EFFECT OF PROPOFOL IN CARDIOPLEGIA SOLUTION ON BIOMARKERS OF MYOCARDIAL INJURY IN CORONARY ARTERY BYPASS GRAFTING SURGERY: A RANDOMIZED DOUBLE-BLIND CLINICAL TRIAL

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Abstract

Introduction: Coronary artery bypass graft (CABG) surgery with cardiopulmonary bypass (CPB) triggers an inflammatory reaction, leading to the development of myocardial damage and dysfunction. It is assumed that propofol, a general anesthetic agent, has a protective role against oxidative stress. The aim of this study was to evaluate the effect of propofol on myocardial protection when added to cardioplegic solution in patients undergoing CABG.

Methods: In this prospective and double-blind RCT study, 120 patients undergoing CABG surgery were randomly assigned into two equal groups. In one group, we added 1200 µg/min (ultimate dose 4 µg/ml) propofol to cardioplegic solution and in the control group, an equal volume of normal saline was added to cardioplegic solution. Serum levels of CPK-MB and Troponin I were checked at four time points, including: just after induction (T1) as baseline, after chest closure (T2), 6 hours after arrival to ICU (T3) and 24 hours after ICU admission (T4).

Results: Cardiac enzyme levels had significant increase over time in both groups (p-value <0.05). It was observed that the enzyme levels in the propofol group increased less compared with the control group; however, this difference was not significant. Both groups were also similar in incidence of post-operative arrhythmia and need for use of IABP.

Conclusion: Adding a dose of 1200 µg/min (ultimate dose 4 µg/mL) propofol to cardioplegia solution does not have an effect on CPK-MB & troponin I level.

***Keywords**:* Coronary Artery Bypass Graft surgery, Cardioplegic Solution, Cardiac Protection, Propofol

Introduction

Cardiovascular diseases are among the most severe chronic diseases (1). Coronary artery disease (CAD), as one of the fatal cardiovascular diseases in industrialized countries, is commonly and efficiently treated with coronary artery bypass grafting (CABG) (1). CABG is performed with or without cardiopulmonary bypass (CPB) (2).

One of the most prevalent CPB surgery techniques is myocardial protection with cardiopulmonary arrest (3, 4). In spite of the development of myocardial protection strategies, ischemia and cardioplegic arrest can still lead to reperfusion injury (5). Death of cardio myocytes and disarrangement of ion homeostasis and metabolism, including sodium and calcium density, are among the complications of this intervention (3, 4, 6). Blood transfusion in the CPB device leads to Systemic Inflammatory Response Syndrome (SIRS) owing to connection of tubes with blood and oxygenator and also reperfusion syndrome which increases inflammatory cytokines (7). The inflammation, initiated by CPB, causes extreme pulmonary edema and secretion which ultimately results in reduction of lung compliance, vascular resistance increment, increased permeability, and changes in lung surfactant (7). The use of CBP has been shown to release more troponin I (a marker of myocardium damage) within 72 hours of postoperative

surgery (7). Arrhythmia happens within four days after surgery; this can lead to heart failure and one of the potential reasons might be inflammatory cytokines (8).

Regarding the relative protection of cardioplegia, it is beneficial to add compounds which might reduce oxidative stress and calcium accumulation and prevent the opening of mitochondrial permeable canals (9). Addition of propofol during CBP might have a helpful consequence on the heart (10). Propofol can act as a free radical reducing agent along with its anesthetic role (11). It can reduce pulmonary function by reducing inflammatory mediators (12). Propofol also plays a supporting role on erythrocytes which are damaged during CPB (13).

Chang et al. (14) has conducted an animal study about the protective effect of propofol against renal ischemia–reperfusion injury (IRI) in rats. They reported the reducing effect of propofol on renal IRI. In another study, Rogers et al. (6) expressed the supportive effect of propofol in cardioplegia in CABG and aortic valve replacement (AVR) surgery at a concentration of 6 µg /mL.

Therefore, in this study we aimed to investigate the effect of 4 µg/mL propofol added to-cardioplegic solution on improving CPK-MB and troponin I levels, in order to measure its cardio-protective effects in patients under CABG surgery.

Materials and Methods

This randomized single-blind clinical trial was performed at Nemazee hospital, affiliated to Shiraz University of Medical Sciences, Shiraz, Iran. The trial protocol was conducted in compliance with the Helsinki Declaration and according to the approved study protocol, Good Clinical Practice guidelines, and all appropriate regulatory requirements. It was approved by the Research Ethical Committee of Shiraz University of Medical Sciences (Ethic Number: IR.SUMS.REC.1397.415). This study is registered in the Iranian Registry of Clinical Trial (IRCT No: 20180922041084N2). The process of this study was completely described to the participants and written consent was received before referring each patient to the operating room.

Our inclusion criteria were 30-75 year-old patients with ASA class I and II who were candidates for elective CABG applying CPB and with the ejection fraction (EF) over 30%. The participants who had liver or renal dysfunction congestive heart failure, allergy to eggs, soy, peanuts or needed coronary and simultaneous valve operation, repeat operation and the patients with preoperative plasma troponin levels more than 3 µg/L, and also patients with severe heart, lung or kidney diseases were excluded from the trial.

Considering previous similar studies, the sample size formula, $\alpha = 0.05$, d100, σ200, the power of 80 % and according to the effect size, the sample size was determined to be 60 patients in each group. The participants were assigned to the intervention or control group using block randomization with a fixed block size of four after referring to http://www.randomizer.org.

All participants were referred to the operation room at Nemazee hospital to perform the elective CABG surgery. All the patients in the present study underwent the same anesthetic technique by an expert anesthesiologist. An arterial catheter was applied for each patient after entering the operating room and carrying out the hemodynamic monitoring. The anesthesia induction was equal in both groups and included 10 µg/kg fentanyl, 0.1 to 0.2 mg/kg midazolam, 0.2 mg/kg morphine and 0.1 mg/kg pancuronium bromide. Along with performing the intubation, the central venous catheter was applied. For maintaining the anesthesia 100 to 150 mg/kg/min propofol, 0.1 to 0.2 µg/kg/min remifentanil and 100% oxygen were used, and were the same in both groups. Induction and maintenance of anesthesia, intubation and insertion of central venous pressure (CVP) was performed by an expert anesthesiologist who was unaware of the trial.

All the patients in the present study underwent the same technique of on pump which was performed with the same surgical team. A surgeon performed the surgery and sternotomy, took the detachment grafts and prescribed 300 U/kg of heparin. Aortic and right atrial cannulations were performed with increasing the activated clotting time (ACT). Each patient was connected to CPB after reaching to an ACT of 480 s. The equal prime solution, including crystalloid ringer, albumin and 100 U/kg of heparin, was used in both groups of the study.

The aorta was clamped after connecting each participant to the pump and the cardioplegic solution, St. Thomas cardioplegic solution in both groups, was injected by means of cardioplegia cannula with an antegrade method and care was taken to be aware of diastolic cardiac arrest. The participants were cooled to 32-34 degrees Celsius.

The cardioplegia solution was injected at a rate of 300 mL/min using a ratio of 1 to 1 (blood & crystalloid). In this technique, the cardioplegic solution and blood were mixed with a valve by Y connection ¼ ¼ ¼. Then the propofol solution was combined with the cardioplegia solution by means of a syringe pump via Y connection valve in the treatment group and normal saline was added to the cardioplegic solution in the control group. We adjusted the rate of propofol administration to 6 cc/min equal with 1200 µg/min (ultimate doses 4 µg/mL).

We entered the final solution into a common pathway to the cardio delivery set, cooled to 8 degrees Celsius and injected into the coronary arteries. 15 mg/kg of this solution was injected and led to diastolic arrest in 30-60 seconds. In a time period of 15-25 minutes after the first dose, a second dose (half of the first dose) of this solution was injected, if required. Rewarming of the participants was started after distal graft anastomosis and after that the cross clamp was opened. The opening time and the time period of the cross clamp were recorded, in addition to any arrhythmias.

In the case of hemodynamic instability after propofol administration, infusions of 0.01 µg/kg/min was prescribed through the CV line with arterial line monitoring. The extubation criteria were adequate ventilation according to arterial blood gas analysis and full consciousness of the patients. The hemodynamic parameters of the patients were also within normal limits.

Myocardial injury, which was assessed by biochemical parameters such as CPK-MB and cardiac troponin I (CTnI) in blood serum, was the primary outcome of this study. Three to five cc of blood samples were collected at 4 time points as follows: 1; just after induction (T1) as baseline, 2; after chest closure (T2) 3; 6 hours after arriving to ICU (T3), 4; 24 hours after ICU admission (T4). CPK-MB (ng/mL) was quantified by an immune inhibition assay, Auto analyzer Hitachi 912 and specific CPK- MB Kits (Parsazmun Co, Tehran, Iran). For determining the concentrations of CTnI, ELISA kits (BioTek-ELX800 and kits from Monobind Inc. USA) were used.

Statistical analysis was performed applying statistical package for the social sciences, version 24 (SPSS, Inc. Chicago, USA). Our data had normal distribution. Independent sample t-test and repeated measurement analysis of variance (ANOVA) was used to analyze the quantitative factors between the groups. The chi-squared test was used to test the relationship between two factors. With reference to the significance of the Mauchly's Test of Sphericity, the changes in the group were assessed by Greenhouse-Geisser correction.

Results

Out of 150 patients who were candidates for CABG operation with CPB, 120 patients were eligible according to inclusion and exclusion criteria, and participated in this trial (Figure 1).

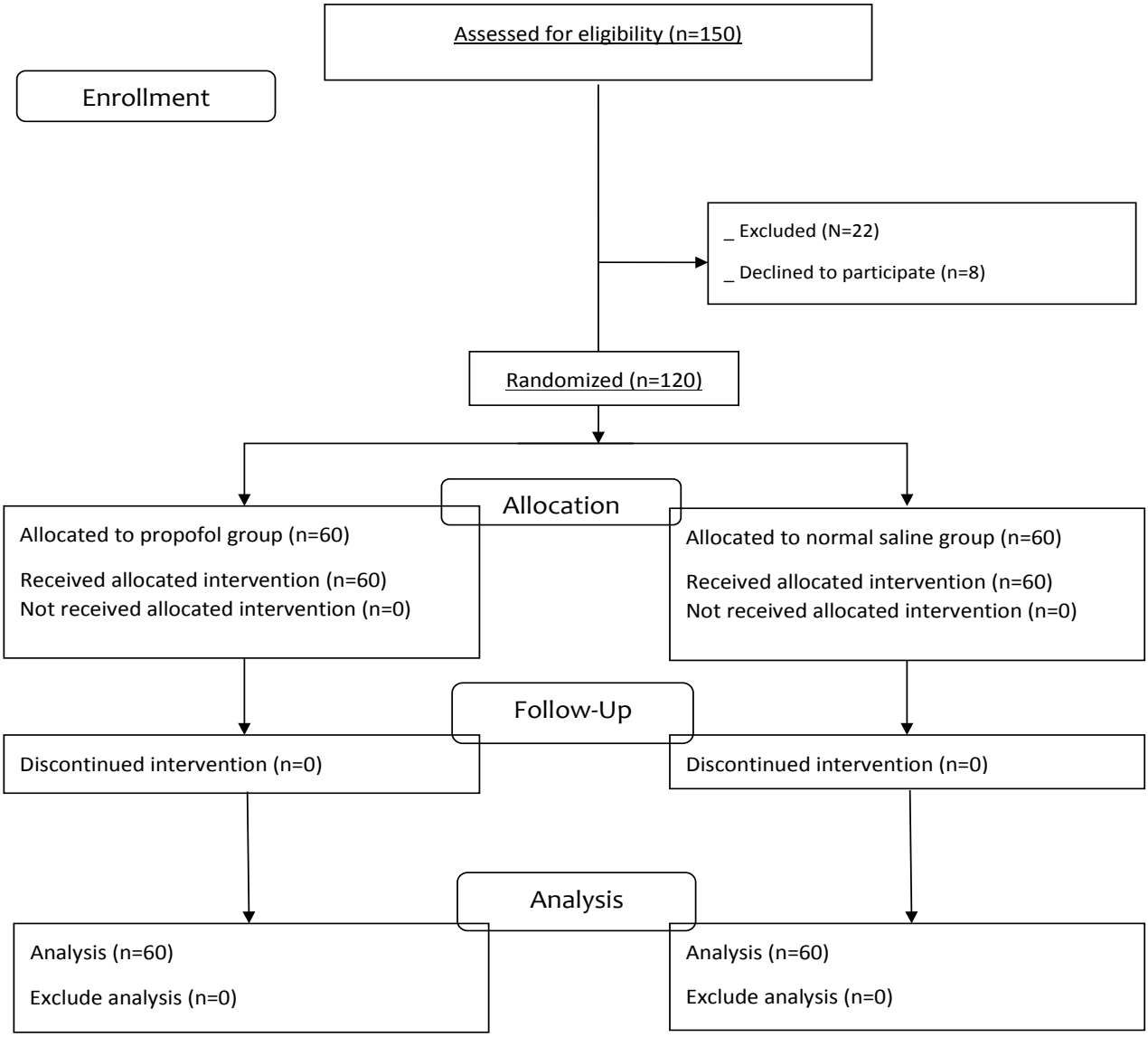

Figure 1: CONSORT flow diagram

Baseline data

Demographic characteristics of the participants, including weight, gender, BSA and EF, were not significantly different between the two groups ($p > 0.05$). There was also no significant difference between the two groups, with respect to the risk factors and underlying diseases ($p > 0.05$). Comparison of baseline laboratory results, hemodynamic and angiography findings and intensity of coronary artery disease between the two groups, revealed no statistically significant difference ($p > 0.05$). Furthermore, CPB Time, total cardioplegic volume, Cross Clamp Time, beating time, number of grafts, ITA Graft, and IABP during surgery, did not have any significant difference in both groups ($p >0.05$) (Table 1).

Table 1: Baseline data

Variable		Propofol	Control	P value
Demographic data				
Gender	female	24(60.0%)	22(63.3%)	0.707
	male	36(40.0%)	38(36.7%)	
Age		63.23±8.47	60.53±11.13	0.138
Weight		66.86±9.95	67.86±13.37	0.643
BSA		1.72±.15	1.73±.20	0.852
EF		50.08±8.05	47.50±8.94	0.099
Underlying disease and risk factors				
HTN		(40)66.7%	(41)68.3%	0.845
HLP		(16)26.7%	(22)36.7%	0.239
DM		(18)30.0%	(15)25.0%	0.540
CVA		(2)3.3%	(1)1.7%	0.505
Family history		(7)11.7%	(9)15.0%	0.591
Smoking		(19)31.7%	(16)26.7%	0.547
Addiction		(12)20.0%	(12)20.0%	1
Hyperthyroidism		(1)1.7%	(0)0.0%	0.315
Hypothyroidism		(2)3.3%	(1)1.7%	0.559
laboratory, hemodynamic, angiography information				
	SVD	(1)1.7%	(2)3.3%	0.757
Angio	DVD	(17)28.3%	(19)31.7%	
	TVD	(42)70.0%	(39)65.0%	
LMCA		(4)6.7%	(3)5.0%	0.679
SBP		133.71±28.41	129.43±26.62	0.396
DBP		77.36±17.43	76.43±15.60	0.758
K		3.61±.56	3.67±.66	0.562
HCT		35.36±6.35	35.00±4.62	0.722
Data during surgery				
CPB Time:		62.58±19.07	61.86±18.69	0.836
Cross Clamp Time		35.78±11.99	35.53±11.45	0.907
Cardioplegic Volume		1121.33±265.30	1199.50±317.37	0.683
Beating Time		159.46±126.87	145.50±139.66	0.567
Number	1	(0)0.0%	(1)1.7%	
of	2	(17) 28.3%	(20)33.3%	
Graft	3	(30) 50.0%	(23)38.3%	
	4	(13) 21.7%	(16)26.7%	.479
ITA Graft		(46)76.7%	(49)81.7%	.500
IABP		(0) 0.0%	(1)1.7%	.315

P <0.05 consider as a significant level
BSA: Body Surface Area; EF: Ejection Fraction; HTN: Hypertension; HLP: Hyperlipidemia; DM: Diabetes mellitus; SVD: Single Vessel Disease; DVD: Double Vessel Disease; TVD: Triple Vessel Disease; LMCA: Left Main Coronary Artery; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HCT: Hematocrit; CPB: Cardio-Pulmonary Bypass; ITA: Internal Thoracic Artery; IABP: Intra-Aortic Balloon Pump

Troponin I and CPK-MB changes

Comparison of enzyme changes in each group over time revealed that CPK-MB and troponin I levels were significantly increased ($p < 0.001$) (Table 2 and Table 3 respectively). The mean values of troponin I level, measured at all four time points, showed that despite the lower level of troponin I in the propofol group in comparison with the control group, a significant difference was only observed in the 6 hours after arrival to ICU stage (p-value = 0.03), but in the other stages there were no significant difference in mean troponin I level between the two groups (p-value > 0.05) (Table 2).

Table 2: Troponin I level

Variable	Propofol mean	Control mean	P value
Troponin I (T1)	13.4917±17.66	13.5900±17.96	.976
Troponin I (T2)	1456.4000±1918.62	1417.6967±1358.44	.899
Troponin I (T3)	3624.7491±2468.99	4851.0814±3442.23	.030
Troponin I (T4)	3444.8051±5609.64	3733.1717±6745.51	.800
	P value<.001	P value<.001	

[1]TI: after induction
[2]T2: after chest closure
[3]T3: 6 hours after arrival to ICU
[4]T4:24 hours after ICU admission

The mean values of CPK-MB level measured at all four time points showed that despite the lower level of CPK-MB in the propofol group in comparison with the control group, there was no significant difference in CPK-MB mean level between the two group (p-value > 0.05) (Table 3).

Table 3: CPK-MB level

Variable	Propofol mean	Control mean	P value
CPK MB (T1)	11.8000±6.95	13.0000±8.57	.402
CPK MB (T2)	32.1833±24.81	38.8475±23.40	.135
CPK MB (T3)	33.2759±44.84	47.9475±91.37	.274
CPK MB (T4)	26.7167±24.86	38.0883±80.28	.297
	P value<.001	P value<.001	

[1]TI: after induction
[2]T2: after chest closure
[3]T3: 6 hours after arrival to ICU
[4]T4:24 hours after ICU admission

Cardiac arrhythmia

Cardiac arrhythmia was recorded during the period of cross-clamp opening time till ICU arrival time. The occurrence of arrhythmia was not significantly different between the groups ($p > 0.5$) (Table 4). No adverse effect as a result of the intervention was observed.

Table 4: Cardiac arrhythmia

Variable	propofol	control	P value
Arrythmia	(24)40.0%	(23)38.3%	.852
Tachycardia	(1)1.7%	(1)1.7%	1
Bradycardia	(3)5.0%	(0)0.0%	.079
Block	(1)1.7%	(1)1.7%	1
PVC	(8)13.3%	(6)10.0%	.570
VF	(6)10.0%	(11)18.3%	.191
VT	(10)16.7%	(8)13.3%	.609
AF	(1)1.7%	(2)3.3%	.559

PVC: Premature Ventricular Contraction; VF: Ventricular Fibrillation; VT: Ventricular Tachycardia; AF: Atrial Fibrillation

Discussion

So far, some studies have been done on the supportive role of propofol on the heart and other body organs during cardiac surgery. In this study, we investigated the effect of adding 1200 µg/min (ultimate concentration 4 µg/ml) propofol to a cardioplegia solution on the reduction of cardiac injury enzymes and incidence of arrhythmia in 120 patients undergoing coronary artery bypass graft surgery under CBP.

Our data shows that CPK-MB and troponin I levels were raised during the surgery due to the use of cardiopulmonary bypass machine and the surgical manipulation of the heart, and these changes were statistically significant in both groups. The highest peak for troponin I level occurred 6 hours after arrival to ICU, between the second and the third time points, and then it decreased at 24 hours after ICU admission (at the fourth time point), which agrees with the findings of the study by Rougers et al. (6). In the present study, the alterations of plasma troponin I level during the surgical procedure were lower in the propofol group than the control group, which was in line with a previous study performed by Rougers et al. (6) however, it was significant only after chest closure till 6 hours after arrival. On the other hand, Rougers et al. showed that cardiac troponin I release was, on average, 15 % lower in the 6 µg/ml propofol group (6).

The CPK-MB level was also lower in the propofol group in comparison with the control group. However, this difference was only significant after chest closure till 6 hours after arrival. Regarding the mean value of the groups, in spite of the lower levels of troponin I and CPK-MB in the propofol group compared with the control group, it can be concluded that 4 µg/ml of propofol does not have significant effects on plasma troponin and CPK-MB levels.

Considering the cardioprotective effect of propofol, this study showed that applying propofol plus isoflurane in the maintenance of anesthesia had a synergistic effect

on reducing plasma levels of cardiac troponin I and CK-MB compared to using each of them individually (15). Isoflurane preconditioning and propofol could significantly reduce ICU stay in addition to increased post-ischemic cardiac index which was parallel to profound decreases in plasma TNF-α and malondialdehyde (MDA) levels as well as decreasing myocardial levels of nitrotyrosine expression (15). There are several other studies supporting the cardioprotective impact of propofol during surgical procedures (6, 16-18).

Propofol has a positive effect on the heart by means of anti-inflammatory mechanisms within the reperfusion time (10) Propofol could act as an anti-oxidant agent along with its anesthetic role in patients under CBP (11) which could improve ischemic stroke (19). Propofol might also perform its cardioprotective role by activating the PI3K (phosphoinositide 3-kinase)/Akt pathway (15).

On the other hand, there are some opposing evidences. Some studies which compared propofol with the volatile anesthetic, sevoflurane, for anesthesia during CABG surgery, reported the protection by sevoflurane individually (20-22). Parts of this contradiction might be due to the role of propofol in interfering with protection mediated by RIPC, that suggests this interference to be located upstream of STAT5 activation (23).

Moreover, when propofol is given at a dose up to 100 μg/kg^{-1} min^{-1} (50–100 μg kg^{-1} min^{-1}), it can significantly reduce myocardial levels of MDA, which is a peroxidation product of lipids, in patients experiencing CABG surgery using CPB. A previous study has shown that the supportive effect of propofol on myocardial function after reperfusion and global myocardial ischemia was dose dependent. Propofol is effective at doses of 30 μM (approximately 5 μg/mL doses) or more. This agent is not efficient at concentrations of 10 μM (approximately 2 μg/mL doses) or less (24).

The length of staying in ICU was shorter in large-dose propofol-receiving patients. This might be due to propofol not deactivating production of oxygen free radicals (which are greatly increased during CPB), at relatively small concentrations. Propofol might maintain viability and function of post-CPB vascular endothelial cells, partly by increasing the bioavailability of nitric oxide, a potent vasodilator, and decreasing tumor necrosis factor α–induced vascular endothelial cell apoptosis. Therefore, reductions in vascular endothelial cell apoptosis by propofol could have led to reduced cardiomyocyte apoptosis within the myocardial ischemia and reperfusion. This could be related to a decline in cardiac enzymatic release and maintenance of function however, further studies are needed. Thus, applying a large dose of propofol during CPB reduces postoperative myocardial cellular damage in comparison with small-dose propofol or isoflurane (24).

In addition, rapid plasma distribution and short half-life of propofol leads to quick onset and short duration of propofol action. As the next dose of cardioplegia is applied, only a small amount of the supplementary propofol stays in the circulation (5). Therefore, considering propofol's dose dependency and short half-life, the present study could not show any significant effect of this agent on troponin I and CK-MB, except after chest closure up to 6 hours after arrival.

In this study, 23 (38.3%) participants in the control group and 24 (40%) patients in the propofol group, after cardiac operation until arrival to ICU, experienced arrhythmia which was not significant between the groups. Therefore, this study showed that propofol has no effect on attenuating the overall rate of arrhythmias from the opening of the cross–clamp until the patients arrived in the ICU.

Strengths and limitations

This study was performed only on CABG patients who did not have any other associated cardiac surgery. This single-center study had some limitations. It was more appropriate to compare two different doses of propofol or use greater doses to assess the myocardial protection by propofol and checking cardiac enzymes during 12 and 48 hours after surgery. Normal saline was used as placebo in the control group; however, it is more appropriate to use intralipid as the placebo in the control group to balance any effect of intralipid on myocardial cells, since propofol contains lipids as solvent.

Conclusion

The goal of this study was to evaluate the protective effect of propofol in cardioplegia solution in cardiac surgery. Our findings show that propofol in the doses used in this study did not change the levels of cardiac enzymes as the surrogate markers of myocardial damage significantly. Thus, further studies on a larger scale are recommended, to find the effect of different propofol concentrations in cardioplegia solution and also to detect the most appropriate dose creating a myoprotective effect.

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Competing interests

None.

Author contribution

R.J. participated in the study conception, proposal writing, data analysis and the article draft and manuscript revision. GA.H. was contributed in proposal preparation, data

collection and the primary draft. R.Kh. was contributed in the study conception, proposal writing and final draft. H.N. was contributed in the proposal writing, data collection and article draft. E.A. participated in data analysis, manuscript preparation, article writing and editing and final draft. Z.E. participated in proposal writing, manuscript preparation, and article writing.

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