Original Article

The Relationship between s100β and Cerebral Oximetry Trend in Patients Undergoing CABG with Cardiopulmonary Bypass

Kamal Fani[1], Mona Hashem-Aghaei[1], Hossein Ali Jelveh-Moghaddam[1], Golnar Radmand[1], Mahnoosh Foroughi[2], Samira Rajaei[3], Ali Dabbagh[1*]

Abstract

Background: Coronary artery bypass grafting (CABG) is among the most common cardiac surgery procedures carried out on heart pump. However, there are always risks for potential neurologic and neurocognitive insults in CABG. One of the biomarker of central nervous system (CNS) is s100β that shows damage. Cerebral oximetry using near-infrared spectroscopy (NIRS) developed for CNS monitoring especially in cardiac surgery. This study was designed to find the relationship between serum levels of s100β and cerebral oximetry in CABG patients.

Materials and Methods: In an observational study, 44 adult patients (40-75 years) entered the study for elective CABG. Serum levels of s100β were assessed at two times during cardiopulmonary bypass (CPB); i.e. just after aortic clamping and immediately after aortic declamping; while the results were compared with right and left cerebral oximetry readings NIRS. It was measured at baseline, during start of cardiopulmonary bypass (CPB), during aortic clamping, and finally at off-clamping the aorta. Repeated Measures ANCOVA (analysis of covariance), multiple linear regression models and Spearman correlation coefficient with scatter plot were used for data analysis. P value less than 0.05 considered significant.

Results: There was no linear correlation between s100β and NIRS according to correlation coefficients. The only positive linear relationship between s100β and right NIRS was observed among patients whose s100β was more than 10 (spearman correlation coefficient= 0.792; P value=0.006).

Conclusion: This study failed to demonstrate a relationship between on-CPB NIRS numbers and serum s100β in adult patients undergoing CABG during the bypass interval; further studies are suggested to evaluate potential predictive value of NIRS in brain ischemia related to CABG.

Keywords: Cardiopulmonary bypass, cerebral oximetry, near infrared spectroscopy, S100 Calcium Binding Protein beta Subunit

Please cite this article as: Fani K, Hashem-Aghaei M, Jelveh-Moghaddam H A, Radmand G, Foroughi M, **Rajaei** S, et al. The relationship between s100β and cerebral oximetry trend in patients undergoing CABG with cardiopulmonary bypass. J Cell Mol Anesth. 2018;3(2):47-53.

1. Anesthesiology Research Center, Cardiac Anesthesiology Department, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Cardiovascular Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3. Department of Immunology, School of Medicine, Tehran University of Medical Science, Tehran, Islamic Republic of Iran

Corresponding Author: Ali Dabbagh, MD, Professor, Anesthesiology Research Center, Taleghani Hospital, Velenjak, Chamran Exp Way, Tehran, Iran; Tel/Fax: +982122432572; cell phone: +989121972368.
Email: alidabbagh@yahoo.com; alidabbagh@sbmu.ac.ir

Introduction

Cardiac diseases impose a great burden on human health and coronary artery diseases are one of the most important titles in this category. Coronary artery bypass grafting (CABG) is among the most common therapeutic options for coronary artery disease (CAD) with an annual number of 400,000 in the US (1-3).

Coronary artery bypass grafting is often performed as on pump surgery. There are a number of drawbacks for CABG when using cardiopulmonary bypass (CPB) including the risk for potential neurologic and neurocognitive insults mainly due to hypoperfusion state, embolic events and inflammatory response. A number of cellular and subcellular biomarkers used for assess the effects of CPB on different organ functions (2, 4-9). The commonly used biomarkers tracking the trend of potential central nervous system (CNS) damage in patients undergoing cardiac surgery with or without CPB is s100β (10-14). On the other hand, a number of CNS monitoring instruments developed to monitor and to help CNS protection during a range of procedures especially cardiac surgery. Cerebral oximetry using near-infrared spectroscopy (NIRS) is mentioned as a relatively novel and common monitoring system (14-19). There is still uncertainty regarding the net predictive value of cerebral oximetry regarding cerebral tissue oxygenation (14, 20). In other words, if cerebral oximetry is valid and reliable monitor for cerebral perfusion, and s100β increases with hypoperfusion and hypoxic injuries in the brain, then there might be a direct relationship between serum levels of s100β and cerebral oximetry readings.

This observational study was designed and implemented to find any potential relationship between serum levels of s100β (considered as one of the CNS neuromarkers of cerebral injury) and cerebral oximetry readings to find out whether the readings of cerebral oximetry by NIRS are in concordance with serum levels of s100β.

Methods

Protocol of the study was confirmed by the Institutional Ethics Committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

For each patient, before commencement of the study, written informed consent was obtained. The study was performed from 1st of April 2017 to the end of November 2017; in cardiac surgery operating room, Shaheed Modarres Hospital affiliated by Shahid Beheshti University of Medical Sciences.

All patients entered the study after written informed consent was taken based on the Institutional Ethics protocols. Patients were aged 40-75 years and patient with emergency procedures were excluded. All were managed by the same surgical, anesthesiology and perfusion team and all were transferred to the same adult cardiac ICU. Likewise, each clinical steps in anesthesia, surgery, cardiopulmonary bypass and ICU care strictly followed standard institutional protocols; including range of temperature manipulation, protocols for anesthetic drugs, organ protection and CPB and blood transfusion guidelines including during CPB.

There was a particular NIRS management protocol which was strictly employed. This protocol was adopted from the protocols described by Denault et al. (21), Murkin et al. (18, 19) and discussed in detail in a number of texts (22). Right and left cerebral oximetry readings NIRS were measured at baseline, at the start of CPB, during aortic clamping, and finally at off-clamping of the aorta.

Human s100β ELISA kit was used (IBL-America; Immuno-Biological Laboratories; Minneapolis, MN; United States). Samples for assessment of serum levels of s100β were collected at two times during CPB (at the time of aortic clamping and immediately after aortic declamping) through the following steps; Non-heparinized blood was drawn from the arterial line of the bypass circuit, then they were centrifuged at 2500 G for 10 minutes at 4°C, the samples were refrigerated at -18°C inside the stat laboratory of the operating room, afterwards, they were transferred using ice box at -70°C to the immunology laboratory, after collecting all the samples, they were defrosted for to undergo ELISA testing. We recorded the right and left side NIRS, arterial blood gas analyses (ABG), blood sugar, temperature and s100β at baseline point, at the starting point of CBP and at the "off-clamp time" for each patient. To prevent s100β release from other sources as much as possible, we never used cell saver

in any of the patients (23).

All quantitative variables demonstrated as mean±SD; also, qualitative variables demonstrated as percentage. To compare quantitative variables in 2 different times, paired t-test or non-parametric Wilcoxon test were used if needed. Repeated Measures ANCOVA (analysis of covariance) was used to adjust the effects of confounding variables (e.g. the baseline values) on comparing variables in different times. The mean differences of variables (between two times), which had significant confounders, are presented in table 4 at different levels of confounder variable. Multiple linear regression models were used for assessing the effect of other variables on the difference of s100β levels between two times and the best models were selected using forward, backward and stepwise methods. The mean difference of s100β at different levels of PaO2 and blood sugar are presented in Table 5. The Spearman correlation coefficient with scatter plot was used to evaluate the linear correlation between NIRS and s100β values. All of the statistical tests were two-tailed at α= 0.05 and SPSS version 18 (SPSS Inc, Chicago, IL, United States) was used for data entry and analysis.

Results

A total of 44 patients including 15 (34.1%) female and 29 (65.9%) male were entered to this study. The main characteristics of patients and the results of diagnostic assessments are presented in Table 1.

The right and left side NIRS, ABG, blood sugar and temperature were evaluated at baseline, on-CBP, aortic clamping and off-clamp times for each patient; while s100β was measured during CPB just at the time of aortic clamping and at aortic declamping (Table 2). The both side NIRS at off-clamp time were significantly more than on-CBP (right side: P value=0.003; left side: P value =0.007). Also the patients had higher PaO_2 (P value<0.001) on CBP rather than off-clamp time. The blood sugar, temperature and s100β at off-clamp time were more than on-CBP (P values: <0.001, 0.002 & 0.002, respectively; Table 2). After adjusting the effect of baseline values just the differences of PaO_2 and temperature remained significant (P value=0.005 & 0.004, respectively).

Table 1: Main characteristics of study patients and results of diagnostic assessments (N= 44)

N= 44	
Age	57.20±13.24
Gender	
Female	15 (34.1%)
Male	29 (65.9%)
Underlying Disease	
Drug History	17 (38.6%)
Cerebrovascular Accidents	1 (2.3%)
Hypertension	7 (15.9%)
Others	6 (13.6%)
None	13 (29.5%)
Carotid Doppler Result	
Normal	27 (61.4%)
Non-significant Stenosis	17 (38.6%)
Significant Stenosis	0 (0.0%)
Ejection Fraction (EF; mean±SD)	51.82 ± 8.83
Pulmonary Artery Pressure (PAP± mean±SD)	32.42 ± 17.34
Time of cross clamp (minutes; mean±SD)	63.82 ± 23.18
Cardiopulmonary Bypass (CPB) time(minutes; mean±SD)	106.86 ± 33.44
Number of used packed cells (mean±SD)	1.41 ± 1.30

The mean differences of on-clamp and off-clamp times for NIRS and temperature were also presented at different levels of their baseline values. The results show that for patients with 60 ≤baseline NIRS ≤69, off-clamp NIRS was more than on-CBP (right side: P value = 0.010; left side: P value=0.025). And for patients with baseline temperature>35, the off-clamp temperature was significantly more than

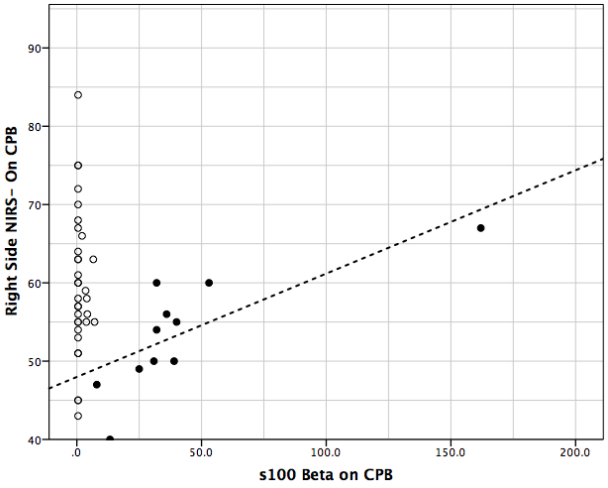

Figure 1. Correlation between s100β and right sided on-CPB NIRS.

Table 2: Results of Outcome Variable Assessments

	Baseline	On-CPB	Off-clamp	difference	P-value	P_{adj}*
NIRS						
Right Side	63.36±10.04	58.22±9.00	62.84±9.66	4.61±9.71	0.003	0.613
Left Side	64.02±10.67	58.98±7.30	62.89±9.76	3.91±0.007	0.007	0.692
HCT	40.57±6.97	24.05±5.04	24.29±3.05	0.25±5.49	0.764	0.266
$PaCO_2$	37.59±8.50	36.77±5.87	35.34±5.44	1.43±5.85	0.112	0.912
PaO_2	227.55±134.16	386.00±69.51	316.05±58.69	69.95±95.81	<0.001	0.005
Blood Sugar	143.93±56.93	162.57±47.04	179.39±46.87	16.82±29.50	<0.001	0.004
Temperature	35.66±1.14	33.80±1.52	34.84±1.26	1.04±2.12	0.002	0.051
s100β	---	11.72±27.05	39.38±58.85	27.66±56.94	0.002	---

* P_{adj}: p-value of difference between on-CPB and off-clamp Adjusted for the baseline value.

Table 3: Difference of NIRS and Temperature between on-CPB & off-clamp at different groups of their baseline values

	Difference between on-CPB & off-clamp values (mean ± SD)	P value
Right side NIRS (Baseline)		
≤59	3.47±10.20	0.209
60-69	6.72±9.80	0.010
≥70	2.73±9.10	0.344
Left side NIRS (Baseline)		
≤59	2.23±9.28	0.403
60-69	5.15±9.47	0.025
≥70	3.64±8.69	0.195
Temperature (Baseline)		
≤35	1.25±2.54	0.068
>35	0.93±1.88	0.015

Table 4: Difference of s100β between on-CPB & off-clamp at different groups of confounders

	Difference (mean ± SD)	P value
PaO_2 (baseline)		
≤102	3.43±32.69	0.690
103-322	10.79±27.43	0.149
>322	71.70±75.32	0.003
Blood Sugar (baseline)		
≤105	28.11±49.27	0.044
106-155	1.84±31.35	0.823
>155	58.79±70.73	0.008

on-CBP (P value=0.015; Table 3).

The patients with PaO_2>322 had higher off-clamp s100β rather than on-CBP time (P value=0.003). Also for patients with blood sugar≤105 or >155, the s100β at off-clamp was more than on-CBP time (P value=0.044 and 0.008, respectively; Table 4).

There was no linear correlation between s100β and NIRS according to correlation coefficients (Table 5). However, the scatter plots showed that there could be a positive linear relationship between s100β and right NIRS among the patients whose s100β>10 (spearman correlation coefficient= 0.792; P value=0.006; Table 5 and Figure 1).

Our follow up for potential neurologic complications was a short time follow (i.e. less than 2 weeks); while in this time period we did not discover any evidence of new onset major clinical neurologic injury as a consequence of operation.

Discussion

The results of the current study demonstrated that in the majority of the measurements, there was no significant correlation between intraoperative s100β

Table 5: Correlation between s100β and NIRS

	Right side NIRS		**Left side NIRS**	
	CC*	P-value	CC*	P-value
s100β (all values)				
On CBP	-0.235	0.124	-0.201	0.190
Off-clamp	-0.058	0.706	-0.165	0.285
	Right side NIRS		**Left side NIRS**	
	CC*	P value	CC*	P value
s100β>10				
On CBP	0.792	0.006	0.567	0.087
Off-clamp	-0.123	0.574	-0.124	0.573

* Spearman Correlation Coefficient.

and NIRS readings in adult cardiac surgery patients. There are many studies measuring serum levels of S100β which focus on cerebral emboli; on the other hand, cerebral oximetry may not be a particularly good monitor for the microembolies that are seen during cardiac surgery. It might be a good monitor for a very large, global embolic phenomenon of the brain, although this would be an extraordinarily rare event. This limitations of cerebral oximetry, as described in our study, could be one of the main reasons for our results.

To our knowledge, this study is the first one assessing such a correlation during the intraoperative period. However, in another study by Harilall et al, the authors found a highly significant relationship between postoperative s100β and intraoperative interventions based on intraoperative clinical interventions suggested by Murkin et al. (18, 19) and Denault et al (21, 22); though, our sample size was twice the sample size of that study (24). The only significant correlation was between on-CPB NIRS numbers and s100β; however, none of the other ones had significant correlation; which suggests a re-thinking about the predictive value of NIRS as a surrogate outcome for assessment of cerebral function and prevention of ischemia. On the other hand, it seems that more sophisticated studies are needed before we could say the final word about this predictive value of NIRS (4, 14).

NIRS explains the balance of the demand/supply of oxygen in the frontal cortex of the brain and is used to assess relative adequacy of cerebral perfusion during hypoperfusion state of CPB with undetermined validity to predict neurologic events. In a number of studies, NIRS was demonstrated as a useful instrument for assessment of cerebral autoregulation; suggesting NIRS as a "means for individualizing MAP during CPB" (25-27). However, this is not a constant finding in all studies; in fact, at times, there is even controversial evidence about correlation of NIRS pathologic findings and postoperative cognitive dysfunction; for example Kok et al. showed high proportion of cognitive dysfunction in CABG patients with low incidence of abnormal NIRS findings (20). Also, Vranken et al have explicitly claimed in their review that there is lack of "clear evidence for a defined desaturation threshold requiring intervention during CPB" (14). In concordance with the two latter studies, the results of our study demonstrated at the neuromarker levels that NIRS readings failed to have a strong correlation with s100β during CPB in adult patients undergoing CABG.

There were a number of limitations in our study which are mentioned here:

1. We had a limited sample size due to budgetary limitations; also, we checked s100β for two times; while, more frequent assessments with a resulting area under curve (AUC) of s100β would be possibly more decisive. Taking into account the inter-individual variability of cerebral oxygen saturation (ScO2) readings and the high variability of biomarkers in the setting of cardiac surgery, a correlation analysis, comparing NIRS values and s100 β levels in two time points could be improved if we could assess and analyze the AUC of perioperative desaturation (in comparison to baseline) and analyzing the time course of s100 beta (up to its maximum that occurs typically 12 to 24 hours after surgery).
2. Our patient population included only the adult patients while the pediatric patients should be assessed in different studies especially considering the type of operations in pediatric population; i.e. congenital heart diseases in the this patients group with more susceptible brain tissue (28, 29)
3. Another limitation of the current study was measuring only s100β; in fact, s100β is a neuromarker that shows neuronal cell damage; while other neuromarkers including neuronspecific enolase (NSE), glial fibrillary acidic protein (GFAP) and

brain-derived neurotrophic factor (BDNF) were studied in other studies but we did not assess them here; meanwhile, our sample size was pretty larger than the sample size of study by Sanchez-de-Toledo et al (29)

4. There are studies demonstrating a heterogeneity of non-brain sources for S100B during surgery; though in the context of surgery there is well documented release of S100B from non-cerebral tissues, this marker was chosen to assess the predictive value of NIRS in brain ischemia since it is the most commonly studied one; however, supplementary studies including cognitive testing or brain imaging could add to our knowledge regarding the predictive value of NIRS in the perioperative period

5. Finally, this study was an observational one and combined interventions in future designs could lead us to more precise determination of the NIRS role as a surrogate outcome and a valid and reliable monitor for potential CNS ischemia and injury.

Conclusion

In brief, this study failed to demonstrate a relationship between on-CPB NIRS numbers and serum s100β in adult patients undergoing CABG during the bypass interval. Further studies are suggested to evaluate potential predictive value of NIRS as a surrogate index in brain ischemia assessment.

Acknowledgment

This research has been financially supported by Anesthesiology Research Center, Cardiac Anesthesiology Department, Shahid Beheshti University of Medical Sciences, Tehran, Iran; research award number: 7129. Also, the authors would like to acknowledge the kind help of all physicians and nurses of cardiac surgery operating room, Modarres Hospital, Shahid Beheshti University of Medical Sciences, Tehran Iran. Besides, the kind help of administrative personnel of Anesthesiology Research Center, Shahid Beheshti University of Medical Sciences is highly acknowledged.

Conflicts of Interest

The authors declare that they have no conflict of interest.

References

1. Alexander JH, Smith PK. Coronary-Artery Bypass Grafting. N Engl J Med. 2016;374(20):1954-64.

2. Dabbagh A, Rajaei S, Bahadori Monfared A, Keramatinia AA, Omidi K. Cardiopulmonary Bypass, Inflammation and How to Defy it: Focus on Pharmacological Interventions. Iran J Pharm Res. 2012;11(3):705-14.

3. Ferasatkish R, Dabbagh A, Alavi M, Mollasadeghi G, Hydarpur E, Moghadam AA, et al. Effect of magnesium sulfate on extubation time and acute pain in coronary artery bypass surgery. Acta Anaesthesiol Scand. 2008;52(10):1348-52.

4. Salameh A, Dhein S, Dahnert I, Klein N. Neuroprotective Strategies during Cardiac Surgery with Cardiopulmonary Bypass. International journal of molecular sciences. 2016;17(11).

5. Warren OJ, Watret AL, de Wit KL, Alexiou C, Vincent C, Darzi AW, et al. The inflammatory response to cardiopulmonary bypass: part 2--anti-inflammatory therapeutic strategies. J Cardiothorac Vasc Anesth. 2009;23(3):384-93.

6. Warren OJ, Smith AJ, Alexiou C, Rogers PL, Jawad N, Vincent C, et al. The inflammatory response to cardiopulmonary bypass: part 1--mechanisms of pathogenesis. J Cardiothorac Vasc Anesth. 2009;23(2):223-31.

7. Dabbagh A, Bastanifar E, Foroughi M, Rajaei S, Keramatinia AA. The effect of intravenous magnesium sulfate on serum levels of N-terminal pro-brain natriuretic peptide (NT pro-BNP) in elective CABG with cardiopulmonary bypass. J Anesth. 2013;27(5):693-8.

8. Aryana P, Rajaei S, Bagheri A, Karimi F, Dabbagh A. Acute Effect of Intravenous Administration of Magnesium Sulfate on Serum Levels of Interleukin-6 and Tumor Necrosis Factor-alpha in Patients Undergoing Elective Coronary Bypass Graft With Cardiopulmonary Bypass. Anesth Pain Med. 2014;4(3):e16316.

9. Foroughi M, Rahimian H, Dabbagh A, Majidi M, Hekmat M, Beheshti M, et al. Postoperative N-terminal pro-brain natriuretic peptide level in coronary artery bypass surgery with ventricular dysfunction after perioperative glucose-insulin-potassium treatment. J Cardiothorac Vasc Anesth. 2012;26(4):631-6.

10. Kawata K, Liu CY, Merkel SF, Ramirez SH, Tierney RT, Langford D. Blood biomarkers for brain injury: What are we measuring? Neuroscience and biobehavioral reviews. 2016;68:460-73.

11. Chong ZZ, Changyaleket B, Xu H, Dull RO, Schwartz DE. Identifying S100B as a Biomarker and a Therapeutic Target For Brain Injury and Multiple Diseases. Current medicinal chemistry. 2016;23(15):1571-96.

12. Zheng L, Fan QM, Wei ZY. Serum S-100beta and NSE levels after off-pump versus on-pump coronary artery bypass graft surgery. BMC cardiovascular disorders. 2015;15:70.

13. van Boven WJ, Morariu A, Salzberg SP, Gerritsen WB, Waanders FG, Korse TC, et al. Impact of different surgical strategies on perioperative protein S100beta release in elderly patients

undergoing coronary artery bypass grafting. Innovations (Philadelphia, Pa). 2013;8(3):230-6.
14. Vranken NPA, Weerwind PW, Sutedja NA, Severdija EE, Barenbrug PJC, Maessen JG. Cerebral Oximetry and Autoregulation during Cardiopulmonary Bypass: A Review. J Extra Corpor Technol. 2017;49(3):182-91.
15. Moerman A, De Hert S. Recent advances in cerebral oximetry. Assessment of cerebral autoregulation with near-infrared spectroscopy: myth or reality? F1000Research. 2017;6:1615.
16. Green DW, Kunst G. Cerebral oximetry and its role in adult cardiac, non-cardiac surgery and resuscitation from cardiac arrest. Anaesthesia. 2017;72 Suppl 1:48-57.
17. Saidi N, Murkin JM. Applied neuromonitoring in cardiac surgery: patient specific management. Semin Cardiothorac Vasc Anesth. 2005;9(1):17-23.
18. Murkin JM, Arango M. Near-infrared spectroscopy as an index of brain and tissue oxygenation. Br J Anaesth. 2009;103 Suppl 1:i3-13.
19. Murkin JM. NIRS: a standard of care for CPB vs. an evolving standard for selective cerebral perfusion? J Extra Corpor Technol. 2009;41(1):P11-4.
20. Kok WF, van Harten AE, Koene BM, Mariani MA, Koerts J, Tucha O, et al. A pilot study of cerebral tissue oxygenation and postoperative cognitive dysfunction among patients undergoing coronary artery bypass grafting randomised to surgery with or without cardiopulmonary bypass*. Anaesthesia. 2014;69(6):613-22.
21. Denault A, Deschamps A, Murkin JM. A proposed algorithm for the intraoperative use of cerebral near-infrared spectroscopy. Semin Cardiothorac Vasc Anesth. 2007;11(4):274-81.
22. Dabbagh A. Postoperative CNS care. In: Dabbagh A, Esmailian F, Aranki S, editors. Postoperative Critical Care for Cardiac Surgical Patients. 1 ed: Springer-Verlag; 2014. p. 245-56.
23. Ishida K, Gohara T, Kawata R, Ohtake K, Morimoto Y, Sakabe T. Are serum S100beta proteins and neuron-specific enolase predictors of cerebral damage in cardiovascular surgery? J Cardiothorac Vasc Anesth. 2003;17(1):4-9.
24. Harilall Y, Adam JK, Biccard BM, Reddi A. The effect of optimising cerebral tissue oxygen saturation on markers of neurological injury during coronary artery bypass graft surgery. Heart Lung Circ. 2014;23(1):68-74.
25. Ono M, Joshi B, Brady K, Easley RB, Zheng Y, Brown C, et al. Risks for impaired cerebral autoregulation during cardiopulmonary bypass and postoperative stroke. Br J Anaesth. 2012;109(3):391-8.
26. Ono M, Brady K, Easley RB, Brown C, Kraut M, Gottesman RF, et al. Duration and magnitude of blood pressure below cerebral autoregulation threshold during cardiopulmonary bypass is associated with major morbidity and operative mortality. J Thorac Cardiovasc Surg. 2014;147(1):483-9.
27. Joshi B, Ono M, Brown C, Brady K, Easley RB, Yenokyan G, et al. Predicting the limits of cerebral autoregulation during cardiopulmonary bypass. Anesth Analg. 2012;114(3):503-10.
28. Tina LG, Frigiola A, Abella R, Tagliabue P, Ventura L, Paterlini G, et al. S100B protein and near infrared spectroscopy in preterm and term newborns. Frontiers in bioscience (Elite edition). 2010;2:159-64.
29. Sanchez-de-Toledo J, Chrysostomou C, Munoz R, Lichtenstein S, Sao-Aviles CA, Wearden PD, et al. Cerebral regional oxygen saturation and serum neuromarkers for the prediction of adverse neurologic outcome in pediatric cardiac surgery. Neurocrit Care. 2014;21(1):133-9.