Investigation of Impact of Trinitroglycerin Conjugated Cardioplegia on Myocardial Protection of Patients With Coronary Artery Bypass Grafting

Mohammad Hasan Nemati, Hasan Badie, Mansour Jannati

Department of Cardiovascular Surgery, Faghihi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

Received: 11 Apr. 2019; Accepted: 18 Sep. 2019

Abstract- Pharmacologic-conjugated-cardioplegia is one of the strategies against ischemia and reperfusion. The aim of this study was to investigate the impact of nitroglycerin on myocardial protection and postoperative outcomes. This was a case-control study performed on 91 patients undergoing coronary artery bypass grafting in Faghihi Hospital, Shiraz University of Medical Sciences. Patients were randomly divided into case and control groups. Trinitroglycerin Conjugated Cardioplegia on Myocardial Protection of Patients with Coronary Artery Bypass Grafting. As a result of nitroglycerin, the number of patients requiring inotrope administration was increased. No other significant alteration was observed between two groups in neither of ischemic features nor postoperative outcomes. In conclusion, nitroglycerin conjugated cardioplegia, with the condition of this study, demonstrated a negative inotrope requirement without improvement in myocardium protection.

Acta Med Iran 2019;57(10):586-591.

Keywords: Coronary artery bypass graft; Cardioplegia; Trinitroglycerine

Introduction

Recently, myocardial protection has become an essential criterion in any cardiac surgery under cardiac arrest or in off-pump coronary artery bypass (OPCAB) procedures to protect myocardium and hinder ischemia or reperfusion-induced damage during cardiac operation. Up to now, a number of myocardial protection procedures during cardiac surgery have been more appealed including temperature modulation (cold, tepid, or warm), delivery single-dose or multi-dose infusion, crystalloid or blood cardioplegia, direction (antegrade or retrograde) of cardioplegia, intermittent or continuous infusion, and cold or warm induction (1).

Cardioplegia protects myocardium by reducing metabolism and thereby increasing cardiac capacity for prolonged ischemia cardiac operations. However, cardioplegia protects the heart during surgery, temporary myocardial ischemia and then reperfusion, result by surgical trauma, manipulation of the heart, pericardial suction or genetic predisposal can trigger a higher systemic inflammatory response (2,3). Warmblood cardioplegia and cold crystalloid cardioplegia are the two main types of cardioplegic solutions used in coronary artery bypass graft (CABG) surgery, but there is still a controversy about the side effects and effectiveness of cardioplegic solutions (1). Although there are a few studies to compare inflammatory response and oxidative stress in different types of cardioplegia (4-7), it has been shown that types of cardioplegia are not specifically associated with neither the systemic inflammatory response nor the oxidative stress (8). Blood cardioplegia protective effects against myocardial damage during ischemia and reperfusion have been shown to be associated with greater oxygen-supply capacity (more aerobic metabolism), greater acid-base balance capacity, and higher osmotic pressure (9).

Pharmacological strategies are additional methods for myocardial protection which have been investigated experimentally and clinically in cardiac surgery. Therapeutic benefits of the non-selective inhibitor of Na+/H+ exchangers, such as amiloride and HOE694, or selective inhibitors, such as Cariporide, were the first demonstrations against ischemia and reperfusion when administered into crystalloid cardioplegic solutions (10-15). Nicorandil drug is known as an activator for both sarcolemmal and mitochondrial KATP (mitoKATP) channels and has been shown to display a cardioprotective effect through the mitoKATP channel activation (16,17). Nicorandil infusion (intravenous) along with antegrade cold-blood cardioplegia significantly reduced postoperative troponin T (18).

Corresponding Author: M. Jannati
Department of Cardiovascular Surgery, Faghihi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran
Tel: +98 713 2351087, Fax: +98 713 2351090, E-mail address: Mansour.jannati@mail.com

Adenosine cold-blood cardioplegia on patients with heart valve replacement has been shown to decrease postoperative troponin I and interleukin levels and also to reduce the extent of myocardial injury assessed by electron microscopy (19). Adenocaine cardioplegia decreases coronary vascular resistance and enhances myocardial oxygen consumption (20) by maintaining the myocardial cell membrane potential at its resting state (21). Esmolol cardioplegia, histidine–tryptophan–ketoglutarate, and natriuretic peptide (hANP shot) are other examples of pharmacological strategies at the time of cardioplegic infusion with enhancing cardioprotective effects (22-25).

Trinitroglycerin (TNG) increases the level of cGMP, by activating Guanly Cyclase, which triggers to inhibition of smooth muscle contraction; so, TNG can affect arteries contraction and as a result dilation of veins (26). TNG cardioplegia on patients with coronary artery bypass surgery has shown the cardioprotective effect by lowering vascular resistance and cardiac infarction (27,28). Regarding the effect of TNG on dilation of veins and limited studies conducted on TNG cardioplegia, in this study, we aimed to investigate the role of TNG on the protective effect of cardioplegia on myocardium with respect to post-operative and ischemic outcomes.

Materials and Methods

Patients

This case-control study was performed on 91 patients with coronary artery occlusion who were candidates for coronary artery bypass grafting.

Inclusion and exclusion criteria

Patients with a history of infarction, arterial fibrillation, and positive serum troponin at zero time (running time of cardiopulmonary pump) were excluded. Patients with all three major vessels involved and with left ventricle ejection fraction (EF) of ≥40% were entered into the study.

Performance

One hour before anesthesia, patients received 0.05-0.1 mg/kg intravenous morphine. The cardiac performance was monitored using precordial leads, and blood pressure were monitored with respect to the left radial artery. Analgesic drug administration were started with midazolam (0.03-0.05 mg/kg), sufentanil (1.5-2 mg/kg), and sodium thiopental (1-2 mg/kg). To facilitate intubation pancuronium bromide (0.15 mg/kg), to keep anaesthesia propofol (50-150 mg/ml) and remifentanil (0.1-1 mg/min) were injected continuously. The temperature of the patient was maintained at 34-32° C during operation and the central venous pressure was kept at about 16-8 mm Hg. Crystalloid cardioplegia was injected at aortic root and with 15-20 cc/kg per 3 min. The cardioplegia compositions were including lactate Ringer solution as the base solution, which the following materials added to it: Potassium meq/L30, bicarbonate meq/45%, magnesium sulfate mg/kg/30%, lidocaine mg/l100. The hematocrit of this solution was 18-22%. For assessment of serum cTnI, Chemiluminescent Enzyme Immunoassay (CLEIA) was performed using the PATHFAST reagent kit (Mitsubishi Chemical Medience Corporation). Heparin sodium, heparin lithium or ethylenediaminetetraacetic acid (EDTA) was used as anticoagulation. Fibrin and coagulation debris was removed by centrifugation.

Ethical consideration

The study was carried out in accordance with the Declaration of Helsinki, and the ethics committee of the X University of Medical Sciences approved the protocols of the study. The study procedure and probable side effects were explained to patients, and written consent was acquired. The patients' records were kept confidential.

Data analysis

Qualitative and quantitative data were reported as frequency (%) and mean±standard deviation, respectively. Statistical analysis was performed with respect to Pearson Chi-square, t-test, ANOVA, and $P<0.05$ was considered significant. All data were analyzed with IBM SPSS Statistics for Windows, version 19.0 (SPSS Inc., Chicago, Illinois, USA).

Patient and public involvement

The patients and participants were aware of the study. They were explained completely about the study process, the reason for the study, the advantages of the study, and the probable side effects. All patients participate in the study according to their desire and willingness. Each stage of the study was explained to them and all participants were notified about the result of the study.

Results

Patients were randomly distributed in each case and control groups. As presented in table 1, except for age, no statistically significant difference was observed between the case and control group. The average age for the case

group was 58.10±39.02, and that of the control group was 62.11±85.3 (*P*=0.05).

Table 1. Demography of patients who underwent cardiac bypass *

		Case	Control	Overall	*P*	CI 95%	Pearson *Chi*-Square
Gender		--	--	--	0.4	--	0.71
Male		36 (81.8)	35 (74.5)	71 (77.2)	--	--	--
Female		8 (18.2)	12 (25.5)	20 (21.7)	--	--	--
Age (year)		58.10 ± 39.02	62.11 ± 85.3	60.10 ± 69.8	0.05	0.003 – 8.9	--
Coronary artery occlusion risk factors	**Diabetes**	20 (45.5)	25 (53.2)	45 (48.9)	0.43	--	--
	Hypertension	27 (61.4)	25 (53.2)	52 (56.5)	0.43	--	--
	Smoking	7 (15.9)	12 (25.5)	19 (20.7)	0.25	--	--
	Hypercholesterolemia	17 (38.6)	30 (63.8)	47 (51.1)	0.016	--	--
	Previous myocardial infarction	0 (0)	2 (4.3)	2 (2.2)	0.16	--	--
Pre-operative EF, %		53.6 ± 22.6	54.56 ± 0.2	53.6 ± 9.4	0.33	-1.4 – 4.07	--

* Data are presented as mean ± standard deviation or No. (%)

To assess TNG efficacy on myocardial protection under cardioplegia and ischemic parameters, some of the trans and postoperative factors were monitored and compared between case and control group. There was no difference between case and control group, except in term of inotropic usage. The number of patients with inotropic usage in the case group was significantly higher than that of the control group (*P*=0.002) (Table 2).

Table 2. Comparison of ischemic and postoperative parameters between study and placebo groups

	Case	Control	*P*	CI 95%
Cardiopulmonary bypass (CPB) time, min	49.6 ± 10.3	48 ± 9	0.45	-5.5 – 2.5
Cross Clamp time, min	26.9 ± 4.6	27.3 ± 5.8	0.7	-1.7 – 2.6
Graft number	4 ± 0.9	4 ± 0.8	0.96	--
Arterial fibrillation	6 (13.6)	3 (6.4)	0.25	--
IABP [1] by the operation	1 (2.3)	0 (0)	0.3	--
IABP after operation	0 (0)	0 (0)	0	--
Postoperative cardiopulmonary resuscitation	0 (0)	1 (2.1)	0.33	--
Administration of antiarrhythmic by the operation	9 (20.5)	12 (25.5)	0.56	--
Administration of antiarrhythmic after the operation	10 (22.7)	8 (17)	0.5	--
Intraoperative DC shocks required	6 (13.6)	10 (21.3)	0.34	--
Inotropic administration	30 (68.2)	17 (36.2)	0.002	--
Time of Inotrope drug, hr	13.6 ± 8.2	19.6 ± 12.5	0.21	-2.8 – 11.4
cTnI, ng/ml	1 ± 0.9	2.4 ± 1.4	0.19	-0.62 – 1.3
Number of inotropes	1.9 ± 1.2	2.4 ± 1.4	0.19	-0.62 – 1.3
ICU stay, day	2.2 ± 0.5	2.2 ± 0.7	0.66	--

* Data are presented as mean ± standard deviation or No. (%).
[1] intra-aortic balloon counterpulsation

Discussion

Myocardial protection protocols aim to reduce metabolic activity through hypothermia, the therapeutic arrest of the myocardial contraction, and all of the electrical activities of the myocardium by the administration of the cardioplegic solution (29-32). Many studies have indicated the role of pharmaceutics, such as β-adrenergic antagonists (β-blockers) to reduce the extent of myocardial ischemia and reperfusion when conjugated with cardioplegia solution (33,34). Also, the infusion of nitroglycerin has shown to the recovery of mechanical function after hypothermic ischemia (35). In this study, the impact of trinitroglycerin conjugation with cardioplegia on myocardial ischemic features was investigated.

As presented in table 1, in terms of gender, the difference between groups of case and control was not significant which demonstrated the random distribution of patients in both groups. However, the average age in the case group was significantly less than the control group. Also, analysis of Coronary artery occlusion risk

factors and ejection fraction (EF) exhibited no significant difference between case and control groups which demonstrated the equal distribution of patients in both groups.

It has been observed that the type of cardioplegia can significantly impact the length of aortic cross-clamp and CPB time. Blood cardioplegia increased the duration of both aortic cross-clamp and CPB time compared with Crystalloid cardioplegia (8). Another study showed that the type of cardioplegia solution significantly affects the aortic cross-clamp time, cardiopulmonary bypass time and the number of doses of cardioplegia (36). According to the findings of the present study, TNG solution increased CPB time and reduced cross-clamp duration; however, these alterations were not statistically significant.

It has been shown that the type of cardioplegia solution might not be associated with either of Intraoperative DC shocks required, IABP usage, or inotropic usage (36). Conversely, our results suggest that there is no difference between control group and that group who received TNG along with cardioplegia solution in term of Intraoperative DC shocks required and IABP usage; however, according to the present results, the number of patients in case group who used inotrope was significantly higher than control group who did not receive TNG. Adversely, conjugation of esmolol (a type of beta-blocker) with cardioplegia reduced post-operative inotropic requirement in patients with open cardiac surgery (37). Moreover, the conjugation of TNG with cardioplegia reduced the number of inotrope administration per patient, but this alteration was not significant. Also, in a study conducted on children undergoing repair of tetralogy of Fallot who received nitric oxide, which is chemically similar to TNG, the length of ICU stay significantly decreased (38). Adversely, in the present study, TNG did not impact the length of the ICU course.

The increase of the TnI level in response to the reperfusion of ischemic myocardium was related to the systemic inflammatory responses induced by ischemia and reperfusion of the myocardium (39). Del Nido cardioplegia (crystalloid) did not impact the concentration of TnI compared with blood cardioplegia group (40). According to our findings, although not statistically significant, conjugation of TNG along with cardioplegia could reduce the concentration of released cTnI which indicated the diminution of necrosis. Similarly, in a study on remote ischemic conditioning-induced cardioprotection during coronary artery bypass grafting, intraoperative nitroglycerine had no significant impact on TnI release (41).

In conclusion, TNG cardioplegia demonstrated no significant impact on ischemic myocardium and postoperative outcomes, although there were observable alterations in investigated parameters as a result of TNG infusion. This study was accompanied by limitations, such as the number of patients participated that can affect the statistical significance of results by increasing the number. Pharmacological cardioplegia has shown to be related by dose, as in the case of adenosine blood cardioplegia higher doses exhibited higher postoperative advantages (42). Similarly, TNG cardioplegia might be dose-dependent, thus requires to be investigated in lower doses to diminish the inotrope usage effect.

References

1. Yamamoto H, Yamamoto F. Myocardial protection in cardiac surgery: a historical review from the beginning to the current topics. Gen Thorac Cardiovasc Surg 2013;61:485-96.
2. Collard CD, Gelman S. Pathophysiology, clinical manifestations, and prevention of ischemia-reperfusion injury. Anesthesiology 2001;94:1133-8.
3. Matata BM, Galinanes M. Cardiopulmonary bypass exacerbates oxidative stress but does not increase proinflammatory cytokine release in patients with diabetes compared with patients without diabetes: regulatory effects of exogenous nitric oxide. J Thorac Cardiovasc Surg 2000;120:1-11.
4. van Boven WJ, Gerritsen WB, Driessen AH, Morshuis WJ, Waanders FG, Haas FJ, et al. Myocardial oxidative stress, and cell injury comparing three different techniques for coronary artery bypass grafting. Eur J Cardiothorac Surg 2008;34:969-75.
5. Kalawski R, Balinski M, Bugajski P, Wysocki H, Olszewski R, Siminiak T. Stimulation of neutrophil activation during coronary artery bypass grafting: comparison of crystalloid and blood cardioplegia. Ann Thorac Surg 2001;71:827-31.
6. Kalawski R, Deskur E, Bugajski P, Wysocki H, Siminiak T. Stimulation of neutrophil integrin expression during coronary artery bypass grafting: comparison of crystalloid and blood cardioplegic solutions. J Thorac Cardiovasc Surg 2000;119:1270-7.
7. Poormoghim H, Moghadam AS, Moradi-Lakeh M, Jafarzadeh M, Asadifar B, Ghelman M, et al. Systemic sclerosis: demographic, clinical and serological features in 100 Iranian patients. Rheumatol Int 2013;33:1943-50.
8. Plicner D, Stolinski J, Rzucidlo-Hymczak A, Kapelak B, Undas A. Acute-phase proteins and oxidative stress in

patients undergoing coronary artery bypass graft: comparison of cardioplegia strategy. Kardiochir Torakochirurgia Pol 2017;14:16-21.
9. Barner H. Historical aspects and current review of myocardial protection. Warm heart surgery Ed Salerno, TA Arnold, London 1995:1-15.
10. Karmazyn M. Amiloride enhances postischemic ventricular recovery: possible role of Na+-H+ exchange. Am J Physiol 1988;255:608-15.
11. Hendrikx M, Mubagwa K, Verdonck F, Overloop K, Van Hecke P, Vanstapel F, et al. New Na(+)-H+ exchange inhibitor HOE 694 improves postischemic function and high-energy phosphate resynthesis and reduces Ca2+ overload in isolated perfused rabbit heart. Circulation 1994;89:2787-98.
12. Choy IO, Schepkin VD, Budinger TF, Obayashi DY, Young JN, DeCampli WM. Effects of specific sodium/hydrogen exchange inhibitor during cardioplegic arrest. Ann Thorac Surg 1997;64:94-9.
13. Koike A, Akita T, Hotta Y, Takeya K, Kodama I, Murase M, et al. Protective effects of dimethyl amiloride against postischemic myocardial dysfunction in rabbit hearts: phosphorus 31-nuclear magnetic resonance measurements of intracellular pH and cellular energy. J Thorac Cardiovasc Surg 1996;112:765-75.
14. Cox CS, Jr., Sauer H, Allen SJ, Buja LM, Laine GA. Sodium/hydrogen-exchanger inhibition during cardioplegic arrest and cardiopulmonary bypass: an experimental study. J Thorac Cardiovasc Surg 2002;123:959-66.
15. Castella M, Buckberg GD, Tan Z. Blood cardioplegic protection in profoundly damaged hearts: role of Na+-H+ exchange inhibition during pretreatment or during controlled reperfusion supplementation. Ann Thorac Surg 2003;75:1238-45.
16. Sato T, Sasaki N, O'Rourke B, Marban E. Nicorandil, a potent cardioprotective agent, acts by opening mitochondrial ATP-dependent potassium channels. J Am Coll Cardiol 2000;35:514-8.
17. Steensrud T, Jakobsen O, Ytrehus K, Sorlie DG. Contractile recovery of heart muscle after hypothermic hypoxia is improved by nicorandil via mitochondrial K(ATP) channels. Eur J Cardiothorac Surg 2006;30:256-62.
18. Yamamoto S, Yamada T, Kotake Y, Takeda J. Cardioprotective effects of nicorandil in patients undergoing on-pump coronary artery bypass surgery. J Cardiothorac Vasc Anesth 2008;22:548-53.
19. Liu R, Xing J, Miao N, Li W, Liu W, Lai Y-Q, et al. The myocardial protective effect of adenosine as an adjunct to intermittent blood cardioplegia during open heart surgery. European Journal of Cardio-Thoracic Surgery 2009;36:1018-23.
20. Dobson GP, Jones MW. Adenosine and lidocaine: a new concept in nondepolarizing surgical myocardial arrest, protection, and preservation. J Thorac Cardiovasc Surg 2004;127:794-805.
21. Sloots KL, Dobson GP. Normokalemic adenosine-lidocaine cardioplegia: importance of maintaining a polarized myocardium for optimal arrest and reanimation. J Thorac Cardiovasc Surg 2010;139:1576-86.
22. Bessho R, Chambers DJ. Myocardial protection with oxygenated esmolol cardioplegia during prolonged normothermic ischemia in the rat. J Thorac Cardiovasc Surg 2002;124:340-51.
23. Fujii M, Chambers DJ. Cardioprotection with esmolol cardioplegia: efficacy as a blood-based solution. European Journal of Cardio-Thoracic Surgery 2012;43:619-27.
24. Braathen B, Jeppsson A, Schersten H, Hagen OM, Vengen O, Rexius H, et al. One single dose of histidine-tryptophan-ketoglutarate solution gives equally good myocardial protection in elective mitral valve surgery as repetitive cold blood cardioplegia: a prospective randomized study. J Thorac Cardiovasc Surg 2011;141:995-1001.
25. Sezai A, Wakui S, Akiyama K, Hata M, Yoshitake I, Unosawa S, et al. Myocardial protective effect of human atrial natriuretic Peptide in cardiac surgery. -hANP Shot" in clinical safety trial. Circ J 2011;75:2144-50.
26. Katzung BG. Basic & Clinical Pharmacology: United States, McGraw-Hill Medical; 2006.
27. Tanaka T, Kazui T, Komatsu K, Sasaki A, Inoue N, Izumiyama O, et al. [Effects of blood-diltiazem-nitroglycerin-cardioplegia in coronary artery bypass grafting]. Kyobu Geka 1992;45:964-7.
28. McKeown PP, McClelland JS, Bone DK, Jones EL, Kaplan JA, Lutz JF, et al. Nitroglycerin as an adjunct to hypothermic hyperkalemic cardioplegia. Circulation 1983;68:107-11.
29. Hearse DJ, O'Brien K, Braimbridge MV. Protection of the myocardium during ischemic arrest. Dose-response curves for procaine and lignocaine in cardioplegic solutions. J Thorac Cardiovasc Surg 1981;81:873-9.
30. Preusse CJ, Gebhard MM, Bretschneider HJ. Myocardial "equilibration processes" and myocardial energy turnover during initiation of artificial cardiac arrest with cardioplegic solution - reasons for a sufficiently long cardioplegic perfusion. Thorac Cardiovasc Surg 1981;29:71-6.
31. Bretschneider HJ. Myocardial protection. Thorac Cardiovasc Surg 1980;28:295-302.
32. Fallah S, Seifi M, Firoozrai M, Godarzi T, Jafarzadeh M, Ghohari L. Influence of Apo E polymorphism on coronary

artery disease. World Acad Sci Eng Technol 2009;57:246-50.
33. Manning AS, Keogh JM, Coltart DJ, Hearse DJ. The effect of beta blockade and partial agonist activity during myocardial ischemia. Adv Myocardiol 1983;4:513-20.
34. Magee PG, Gardner TJ, Flaherty JT, Bulkley BH, Goldman RA, Gott VL. Improved myocardial protection with propranolol during induced ischemia. Circulation 1980;62:I49-56.
35. Kawata H, Aoki M, Mayer JE, Jr. Nitroglycerin improves functional recovery of neonatal lamb hearts after 2 hours of cold ischemia. Circulation 1993;88:366-71.
36. Mishra P, Jadhav RB, Mohapatra CK, Khandekar J, Raut C, Ammannaya GK, et al. Comparison of del Nido cardioplegia and St. Thomas Hospital solution - two types of cardioplegia in adult cardiac surgery. Kardiochir Torakochirurgia Pol 2016;13:295-9.
37. Fazelifar S, Bigdelian H. Effect of esmolol on myocardial protection in pediatrics congenital heart defects. Adv Biomed Res 2015;4:246.
38. Checchia PA, Bronicki RA, Muenzer JT, Dixon D, Raithel S, Gandhi SK, et al. Nitric oxide delivery during cardiopulmonary bypass reduces postoperative morbidity in children--a randomized trial. J Thorac Cardiovasc Surg 2013;146:530-6.
39. Huang WH, Lee JF, Wang D, Gou WH, Chang CY, Wei J. Postischemia myocardial injury in coronary artery bypass patients (PP6). Transplant Proc 2010;42:725-8.
40. Kim JS, Jeong JH, Moon SJ, Ahn H, Hwang HY. Sufficient myocardial protection of del Nido cardioplegia regardless of ventricular mass and myocardial ischemic time in adult cardiac surgical patients. J Thorac Dis 2016;8:2004-10.
41. Kleinbongard P, Neuhauser M, Thielmann M, Kottenberg E, Peters J, Jakob H, et al. Confounders of Cardioprotection by Remote Ischemic Preconditioning in Patients Undergoing Coronary Artery Bypass Grafting. Cardiology 2016;133:128-33.
42. Mentzer RM, Jr., Birjiniuk V, Khuri S, Lowe JE, Rahko PS, Weisel RD, et al. Adenosine myocardial protection: preliminary results of a phase II clinical trial. Ann Surg 1999;229:643-9.