Research Article

Effect of Selenium on Ischemia-Reperfusion Injury in the Coronary Artery Bypass Graft Surgery: A Clinical Trial Study

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Abstract

Background: In patients with coronary artery stenosis, coronary artery bypass graft surgery (CABG) is the most effective strategy to limit infarct size and improving outcomes. However, the rapid restoring of blood flow to the tissue can paradoxically induce cardiac damage. This phenomenon termed as myocardial ischemic/reperfusion (I/R) injury which is exacerbated under cardiopulmonary bypass (CPB) and is the cause of poor clinical outcomes. Therefore, it is essential to search for novel strategies with further cardio protective effects.

Objectives: In the current study, we investigated the effects of selenium (Se) administration on I/R injury in CABG patients.

Methods: This randomized double-blind clinical trial was conducted in the department of cardiac surgery of a university hospital in North of Iran from May 2015 to September 2015. One hundred and ten patients undergoing an elective isolated CABG surgery were divided into two groups using randomized fixed quadripartite blocks. They received either intravenous Se before induction of anesthesia, or normal saline as placebo. Cardiac troponin I (CTnI) and creatine kinase-MB (CKMB) were measured as biomarkers at four measurement point times, before the intervention (T0), at 6, 12, 24 and 48 hours after the surgery (T1-T4).

Results: Finally, data from 104 patients were analyzed, the Se (n = 53) and control (n = 51) groups. There was no significant difference between the two groups regarding the baseline characteristics. In both groups CPB caused a markedly increase in CKMB and CTnI plasma concentrations compared to the baseline (P = 0.0001). Based on CKMB, there was no significant difference between the two groups at any point times, T0 (P = 0.357), T1 (P = 0.751), T2 (P = 0.46), T3 (P = 0.16) and T4 (P = 0.053). According to CTnI, there was just a significant difference between the two groups at T1 (P = 0.011) but not at T2 (P = 0.116), T3 (P = 0.09) and T4 (P = 0.634). No adverse effect was recorded linked to our intervention.

Conclusions: Selenium can alleviate I/R injury in short time. Further well-planned trials are needed to find the optimized administration method to achieve the most beneficial effects to the patients.

Keywords: Coronary Artery Bypass Graft Surgery, Selenium, CKMB, CTnI

1. Background

In patients with coronary artery stenosis, the most effective strategy is the coronary artery bypass graft (CABG) surgery. However, myocardial reperfusion itself causes tissue damage, which is known as an ischemic/reperfusion (I/R) injury [1-5]. Accumulating evidence suggests that generation of reactive oxygen species (ROS) following neutrophil activation and inflammatory reactions is the main triggering factor of the I/R injury. Oxidative stress results in membrane lipid peroxidation which leads to irreversible tissue damage, which could translate to adverse outcomes. Therefore, it is supposed that any intervention to restrict the inflammation might have cardiac protection against cell injury [6, 7]. Despite considerable advances in surgical and anesthesia techniques and applying various anti-inflammatory interventions with different degrees of success, I/R still occurs and is associated with short- and long-term poor outcomes [6, 8].

By the way, in recent years because of the increased

ageing population and the prevalence of comorbidities such as diabetes, heart failure, previous myocardial infarction and renal impairment, much higher risk patients are undergoing the CABG surgery (8-10) consequently an enhanced degree of oxidative stress. Therefore, novel therapeutic approaches are needed to provide further cardiac protection. It has been suggested that trace elements such as Se might serve this goal. Selenium as an essential metabolic agent is cost effective and simple to use with antioxidant and anti-inflammatory properties (11-15). It is a large body of literature which indicates that the cardiac surgery is correlated with a decrease of antioxidant capacity related to a significant depletion of Se circulating levels during the CABG surgery. By the way, correction of suboptimal Se statue after the onset of inflammation reaction does not prevent the worsening of tissue damage. Hence, a preemptive strategy is logical (16-20). A few related experimental and animal studies with meaningful results are available (21-24). Whether these findings hold true in humans is yet unclear. Considering the lack of enough data in this field, as we found no similar studies investigating the efficacy of Se focusing on the amount of cardiac injured cells and the role of race and genetic in inflammatory reactions and the different types of diets in different areas, performing this trial in Iranian population might represent the novelty of this work.

2. Objectives

The aim of the current study was to test the hypothesis that Se administration prior to surgery could limit the myocardial injury in patients undergoing elective CABG by CPB.

3. Methods

3.1. Setting

This randomized double-blind clinical trial was conducted at Dr. Heshmat hospital, an academic center, specialized for different types of cardiac surgeries affiliated to Guilan University of Medical Sciences, Rasht, Iran. It was a referral hospital with one hundred and eighty beds and consisted of different sections including angiography, angioplasty, echocardiography, electrophysiology study, the intensive care unit (ICU), coronary care unit (CCU) and surgical wards for men, women and pediatric. The trial protocol was approved by the research ethical committee of the university and also was registered in Iranian registry of clinical trial (IRCT) with the number of IRCT2015041313456N4.

3.2. Study Participants

Between May 2015 and September 2015, consecutive patients referred for the CABG surgery were screened for eligibility. Before the enrolment, an informed consent was obtained from all patients.

3.3. Inclusion Criteria

Patients with ASA class I and II who were candidates for elective CABG as an isolated procedure using CPB, aged 30 - 65 years old, had 3-vessel disease, and ejection fraction> 40% - 45%.

3.4. Exclusion Criteria

Emergency or urgent surgery, myocardial infarction during 6 months ago, who had taken antioxidant supplements during the previous month, a concomitant malignant disease, uncontrolled diabetes, thyroid disease, liver or renal dysfunction, pregnancy, major trauma or major surgery during less than three months, skeletal muscle damage, infection and inflammatory, history of previous angioplasty and those who were unable to give informed consent.

3.5. Sample Size

With a margin of error α = 0.05 and β = 10%, an expected power of 90%, a Z value of 1.28, and the mean $\pm$ SD in the two groups, the Se group: 4.77 $\pm$ 0.09 (mean $\pm$ SD), and the control group: 4.76 $\pm$ 0.13 (mean $\pm$ SD), it was calculated that a sample of at least 50 patients in each group was required. We decided to include 55 patients in each group.

3.6. Randomization and Blinding

One hundred and ten eligible patients were randomly allocated to either the Se group (S) or control group (C) using randomized fixed quadripartite blocks. They had an equal probability of being assigned to each of the two groups. A responsible anesthesiologist was aware of the type of the groups. However, the patients and investigator collecting the data were unaware of treatment assignment.

3.7. Intervention

Before the surgery to assure physical and mental health, a 12- lead ECG, a medical history and physical exam were conducted. Baseline patients' demographic characteristics were also recorded. Patients in the Se group received an intravenous bolus of 500 μg Se in the form of sodium-selenite (Biosyn Arzneimittel GmbH. Fellbach, Germany. vial 50 micrograms/mL) in NaCl 0.9% within 30 minutes at 8:0 am through 48 hours hospitalization before the surgery and just before the induction of anesthesia.

In the control group, normal saline was administered in the same manner. Blood samples were routinely acquired from all patients targeting cardiac troponin I CTnI and creatine kinase-MB CK-MB before the intervention (T0) and at 6, 12, 24 and 48 hours after the surgery (T1-T4). During the study period, patients were observed for any adverse events, which was defined as undesirable signs or symptoms not necessary related to our intervention. If the patients showed any clinical signs of Se overdose such as, gastrointestinal disturbances, garlic smell in the exhaled air, nausea, vomiting, dizziness, pulmonary edema, and muscle cramps (15, 25, 26), they were excluded and immediate measurement of the Se serum level and symptomatic therapy were performed.

3.8. Laboratory Measurements

All the tests were performed in our hospital clinical chemistry laboratory by an experienced lab technician who was employed for this purpose. The samples were collected four times targeting CKMB and CTnI. Before the intervention (T0), at 6, 12, 24 and 48 hours after the surgery (T1-T4), venous blood samples (5 mL) were obtained and within a few minutes plasma was separated by centrifuging at 1200 g for 10 minutes. To measure CKMB (ng/mL) values, an immunoinhibition assay, Autoanalyzer Hitachi 912 and specific CK-MB Kits (Pars Azmoon Tehran, Iran) were used. Also, concentrations of CTnI were recorded using the enzyme-linked immunosorbent sandwich assay (ELISA) (BioTek-ELX800) and kits from Monobind Inc (USA).

3.9. Anesthesia and Surgical Methods

Surgery always started in the morning between 8: 00 am and 9: 00 am to avoid bias caused by the circadian rhythm of circulating stress hormones. On arrival in theatre, an intravenous catheter (18 gauge) was inserted into the forearm vein. Standard monitoring included electrocardiography with both leads II and V5, pulse oximetry, continuous arterial blood pressure, central venous pressure, nasopharyngeal thermometer, Bispectral index (BIS) and End Tidal Co2 (Etco2). The patients were premedicated with oral lorazepam. Anesthesia was inducted with 20 μg/kg fentanil and 0.2 mg/kg etomidate. To prevent myoclonus due to etomidate, a low dose of this hypnotic agent (0.03 mg/kg) was administered before the induction dose (27). After neuromuscular blockade was achieved with 0.2 mg/kg cisatracurium, patients underwent tracheal intubation and mechanical ventilation was started thereafter. Anesthesia was maintained with continuous infusion of propofol 50 - 150 mg/kg/min, remifentanil 0.01 μg/kg/h and 0.6 mg/kg/h cisatracurium. An initial dose of 300 u/kg of heparin was administered to achieve an activated coagulation time greater than 480 seconds, and then

CPB was performed. To induce cardiac arrest, a cold cardioplegic solution was injected into the coronary arteries during the pump time. The patients went under the median sternotomy and a standard technique was used to establish heart-lung pump (standard membrane oxygenator Medtronic). At the end of the surgery heparin was reversed by protamine and the vascular graft completed patients were admitted into the cardiac intensive care unit (CCU) for at least 48 hours. After standard criteria were full filled, tracheal extubation was performed within 6 - 8 hours (28).

3.10. Statistical Analysis

All the statistical analyses were carried out using the SPSS statistical software version 16 (SPSS Inc, Chicago, Illinois, USA). Chi-square test was used to compare the categorical variables between the two groups. The K-S test was also used to describe the normality of our variables and followed by parametric tests. Independent t-test was used to compare and determine the parametric data between the two groups and repeated measurement test to compare the parametric data in five point times. The data were represented as mean $\pm$ standard deviation. P value < 0.05 was considered as statistically significant.

4. Results

In the present study, one hundred and ten eligible subjects were divided into the selenium (Se) and control groups. In the Se group, one patient was affected by malignant hyperthermia and one needed valve repair during the surgery. In the control group, an intra-aortic balloon pump was used for two patients and two could not be extubated within the expected time. After excluding these cases from the survey, data from 104 cases were analyzed (Figure 1).

The mean age of the patients in the Se and control groups were 55.9 $\pm$ 8.95 and 56.84 $\pm$ 9.02 years, respectively (P = 0.59). In the Se group, 32 cases (60.4%) and in the control group 36 (70.6%) of the participants were men (P=0.274). There was no significant difference between the two groups regarding the other baseline characteristics, including BMI (Kg/m^2) (P = 0.888), ejection fraction (P = 0.59), surgery duration (P = 0.511), pump time (P = 0.36), clamp time (P = 0.197), cardiovascular risk factors and patients' medication, diabetes mellitus (P = 0.69), hypertension (P = 0.81) hyperlipidemia (P = 0.83), family history (P = 0.24), and smoking (P = 0.57) (Tables 1 and 2). Baseline plasma concentrations of CKMB (P = 0.357) and CTnI (P = 0.723) showed no significant difference as well (Table 1). Based on the CKMB, there was no significant difference between the two groups at any point times, T0 (P = 0.357), T1 (P = 0.751), T2 (P = 0.46), T3 (P = 0.16) and T4 (P = 0.053). However, the trend of changes was statistically significant in
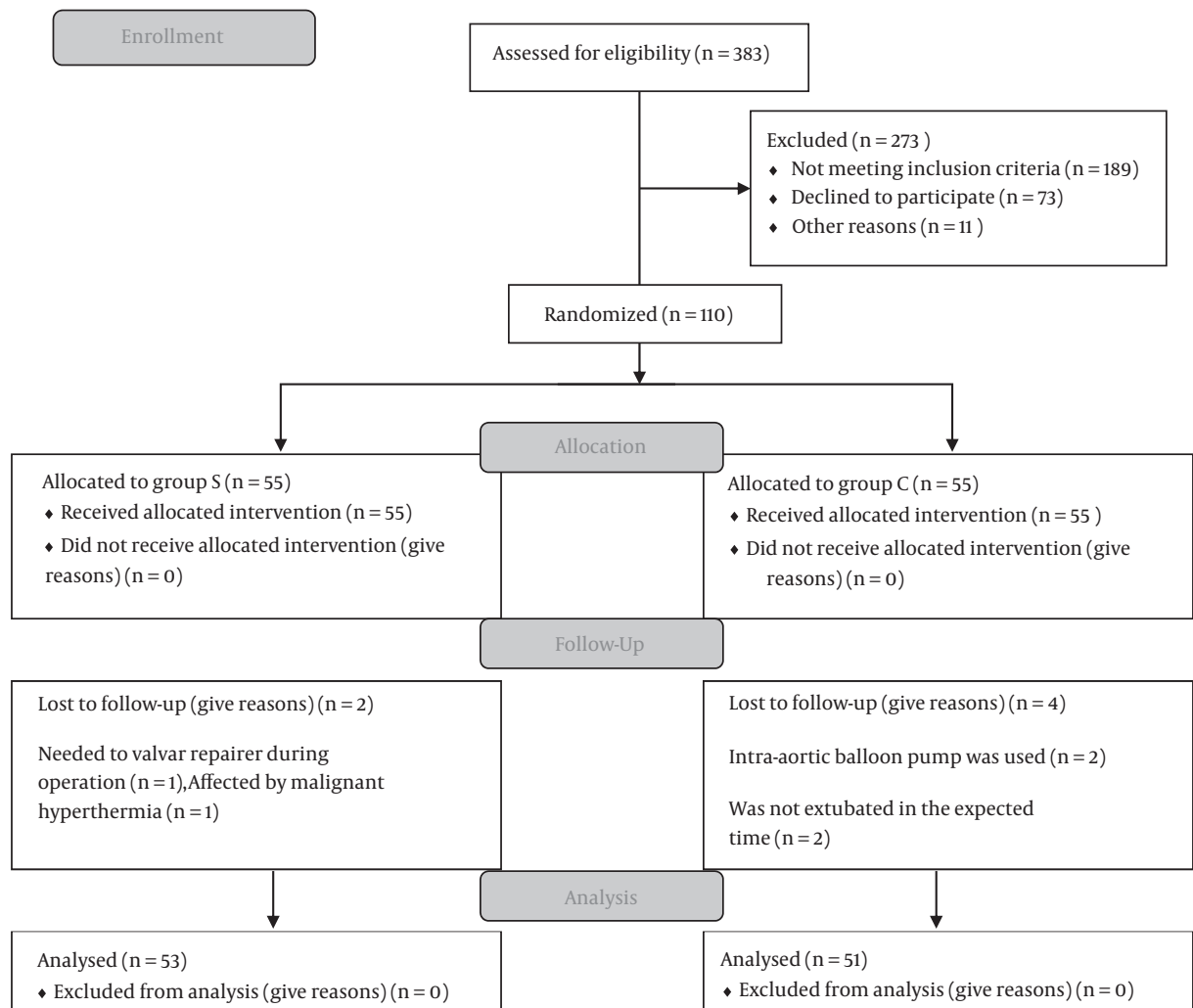
Figure 1. Progress of the Participants During the Study

each group (P = 0.0001). According to the CTnI, the trend of changes was statistically significant in each group (P = 0.0001). However, comparison of the two groups showed that there was just a significant difference between them at T1 (P = 0.011) but not at T2 (P = 0.116), T3 (P = 0.09) and T4 (P = 0.634) (Table 3) (Figures 2 and 3). None of the patients in the Se group experienced adverse effects due to the intervention.

5. Discussion

Selenium has been applied safe in a wide range of doses from 50 μg /day up to 2000 μg /day in different therapeutic durations (6, 11, 29). Clinical studies have claimed that to achieve acceptable results the Se supplementation should

Figure 2. Changes of CTnI Concentrations at Five Point Times
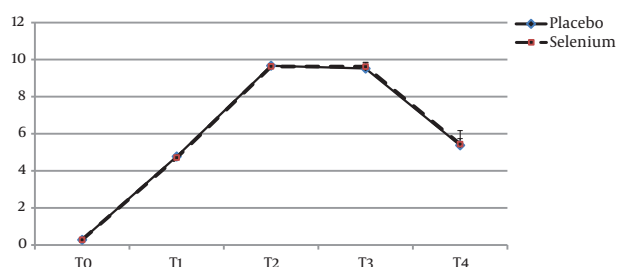
Before the intervention (T0) and at 6, 12, 24 and 48 hours after the surgery (T1-T4).

be started at least 48 hours before the surgery and also if

Table 1. Baseline Characteristics and Data of Surgery[a]

	Group		
Variable	**Placebo (n = 51)**	**Selenium (n = 53)**	**P Value**
Age, y	56.84 ± 9.02	55.9 ± 8.95	0.59
Weight, kg	70.72 ± 6.99	72 ± 11.97	0.511
Height, Cm	161.6 ± 5.72	162.9 ± 8.71	0.368
BMI, Kg/m^2	27.05 ± 2.29	26.98 ± 3.05	0.888
Gender			
Female	15 (29.4)	21 (39.6)	0.274
Male	36 (70.6)	32 (60.4)	
Operation Time, min	169.6 ± 17.09	172.13 ± 21.01	0.511
Pump Time, min	60.7 ± 18.45	57.81 ± 13.6	0.36
Clamp Time, min	37.07 ± 10.03	34.64 ± 9.11	0.197
Ejection Fraction, %	48.23±3.71	47.64 ± 6.97	0.59

[a]Values are expressed as mean ± SD or No. (%).

Figure 3. Changes of CKMB Concentrations at Five Point Times
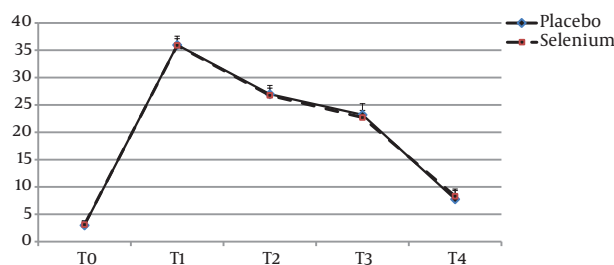
Before the intervention (T0) and at 6, 12, 24 and 48 hours after the surgery (T1-T4).

administrated equal or less than 500 μg, it would not be beneficial to patients (11, 12, 20). In this study, due to the patients' condition and presumed adverse effects, high doses were avoided (30, 31). However, the chosen pattern of supplementation was safe with presumed promising effects. Our results showed that the pattern of changes of the mentioned biomarkers were constantly in line with the previous studies. This study suggested that CKMB and CTnI were involved in the ischemic reperfusion injury, as a sharp rise of cardiac enzymes just after CPB was observed. It was notable that no significant difference was observed between the two groups except of T1 based on CTnI. It shows that the positive effects of the Se remains just for a short time and following the Se serum levels drop the applied dosage could not cope with the inflammatory reactions. During

the I/R injury, when the myocytes' membrane is ruptured or permeable, cytosolic enzymes are released into blood stream. The peak serum levels of CKMB and troponins tend to be found within 24 - 48 hours, and decrease over a few days, which is largely similar to the patients after the acute myocardial infarction (32). Following promising studies focusing on antioxidant properties of trace elements we investigated the effects of Se on the I/R injury in patients undergoing the CABG surgery. In On-pump CABG with cardioplegic arrest and elective global ischemia, as the surgeon controls the onset and duration of ischemia, the onset of oxidative injury is predictable and reproducibly prompts I/R injury. Therefore, this type of surgery could be an ideal model to study the efficacy of preemptive Se (33). Selenium is an essential trace element that exerts its antioxidant and anti-inflammatory effects via its selenoproteins and acts as an antioxidant enzymes co-factor, such as super oxidase (GPX), thioredoxin reductase and prevents Lipopoly saccharide induced pro-inflammatory gene expression, by adjusting nuclear factor- kappa.B (NF- KB) (34-38). Depletion of Se state during the surgery triggers neutrophil accumulation in reperfused sites, which is the primary source of ROS and proteolytic enzyme generation (39). Crucially, the myocardial injury has been measured by serum cardiac enzymes (5, 40). Although the value of cardiac biomarkers for adverse outcome following CABG is poorly understood, it is suggested that among myocardial necrosis markers, cardiac troponins are the gold standard for detection of the cardiac damage (9, 32) Multiple Tn isoforms have been detected in muscles, but CTnT and CTnI are known as cardiac specific isoforms. CTnI with a high specificity detects even small areas of necrosis. CKMB with a limited specificity is expressed in skeletal muscle injuries; however, it represents the same role to CTnI in levels upper than 20 ng/mL (5). Irrespectively of the mechanism, cardioplegia, hypotension, ventricular arrhythmia, manipulation of the heart, and coronary microemblolism whenever myocardial injury occurs these markers are released (2, 4, 9). Recent trails have made clear that even minor rise of cardiac enzyme after the surgery are associated with delayed recovery and short- and long-term morbidity and mortality (2, 3, 9, 41). Indeed, measuring of these markers as prognostic guidance is recommended to detect high-risk patients who need more careful management (32, 41). Based on the above data the amount of damaged cardiac cells was assessed by CTnI and CKMB. In this study, we attempted to review the current literature and knowledge on different cardio protective strategies with the especial emphasis on the anti-inflammatory role of Se. ven den Berg et al. 2016 (1) investigated the effects of eplerenone on the I/R injury in human cardiac tissue. They observed no cardio protective effects from mineralocorticoid receptor an-

Table 2. Cardiovascular Risk Factors and Patients' Medication[a]

Variable		Placebo (n = 51)	Selenium (n = 53)	P Value
		Group		
Diabetes mellitus	Yes	24 (47.1)	27 (50.9)	0.69
	No	27 (52.9)	26 (49.1)	
Hypertension	Yes	30 (58.8)	30 (56.6)	0.81
	No	21 (54.9)	26 (43.4)	
Hyperlipidemia	Yes	28 (58.8)	30 (56.6)	0.83
	No	23 (45.1)	25 (47.2)	
Family history	Yes	25 (49.0)	20 (37.7)	0.24
	No	26 (51.0)	33 (62.3)	
Smoking	Yes	29 (56.9)	33 (62.3)	0.57
	No	22 (43.1)	20 (37.7)	
ACE-inhibitor	Yes	38 (74.5)	34 (64.2)	0.25
	No	13 (25.5)	19 (35.8)	
Statin	Yes	42 (82.4)	45 (84.9)	0.72
	No	9 (17.6)	8 (15.1)	
Beta Blocker	Yes	28 (54.9)	27 (50.9)	0.68
	No	23 (45.1)	26 (49.1)	
Aspirin	Yes	46 (90.2)	44 (83.0)	0.28
	No	5 (9.8)	9 (17.0)	
Nitrate	Yes	25 (49.0)	32 (60.4)	0.24
	No	26 (51.0)	21 (39.6)	

[a]Values are expressed as mean $\pm$ SD or No. (%).

Table 3. CKMB and CTnI Concentrations at Five Point Times, Before Intervention (T0) and at 6, 12, 24 and 48 Hours After the Surgery (T1-T4)

Variable	Groups	T0	T1	T2	T3	T4	P Value	P Value
CKMB, ng/mL	Placebo	2.99 ± 0.7	35.97 ± 1.61	26.96 ± 1.61	23.18 ± 2.05	7.74 ± 1.6	F = 11791; P = 0.0001	F = 6.24; P = 0.003
	Selenium	3.12 ± 0.7	35.88 ± 1.24	26.74 ± 1.34	22.7 ± 1.31	8.3 ± 1.32	F = 20372; P = 0.0001	
	P value	0.357	0.751	0.46	0.16	0.053		
CTNI, ng/mL	Placebo	0.28 ± 0.1	4.77 ± 0.09	9.67 ± 0.09	9.52 ± 0.3	5.38 ± 0.36	F = 19986; P =0.0001	F = 1.33; P = 0.26
	Selenium	0.28 ± 0.09	4.71 ± 0.13	9.63 ± 0.15	9.62 ± 0.24	5.44 ± 0.73	F = 6641.3; P = 0.0001	
	P value	0.723	0.011	0.116	0.09	0.634		

tagonism. Moludi et al. 2016 (42) reported that administration of 150 mg of Q10 supplement per day for 7 days before the surgery could not reduce myocardial damage in the CABG surgery under CPB. Alam et al. 2015 (43) in a randomized double-blind placebo-controlled clinical trial investigated whether intravenous Elafin 200 mg as a potent endogenous neutrophil elastase inhibitor could inhibit myocardial I/R injury during the CABG surgery. They found no strong evidence supporting their hypothesis. Xiaohui et al. 2016 (40) carried out a prospective, randomized, controlled study among off-pump coronary artery bypass grafting (OPCAB) surgery patients. They found that myocardial injury was limited by the administration of a 1 μg/kg loading dose and a 0.6 μg/kg/h infusion dose of dexmedetomidine. CTnI and CK-MB serum levels were measured as cardiac biomarkers. Thielmann et al. 2013 (41)

in a randomized controlled clinical trial examined the hypothesis that whether remote ischemic preconditioning attenuate CTnI serum levels in elective isolated on pump CABG surgery. They reported that the mentioned intervention could be recommended as a cardio protective promising strategy. In a study conducted by Jouybar et al. 2012 (44), no cardio protective effect of ascorbic acid was reported. Their evaluation was based on IL-6 and IL-8 serum levels. Leong et al. 2010 (10) believed that if antioxidants worked as a network they would act more effectively. They achieved therapeutic effects of two weeks 200 μg /day Se but in combination with, coenzyme Q10, omega3, lipid acid and orthotic acid. Of course the exact role of each supplement was not obvious. The results of some similar studies indicated that the severity of inflammatory reactions is not the same among different types of cardiac surgeries. Indeed, a wide range of cardiac enzymes elevation is observed in different cardiac procedures (7, 32), all combined procedures were excluded from this study. Their subjects were selected among both elective CABG and valve surgery patients; consequently our patients were burdened greater degree of stress response. Comparing two studies, it seems that longer duration of Se supplementation combined with other antioxidant agents and the lower level of stress response were responsible factors for the superiority of their results. Altaei et al. 2012 (45) reported that Se treatment (140 μg $\times$ 3 Cap per day) three days before the CABG significantly diminished concentration of IL-6 and TNF-α. It is considerable that Se dosage, timing and the route of administration and also their studied cases who were selected from both on-pump and of-pump CABG patients were the differences between the two studies. Although strong evidence is required to confirm but it is thought that these types of interventions might be more effective in conditions with less degree of stress, such as off-pump compared to on- pump surgery. Stopp et al. 2013 (6) conducted a study on patients undergoing elective cardiac surgery who received an intravenous bolus of 2000 μg Se after the induction of anesthesia and 1000 μg/day within the intensive care unit stay. Selenium serum levels were recorded at regular intervals. They reported normal Se serum levels, which was associated with a decrease in SOFA scores at ICU admission time. It was noticeable that the high dose Se supplementation could not prevent Se level drop on the next postoperative days and patient's outcome was not improved.

Sedighinejad et al. 2016 (46) studied the cardio protective effects of intravenous Se (600 μg) before the surgery reflected by CRP, IL-6, TNF-α in on-pump CABG patients. Their results presented just a borderline significant superiority of the Se group according to CRP concentrations within the first hours of surgery not at the next mea-

surement point times. They support the present study which rule outs the long-term effects of these metabolic agents. As noted above the challenging comparing studies are limited although it emphasizes the novelty of the current work. On the whole a number of responsible factors could explain these controversial results. The stress response to CPB is significantly different among patients population and it is believed that no single approach is ideal for all cases. In addition, the predominant factors in the onset of systemic stress reactions are not completely understood (i.e., cardiopulmonary bypass or the surgical trauma) (21). Clinical evidence has established that the choice of the main anesthetic agent influences the degree of inflammatory reactions by modulating the pathophysiologic pathways (47, 48). Surgeon's experience the method of drug administration (root, dosage, and timing) might affect the outcomes as well (22). Moreover, it is believed that Se biology is cell-tissue dependent, complex and is affected by the disease process and it can have effects on the other metabolic pathways (15, 49). The human pharmacodynamic conditions are not well-known; it is largely unknown whether genetic background of patients, their genotype and phenotype might contribute to Se distributions (22, 50).

5.1. Strengths

To the best of our knowledge, no similar study has been conducted to examine the effects of pretreatment with Se on the severity of myocardial damage measured by cardiac enzymes.

5.2. Weaknesses

The authors acknowledge the fact that regarding to the study exclusion criteria, higher risk patients were not enrolled. Indeed, it is not clear that our findings are also applicable to these patients' groups or not. Moreover, the selected mentioned point times might not have been optimal to determine the peak values and restricted indexes as cardiac damage could also be mentioned as the weakness of this study.

5.3. Limitations

There were certain limitations in this study. First, it was a single center trial with a small sample size. Second, postoperative left ventricular ejection fraction (LVEF) and other major adverse cardio vascular events such as different types of arrhythmias as the other endpoints of Se cardio protective properties were not recorded in this study. Third, rather to select one surgeon and matched patients

in the two groups regarding to known modulating factors, the multiple unknown causes for cardiac enzyme release might bias the results and false diagnosis is problematic. Forth, due to the mentioned follow-up time as long as 48 hours, later changes of these enzymes may have been missed. Considering the mentioned limitations, our findings are mainly hypothesis and not applicable for whole community.

5.4. Suggestions

With great interest, we await the results of future large well-planned multicenter trials with longer follow-up durations in different populations to establish the impact of this intervention on patients' outcome. Searching for further factors in addition to our current knowledge that lead to cardiac biomarker release and also understanding the optimal mode for their evaluation and interpretation are strongly recommended.

5.6. Conclusions

The findings of the current study show that selenium can reduce myocardial damage in short time. Theoretically longer infusion duration or administration combined with the other antioxidants might lead to superior results. However, future trials should also address this issue with functional end points before this strategy to be implemented in the clinical setting.

Acknowledgments

Footnotes

Authors' Contribution: Abbas Sedighinejad and Vali Imantalab: design and concept of the study and manuscript preparation. Ali Mirmansouri and Ali Mohammadzadeh Jouryabi: manuscript preparation and data collection. Bahram Naderi Nabi and Nassir Nassiri Sheikhani: manuscript preparation. Mohammad Haghighi and Gelareh Biazar: data collection and preparation of the manuscript. Zahra Atrkarroushan: data analysis.

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