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Evaluation of Vasodilatory Effect of Nitroglycerin in Cardioplegia Solution on Patients Undergoing Coronary Artery Bypass Graft Surgery

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Original Article

Abstract

INTRODUCTION: This study aimed to evaluate the vasodilatory effect of nitroglycerin (NTG) in cardioplegia solution on changes in troponin I and creatine phosphokinase-MB (CPK-MB) levels during coronary artery bypass graft (CABG) surgery.

METHOD: A randomized controlled double-blind clinical trial was performed on 44 patients who were candidates for CABG surgery. These patients were divided into two groups. In the first group (NTG group), 3 mg/kg NTG was added to the cardioplegia solution, while 10 cc placebo (distilled water) was added to the cardioplegia solution in the second group (control group). Troponin I and CPK-MB levels were then assessed before and after the surgery.

RESULTS: In this study, 72.7% and 27.3% of patients in the NTG group and 68.2% and 31.8% of patients in the control group were male and female, respectively. In addition, 9.1% within the age range of 40-50 years, 27.3% within the age range of 50-60 years, and 63.6% within the age range of more than 60 years were present in the NTG group. Moreover, 18.2% within the age range of 40-50 years, 36.4% within the age range of 50-60 years, and 45.5% within the age range of more than 60 years were present in the control group. Although the mean cardiopulmonary bypass (CPB) and cross-clamp time was insignificantly higher in the NTG group compared to the control group. In addition, troponin I and CPK-MB levels after surgery in the NTG group with the mean of 2090.68 ± 1856.07 and 97.27 ± 38.17 were significantly lower than those of the control group with the mean of 2697.02 ± 5586.56 and 137.95 ± 227.99, respectively (P-value <0.05).

CONCLUSION: According to the results of this study, although troponin I and CPK-MB levels increased significantly after CABG surgery, this increase was significantly lower in the intervention group compared to the control group following the administration of NTG.

Keywords: Nitroglycerin, Troponin I, CPK-MB, Cardioplegia, Coronary artery bypass graft surgery

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Introduction

Myocardial ischemia is a cardiovascular disease that occurs due to partial or complete blockage of coronary arteries, leading to decreased blood flow to the myocardial cells [1]. Ischemic-induced lesions in the heart result in the death of myocardial cells. Specifically, during ischemia, reduced blood flow and insufficient oxygen delivery to the tissue disrupt cellular respiration, leading to irreversible damage to the myocardium, including myocardial infarction in less than a few minutes [2]. Therefore, the use of reperfusion is one of the primary and immediate treatment priorities in myocardial ischemia. However, with the restoration of

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blood flow after myocardial ischemia, oxygen and nutrients become available to cells that have previously been exposed to ischemia. This can be associated with inhibition of oxidative phosphorylation (increased oxidative stress), nitric oxide (NO), and the production of free radicals, exacerbating local damage such as endothelial dysfunction. This phenomenon, known as ischemia-reperfusion injury (IRI), causes irreversible damage to the myocardium by increasing apoptosis (cell death) [3].

It is important to note that ischemia-reperfusion, which occurs during certain cardiac surgeries including coronary artery bypass grafting (CABG), is also a major cause of heart failure, morbidity, and mortality. CABG is currently the most common treatment procedure performed by cardiac surgeons, with more than 800,000 patients worldwide undergoing CABG annually [4,5]. Although this treatment option saves patients with coronary artery occlusion, the complications of this surgery may have some consequences.

The establishment of blood flow in CABG surgery is associated with a number of events such as the inhibition of oxidative phosphorylation, inhibition of NO production, the production of free radicals, and the death of endothelial cells [6, 7]. The mechanisms involved in hypoxic endothelial cell death are not yet fully understood; however, researchers cite changes in calcium ion concentrations, mitochondrial dysfunction, and purine nucleotide depletion as possible causes of endothelial cell death [8].

The healthy endothelium maintains vascular homeostasis and normal tone in arteries by producing NO. Under pathophysiological conditions, overproduction of reactive free radicals, especially superoxide anion (-O2), may reduce the biological activity of NO and its bioavailability. Recent studies have indicated that NO emission from the coronary artery endothelium decreases after myocardial ischemia and reperfusion. This process is due to an incomplete response to endothelium-dependent vasodilators [9]. Researchers believe that rapid hypoxic contraction is dependent on the response of the coronary artery endothelium to these events and is associated with a decrease in NO and soluble guanylyl cyclase (sGC) [10].

In this regard, some studies have suggested that the addition of an NO releaser to the cardioplegia solution in CABG surgery can improve cardiac function and post-ischemic myocardial function [11]. Furthermore, studies have indicated that drugs such as nitroglycerin (NTG), which mediates NO production, may be able to reduce ischemia-reperfusion injury [12]. NTG is used to treat ischemic heart disease and systemic hypertension due to its dilation of the coronary arteries [13]. After conversion to NO or NO-related mediators in the cytoplasm, the drug causes vasodilation, which in turn increases cGMP due to the activation of sGC and PKG [14]. The pharmacological effects of this drug on coronary arteries are not limited to the vasodilation effects, but also reduce cardiac afterload [15].

The results of one study showed that NTG prevents the stable endothelium-dependent vasoconstriction by inhibition of the PI3K/Akt pathway [16].

Additionally, some researchers believe that the direct effects of NO on cardiac myocytes and coronary arteries may contribute to the damage caused by cardioplegia and cardiopulmonary bypass (CPB) [17]. Another study revealed that ischemia-reperfusion during CABG surgery reduced NO levels, leading to endothelial dysfunction. They suggested that the use of an NO releaser in the cardioplegia solution, such as L-arginine, could reduce the rate of these injuries during CABG surgery [18]. The effects of using NTG in the cardioplegia solution were then evaluated, and the results indicated that the use of this drug in the cardioplegia solution in patients undergoing CABG reduces ischemia-reperfusion-induced lipid peroxidase activities [12].

Therefore, considering that cardioplegia is a crucial method in CABG surgery and the type of this solution can play a significant role in stopping and protecting the heart during surgery, selecting an appropriate cardioplegia solution with more efficiency and safety can promote successful surgery and remains one of the most significant challenges for researchers and surgeons.

Therefore, the current study was conducted to investigate the vasodilatory effects of NTG in the cardioplegia solution on ischemia-reperfusion during CABG surgery.

Materials and Methods

The present randomized controlled double-blind clinical trial was conducted on 44 patients who were candidates for CABG surgery at Chamran Hospital in Isfahan, Iran during 2021. The inclusion criteria included patients with coronary artery disease who were candidates for non-emergency CABG, within the age range of 35-70 years, with an Ejection Fraction (EF) of more than 40%, with a CPB time range of 1-2 hours, and an arrest time range of 30-100 minutes. Additionally, patients with cardiogenic shock and those receiving known antioxidants such as captopril, mannitol, or allopurinol were not included in the study. In the event of unpredictable events that disrupted the normal surgical process such as the use of an intra-aortic balloon pump (IABP) and extracorporeal membrane oxygenation (ECMO), cardiac arrest, and more than five days of ICU stay, the patient was excluded from the study and replaced with another sample.

After obtaining the code of ethics from the Ethics Committee of Isfahan University of Medical Sciences (approval code: IR.MUI.MED.REC.1400.497), the code of clinical trial (Code: IRCT20211225053517N1), and written consent from eligible patients, 44 patients were selected using the convenience sampling method. At the beginning of the study, patients' basic information including age, sex, height, weight, and smoking status were recorded. Then, the patients were divided into two groups of 22 using random allocation software.

All patients were instructed to stop taking aspirin 7 days prior to the surgery. Troponin I and creatine phosphokinase-MB (CPK-MB) levels were tested in all patients before surgery. In the first group (NTG group), 3 mg/kg NTG was added to the cardioplegia solution, while 10 cc placebo (distilled water) was added to the cardioplegia solution in the second group (control group).

It should be noted that the anesthesia and surgical methods were identical for all patients. Surgery was performed on all patients by a single skilled surgeon using a similar technique. Sodium thiopental, pancuronium bromide, and fentanyl were used to induce anesthesia, and propofol was used for its maintenance. The same cardioplegia solution was used to protect the myocardium and induce cardiac arrest, with only NTG or distilled water being blindly added to each patient's cardioplegia solution.

The prime solution contained Ringer's lactate, voluven, and 10,000 units of heparin. A single type of CPB machine, oxygenator, and arterial filter were used for all patients. Cooling was performed with a heat exchanger up to 32 °C. The mean arterial blood pressure was maintained within the range of 60-90 mmHg. Troponin I and CPK-MB levels were checked again in both groups after surgery.

It is worth mentioning that a 3 cc blood sample was taken from the patients to examine the troponin I level. This protein was measured by the ELISA method using a Vidas device. The immunoinhibition method was also used to evaluate the CPK-MB enzyme.

Statistical analysis

Finally, the collected data were entered into SPSS software (Ver. 26). Continuous and categorical variables were presented as Means ± standard deviation (SD) or n (%). The Kolmogorov-Smirnov (K-S) test was used to evaluate the normality of data distribution. Troponin I and CPK-MB did not have a normal distribution, so the Mann-Whitney test was used to compare the mean of these two variables between the two groups before surgery. To compare the mean of these two variables between the two groups after surgery, the ANCOVA test was used by adjusting the baseline variable. Also, the Wilcoxon test was used to compare the mean of these two variables after surgery compared to before surgery. According to the result of the K-S test that the distribution of other quantitative variables was normal, the independent sample t-test was used to compare their average between the two groups in each of the studied times. In addition, the chi-square test was used to compare the frequency distribution of discrete variables between two groups. The significance level was considered to be less than 0.05 in all analyses.

Results

In this study, 44 patients with coronary artery disease who were candidates for CABG surgery were randomly divided into two groups of 22 cases. During surgery in the NTG group, 3 mg/kg of nitroglycerin was added to the cardioplegic solution, and 10 cc of placebo was added to the cardioplegic solution in the control group (Figure 1).

In the NTG group, 16 (72.7%) patients were male and 6 (27.3%) were female, while in the control group, 15 (68.2%) patients were male and 7 (31.8%) were female.

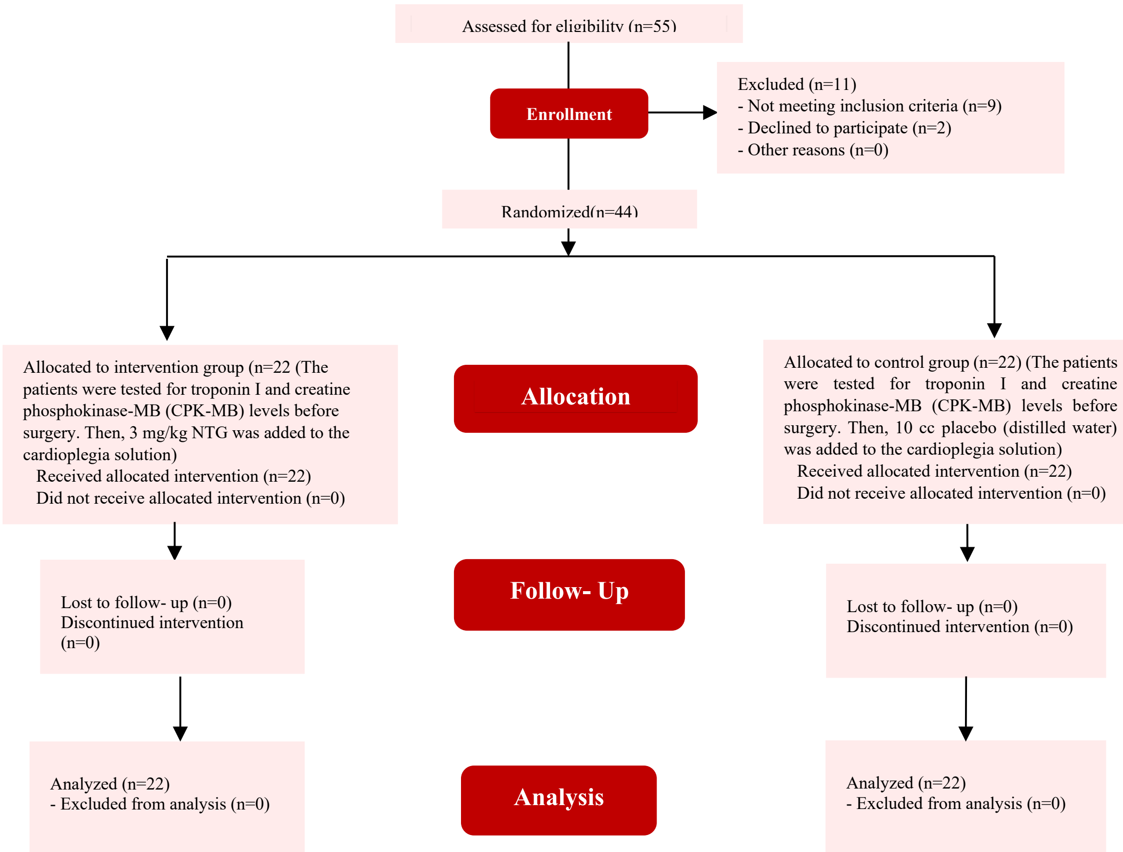

Figure 1. Consort flowchart of patients

There was no significant difference between the two groups in terms of age, sex, height, weight, and smoking status (P-value > 0.05) (Table 1).

The intraoperative DC shocks required were reported only in one case in the control group. The mean of body surface area (BSA), flow, CPB time, cross-clamp time, graft number, and length of ICU stay were not significantly different between the two groups (P-value > 0.05) (Table 2).

Finally, the mean of troponin I and CPK-MB levels before surgery was not significantly different between the two groups (P-value > 0.05). However, after surgery, the increase of these two variables in the NTG group with the mean of 2090.68 ± 1856.07 and 97.27 ± 38.17 were significantly less than that of the control group with the mean of 2697.02 ± 5586.56 and 137.95 ± 227.99, respectively (P-value < 0.05) (Table 3).

Table 1. Baseline characteristics of patients in the two groups

Characteristics		NTG group (n=22)	Control group (n=22)	P-value
Sex	**Male**	16(72.7%)	15(68.2%)	0.741†
	Female	6(27.3%)	7(31.8%)	
Age range				
	40-50 year	2(9.1%)	4(18.2%)	0.169†
	50-60 year	6(27.3%)	8(36.4%)	
	> 60 year	14(63.6%)	10(45.5%)	
	Height; cm	166.77±7.73	167.73±9.41	0.713††
	Weight; kg	73.82±11.51	75.32±8.42	0.624††
	Smoker	5(22.7%)	7(31.8%)	0.498†

†: Significance level of the Chi-Square test to compare the frequency distribution of qualitative variables between two groups
††: Significance level of the independent sample t test to compare the mean of the quantitative variables between the two groups

Table 2. Comparison of surgical parameters during surgery and the length of ICU stay between the two groups

Variables	NTG group (n=22)	Control group (n=22)	P-value
Intraoperative DC shocks required	0(0%)	1(4.5%)	>0.99†
body surface area (BSA); m^2	1.82±0.16	1.84±0.20	0.716††
Blood Flow	4.42±0.38	4.49±0.33	0.517††
Cardiopulmonary bypass (CPB) time, min	99.22±10.63	97.77±10.41	0.649††
Cross-clamp time, min	64.01±1.67	59.12±1.71	0.088††
Graft number	3.45±0.73	3.14±0.78	0.181††
ICU stay, day	3.22±0.73	3.33±0.77	0.629††

†: Significance level of the Chi-Square test to compare the frequency distribution of qualitative variables between two groups
††: Significance level of the independent sample t test to compare the mean of the quantitative variables between the two groups

Table 3. Comparison of troponin I and CPK-MB levels before and after the surgery between the two groups

Variables	Time	NTG group (n=22)	Control group (n=22)	P-value
Troponin I	**Before surgery**	180.69±417.92	45.00±117.2	0.150†
	After surgery	2090.68±1856.07	2697.02±5586.56	0.031††
P-value†††		<0.001	<0.001	
CPK-MB	**Before surgery**	30.68±31.52	27.77±26.95	0.743†
	After surgery	97.27±38.17	137.95±227.99	0.045††
P-value†††		<0.001	<0.001	

†: Significance level of the Mann-Whitney U test to compare the mean of the variables between the two groups before surgery
††: Significance level of ANCOVA test to compare the mean of variables between two groups after surgery by adjusting the baseline variable.
†††: Significance level of the Wilcoxon test to compare the mean of variable after surgery as compared to before surgery in each of the two groups

Discussion

The results of this study revealed that risk factors such as age, sex, height, weight, smoking, and EF were not significantly different between the two groups. Moreover, intraoperative DC shocks were required for only one case in the control group. The CPB and aortic cross-clamp time were not significantly different between the two groups.

In this regard, a study by Nemati et al. showed that the length of CPB and aortic cross-clamp time were significantly affected by the type of cardioplegia such that NTG solution could increase CPB time and reduce cross-clamp duration, although these changes were not statistically significant [19]. In this study, the increase in CPB and aortic cross-clamp time was negligible. However, some other studies have reported that blood cardioplegia, compared to crystalloid cardioplegia, led to an increase in the duration of CPB and aortic cross-clamp time [20]. The results of another study indicated the significant effect of the type of cardioplegia solution on CPB time, number of doses of cardioplegia, and aortic cross-clamp time [21]. Moreover, no association was reported between the type of cardioplegia solution and either inotropic usage, IABP usage, or intraoperative DC shocks required [21]. In contrast, the findings of the current study revealed no significant difference between the NTG group and the control group in terms of the intraoperative DC shocks required.

Moreover, a study addressing the repair of tetralogy of Fallot (TOF) indicated a significant decrease in the length of ICU stay in children receiving NO that is chemically comparable to NTG [22]. However, the length of ICU stay was not affected by NTG in the present study.

It should be noted that myocardial ischemia, induced by aortic cross-clamping, leads to an increase in the serum levels of typical biochemical markers, including troponin I or T and CK-MB [23]. It has been acknowledged that the specificity of CK-MB, compared with cardiac troponin I and T, might be lower in detecting myocardial injury[24]. The association of cTnI release with the extent of ischemic injury has been reported by Chocron et al. [25]. These findings suggest that the release of cardiac troponin after cardiac surgery is a good indicator of the extent of myocardial damage caused by ischemic injury [25]. In addition, the specificity of cardiac troponin I (cTnI), compared with cardiac troponin T, has been suggested to be greater in detecting myocardial injury [24]. That's why the effect of NTG on serum cardiac Tn I and CPK-MB levels were measured in this study to detect reperfusion and ischemia.

The findings of this study showed that troponin I and CPK-MB levels in both groups increased significantly after surgery compared to before surgery. However, this increase was significantly lower in the NTG group, compared to the control group. In fact, the administration of NTG has been successful in controlling the increase of these two factors.

The study conducted by Hisatomi et al. revealed a decrease in the concentration of creatine kinase-MB in the heart of rats following the addition of NTG to the cardioplegic solution [26]. However, this study did not provide any information regarding the mediation of the pharmacologic effects of NTG by NO. Conversely, early intravenous NTG therapy via production of NO has been suggested to improve the survival rate and decrease the infarct size in acute myocardial infarctions [27]. A number of studies have also reported that peak values of TnI were obtained 12 hours after aortic unclamping, then decreased, and disappeared 5 days after the surgery without any complications [28]. Therefore, it can be conjectured that the levels of TnI could not reach the preoperative levels 24 hours after the surgery.

There are indeed controversies regarding the role of NO in ischemic-reperfusion injury [29]. Numerous experimental studies have reported a cardioprotective effect during myocardial ischemic-reperfusion. However, another set of studies proposed that NO exacerbates reperfusion injury by inducing the production of peroxynitrite [30].

This study did not assess NO levels, which can be considered a limitation. Additionally, the study did not evaluate intra-aortic balloon counter pulsation, blood pressure, and lipid peroxidation during surgery. However, the evaluation of CPK-MB and troponin I levels, which increased due to aortic cross-clamping and increased the chance of myocardial ischemia, has been a less explored topic and can be considered one of the strengths of this study. Nevertheless, further studies with larger sample sizes and longer follow-up periods are recommended.

Conclusion

The results of this study indeed suggest that while troponin I and CPK-MB levels increased significantly after CABG surgery, this increase was significantly lower in the group where NTG was administered. This could potentially indicate a protective effect of NTG against myocardial damage during surgery. However, further research is needed to confirm these findings and fully understand the mechanisms involved.

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