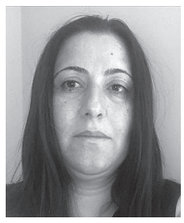
Neurocognitive dysfunction after cardiac surgery process



Gülseren Keskin

Ege University, Atatürk Medical Vocational Training School, Bornova (İzmir), Turkey

Pielęgniarstwo Chirurgiczne i Angiologiczne 2021; 2: 68–73

Submitted: 5.08.2020; accepted: 9.12.2020

Address for correspondence:
Prof. **Gülseren Keskin**, Ege University, Atatürk Medical Vocational Training School, Bornova (İzmir), Turkey, e-mail: gulseren.keskin@ege.edu.tr

Summary

Aim of the study: This study identified risk factors and causes for neurocognitive dysfunction after cardiac surgery.

Material and methods: A systematic literature search was conducted on academic databases by using keywords. The literature on neurocognitive dysfunctions after cardiac surgery procedures has been reviewed, and the risk factors of cognitive dysfunction occurrence have been analysed.

Results: Postoperative neurocognitive dysfunction is significantly reduced compared to preoperative cognitive status. Especially after coronary artery surgery, the permeability of the blood-brain barrier increases and micro embolism occurs, which may affect cognitive function. On the other hand, generalized inflammatory response associated with anaesthesia and major surgical procedures may also be associated with cognitive impairment other than cardiopulmonary bypass.

Conclusions: In the postoperative neurocognitive dysfunction process, it was found that genetic structure, process of inflammation, functional change in neurotransmitters, stress response, anaesthesia, and cardiopulmonary bypass technique (off pump on pump) can be effective.

Key words: cardiopulmonary bypass, off-pump coronary artery bypass grafting, on-pump coronary artery bypass grafting, neuro-cognitive.

Introduction

Postoperative cognitive dysfunction is a common complication after cardiac surgery. Although many new techniques have been developed in cardiac surgery, the incidence of postoperative neurocognitive destruction has not changed much, although mortality rates have decreased, and it remains the most common complication after cardiac surgery. This cognitive dysfunction can result in a serious deterioration in quality of life and an increased duration of hospital stay. Cognitive impairment may persist for many years and may lead to dementia in later years [1].

Postoperative cognitive dysfunction affects 25–40% of non-cardiac surgery patients, with the highest incidence after major cardiovascular surgery. The incidence of post-operative neurocognitive damage decreases over time. The highest rate, after hospital discharge, is 30–70%, followed by 20–30% 6 months after surgery [2]. Postoperative cognitive dysfunction is more common in elderly patients and in patients with postoperative delirium. Postoperative cognitive loss increased the risk of postoperative mortality [3]. It was determined that 22% of patients who had coronary artery bypass surgery had statistically significant cognitive impairment after the postoperative period. While some of the patients return to the start date within weeks or months, a small group of patients never fully heal [4].

Risk factors for postoperative cognitive decline after cardiac surgery include advanced age, non-coronary atherosclerosis (carotid, peripheral vascular), low educational level, pre-existing neurological deficit, diabetes, inverse intraoperative and postoperative events, and the presence of small cerebral infarction in elderly patients [5]. Cognitive decline is characterized by a significant decrease in the performance of at least one of the four cognitive domains such as verbal memory, abstraction and visual spatial orientation, attention, psychomotor processing speed and concentration, and visual memory [4, 5]. Lesions underlying postoperative cognitive impairment are probably in the hippocampus, which is clearly susceptible to hypoxic damage [6]. In particular, high levels of interleukin-1 pta (IL-1b) and tumour necro sistor-alpha (TNF-a) and insulin resistance have been shown to lead to decreased postoperative learning abilities and memory problems [7]. Postoperative cognitive impairment was associated with cerebral micro embolism, cerebral hypo perfusion, surgical and systemic inflammatory response, anaesthetic response, genetic susceptibility, and depression [6, 7].

Many investigators have reported that anaesthesia or surgical procedures can impair postoperative cognitive functions. Especially in coronary artery bypass surgery, surgical perfusion, and patient- and anaesthesia-related risk

factors are responsible for postoperative neurocognitive destruction. Coronary artery bypass grafting surgery is in the heart surgery group that includes short- and long-term risks that may lead to cognitive impairment such as stroke and delirium. Coronary artery bypass grafting is a commonly performed surgical procedure. Modern coronary artery bypass surgery has been practiced since the 1950s [1]. However, working in the throwing heart is technically challenging. Nonetheless, the number of operations performed for myocardial revascularization is increasing. Cardioplegic practices are required for myocardial revascularization after cardiopulmonary bypass surgery [8, 9].

This review focuses on the recent literature concerning the timeline, risk factors, diagnostic tools, and interventions for cognitive decline after coronary artery bypass grafting. The aim of this review is to highlight recent trends in the assessment of postoperative neurocognitive dysfunction and to discuss contemporary practices in its management.

Material and methods

A systematic literature search was conducted on academic databases such as Pubmed, EBSCO, and Science Direct using the keywords "cardiopulmonary bypass, coronary artery bypass grafting, off-pump coronary artery bypass grafting, on-pump coronary artery bypass grafting, neuro-cognitive". During the period 2012–2018, 2262 articles were found; and since 2013–2018, 530 articles were indicated. The search terms included off-pump, on-pump, with/without cardiopulmonary bypass, randomized trial, and trial. The authors chose to focus on only well conducted, appropriately blinded trials and their sub studies. No language, publication date, or publication status restriction was imposed. Both blinded and open-label trials were considered eligible. The most updated or inclusive data for each study were used for abstraction. References of original and review articles were cross-checked. In the selected works, we primarily included studies on humans, as well as studies involving animals to obtain sufficient data. We received very little review work on the article. To limit the reference number, inclusion of articles in our research was based on a combination of the level of evidence and the time of publication. Accordingly, the number of references was limited to 43.

Citations were screened at the title/abstract level and retrieved as full reports if they fulfilled the inclusion criteria: human study and off-pump and on-pump method for cardio pulmonary surgery. The exclusion criteria were a prospective cohort and quasi-randomized study and a study with paediatric cardiac surgery

Results and discussion

Postoperative cognitive dysfunction is an intellectual decrease due to surgery. The incidence of neurological damage after adult cardiac surgery increases with age. After major surgical intervention, patients in the elderly group are characterized by severe cognitive disturbances that can range from delirium to mild concentration difficulties on the clinical spectrum. The problem may be temporary or it may continue for a longer period. This deterioration is a risk factor for diseases such as dementia and Alzheimer's [10, 11].

Cognitive decline after cardiac surgery is more frequent than non-cardiac major surgery. Recent developments in perioperative management, including surgical techniques, anaesthetic selection, and perfusion strategies, have reduced the incidence rate of major complications [12]. The frequency of subclinical neurological damage is 50–70%. Cardiac surgery is known to cause neurocognitive dysfunctions such as ischaemic and haemorrhagic stroke, seizures, delirium, cognitive dysfunction, cerebral hyper-perfusion syndrome, cranial nerve injuries, and peripheral neuropathies [13, 14]. Postoperative cognitive deficits have an adverse effect on the quality of life of the individual. This cognitive impairment may in time affect the functional independence in the individual, and an increase in care needs may lead to reduced participation in the workforce [15].

Coronary artery bypass surgery is one of the most common surgical procedures for treating ischaemic heart disease and is among the high-risk cardiovascular interventions. Such postoperative neurological injury is still a frequent cause of perioperative mortality and morbidity [16]. As reported in various studies, the incidence of permanent neurological dysfunction is 2–5% for elective cases and 9–16% for emergency cases. In addition, neurological damage may be seen as transient neurological dysfunction. Neurocognitive impairment after cardiac surgery is due to cardiopulmonary bypass in 80% of cases. It has been determined that cardiopulmonary bypass increases the permeability of the blood-brain barrier and produces micro emboli that can affect cognitive function. However, the effect of the pump output on the cognitive functions is not proven [17, 18].

Cardiopulmonary bypass surgery also has a structure that can cause postoperative neurocognitive dysfunction associated with oxygen toxicity. During cardiopulmonary bypass surgery, the cellular response caused by hyper-oxidative exposure leads to an increase in oxidative stress, in particular – free radical, which in turn impairs brain functioning. Oxidative stress is highly deleterious to neuronal homeostasis and may lead to decreased synaptic plasticity, increased blood-brain barrier permeability, and possibly neuronal cell dysfunction and death [19, 20].

When the clinical outcomes are evaluated separately, these rates are given as 1–9% for stroke, 13–30% for delirium, 60% for early onset, and 25–30% for late regression in cognitive functions such as memory and attention deficits and motor slowdown [11, 19, 20].

Aetiology

In the aetiology of postoperative cognitive dysfunction, genetic factors, inflammation process, stress response, anaesthesia, and cardiopulmonary bypass technique (off-pump, on-pump) are included [19, 20].

Genetic factors and neurocognitive disorder

The ApoEε4 allele is a known risk factor for Alzheimer's disease and has been associated with a decline in cognitive functions after haemorrhagic and ischaemic stroke in humans. Apolipoproteins cannot cross the blood-brain barrier; however, Apo E is expressed in the central nervous system by astrocytes, microglia, and oligodendrocytes, wherein the neuronal membrane carries phospholipids and cholesterol for regeneration and re-myelination. ApoE4 is more susceptible to degradation than other isoforms, thus limiting lipid mobilization for repair. The E4 allele is also associated with the accumulation of amyloid plaques, even in the absence of dementia [21].

Inflammation process and neurocognitive disorder

Systemic inflammation gradually increases with age, often called inflammation-aging. Inflammation interleukin-6 (IL-6), one of the cytokines applied during the aging process, is considered to be one of the main inflammatory components leading to age-related pathologies. IL-6 is a hormone-like cytokine with pleiotropic properties, including roles in immunological homeostasis, which physiologically rearranges acute phase response proteins (e.g. C-reactive protein) and regulates signals within the central nervous system. High systemic inflammation biomarkers have been reported in individuals with cognitive decline [22].

Stress response and neurocognitive disorder

In general, the effect of acute stress on high-level functions such as working memory is thought to be mediated by central catecholamine activity for a significant proportion. Neuroendocrine responses to stress (cortisol and a -amylase) relate to fronto-parietal working memory activity changes in response to atomoxetine, a noradrenaline transporter inhibitor that selectively increases extracellular cortical dopamine and noradrenaline. Hernaus *et al*. reported positive correlations between stress-induced cortisol and a-amylase increases and catecholamine-dependent working memory-related activity in the dorsolateral prefrontal cortex. Furthermore, stress-induced cortisol increases correlated with supra-marginal gyrus working memory-related activity [23].

Anaesthesia-related aetiology

The effect of mechanical ventilation time in the intensive care unit is inevitable in the formation of postoperative neurocognitive destruction [24]. However, the results of repeated exposure to anaesthesia and the effects of depth of anaesthesia remain unclear. It is controversial that the inhaled anaesthetic agents used in these patients are most useful in terms of clinical neurological outcomes. According to various preclinical and animal studies, intestinal anaesthetics interact with known neurodegenerative pathways and increase cellular stress. Unlike inhaled anaesthetics, propofol has a strong anti-inflammatory effect and less cognitive impairment [25, 26]. Postoperative cognitive functions after anaesthesia with isoflurane yielded better results than anaesthesia with sevoflurane and desflurane [27].

Recent clinical trials have shown that inhaled anaesthetics are useful for early postoperative cognitive function in patients with on-pump coronary artery bypass grafting. Surgical stimulation itself induces an inflammatory response even without cardiopulmonary bypass. According to various preclinical and animal studies, intestinal anaesthetics interact with known neurodegenerative pathways and increase cellular stress [26].

A study that examined inflammatory markers showed that IL-6β and tumour necrosis factor-α were lower in extracorporeal cardiopulmonary bypass patients than in conventional bypass patients postoperatively. The off-pump method was found to limit the complications associated with cardiopulmonary bypass and cognitive impairment by limiting inflammation and emboli formation [28, 29].

Cardiopulmonary bypass techniques and neurocognitive damage

Neurological injury, including stroke and transient ischaemic attack, are the most important complications concerning the heart surgeon. Several techniques have been developed to reduce neurological damage during cardiac surgical procedures. These include non-pump coronary artery bypass grafting, antegrade cerebral perfusion and hypothermia during aortic arch surgery, distal aortic perfusion in the thoraco-abdominal aortic surgeon, and cerebrospinal fluid drainage. These techniques have positive contributions in neurological recovery. Avoiding cardiopulmonary by-pass or percutaneous coronary intervention during off-pump coronary artery bypass grafting does not improve cognitive outcome [20, 30].

Although no-aortic-touch multi-arterial revascularization, extracorporeal perfusion techniques, and off-pump approaches to reduce unwanted neurological events were the least common, these events are the leading cause of morbidity associated with coronary

artery bypass grafting surgery. Adverse neurological events are often caused by aortic manipulation caused by aortic manipulation, which can occur in any part of the procedure, including aortic clamping, cannulation placement and removal, and bypass initiation [31, 32].

Off-pump coronary artery bypass has been shown to reduce mortality and morbidity, especially stroke, transfusion requirements, rates of atrial arrhythmia, and renal dysfunction [25].

Patients with coronary artery disease undergoing revascularization are at risk of cognitive dysfunction. During these procedures, cerebral micro-embolization of air, atheromatous material, or oil in the circulation has been suggested as an aetiological factor. Cerebral micro-embolization is the most important cause of cognitive dysfunction. Coronary artery disease patients with coronary revascularization traits were found to have lower brain volumes than controls [31, 33].

In patients with chronic renal insufficiency, off-pump coronary artery bypass surgery reduces in-hospital mortality rates. In a retrospective study, postoperative stroke rates of patients with renal insufficiency were 8.4% for the pump method and 10.4% for the on-pump method [31, 33].

Coronary artery bypass grafting reduces the risk of death in patients with diffuse coronary artery disease. Despite continuous evolution, researchers cannot ignore the fact that cardiopulmonary bypass can lead to pathophysiological processes that can result in tissue damage and organ dysfunction [34]. Furthermore, cardiovascular surgeons are at a greater risk of cerebrovascular accident resulting from coronary artery bypass-related events. Usually, cardiopulmonary bypass is performed with the off-pump method [35].

On-pump or off-pump coronary artery bypass techniques are used to reduce the perioperative complications associated with the use of coronary artery bypass. In the 1970s, almost all revascularization surgeries were performed "on pump" despite increased awareness of biological stress and potential damage associated with extracorporeal circulation. By the mid 1990s, "off pump" led to a renewed interest in revascularization, followed by a dramatic increase in the number of off-pump procedures performed [35, 36].

With this approach, perioperative mortality, neurological damage, myocardial infarction, and stroke risk decreased. Both perioperative and long-term complications may be associated with aortic cross clamping in conjunction with cardiopulmonary bypass use and aortic pump coronary artery bypass grafting procedure [37].

Neurological damage after coronary artery bypass graft surgery is an important complication. Two types of neurological damage develop. Type 1 neurological damage is seen in 3–6% of symptomatic cases such as stroke or transient ischaemic attack. On the other hand, cognitive dysfunction, including attention deficit, concentration, short-term memory, fine motor function, and speed of mental and motor reactions, is seen in the second type and is milder (Tab. 1) [12, 38, 39].

Risk factors

The risk of postoperative cognitive impairment in elderly patients undergoing cardiac and non-cardiac surgery increases with age. Postoperative cognitive impairment rates are low in patients with higher education level. In the educated population, the brain constantly activates mental abilities and delays the symptoms of dementia using neuronal reserves and increasing the effectiveness of redirection around damaged areas of synapses [40]. In the studies, the number of POCDs was found to be high among low educated subjects. This result may be because highly educated individuals can implement better compensation strategies at behavioural and neuronal levels [41].

It is thought that the pumping method increases the rate of neurological complications especially during coronary artery bypass graft surgery in DM patients. The incidence of cerebrovascular disease in diabetes mellitus patients is higher than in the general population. DM is considered to be an independent risk factor for neurological complications following coronary artery bypass grafting procedures, the most common of which is delirium and descent. Hyperglycaemia may cause serious arrhythmia, bradycardia, and post-op infection during coronary artery bypass grafting surgery. The hyperglycaemic state triggered by cardiac surgery may also be harmful to the hypoperfusion brain and may cause neurological deterioration similar to that seen in stoke patients (Fig. 1) [33, 42, 43].

Table 1. Aetiology of major neurologic complications after vascular and cardiac surgeries

Aetiology	
Genetic factors and neurocognitive disorder	E4 allele-amyloid plaques-dementia
Inflammation process and neurocognitive disorder	High systemic inflammation biomarkers-cognitive decline
Stress response and neurocognitive disorder	High cortisol-neurotoxic effects on the hippocampus
Anaesthesia-related neurocognitive disorder	On-pump procedures-cognitive impairment
Cardiopulmonary bypass techniques and neurocognitive damage	Extracorporeal perfusion techniques-neurological deficit

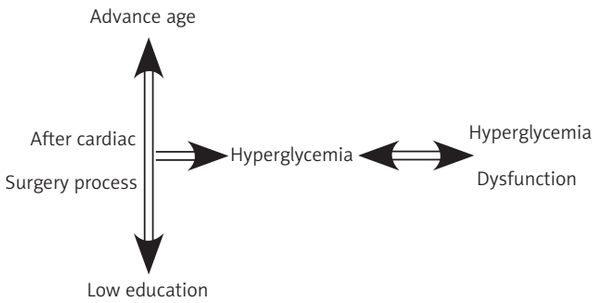


Fig.1. Risk factors related to neurological complications after vascular and cardiac surgeries

Conclusions

Cardiopulmonary bypass requires aortic cannulation, and perioperative cerebral hypo-perfusion and thromboembolism can result in non-pulsatile flow and micro-thrombosis. Plaques falling from the aortic arch can also cause infarction. Pulsatile flow is protected by the off-pump method and the aorta remains intact [28, 29]. Thus, adequate perioperative cerebral perfusion can be maintained. It has been determined that the off-pump method is superior to the on-pump method in terms of post-operational neurological complications in patients with cardiopulmonary bypass.

The author declares no conflict of interest.

References

1. Van Harten AE, Scheeren TW, Absalom AR. A review of postoperative cognitive dysfunction and neuroinflammation associated with cardiac surgery and anaesthesia. Anaesthesia 2012; 67: 280-293.
2. Ghaffary S, Ghaeli P, Talasaz AH, et al. Effect of memantine on post-operative cognitive dysfunction after cardiac surgeries: a randomized clinical trial. Daru 2017; 25: 24.
3. Green CM, Schaffer SD. Postoperative cognitive dysfunction in noncardiac surgery: a review. Trends Anaesth Crit Care 2019; 24: 40-48.
4. Johnson KB, Bailey T, Thackeray E. Anesthetic toxicity in neonates and ınfants. physiology and pharmacology of obesity, pediatrics, and the elderly. Elsevier 2019: 91-112.
5. Beca J, Sidebotham D. Neurologic dysfunction. cardiothoracic critical care, Butterworth Heinemann. Elsevier, Philadelphia 2007.
6. Salameh A, Dhein S, Dähnert I, Klein N. Neuroprotective strategies during cardiac surgery with cardiopulmonary bypass. Int J Mol Sci 2016; 17: 1945.
7. Tang N, Jiang R, Wang X, et al. Insulin resistance plays a potential role in postoperative cognitive dysfunction in patients following cardiac valve surgery. Brain Res 2017; 1657: 377-382.
8. Diodato M, Chedrawy EG. Coronary artery bypass graft surgery: the past, present, and future of myocardial revascularisation. Surg Res Pract 2014; 2014: 726158.
9. Kim K, Joung KW, Ji SM, et al. The effect of coronary angiography timing and use of cardiopulmonary bypass on acute kidney injury after coronary artery bypass graft surgery. J Thorac Cardiovasc Surg 2016; 152: 254-261.e3.
10. Oh CS, Park S, Wan Hong S, Kang WS, Kim SH. Postoperative delirium in patients undergoing off-pump coronary artery bypass grafting according to the anesthetic agent: a retrospective study. J Cardiothorac Vasc Anesth 2017; 31: 1988-1995.
11. Krenk L, Rasmussen LS. Postoperative delirium and postoperative cognitive dysfunction in the elderly – what are the differences? Minerva Anestesiol 2011; 77: 742-749.
12. Monk TG, Weldon BC, Garvan CW, et al. Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology 2008; 108: 18-30.
13. Orhan G, Biçer Y, Taşdemir M, et al. Comparison of norocognitive functions in patients undergoing coronary bypass surgery under cardiopulmonary bypass or beating heart. J Turk Gogus Kalp Damar 2007; 15: 24-28.
14. Kurnaz P, Sungur Z, Camci E, et al. The effect of two different glycemic management protocols on postoperative cognitive dysfunction in coronary artery bypass surgery. Rev Bras Anestesiol 2017; 67: 258-265.
15. Indja B, Seco M, Seamark R, Kaplan J, Michael P. Vallely neurocognitive and psychiatric ıssues post cardiac surgery. Heart Lung Circ 2017; 26: 779-785.
16. Velazquez EJ, Lee KL, Jones RH et al. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. N Engl J Med 2016; 374: 1511-152.
17. Farhoudi M, Mehrvar K, Afrasiabi A, et al. Neurocognitive impairment after off-pump and on-pump coronary artery bypass graft surgery – an Iranian experience. Neuropsychiatr Dis Treat 2010; 6: 775-778.
18. Pérez-Belmonte LM, San Román-Terán CM, Jiménez-Navarro M, Barbancho MA, Lara JP. Assessment of long-term cognitive impairment after off-pump coronary-artery bypass grafting and related risk factors. J Am Med Dir Assoc 2015; 16: 263.e9-263.e11.
19. Salim S. Oxidative stress and the central nervous system. J Pharmacol Exp Ther 2017; 360: 201-205.
20. Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS. Group I. Long-term consequences of postoperative cognitive dysfunction. Anesthesiology 2009; 110: 548-555.
21. Caplan GA, Tai J, Mohd Hanizan F, McVeigh CL, Hill MA, Poljak A. Cerebrospinal fluid apolipoprotein e levels in delirium. Dement Geriatr Cogn Dis Extra 2017; 7: 240-248.
22. Bradburn S, Sarginson J, Murgatroyd CA. Association of peripheral Interleukin-6 with global cognitive decline in non-demented adults: a meta-analysis of prospective studies. Front Aging Neurosci 2018; 9: 438.
23. Hernaus D, Quaedflieg CWEM, Offerman JS, Casales Santa MM, van Amelsvoort T. Neuroendocrine stress responses predict catecholamine-dependent working memory-related dorsolateral prefrontal cortex activity. Soc Cognit Affect Neurosci 2018; 13: 114-123.
24. Glumac S, Kardum G, Sodic L, Supe-Domic D, Karanovic N. Effects of dexamethasone on early cognitive decline after cardiac surgery: a randomised controlled trial. Eur J Anaesthesiol 2017; 34: 776-784.
25. Ueki C, Miyata H, Motomura N, et al. Off-pump technique reduces surgical mortality after elective coronary artery bypass grafting in patients with preoperative renal failure. J Thorac Cardiovasc Surg 2018; 12: 30934-30936.
26. Oh CS, Park S, Wan Hong S, Kang WS, Yoon TG, Kim SH. Postoperative delirium in patients undergoing off-pump coronary artery bypass grafting according to the anesthetic agent: a retrospective study. J Cardiothorac Vasc Anesth 2017; 31: 1988-1995.
27. Kanbak M, Saricaoglu F, Akinci SB, et al. The effects of isoflurane, sevoflurane, and desflurane anesthesia on neurocognitive outcome after cardiac surgery: a pilot study. Heart Surg Forum 2007; 10: E36-41.
28. Okgün Alcan A, Demir Korkmaz F, Çakmakçı H. An evaluation of health-promotion lifestyle behaviors following coronary artery bypass graft surgery. Turk Gogus Kalp Damar 2017; 25: 45-51.
29. Altaei T. Protective effect of silymarin during coronary artery bypass grafting surgery. Exp Clin Cardiol 2012; 17: 34-38.
30. Seco M, Edelman JJ, Van Boxtel B, et al. Neurologic injury and protection in adult cardiac and aortic surgery. J Cardiothorac Vasc Anesth 2015; 29: 185-195.
31. Pawliszak W, Kowalewski M, Maria Raffa G, et al. Cerebrovascular

events after no-touch off-pump coronary artery bypass grafting, conventional side-clamp off-pump coronary artery bypass, and proximal anastomotic devices: a meta-analysis. J Am Heart Assoc 2016; 5: e002802.
32. Lamy A, Devereaux PJ, Prabhakaran D, et al. Five-year outcomes after off-pump or on-pump coronary-artery bypass grafting. N Engl J Med 2016; 375: 2359-2368.
33. Benedetto U, Caputo M, Vohra H, et al. Off-pump versus on-pump coronary artery bypass surgery in patients with actively treated diabetes and multivessel coronary disease. J Thorac Cardiovasc Surg 2016; 152:1321-1330.
34. Shroyer AL, Hattler B, Wagner TH, et al. Five-year outcomes after on-pump and off-pump coronary-artery bypass. N Engl J Med 2017; 377: 623-632.
35. Dieberg G, Smart NA, King N. On- vs. off-pump coronary artery bypass grafting: a systematic review and meta-analysis. Int J Cardiol 2016; 223: 201-211.
36. Shaefi S, Mittel A, Loberman D, Ramakrishna H. Off-pump versus on-pump coronary artery bypass grafting-a systematic review and analysis of clinical outcomes. J Cardiothorac Vasc Anesth 2019; 33: 232-244.
37. Ko SB. Perioperative stroke: pathophysiology and management. Korean J Anesthesiol 2018; 71: 3-11.
38. Gottesman RF, McKhann GM, Hogue CW. Neurological complications of cardiac surgery. Semin Neurol 2008; 28: 703-715.
39. Krenk L, Rasmussen LS, Kehlet H. New insights into the pathophysiology of postoperative cognitive dysfunction. Acta Anaesthesiol Scand 2010; 54: 951-956.
40. Kotekar N, Shenkar A, Nagaraj R. Postoperative cognitive dysfunction – current preventive strategies. Clin Interv Aging 2018; 13: 2267-2273.
41. Soenarto RF, Mansjoer A, Amir N, Aprianti M, Perdana A. Cardiopulmonary bypass alone does not cause postoperative cognitive dysfunction following open heart surgery. Anesth Pain Med 2018; 8: e83610.
42. Nath SS, Das PK. A Commentary: effects on glargine insulin on glycemic control in patients with diabetes mellitus type II undergoing off-pump coronary artery bypass graft. Ann Card Anaesth 2018; 21: 173-174.
43. Gandhi H, Sarvaia A, Malhotra A, Acharya H, Shah K, Rajavat J. Effects of glargine insulin on glycemic control in patients with diabetes mellitus type IIundergoing off-pump coronary artery bypass graft. Ann Card Anaesth 2018; 21: 167-172.