legend: S100B=brain-derived protein; sTNFR=soluble tumor necrosis factor receptor; ScvO2=central vein saturation.

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