Iran Red Crescent Med J. 2019 October; 21(10):e92737. doi: 10.5812/ircmj.92737.
Published online 2019 October 21.

Research Article

Effect of Selenium Added to the Cardioplegic Solution on Cardiac Protection in Coronary Artery Bypass Grafting Surgeries: A Randomized, Double-Blinded, Clinical Trial Study

Masih Shafa[1], Simin Azemati[1], Masood Abasi[1,*] and Rahim Hemati[1]
[1]Shiraz University of Medical Sciences, Shiraz, Iran

[*]*Corresponding author*: MSc of Circulation Technology, Shiraz University of Medical Sciences, Shiraz, Iran. Tel: +98-9171488132, Email: masooda1361@gmail.com

Received 2019 April 30; **Revised** 2019 September 13; **Accepted** 2019 September 15.

Abstract

Background: Coronary artery bypass graft (CABG) surgery with cardiopulmonary bypass (CPB) triggers an inflammatory reaction, leading to the development of myocardial damage and dysfunction. Selenium is the main cofactor for many antioxidant enzymes. Selenium level is decreased during heart surgeries affecting the cardiopulmonary pump, which in turn can aggravate the organ and heart dysfunction and mortality.
Objectives: The aim of this study was to evaluate the cardiac protective effects of adding selenium to cardioplegia solution in these surgeries.
Methods: In this randomized, double-blind, clinical trial study that was conducted in the department of cardiac surgery of Shiraz University of Medical Sciences (SUMS) in Shiraz, Iran, 67 elected CABG patients were allocated to the two control or selenium groups. In the intervention group, 1000 μg sodium selenite was added to cardioplegia solution. The same amount of normal saline was added to the cardioplegia solution in the control group. Arterial blood samples were withdrawn before anesthesia induction (T1), immediately after the surgery (T2), as well as, 6 and 24 hours after the surgery (T3 and T4 respectively), to determine the CK-MB and Troponin I levels.
Results: According to our findings, the CK-MB and Troponin I cardiac enzyme levels were significantly different, considering different time points ($P < 0.05$). Despite lower enzyme levels in the selenium group, the differences were not statistically significant between the two groups ($P > 0.05$). There were also no significant differences between the two groups regarding systolic and diastolic blood pressures.
Conclusions: The administration of 1000 μg sodium selenite via cardioplegia solution had no significant cardioprotective effect during coronary bypass surgery in CABG patients.

Keywords: Cardiac Enzymes, Cardioplegia Solution, Coronary Bypass Surgery, Creatine Kinase MB Form, Induced Heart Arrest, Heart Protection, Myocardium, Selenium, Sodium Selenite

1. Background

Cardiovascular disease (CVD) is among the main causes of mortality in men and women in different ethnic groups (1-3). Coronary artery disease (CAD) is the most common CVD in adults and is characterized by abnormal accumulation of lipids, fats, and fibrous tissue on vessel walls, leading to their obstruction, constriction, and finally, to reduced blood flow through the myocardium (1, 2).

One treatment for coronary vessel obstruction is coronary artery bypass graft (CABG), which is the most frequent heart surgery performed around the world. Nowadays, many cardiac surgeries are feasible via cardiopulmonary bypass (CPB). The cardiac surgery complicated with increased oxidative stress indicates a dramatic decline in antioxidant and anti-inflammatory capacities post-operation. These events can be associated with organ dysfunctions and elevated mortality (4). After initiation of CPB and subsequent to blood contact with artificial surfaces, a systemic inflammatory response rises, leading to the activation of neutrophils, nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase), and Xanthine oxidase. All these events contribute to the production of free oxygen and nitrogen radicals (RNOS) (5).

The free oxygen and nitrogen radicals induced by CPB can trigger harmful effects. The systemic release of free radicals during CPB disturbs the reperfusion of ischemic heart and probably participates in secondary myocardium damage (6, 7). During ischemia and reperfusion, free oxygen radicals exert their harmful effects by inflicting mitochondria, sarcoplasm, vascular endothelium, adenosine, and nitric oxide (which is a vasoactive and anti-inflammatory mediator). These effects cause augmented myocardial damage, presenting as arrhythmia, contraction abnormalities, and necrosis (8). Because of aortic clamping during on-pump CABG, blood flow toward the heart is compromised, which aggravates oxidants accumulation within the heart. Accordingly, the cross-clamp aorta has been directly associated with oxidative stress-induced cardiac damage (9, 10).

Selenium is a vital element in the structure of selenoproteins with antioxidative activities such as GPX, selenoprotein p, and thioredoxin. Particularly, GPX is highly dependent on selenium in a way that a slight reduction in the selenium level (below the reference range (90 - 100 μg/L) can directly reduce GPX activity (11). Also, selenium deficiency may be involved in the development and progression of CVDs, possibly by 1-increasing thromboxane B2 synthesis, which subsequently leads to platelet aggregation and 2-decreasing prostacyclin production, which inhibits platelet aggregation (12). The level of selenium dramatically declines following heart surgeries and dialysis (13), resulting in unwanted complications and morbidities in both conditions (14, 15). A previous study also indicated a reduction in selenium level in patients under CABG surgery (14). Because of this, patients under cardiac surgery are administered with high dose sodium selenite to prevent selenium reduction during the surgery and to restore both selenium level and GPX activity postoperation. Meanwhile, the administration of high-dose sodium selenite has been approved as a safe intervention in CABG surgery (4). The results of a recent study revealed that selenium was reduced on the first day of postoperation despite high-dose sodium selenite administration. However, their study supported the safety and efficiency of high-dose sodium selenite in preventing selenium fall during cardiac surgery (4). Sedighinejad et al. in their study in 2015, investigated the effects of selenium on inflammatory markers in patients undergoing CABG. According to their results, the infusion of 600 μg selenium was safe with no adverse effects in these patients. Nevertheless, selenium did not significantly affect CABG-pump induced systemic inflammatory markers in comparison to the control group (16).

Considering the fall of selenium during CABG surgery and the subsequent depletion of antioxidant mediators, on the one hand, and high production of free radicals, on the other hand, it seems that selenium-supplemented cardioplegia solution can help to restore antioxidant and cardioprotective capacities.

2. Objectives

In this study, the cardioprotective and antioxidative effects of selenium administration through selenium-supplemented cardioplegia solution were investigated. Cardiac enzymes (Troponin I and CK-MB) were used to assess cardioprotective effects. The previous studies evaluated the role of selenium administration during cardiac surgery in antioxidant capacity. Based on our searches no study has reported the efficiency of indirect selenium infusion to coronary arteries by adding selenium (sodium selenite) to cardioplegia solution.

3. Methods

3.1. Design and Ethical Criteria

This randomized, double-blind clinical trial took place at Namazi Educational Hospital, from May 2018 to September 2018. This governmental and academic center is affiliated with Shiraz University of Medical Sciences (SUMS) in Shiraz, Iran. This study approved by the Ethics Committee of Shiraz University of Medical Sciences (approval code: ir.sums.rec.1396.49), and has been registered as a clinical trial (IRCT20180422039383N1). Overall, 68 patients were allocated to the control and intervention groups. for the patients, informed consent was obtained and the cost of the complications associated with this plan was the responsibility of the program administrators.

3.2. Randomization and Blinding

Sixty-eight eligible patients were randomly allocated to either the Se group (S) or control group (C) using the random-number table. They had an equal probability of being assigned to each of the two groups. A responsible anesthesiologist was aware of the type of groups. However, the patients and the investigators collecting the data were unaware of the treatment assignment (double-blinded).

3.3. Inclusion Criteria

The inclusion criteria were comprised of a scheduled CABG surgery, consent to participate in the study, the absence of renal or hepatic failure, age of > 30 and < 80 years old, and being non-pregnant.

3.4. Exclusion Criteria

Patients with complex surgeries or previous CABG surgery, a history of the recent infraction (within the past one week), EF $< 30\%$, and elevated troponin level (> 0.33 μg/L), as well as the patients in whom the surgery process altered from ON PUMP to OFF PUMP were excluded.

3.5. Anesthesia and Surgical Methods

After referring to the operation room, the patients were monitored by standard procedures, including Leads II and V5 electrocardiography, pulse oximetry, continuous arterial blood pressure, central venous pressure, nasopharyngeal thermometer, Bispectral index (BIS), and End-Tidal Co2 (Etco2). The anesthesia method was the same in both control and intervention groups, including administration of Midazolam (0.2 - 1 mg/kg), Fentanyl (5 - 10 μg/kg), Morphine (2 mg/kg), and Pancuronium Bromide (1 mg/kg). Anesthesia maintenance was achieved by administering Propofol (50 - 100 μg/kg/m), Remifentanil (0.1 - 0.2 μg/kg/min), and 100% oxygen. Following the sternotomy and removing the graft by the surgeon, the primary dose of heparin (300 mg/kg) was infused. After reaching to ATC > 400s, the cannulation of aorta and right atrium was conducted, and the patient was connected to the cardiopulmonary pump. The patients underwent the median sternotomy and a standard technique was used to establish cardiopulmonary bypass pump. At the end of the surgery, heparin was reversed by protamine, and the vascular graft-completed patients were admitted to the intensive care unit (ICU) of cardiac surgery for at least 48 hours. After standard criteria were fulfilled, tracheal extubation was performed within 6 - 8 hours (17).

3.5.1. CPB

CPB was performed on a conventional CPB circuit (Stockert S5, Sorin group, Germany). Cardiac arrest was started by the antegrade infusion of cold crystalloid cardioplegia (i.e. del Nido). A non-pulsatile pump flow of 2.2 L/min/m^2 was maintained throughout CPB. Ringer crystalloid supplemented with heparin (5000 IU) was used as the prime solution in all patients.

3.5.2. Intervention

Twenty ml (1000 μg) sodium selenite and the same amount (20 mL) of normal saline were added to the cardioplegia solution in the intervention and control groups, respectively.

3.5.3. CK-MB and Cardiac Troponin I Measurement

To this aim, blood samples were withdrawn from the arterial line in the following time points: 1- after anesthesia induction (T1), 2- immediately following the surgery (T2), 3- six hours after the surgery (T3), and 4- twenty-four hours after the surgery (T4). The CK-MB (ng/mL) were quantified by an immune inhibition assay, Auto-analyzer Hitachi 912, and specific CK-MB Kits (Pars Azmoon Co, Tehran, Iran). To determine the concentrations of CTnI, we used ELISA kits (BioTek-ELX800 and kits from Monobind Inc. USA). Moreover, the patients' hematocrit was checked before, during, and after pumping.

3.6. Statistical Analysis

Statistical analysis was performed using statistical package of IBM SPSS Statistics for Windows, version 24 (IBM Corp, Armonk, N.Y., USA). The parametric independent sample student *t*-test was used to compare quantitative variables between the two studied groups. Repeated measures ANOVA was used to screen time-dependent and between-group changes in quantitative variables. In order to check the association between categorical variables, chi-square or Fisher's exact test were applied. Also, paired sample student *t*-test was performed for within-group comparisons between quantitative variables. The data were expressed as mean $\pm$ standard deviation. P values of less than 0.05 were considered statistically significant.

4. Results

In this study, 68 patients undergoing CABG by the use of pulmonary pump were categorized into two selenium-treated and control groups. After screening laboratory tests, one patient in the control group was excluded from the study due to the high initial troponin level. The data of the remaining 67 patients were analyzed. The patients' demographic information is displayed in Table 1. According to the indicated demographic data in this table, there were no significant differences between the two groups.

Hemodynamic markers, including systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded before, during, and after pumping in the two studied groups. Systolic and diastolic blood pressures were significantly decreased during pumping and showed an increasing trend afterward ($P < 0.001$). Nevertheless, neither systolic nor diastolic blood pressures showed significant differences between the studied groups (Figure 1).

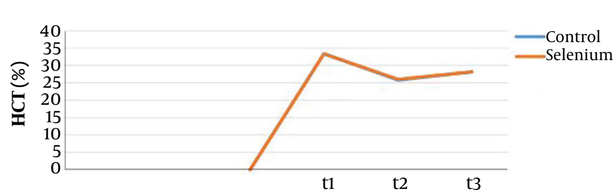

Figure 1. Comparison of hematocrit at three time-points (before, during and after pump)

Based on statistical analysis results regarding troponin fluctuations revealed significant time-dependent changes

Table 1. Demographic Information and History of Underlying Diseases in the Studied Groups

Variables	Selenium Group	Control Group	P Value
Gender (male/female)	42/58	44/56	0.32
Age, y	54.5	58.3	0.06
Weight, kg	68.6 ± 8.5	70.3 ± 10.6	850.
BSA, m²	1.8 ± 0.11	1.75 ± 0.12	0.89
Preoperative EF, %	48.3333	48.5294	77.0
HTN, %	32.8	32.8	0.535
DM, %	13	9	0.24
HLP, %	10.4	11.9	0.474
Hyperthyroidism	0	0	0.353
Hypothyroidism, %	1.5	0	0.32
Smoking, %	19.4	14.9	0.49
Addiction, %	7.5	10.4	3540.
Renal failure	0	0	0.335
CVA, %	1.5	1.5	0.74

Abbreviations: BSA, body surface area; CVA, cerebral vascular attack; EF, ejection fraction; HLP, hyperlipidemia; HTN, hypertension.

Table 2. Comparison of the Mean Troponin Levels Between the Studied Groups in Four Time-Points (T1 - T4)

Group		Mean ± SD	P Value
T1			0.71
	Control	47.0667 ± 95.02269	
	Selenium	56.9214 ± 104.43976	
	Mean	52.0836 ± 99.12617	
T2			0.35
	Control	1286.1741 ± 1252.51421	
	Selenium	1302.5036 ± 1759.61046	
	Mean	1294.4873 ± 1517.73733	
T3			0.11
	Control	5372.1519 ± 4346.32917	
	Selenium	3856.1071 ± 2651.21446	
	Mean	4600.3473 ± 3632.48913	
T4			0.54
	Control	4508.7889 ± 9329.68025	
	Selenium	3189.2107 ± 7552.26797	
	Mean	3837.0036 ± 8418.50182	

in troponin in both groups ($P < 0.001$). Paired comparisons demonstrated that significant differences were related to the differences between the first measurement to the other time points ($P < 0.001$) and also between the second and third measurements ($P < 0.001$). As shown in Figure 2, the troponin level showed a steadily increasing trend until the third measurement (T3) and then reduced. Overall, the mean troponin level was higher in the control group in comparison to the selenium group (Table 2). Despite the higher troponin level in the control group, the repeated measures ANOVA showed that this was not statistically significant ($P = 0.31$).

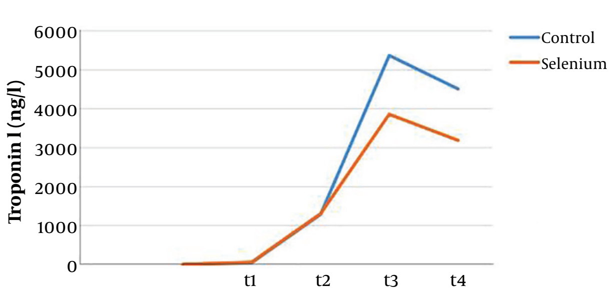

Figure 2. Comparison of serum levels of troponin between the two groups at four time-points

According to the evidence of repeated measures ANOVA, the within-group CK-MB alternations were not statistically significant in neither of the studied groups at any time points (P values of 0.45, 0.22, 0.12, and 0.28 for T1, T2, T3, and T4, respectively). This indicated no overall significant impact on CK-MB ($P = 0.8$). The mean values of CK-MB in the studied groups at different time points are shown in Table 3. As it is indicated, the mean values of CK-MB were higher in the control than the intervention group at all time-points after the surgery. As shown in Figure 3, except for the first measurement (T1), CK-MB values were higher in the control than the selenium group at other time points (i.e. in T2, T3, and T3). Nevertheless, the differences were not statistically significant ($P = 0.16$).

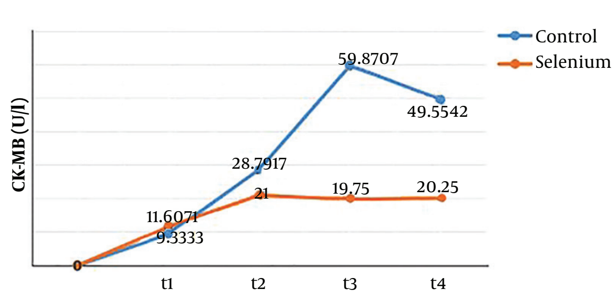

Figure 3. The CK-MB(U/l) measurements at four time-points

Table 3. The Comparison of CK-MB Values Between the Control and Selenium Groups at Four Time-Points

Group	Mean ± SD	P Value
CK-MB1		0.45
Control	9.3333 ± 5.88045	
Selenium	11.6071 ± 9.46079	
Mean	10.5577 ± 8.01815	
CK-MB2		0.22
Control	28.7917 ± 22.64274	
Selenium	21.0000 ± 21.150266	
Mean	24.5962 ± 21.9868	
CK-MB3		0.12
Control	59.8708 ± 143.02955	
Selenium	19.7500 ± 17.46663	
Mean	38.2673 ± 98.97125	
CK-MB4		0.28
Control	49.5542 ± 126.47067	
Selenium	20.2500 ± 19.44341	
Mean	33.7750 ± 87.35614	

5. Discussion

Cardiac surgery complicated with oxidative stress refers to the prominent reduction in antioxidative and anti-inflammatory capacities following the surgery. This phenomenon can disturb organ functions and increase the mortality rate (4). Cardiopulmonary bypass is associated with the activation of inflammatory and hemostatic cascades along with altered oxidative balance. Contact of blood with artificial beds triggers a systemic inflammatory response, leading to the activation of neutrophils, NADPH oxidase, and xanthine oxidase, which in turn produce oxygen and nitrogen free radicals (RNOS) (8). The free radicals subsequently lead to unbalanced Ca^{2+} hemostasis and its intracellular accumulation causes the increment of cardiac enzymes such as CK-MB, troponin, and LDH (18).

Selenium is a vital element in most antioxidant mediators, including glutathione peroxidase, selenoprotein P (SE-P), and selenoprotein W (SE-W). A reduction in the selenium level attenuates the activity of the body's antioxidant system (11). Many studies have reported the relationship between selenium deficiency during cardiac surgery and postoperative complications. Also, some studies have assessed the relationships between intravascular injected selenium (sodium selenite) and inflammatory and cardioprotective markers. In this study, we studied the effects of selenium administered via cardioplegia solution on the levels of cardiac enzymes and arrhythmias in 67 patients who were candidates for CABG surgery. As mentioned, we found no previous reports applying this method to deliver selenium.

Our results demonstrated a remarkable reduction in patients' blood pressure during pumping. It appears that hemodilution is one of the most important factors contributing to blood pressure reduction in this condition. Hemodilution is triggered following the infusion of 1.5 L (in adults) prime solution, which then results in reduced blood viscosity and pressure. Abnormal blood pumping and thereafter non-elastic vessels may further aggravate the hypotension during cardiopulmonary pumping. Nonetheless, the observed hypotension revealed similar descending and ascending patterns between the two studied groups with no significant differences. This phenomenon suggested no evident impacts for the sodium selenite on hemodynamic parameters.

As our results revealed, the time-dependent troponin alternations were significant in both studied groups. The noticeable increment in troponin level in T2 respective to T1 demonstrated an increase in the enzyme level during the surgery likely due to the surgical manipulations and application of the cardiopulmonary pump. The highest increment in troponin level was related to the interval between T2 (i.e., 1-hour postoperation) and T3 (i.e., six hours postoperation). Furthermore, the enzyme level was reduced in the transition between T3 to T4 (i.e., 24 hours postoperation). These results are in accordance with the findings of Carrier et al. (19) and Sedighinejad et al. (20). In between groups comparisons, although troponin levels were higher in the control group than intervention at 1 hour after surgery (i.e. T2), the differences were not statistically significant. However, this observation was opposed to the finding of Sedighinejad et al. (20) at 6 hours postoperation (i.e. T2). According to the recent report, the troponin level showed a significant difference between the control and selenium groups at 6 hours postoperation. Nevertheless, the results of Sedighinejad et al. were in line with ours, indicating no significant differences in troponin levels between the groups in other time points.

Also, there were no significant differences comparing the two studied groups regarding CK-MB isoenzyme at any of the time points. The mean levels of CK-MB were higher in the control group than the intervention group at all timepoints evaluated postoperatively. Nevertheless, these differences did not show a statistically significant threshold. According to our results, selenium administration via cardioplegia solution did not effectively reduce CK-MB level in the patients undergoing CABG, which agreed with the findings of Sedighinejad et al. (20).

In the present study, 1000 μg selenium (sodium selenite) was infused (via cardioplegia solution) to the patients who were candidates for CABG. The two studied cardiac enzymes; troponin and CK-MB, remarkably raised after the surgery, indicating the contribution of these enzymes to the reperfusion ischemic damage secondary to cardiac manipulation and pumping during the surgery. Although selenium reduced the troponin and CK-MB levels, these effects were not efficient, and no statistically significant differences were detected between the intervention and control groups. Furthermore, there were no significant differences between the two groups regarding hematocrit, potassium level, blood pressure, and beating time.

5.1. Conclusions

It was found that selenium decreases the markers of troponin and CK-MB, but this reduction is not effective, and the difference between the two groups is not statistically significant. According to our study, we recommended that a higher dose of selenium should be used before the operations, considering the enhancement of cardiac markers during the surgery. Regarding the role of various antioxidants as a chain in the prevention and reduction of oxidative damages, it sounds that combined administration of these antioxidants may be more effective in the prevention or limitation of oxidative damages.

Footnotes

Authors' Contribution: Masih Shafa and Rahim Hemati conceived of the presented idea. Masood Abasi developed the theory and performed the computations. Simin Azemati and Rahim Hemati verified the analytical methods. Masih Shafa encouraged Masood Abasi to investigate [a specific aspect] and supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

Conflict of Interests: The authors declare that there is no conflict of interest.

Ethical Approval: The project has been approved by the Ethics Committee of Shiraz University of Medical Sciences and the patient consent form has been completed.

Funding/Support: The present article was extracted from the thesis written by Masood Abbasi This study was financially supported by Shiraz University of Medical Sciences grants No. 12811.

References

1. Castelli WP. Epidemiology of coronary heart disease: The Framingham study. *Am J Med*. 1984;**76**(2A):4–12. doi: 10.1016/0002-9343(84)90952-5. [PubMed: 6702862].
2. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med*. 2005;**352**(16):1685–95. doi: 10.1056/NEJMra043430. [PubMed: 15843671].
3. Bhatnagar P, Wickramasinghe K, Williams J, Rayner M, Townsend N. The epidemiology of cardiovascular disease in the UK 2014. *Heart*. 2015;**101**(15):1182–9. doi: 10.1136/heartjnl-2015-307516. [PubMed: 26041770]. [PubMed Central: PMC4515998].
4. Stoppe C, Spillner J, Rossaint R, Coburn M, Schalte G, Wildenhues A, et al. Selenium blood concentrations in patients undergoing elective cardiac surgery and receiving perioperative sodium selenite. *Nutrition*. 2013;**29**(1):158–65. doi: 10.1016/j.nut.2012.05.013. [PubMed: 23010420].
5. McDonald CI, Fraser JF, Coombes JS, Fung YL. Oxidative stress during extracorporeal circulation. *Eur J Cardiothorac Surg*. 2014;**46**(6):937–43. doi: 10.1093/ejcts/ezt637. [PubMed: 24482384].
6. Clermont G, Vergely C, Jazayeri S, Lahet JJ, Goudeau JJ, Lecour S, et al. Systemic free radical activation is a major event involved in myocardial oxidative stress related to cardiopulmonary bypass. *Anesthesiology*. 2002;**96**(1):80–7. doi: 10.1097/00000542-200201000-00019. [PubMed: 11753006].
7. Martins GF, Martins G. Role of trimetazidine in coronary artery bypass graft surgery. *World Jo Cardiovasc Surg*. 2017;**7**(7):87–102. doi: 10.4236/wjcs.2017.77011.
8. Koskenkari J. Myocardial ischemia-reperfusion injury and systemic inflammatory response in high-risk cardiac surgery. *Medica*. 2006;**500**:892.
9. Garcia-de-la-Asuncion J, Pastor E, Perez-Griera J, Belda FJ, Moreno T, Garcia-del-Olmo E, et al. Oxidative stress injury after on-pump cardiac surgery: Effects of aortic cross clamp time and type of surgery. *Redox Rep*. 2013;**18**(5):193–9. doi: 10.1179/1351000213Y.0000000060. [PubMed: 24020718].
10. Zweier JL, Talukder MA. The role of oxidants and free radicals in reperfusion injury. *Cardiovasc Res*. 2006;**70**(2):181–90. doi: 10.1016/j.cardiores.2006.02.025. [PubMed: 16580655].
11. Neve J. New approaches to assess selenium status and requirement. *Nutr Rev*. 2000;**58**(12):363–9. doi: 10.1111/j.1753-4887.2000.tb01837.x. [PubMed: 11206845].
12. Beck MA, Shi Q, Morris VC, Levander OA. Rapid genomic evolution of a non-virulent coxsackievirus B3 in selenium-deficient mice results in selection of identical virulent isolates. *Nat Med*. 1995;**1**(5):433–6. doi: 10.1038/nm0595-433. [PubMed: 7585090].
13. McDonald CI. *Selenium and oxidative stress modulation during extracorporeal circulation*. University of Queensland; 2016.
14. Stoppe C, Schalte G, Rossaint R, Coburn M, Graf B, Spillner J, et al. The intraoperative decrease of selenium is associated with the postoperative development of multiorgan dysfunction in cardiac surgical patients. *Crit Care Med*. 2011;**39**(8):1879–85. doi: 10.1097/CCM.0b013e3182190d48. [PubMed: 21460705].
15. Fujishima Y, Ohsawa M, Itai K, Kato K, Tanno K, Turin TC, et al. Serum selenium levels are inversely associated with death risk among hemodialysis patients. *Nephrol Dial Transplant*. 2011;**26**(10):3331–8. doi: 10.1093/ndt/gfq859. [PubMed: 21372251].
16. Sedighinejad A, Imantalab V, Mirmansouri A, Mohammadzadeh Jouryabi A, Kanani G, Nassiri Sheikhani N, et al. Effects of low-dose selenium on the inflammatory response in coronary artery bypass graft surgery: A clinical trial. *Iran Red Crescent Med J*. 2016;**18**(8). e37918. doi: 10.5812/ircmj.37918. [PubMed: 27795837]. [PubMed Central: PMC5070486].
17. Imantalab V, Mirmansouri A, Sedighinejad A, Naderi Nabi B, Farzi F, Atamanesh H, et al. Comparing the effects of morphine sulfate and diclofenac suppositories on postoperative pain in coronary artery bypass graft patients. *Anesth Pain Med*. 2014;**4**(4). e19423. doi: 10.5812/aapm.19423. [PubMed: 25346897]. [PubMed Central: PMC4205802].

18. Moludi J, Keshavarz S, Tabaee AS, Safiri S, Pakzad R. Q10 supplementation effects on cardiac enzyme CK-MB and troponin in patients undergoing coronary artery bypass graft: A randomized, double-blinded, placebo-controlled clinical trial. *J Cardiovasc Thorac Res*. 2016;**8**(1):1–7. doi: 10.15171/jcvtr.2016.01. [PubMed: 27069560]. [PubMed Central: PMC4827133].
19. Carrier M, Pellerin M, Perrault LP, Solymoss BC, Pelletier LC. Troponin levels in patients with myocardial infarction after coronary artery bypass grafting. *Ann Thorac Surg*. 2000;**69**(2):435–40. doi: 10.1016/s0003-4975(99)01294-1. [PubMed: 10735677].
20. Sedighinejad A, Imantalab V, Mirmansouri A, Mohammadzadeh Jouryabi A, Nassiri Sheikhani N, Naderi Nabi B, et al. Effect of selenium on ischemia-reperfusion injury in the coronary artery bypass graft surgery: A clinical trial study. *Iran Red Crescent Med J*. 2016;**19**(4). doi: 10.5812/ircmj.42562.