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ORIGINAL RESEARCH **CARDIAC ANESTHESIA**

Neuroprotection role of cooling helmet on neuron specific enolase (NSE) and post-surgery delirium levels in open heart surgery patients: a randomized controlled trial

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Abstract

Background & objective: This study aims to assess the effect of cooling helmet during surgery on neuron specific enolase (NSE) and delirium levels following open heart surgery patients with cardiopulmonary bypass (CPB) using a heart-lung machine.

Methodology: This double-blind randomized clinical trial took place from October to December 2021 in a tertiary care hospital. The research used a modified cooling helmet to decrease brain temperature. Inclusion criteria were adult patients who were scheduled for open heart surgery with CPB. The subjects were randomized into two groups: patients with the cooling helmet on as the treatment group (n = 12) and the patients with the non-cooling helmet on as the control group (n = 13). The differences between NSE and delirium levels in both groups were assessed at specific times.

Results: NSE levels in the treatment group were lower than the control group (7.13 ± 7.63 vs. 12.49 ± 6.81; $P < 0.05$). Regarding the delirium, no statistically significant difference was found in both groups ($P > 0.05$).

Conclusion: The hypothermia effect of the cooling helmet is associated with a decrease of neuron specific enolase levels, but it did not significantly correlate to prevent the delirium after open heart surgery patients with the cardiopulmonary bypass machine.

Abbreviations: CABG: coronary artery bypass graft; CPB: Cardiopulmonary Bypass; $CMRO_2$: cerebral metabolic rate of oxygen; HLM: Heart-lung machine; NSE: Neuron Specific Enolase; ROS: reactive oxygen species

Key words: Adult; Brain / physiopathology; Brain / enzymology; Brain Injuries / therapy; Delirium; Head Protective Devices; Humans; Hypothermia, Induced / instrumentation; Immunoenzyme Techniques; Isoenzymes / analysis

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1. Introduction

Open heart surgery is a common procedure now a days. The use of cardiopulmonary bypass (CPB) using a heart-lung machine (HLM) is often compulsory for this procedure and it is not risk-free. Brain injury is one of the most notable complication for open heart surgery that utilize cardiopulmonary bypass (CPB) made possible by the heart-lung machine (HLM). Neurological complications following this procedure could increase the morbidity and the mortality for patients during their hospital stay.[1,2]

There are a number of mechanisms that can lead to neurological injury during the utilization of CPB. Hypoperfusion, micro emboli and systemic inflammatory response syndrome (SIRS) may bring negative impact to neurological well-being during open heart surgery.[2,3] These mechanisms could cause cerebral ischemia that will decrease adenosine triphosphate (ATP) supply and increase intracellular calcium level and glutamate release. This event (neurotoxicity) will further lead to neuronal cell necrosis and finally cause brain injury.[3,4]

Neuron Specific Enolase (NSE) is known as one of the brain injury biomarkers.[2,3] It is also believed to be highly correlated to neurocognitive dysfunction rather than S-100B.[5] The increment of NSE levels before and after open heart surgery with CPB is a sensitive surrogate of neuronal injury.[2] After six hours of open heart surgery NSE was found significantly high in patients that had neurocognitive dysfunction compared to normal patients.

Post open heart surgery neurological complications manifest clinically as delirium after 24-72 h of surgery and evolve to neurocognitive dysfunction in weeks and months later.[6] In general, the incidence of post open heart surgery neurological dysfunction is 25-50%. Neurological dysfunction in Cipto Mangunkusumo Hospital had been reported to be about 40.7% in open heart surgery patients.[7]

Delirium is defined as a disturbance of the consciousness that develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day. The disturbance is caused by direct physiological consequences of a general medical condition and may have one or more etiologies. Post open heart surgery delirium needs to be addressed, because it is often misdiagnosed and could lead to nosocomial complications and permanent cognitive decline.[6,8] There are a few neuroprotective measures that can help by suppressing cerebral ischemia and inflammation response during open heart surgery. Hypothermic therapy has been reported as one of the fundamental method that can reduce brain injury incidence.[4] Hypothermia could reduce cerebral metabolic rate of oxygen ($CMRO_2$) consumption by 7% for each 1°C below normal body temperature.[9] Hypothermic therapy can be used during most of the open heart surgeries by lowering patients body temperature in slight hypothermic approach to 33-36° C, or in moderate hypothermic approach to 32-34° C). This approach will block glutamate excitation, reduce calcium influx and suppress reactive oxygen species (ROS) production.[4]

The incidence of cognitive dysfunction in coronary artery bypass graft (CABG) patients after one week of surgery was reported in 62% at normothermia group and 48% at the hypothermia group.[10] One of the interface method to achieve neurological hypothermia is by using surface cooling helmet. This non-invasive method causes selective brain hypothermia. Cooling helmet device works by flowing cool liquid to all regions inside the helmet surface that is incontact with the patient's head. Wang et al. conducted an experiment using cooling helmet and reported that the brain temperature decrement ranges between 0.9−2.4 °C after one hour of helmet application. He did not find any clinically significant complication for this procedure.[11] Currently ice packs are used for selective neuroprotective hypothermic in open heart surgery patients. This method has few drawbacks such as the melted ice could wet the environment and temperature may fluctuate. The application of ice packs is also not an ideal choice as the surface contact area to the head is less optimal.[12]

Available literature about use of cooling helmet for open heart surgery with HLM is still very limited. The consensus that incorporates hypothermia therapy for neuroprotective measure during open heart surgery is not available. Considering the benefits of selective hypothermia therapy as neuroprotective measure mentioned above, we conducted this study to evaluate cooling helmet application during open heart surgery with HLM.

2. Methodology

This prospective study was reviewed and approved by the Ethics and Research Committee of the University of Indonesia (1117/UN2.F1/ETIK/PPM.00.02/2021). This study was registered in the ClinicalTrials.gov No. NCT05264766. This study was a randomized, double-blind clinical trial, conducted from October to December 2021 at Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia.

The sample size was calculated using the formula given below, and it came out to be 26

patients.

$$n1 = n2 = 2\left[\frac{(Z\alpha + Z\beta)s}{(x1 - x2)}\right]^2$$

Patients scheduled for open-heart surgery with CPB in the Integrated Cardiac Centre / *Pusat Jantung Terpadu* (PJT) of Cipto Mangunkusumo Hospital, were selected according to the inclusion and exclusion criteria.

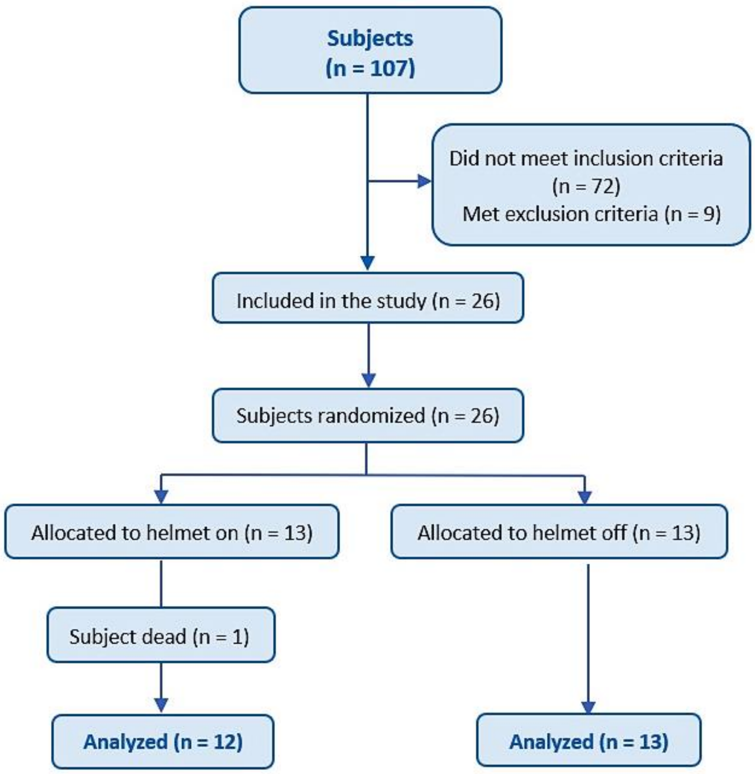

Figure 1: CONSORT flow diagram

Patients above 18 years old, ASA - III, fully conscious with Glasgow Coma Scale score of 15, were selected. Exclusion criteria were patient refusal to be included in the study, central nervous system disorders such as stroke or intracranial tumors, any psychiatric disorder (schizophrenia, depression, etc.), lung cancer, cognitive impairment, blind and/or deaf, and those using psychotropic drugs/narcotics were excluded.

The selected patients were randomly divided into the treatment group and the control group. The treatment group wore the cooling helmet filled with ice water, while the control group had their cooling helmet filled with water on room temperature (Figure 1). The subject and/or their guardians were informed the content and purpose of this study and signed informed obtained.

Blocked randomization was conducted by using 4 subjects for each block. The selection number was done randomly using a computerized software (www.randomizer.org). Furthermore, the allocation sequence was concealed by using opaque and sealed envelopes. The participants and the study investigators were blinded of the treatment assignment.

On the day of surgery, all actions related to anesthesia were carried out by a cardiovascular anesthesiologist assisted by an independent resident anesthesiologist. NIBP, ECG and pulse oxygen saturation of all subjects were monitored. A central venous catheter (CVC) and an arterial line were inserted under local anesthesia. The patient was induced general anesthesia, then the helmets were applied. Nasopharyngeal and rectal temperature probes were placed to record the temperature. The initial temperature (T0) was measured in both groups. Second measurement (T1) was done 20 min after the helmet had been installed.

The helmet was made by a plastic hose and it used to wrap the subject's head (Figure 2). The water was pumped with Lion L-3900 aquarium pump from the reservoir to be circulated in the helmet. The water reservoir was equipped with a adigital thermometer to measure the temperature of the circulating water. The procedure for installing a HLM was carried out according to the hospital protocol. The perfusion machine worked according to the protocol and during the cross-clamp period, the temperature was recorded (T2) and maintained at 32–34 ºC. Patients were monitored in the CICU room to assess delirium after surgery.

The primary objective of this study was to assess the effect of cooling hat on NSE levels and the delirium after open heart surgery with CPB. The second clinical parameter observed was nasopharyngeal and rectal temperature between the two groups.

Figure 2: The Cooling Helmet

Blood samples to measure the first NSE levels were collected before the cooling helmet switched on and the second sample was collected after 6 h of CPB off. The blood serum was centrifuged and stored in a refrigerator at −80 ºC until it was analyzed in the University of Indonesia integrated laboratory.

Delirium was assessed using the CAM-ICU instrument two times a day for 48 h postoperatively. The CAM-ICU assessment was performed when the RASS score was – 3 to +4 by the resident anesthesiologist on duty.

Basic demographic and clinical characteristics of all subjects were recorded; including age, sex, body weight, height, body mass index, education, comorbids (diabetes mellitus, hypertension), CPB time, cross-clamp time, length of stay in ICU, nasopharyngeal and rectal temperatures.

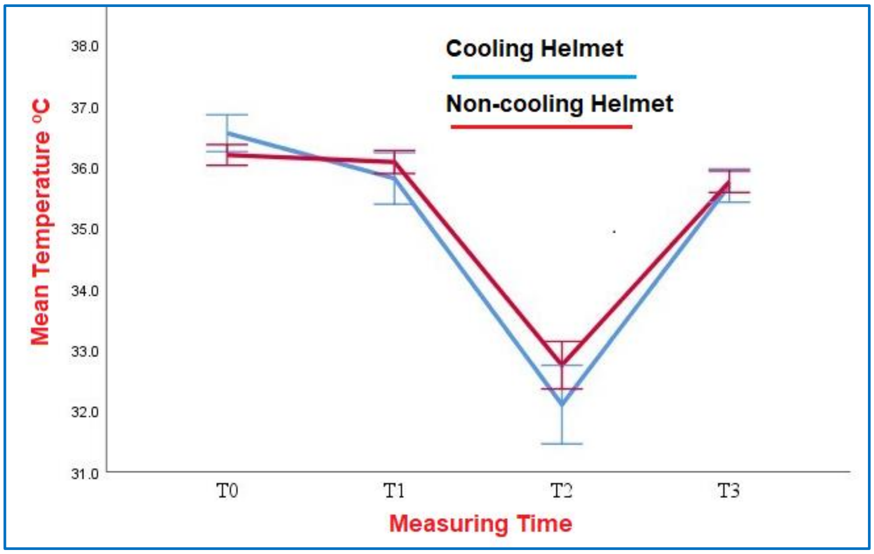

Figure 3-A: Comparative nasopharyngeal temperatures in two groups

Statistical Analysis

The data from both groups was processed and analyzed in this study using SPSS 25.0 for Windows. $P < 0.05$ was deemed to be significant. A bivariate analysis was carried out to determine the relationship between all parameters using the cooling helmet and the non-cooling helmet. Numeric data (NSE levels, ages,body weight, body height, body mass index, CPB time, cross-clamp time) was presented as mean ± standard deviation and the categoric data (sex, education, comorbid, length of stay in ICU, delirium) was presented as n, or n (%). The numeric data was analyzed through Wilcoxon test and the categoric data was analyzed with Fisher's exact test

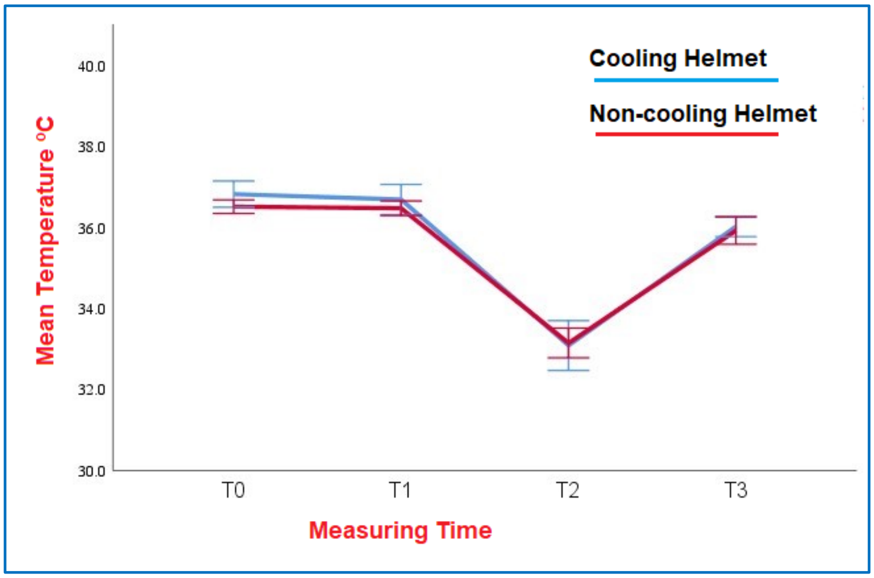

Figure 3-B: Comparative rectal temperatures in two groups

3. Results

Among the subjects, the mean age in the treatment group was 51.83 ± 14.95 y and in the control group it was 54.67 ± 9.58 y. Male gender dominated with 75% of the treatment group and 66.7% of the control group. For education, most of the subjects were highly educated in both groups (75% and 66.7%).

The duration of CPB on the treatment group (110.58 ± 34.02) was slightly longer than the control group of (104.23 ± 27.17). The length of the cross-clamp time on the treatment group (83.08 ± 35.5) was not much different from the control group (78.33 ± 19.39). In the treatment group, the majority of patients stayed in the ICU ≤ 48 h (50%), while the control group dominated more than 48 h after surgery (53.8%). The subjects who died after 48 h in the control group (30.8%) was higher than the treatment group (8.3%).

The mean of nasopharyngeal temperature before the cooling helmet installed was not significantly different between both groups (36.5 ± 0.5 on the treatment group vs 36.2 ± 0.3 on the control group). When cooling helmet had been installed and turned on, the mean of treatment group (35.8 ± 0.7) was lower than the control group (36.1 ± 0.3). Likewise, the temperature when using the CPB machine in the treatment group (32.1 ± 1.01) was lower than the control group (32.7 ± 0.6). Meanwhile, when the

Table 1: Subjects Baseline Characteristic Data

Variable	Cooling Helmet Group (n = 12)	Non-cooling Helmet Group (n = 13)
Age (y)	51.92 ± 15.07	55.31 ± 9.38
Sex		
Male	9 (75%)	9 (69.2%)
Female	3 (25%)	4 (30.8%)
Body Weight (kg)	70.79 ± 11.68	63.15 ± 9.43
Body Height (cm)	165.08 ± 6.32	163.38 ± 7.79
Body Mass Index (kg/m^2)	26 ± 4.18	23.66 ± 3.16
Education		
• Well	9 (75%)	9 (69.2%)
• Low	3 (25%)	4 (30.8%)
Comorbids		
• Diabetes mellitus	5 (41.7%)	6 (46.2%)
• Hypertension	8 (66.7%)	11 (84.6%)
• CPB Time (min)	110.58 ± 34.02	104.23 ± 27.17
• Cross-Clamp Time (min)	83.08 ± 35.5	78.33 ± 19.39
Length of Stay in ICU		
• < 48 h	6 (50%)	2 (15.4%)
• ≥ 48 h	5 (41.7%)	7 (53.8%)
• Died ≥ 48 h	1 (8.3%)	4 (30.8%)
Nasopharyngeal Temperature (ºC)		
• T0	36.5 ± 0.5	36.2 ± 0.3
• T1	35.8 ± 0.7	36.1 ± 0.3
• T2	32.1 ± 1.0	32.7 ± 0.6
• T3	35.7 ± 0.4	35.7 ± 0.3
Rectal Temperature (ºC)		
• T0	36.8 ± 0.5	36.5 ± 0.3
• T1	36.7 ± 0.6	36.5 ± 0.3
• T2	33.1 ± 0.9	33.1 ± 0.6
• T3	36 ± 0.4	35.9 ± 0.6

The data are mean ± standard deviation, n, or n (%). CPB, Cardiopulmonary Bypass; ICU,Intensive Care Unit; T0, The temperature before the helmets were switched on; T1, The temperature 20 min after the helmets were switched on; T2, The temperature when started the CPB; T3, The temperature when the CPB and the helmets were switched off

CPB was stopped, both off groups temperature were almost the same (35.7 ± 0.4 on the treatment group vs 35.7 ± 0.3 on the control group) (Figure 3). There were no patients who experiencing any adverse events during the assignment of treatment.

All the baseline characteristics are shown in Table 1.

The change from 1st NSE level to the 2nd level for each group were measured. The results of these tests found that each group had statistically significant difference in NSE levels between the first and second measurements. (Table 2). The mean change of NSE levels in the treatment group was smaller than the control group with statistically significant value (P = 0.018). These findings suggest that the use of the hypothermia technique on a cooling helmet can reduce NSE levels lower after open heart surgery than without using a cooling helmet (Table 3).

The delirium was only noticed in the control group in 3 (23.1%) patients, while no subject in the treatment group experienced delirium. The difference was statistically not significant P = 0.220). The RR value = 2.2 means that the control group had 2.2 times higher chance with 95% CI 1.39 – 3.48 to experience delirium compared to the treatment group.

4. Discussion

Central nervous system (CNS) disorder is one of the most common neurological complications in patients after open heart surgery.[13] Neurocognitive dysfunction can be seen from the increase in serological markers due to transient ischemia or persistent cell damage. NSE is a serologic marker of brain damage that can be used to predict the onset of neurocognitive dysfunction in patients after cardiac surgery.[5,14,15] Postoperative delirium is one of the neurocognitive dysfunction that can be found after cardiac surgery.[6] Therefore, early diagnosis and treatment is important to improve patients' neural function and protecting them against neural injury after open heart surgery. In the recent years, hypothermia techniques to lower core body temperature have been used to reduce the incidence of neurocognitive dysfunction after CABG surgery. There have been several studies that compared neurologic deficit in normothermia vs. hypothermia in CABG surgery with CPB.[10,16] Nathan et al. conducted a study, which randomized 223 patients undergoing CABG surgery, and showed that the incidence of cognitive decline one week postoperative time was lower in the

Table 3: The NSE levels difference between the cooling helmet on group vs the cooling off group.

NSE Level	Cooling Helmet Group (n = 12)	Non-cooling Helmet Group (n = 13)	P-value
Delta in NSE level	7.13 ± 7.63	12.49 ± 6.81	0.018 [a]

The data are mean ± standard deviation. [a] Mann-Whitney test

non-cooling helmet group. In the present study we

Table 2. The NSE levels in the cooling helmet on group and non-cooling helmet group between the 1st and 2nd measurements

Group	1st NSE Level	2nd NSE Level	P-*value*
Cooling helmet group	6.71 ± 3.48	13.84 ± 7.64	0.002 [a]
Non-cooling helmet group	5.99 ± 2.32	18.49 ± 7.51	0.001 [a]

The data are mean ± standard deviation. [a] Wilcoxon Test

hypothermic group than the control group (48% vs 62%).[10] However, the mechanisms that create hypothermic neural protection remain unclear and clinical evidence remains inadequate. In the present study, we carried out a treatment strategy by given a cooling helmet to patients undergoing open heart surgery with CPB. We found that the NSE levels in cooling helmet group were better than the non-cooling helmet group, and it showed a reduced risk of neurologic dysfunction manifested by no delirium after surgery in this group.

A researcher studied the correlation between the type of surgery and the frequency of postoperative delirium. The results showed the combination of CABG and heart valve surgeryhad a risk of postoperative delirium to be about 86% ,whereas it was 70% if only CABG surgery was undertaken.[17] Similarly, Liu et al. explained that the incidence of delirium was 14-50% after heart surgery.[1] In the present study, although the incidence of delirium in the cooling helmet group was zero and in the cooling helmet group it was 23,1%, the difference was statistically not significant. Nevertheless, our results were supported by a study by Sirvinskas et al., which showed that the intraoperative external head cooling technique had a neuroprotective effect after CABG surgery.[16] Some discrepancies in the subjects characteristics such as older age, longer ICU stay, longer CPB time, and longer mechanical ventilation time might have correlation with the frequency of delirium after open heart surgery.[6,17,18]

Ramlawi B. et al. found significant increase in NSE levels after 6 h of CABG surgery with CPB in the group which had neurocognitive dysfunction than the group without neurocognitive dysfunction (68.8% vs. 29.2%) after surgery.[5] In this present study,we showed that NSE levels in the cooling helmet group were lower than the showed that the hypothermia produced by our cooling helmet can reduce NSE levels, and clinically could reduce the risk of delirium in patients after open heart surgery with HLM. It could be an alternative tool to monitor neuroprotection management in open heart surgery patients.

5. Limitations

The present study has some limitations. The NSE value is strongly influenced by temperature regulation during surgery. In the present study, there were difficulties in maintaining constant temperatures. The temperature of the water in the cooling helmet remained between 4−11 ºC. The ice cubes used to cool the water could melt because of the environment temperature. The size of the cooling helmet also needs to be adjusted to the subject's head. Future studies are recommended to assess the relationship between NSE levels at each level of temperature produced by cooling helmets in open heart surgery patients with CPB machine. Electronic machine models might be manufactured and used to keep the head temperature at the desired level.

6. Conclusion

We conducted a randomized, controlled study to investigate the efficacy of cooling helmet as the neuroprotection role management in open hearts surgery patients.

The results of our study show that the hypothermia produced by the cooling helmet during open heart surgery, on heart-lung machines, can reduce neuron specific enolase (NSE) levels; although, the statistical results showed no significant differences in the frequency of delirium. Future larger studies might provide more clinical evidence and new insight for application of hypothermia in the management of open-heart surgery patients.

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8. Disclaimer

This manuscript is not currently under consideration in another journal nor it was submitted toanother journal.

9. Conflict of interest

The authors have no conflicts of interest to declare.

10. Funding disclosure

None to declare.

Data availability

Numerical dat generated in this study can be requested from the corresponding author.

11. Authors' contribution

MPA: Concept, Data Acquisition, Data analysis, Manuscript writing, The guarantor of the study

JKH, AH: Study design, Interpretation of data, Manuscript writing, Review & Editing, Supervision, The guarantor of the study

12. References

1. Liu Y, Chen K, Mei W. Neurological complications after cardiac surgery: anesthetic considerations based on outcome evidence. Curr Opin Anaesthesiol. 2019;32(5):563-7. [PubMed] DOI: 10.1097/ACO.0000000000000755
2. Demir T, Demir H, Tansel T, Kalko Y, Tireli E. Dayioglu E, et al. Influence of methylprednisolone on levels of neuron-specific enolase in cardiac surgery: a corticosteroid derivative to decrease possible neuronal damage. J Card Surg. 2009;24:397-403. [PubMed] DOI: 10.1111/j.1540-8191.2009.00842.x
3. Ahonen J, Salmenperä M. Brain injury after adult cardiac surgery. Acta Anaesthesiol Scand. 2004;48(1):4-19. [PubMed] DOI: 10.1111/j.1399-6576.2004.00275.x
4. Otto KA. Therapeutic hypothermia applicable to cardiac surgery. Vet Anaesth Analg. 2015;42(6):559–69. [PubMed] DOI: 10.1111/vaa.12299
5. Ramlawi B, Rudolph JL, Mieno S, Khabbaz K, Sodha NR, Boodhwani M, et al. Serologic markers of brain injury and cognitive function after cardiopulmonary bypass. Ann Surg. 2006;244(4):593–601. [PubMed] DOI: 10.1097/01.sla.0000239087.00826.b4
6. Berger M, Terrando N, Smith SK, Browndyke JN, Newman MF, Mathew JP. Neurocognitive function after cardiac surgery: from phenotypes to mechanisms. Anesthesiology. 2018 Oct;129(4):829-851. [PubMed] DOI: 10.1097/ALN.0000000000002194
7. Farida R, Perdana A, Aprianti M, Amir N, Mansjoer A. Pengaruh Usia, Pendidikan, Diabetes Mellitus, Lama CPB Dan Klem Silang Terhadap Penurunan Fungsi Kognitif Pascabedah Jantung Terbuka Di RSUPN DR. Cipto Manungkusumo. Universitas Indonesia. 2017.
8. O'Neal JB, Billings FT, Liu X, Shotwell MS, Liang Y, Shah AS, et al. Risk factors fordelirium after cardiac surgery: a historical cohort study outlining the influence of cardiopulmonary bypass. Can J Anesth. 2017;64(11):1129-37. [PubMed] DOI: 10.1007/s12630-017-0938-5
9. Joshi S, Ornstein E, Young WL. Cerebral and spinal cord blood flow. In: Cottrell JE, Young WL, editors. Cottrell and Young's Neuroanesthesia. 5th ed. Philadelphia: Elsevier Saunders; 2010. p. 17–59 41.
10. Nathan HJ, Wells GA, Munson JL, Wozny D. Neuroprotective effect of mild hypothermia in patients undergoing coronary artery surgery with cardiopulmonary bypass. Circulation. 2015;104(1):I-85-I91. [PubMed] DOI: 10.1161/hc37t1.094710
11. Wang H, Olivero W, Lanzino G, Elkins W, Rose J, Honings D, et al. Rapid and selective cerebral hypothermia achieved using a cooling helmet. J Neurosurg. 2004;100(2):272–7. [PubMed] DOI: 10.3171/jns.2004.100.2.0272
12. Harris B, Andrews PJD, Murray GD, Forbes J, Moseley O. Systematic review of headcooling in adults after traumatic brain injury and stroke. Health Technol Assess (Rockv). 2012;16(45):1-175. [PubMed] DOI: 10.3310/hta16450
13. Hogue CW, Gottesman RF, Stearns J. Mechanisms of cerebral injury from cardiac surgery. Crit Care Clin. 2008 Jan;24(1):83-98, viii-ix. [PubMed] DOI: 10.1016/j.ccc.2007.09.004
14. Rasmussen LS, Christiansen M, Eliasen K, Sander-Jensen K, Moller JT. Biochemical markers for brain damage after cardiac surgery - time profile and correlation with cognitive dysfunction. Acta Anaesthesiol Scand. 2002;46(5):547–51. [PubMed] DOI: 10.1034/j.1399-6576.2002.460512.x
15. Tomaszewski D. Biomarkers of brain damage and postoperative cognitive disorders in orthopedic patients: an update. Biomed Res Int. 2015;2015:402959. [PubMed] DOI: 10.1155/2015/402959
16. Sirvinskas E, Usas E, Mankute A, Raliene L, Jakuska P, Lenkutis T, et al. Effects of intraoperative external head cooling on short-term cognitive function in patients after coronary artery bypass graft surgery. Perfusion. 2014;29(2):124–9. [PubMed] DOI: 10.1177/0267659113497074
17. Lin Y, Chen J, Wang Z. Meta-analysis of factors which influence delirium followingcardiac surgery. J Card Surg. 2012;(2):481–92. [PubMed] DOI: 10.1111/j.1540-8191.2012.01472.x
18. Marcantonio ER. Delirium in hospitalized older adults. N Engl J Med. 2017;377(15):1456–66. [PubMed] DOI: 10.1056/NEJMcp1605501

