To cite this article: Cicek MC, Gormus N, Durgut K, Kayrak M, Toker A, Gormus IS, Cicek OF. Comparison of effect of antegrade with combined antegrade-retrograde cardioplegia on inflammatory response and left ventricular systolic function in coronary bypass surgery: A prospective randomized Study. Turk J Clin Lab 2018; 9(3): 179-184.

Original Article

Comparison of effect of antegrade with combined antegrade-retrograde cardioplegia on inflammatory response and left ventricular systolic function in coronary bypass surgery: A prospective randomized Study

Koroner bypass cerrahisinde antegrad kardiyopleji yönteminin antegrad-retrograd kardiyopleji yöntemi ile inflamatuar cevap ve sol ventrikül sistolik fonksiyonları açısından kıyaslanması: Prospektif randomize çalışma

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ABSTRACT

Aim: Nonhomogeneous distribution of antegrade cardioplegia especially in cases with severe myocardial hypertrophy or proximal stenosis of coronary arteries may be a serious problem. This prospective randomized study was designed to determine whether combined antegrade–retrograde cardioplegia provides improved myocardial protection in the early period and is associated with better laboratory results compared with antegrade technique alone.

Material and Methods: A total of 60 patients who underwent coronary artery bypass grafting surgery, 45 (75%) males and 15 (25%) females, were included in the study as 2 groups: In Group 1, 30 patients were given the combined cardioplegia solution antegrade via the aortic root and retrograde via the coronary sinus, in Group 2, 30 patients were given only antegrade cardioplegia solution via the aortic root. The CK-MB, TpI, TNF- α, IL-1, IMA, ICAM-1, and BNP parameters were studied in the blood samples which were taken preoperatively, intraoperatively and postoperative sixth day. The patients were evaluated preoperatively and on the sixth postoperative day using transthoracic echocardiography.

Results: The postoperative mean EF decrease was significantly lower in Group 1 compared to Group 2 (4.13 ± 9.09 vs 8.90 ± 10.76 in Group 1 vs. Group 2, respectively, p=0.046). When the change in TNF-α levels were compared between groups 1 and 2, the magnitude of increase in TNF-α was significantly higher in Group 2 (p=0.047).

Conclusion: We concluded that co-administration of antegrade and retrograde cardioplegia may provide improved myocardial protection compared to antegrade cardioplegia method alone in the early postoperative period.

Keywords: antegrade; cardioplegia; inflammation; myocardial protection; retrograde

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Email: drmcuneyt@hotmail.com
Received 08.06.2018 accepted 12.08.2018
Doi: 10.18663/tjcl.432111

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ÖZ

Amaç: Özellikle proksimal darlığı olan koroner arter hastalarında veya ciddi miyokardiyal hipertrofisi olan hastalarda antegrad kardiyoplejinin homojen olmayan dağılımı ciddi bir problemdir. Bu prospektif randomize çalışmada, kombine antegrad-retrograd kardiyoplejinin sadece antegrad tekniğe kıyasla erken dönemde daha iyi miyokardiyal koruma sağlaması ve daha iyi laboratuar sonuçları ile ilişkisi değerlendirilmiştir.

Gereç ve Yöntemler: Koroner bypass cerrahisi uygulanan 60 hasta (45 (%75) erkek, 15 (%25) kadın) çalışmaya dahil edilmiştir ve iki grupta incelenmiştir: Grup 1'de 30 hastaya aort kökünden antegrad ve koroner sinusten retrograd yolla kombine kardiyopleji; Grup 2'de ise 30 hastaya aort kökünden antegrad kardiyopleji verildi. Preoperatif, intraoperatif ve postoperative altıncı günde alınan kan örneklerinden CK-MB, TpI, TNF- α, IL-1, IMA, ICAM-1 ve BNP parametreleri çalışıldı. Hastalar preoperative olarak ve postoperative altıncı günde transtorasik ekokardiyografi ile değerlendirildi.

Bulgular: Postoperatif ortalama EF düşüşü Grup 1'de Grup 2'ye kıyasla istatistiksel olarak anlamlı şekilde daha az oldu (4.13 ± 9.09 ve 8.90 ± 10.76, sırayla Grup 1 ve Grup 2, p=0.046). TNF- α seviyelerindeki değişimin büyüklüğü kıyaslandığında Grup 2'deki artışın daha fazla olduğu bulunmuştur (p=0.047).

Sonuçlar: Antegrad ve retrograd kardiyoplejinin birlikte uygulanmasının, erken postoperatif dönemde tek başına antegrad kardiyoplejiye göre daha iyi miyokardiyal koruma sağlayabileceği sonucuna vardık.

Anahtar Kelimeler: antegrad; inflamasyon; kardiyopleji; miyokardiyal koruma; retrograd

Introduction

Since the time when open heart surgery first began, intra-operative myocardial protection has been one of the most serious problems associated with cardiovascular surgery, and its topicality as a subject which has been studied throughout the world has continued to this day. Myocardial damage which has occurred as a result of inadequate or false protection generally manifests itself as myocardial contractile dysfunction which appears minutes or hours after a cardiopulmonary bypass (CPB). Sufficient myocardial protection during open heart surgery may be provided by the rapid infusion of cold potassium cardioplegia together with systemic and topical hypothermia resulting diastolic arrest. Sufficient myocardial protection using cardioplegic solutions might, however, be possible in case where cardioplegia has been distributed homogeneously on every side of the myocardium [1]. Many studies hitherto have been carried out on the composition of these solutions and the manner in which they are given. While in a section of the literature concerned with the method of giving cardioplegic solutions, the better efficacy of antegrade cardioplegia on myocardial protection is defended, a portion of researchers advocate that cardioplegic solutions given using the retrograde method can better protect the myocardium. On the other hand, some other researchers, who see the antegrade and retrograde cardioplegia techniques as methods which supplement each other, have carried out studies on the combined cardioplegia method, in the assumption that these two methods may be used in combination [2,3,4].

This study was designed to determine whether combined antegrade–retrograde cardioplegia provides improved myocardial protection in the early postoperative period and is associated with better laboratory results compared with antegrade technique alone. In our prospective, randomized study, the parameters of echocardiography, creatine kinase MB isoenzyme (CK-MB), troponin-I (TpI), brain natriuretic peptide (BNP), tumor necrosis factor- alpha (TNF- α), interleukin-1 (IL-1), ischaemia modified albumin (IMA), and intercellular adhesion molecule -1 (ICAM-1) were compared, in patients who underwent coronary artery bypass graft surgery (CABG) with different cardioplegia application strategies.

Material and Methods

The study protocol was approved by Ethics Committee and written informed consent was obtained from all patients who participated to the study. The study was conducted according to the principles of Helsinki declaration. This prospective study was carried out on 60 patients who underwent elective CABG with CPB between June 2011 and December 2011.

The participants were block randomized into two groups: In Group 1, 30 patients were given the combined cardioplegia solution, antegrade via the aortic root and retrograde via the coronary sinus. In Group 2, 30 patients were given only antegrade cardioplegia solution via the aortic root. In emergency cases, patients who had an ejection fraction (EF) value of below 35% and those with chronic kidney failure were not included in the study.

Surgical Technique and Protection of the Myocardium

All the patients underwent elective operation through a standard median sternotomy. The left internal mammarian artery (LIMA) and saphenous vein graft (SVG) were harvested. The ascending aorta and right atrium were cannulated after administration of heparin. Antegrade and retrograde cardioplegia cannulae were placed in all the patients. The aim of the retrograde cardioplegia cannula placed in patients in Group 2 was to obtain blood samples from the coronary sinus for evaluation. The pump with a non-pulsatile flow was set so that the flow-rate would be between 1.8 and 2.4 L/min/m2. Moderate hypothermia (28-32oC) was used. During the CPB, haematocrit was maintained at between 20-25% and mean artery pressure between 50-70 mmHg. Activated clotting time (ACT) was maintained at 480 seconds. After cross clamping the aorta, cold blood cardioplegia (4oC) was applied from 15-20 ml/kg at the beginning. In Group 2, the heart was stopped using cold blood cardioplegia given via the antegrade route. In Group 1, the heart was stopped using cold blood cardioplegia given, at intervals, first via the antegrade route (2/3 of the cardioplegia) then via the retrograde route (1/3 of the cardioplegia). During the cross-clamp time, for redosing, 10-15 ml/kg dose of cold blood cardioplegia was given every 20 minutes via the antegrade, retrograde routes and through the grafts to completed distal anastomosis in Group 1; while for the patients in Group 2 the cardioplegia was given via the aortic root and through the grafts to the completed distal anastomosis. After the distal anastomoses had been completed, a hot-shot (34-36oC) cardioplegia solution was given to both groups before the cross clamps were removed. Rewarming was initiated during the last distal coronary anastomosis. Proximal anastomoses were constructed with side clamps after the cross-clamp release.

The cold blood cardioplegia (4oC) used in our clinic was prepared in a manner where there is a ¼ ratio between the blood and a crystalloid solution of 500 cc of 40 mEq of potassium within 0.9% NaCl, 5 cc of 10% calcium, 10 cc of magnesium, and 10 mEq of sodium bicarbonate. For the hot-shot (warm blood) cardioplegia, 1 ampule (1.5 grams) of MgSO4 and 2 ampules (1.68 grams totally) of NaHCO3 were added to 100 cc of 0.9% NaCl and prepared by mixing it with blood to a ratio of ¼ to a temperature of between 34-36oC.

Biochemical Measurements

Routine biochemical parameters and CK-MB, TpI, BNP, TNF- α, IL-1, IMA, and ICAM-1 were studied in the blood samples taken from the patients just before the induction of anesthesia. The CK-MB, TpI, TNF-α, IL-1, IMA, and ICAM-1 parameters were studied in the coronary sinus blood samples that were taken before aorta cross-clamping and at the beginning of reperfusion. The BNP and IMA were looked in the blood samples at the sixth postoperative day.

The CK-MB, BNP, and TpI analyses were performed with chemiluminescent methods using original Beckman Coulter brand commercial kits in a Beckman Coulter Unicel DxI-800 brand immune analyzer. The IL-1, TNFα, and ICAM-1 were measured using an eBioscience brand kit worked using ELISA method. The IMA level was analyzed manually using the method specified by Bar-Or et al [5].

Echocardiographic Evaluation

The patients were evaluated preoperatively and on the 6th postoperative day using transthoracic echocardiography. The evaluation was carried out by the same cardiologist blinded to the study. Standard cardiac diameters and routine values were determined.

Statistical Analysis

The SPSS for Windows v20.0 software (SPSS Inc, Chicago, IL, USA) was used in the analysis of the statistical data. The Student-t test (those conforming to normal distribution) and the Mann-Whitney U Test (those not conforming to normal distribution) were used in the comparison between the two groups of numeric variables acquired by taking measurements from the patients on one occasion. All statistical hypothesis controls were applied at a significance level of α=0.05. Results which came out as $p<0.05$ were interpreted as being significant.

Results

A total of 60 patients who underwent coronary artery bypass grafting surgery, 45 (75%) males and 15 (25%) females, were included in the study.

The preoperative characteristics of the patients included in the study are presented in Table 1. There was no significant difference between 2 groups in terms of age, gender, comorbid conditions, additional procedures, coronary artery lesions, blood lipid parameters, and inflammatory status ($p>0.05$).

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Table 1: Preoperative demographic, laboratory, and echocardiographic characteristics of the patients			
	Group 1 (n=30)	**Group 2 (n=30)**	**p value**
Age (years)	62.27 ± 9.15	60.57 ± 8.26	0.45
Male/female	24/6	21/9	0.37
Body surface area (m2)	1.85 ± 0.11	1.86 ± 0.19	0.89
Diabetes mellitus	14 (46.17%)	11 (36.17%)	0.43
Hypertension	20 (66.7%)	22 (73.3%)	0.57
Hyperlipidemia	15 (50%)	19 (63.3%)	0.30
Chronic obstructive pulmonary disease	7 (23.3%)	2 (6.7%)	0.15
Peripheral arterial disease	3 (10%)	1 (3.3%)	0.30
Left main stem stenosis	0	3 (10%)	0.07
Two vessel disease	11 (36.7%)	5 (16.7%)	0.07
Three vessel disease	19 (63.3%)	22 (73.3%)	0.07
Additional procedure	4 (13.3%)	0	0.11
Preoperative myocardial infarction	6 (20%)	9 (30%)	0.37
Creatinine (mg/dL)	0.96 ± 0.25	0.85 ± 0.21	0.06
High-density lipoprotein cholesterol (mg/dL)	33.30 ± 8.63	32.57 ± 9.84	0.76
Low-density lipoprotein cholesterol (mg/dL)	102.97 ± 32.30	97.97 ± 44.79	0.62
CKMB	1.54 ± 0.72	2.10 ± 1.72	0.11
TpI	0.09 ± 0.18	0.29 ± 0.66	0.13
BNP	240.57 ± 363.73	148.60 ± 140.58	0.20
TNF-α	18.99 ± 5.55	17.45 ± 0.59	0.14
IL1	19.51 ± 3.09	19.40 ± 3.84	0.89
IMA	1.38 ± 0.09	1.42 ± 0.1	0.11
ICAM-1	361.43 ± 107.28	343.53 ± 106.69	0.52

There was no statistically significant difference between the groups with respect to number of distal anastomosis per patient, aortic cross-clamping time, cardiopulmonary bypass time, volume of cardioplegia, spontaneous cardiac activity, need of inotropic agents, ventilation time, bleeding amount, postoperative arrhythmia, intensive care unit duration, and length of stay in hospital (Table 2).

Table 2: Comparison of surgical and postoperative variables between the 2 groups			
	Group 1 (n=30)	**Group 2 (n=30)**	**p value**
Number of distal anastomosis per patient	3.40 ± 0.86	3.50 ± 0.97	0.67
Aortic cross-clamping time (minutes)	66.83 ± 27.55	59.23 ± 18.29	0.21
Cardiopulmonary bypass time (minutes)	117.80 ± 31.30	113.73 ± 38.08	0.65
Volume of cardioplegia (ml)	2678.33 ± 783.31	2671.67 ± 592.29	0.97
Spontaneous cardiac activity	19 (63.3%)	15 (50%)	0.30
Need of inotropic agents	27 (90%)	27 (90%)	1.00
Ventilation time (hours)	18.97 ± 23.52	13.83 ± 5.45	0.25
Bleeding amount (mL)	1561.67 ± 1343.35	1673.33 ± 1208.14	0.09
Intensive care unit duration (days)	3.87 ± 3.19	2.93 ± 1.02	0.13
Length of stay in hospital (days)	8.90 ± 4.71	8.30 ± 2.38	0.54
Postoperative arrhythmia	6 (20%)	6 (20%)	1.00

When both groups were compared, the magnitude of the changes (difference between pre and post CPB) in the CK-MB, TpI, IL-1, IMA, and ICAM-1 values were not statistically significant (p=0.112, p=0.394, p=0.391, p=0.13, and p=0.182, respectively). The magnitude of increase in TNFα was significantly higher in Group 2 (p=0.047) (Table 3).

Table 3: Comparison of the magnitude of the changes after CPB between 2 groups

	Group 1 (n=30)	Group 2 (n=30)	p value
CKMB	11.20 ± 8.93	14.77 ± 8.20	0.112
TpI	0.75 ±0.86	0.58 ±0.61	0.394
TNF α	9.77 ± 10.12	16.38 ± 14.72	0.047
IL-1	-0.53 ± 5.61	-1.67 ± 4.51	0.391
IMA	-0.03 ± 0.14	-0.10 ± 0.20	0.130
ICAM-1	-38.47 ± 15.09	-65.17 ± 68.61	0.182

The values from echocardiography revealed that mean EF decreased after operation in both groups. However, the magnitude of decrease in EF was significantly higher in Group 2 compared to Group 1 (p=0.046). The mean BNP values increased after operation in both groups. The magnitude of increase in BNP was significantly higher in Group 2 (p=0.032) (Table 4).

Table 4: Comparison of the magnitude of the changes after operation between 2 groups

	Group 1 (n=30)	Group 2 (n=30)	p value
BNP	251.6 ± 257.8	295.9 ± 282.9	0.032
EF	-4.13 ± 9.09	-8.9 ± 10.76	0.046

Discussion

Most favorable myocardial protection requires homogeneous delivery of cardioplegic solution throughout the heart. Despite developments in surgical techniques and progress in myocardial protection methods, there is no consensus on applying an ideal method for the protection of myocardium during open heart surgery. Reperfusion damage generally manifests itself as myocardial systolic and diastolic dysfunction which appears minutes or hours after CPB.

A number of authors who argue for the supremacy of antegrade cardioplegia have reported that the infusion of cardioplegic solution through the aortic root is a simple delivery method used by cardiac surgeons. Antegrade cardioplegia provides diastolic arrest more quickly than retrograde cardioplegia. However, when there is a critical stenosis in proximal parts of coronary arteries especially in proximal left anterior descending lesion accompanied by poor collaterals, this method can cause nonhomogeneous distribution of cardioplegic solution to the myocardium. On the other hand, the inability for cardioplegia given via the aortic root in patients who have coronary lesions accompanied by aortic insufficiency is an important restrictive factor in the usage of the antegrade cardioplegia method [6]. Clinical trials regarding the risk of athero-embolisms and air embolisms by using different cardioplegia methods demonstrate that antegrade cardioplegia can cause more embolic complications compared to retrograde one [7]. When there is a severe left ventricular hypertrophy (for any reason), the cardiac tissue will not be protected adequately due to disproportional increment of myocardial thickness relative to the myocardial vascular network. Consequently, this situation increases the possibility of myocardial ischemia resulting cardiac injury during aortic cross-clamping [8]. On the other hand, because of reasons such as slow flow rate, heterogeneous distribution, and poor protection of the right ventricle wall, the use of the retrograde cardioplegia method on its own is also restricted. For this reason, the use of the antegrade and retrograde cardioplegia methods together can increase its efficacy [6,9]. The aim in using antegrade and retrograde cardioplegia in combination is to supplement each other. It has been reported that, by the combined antegrade-retrograde cardioplegia method, myocardial functions are better preserved, that the production of myocardial lactate is lower, the ATP is better preserved, arrhythmias and hospitalization duration in the postoperative period are lower [10,11].

This prospective study examines the impact of different cardioplegic solution delivery systems to left ventricular systolic functions and the levels of some biochemical markers which increased in response to ischemic and inflammatory conditions in randomized patients undergoing first time one or more vessel CABG.

The TNF-α is released in the early stages of acute inflammation. This biochemical marker was also examined in the samples taken from the coronary sinus before and after the cardioplegia, while the TNF-α level increased much more significantly in antegrade cardioplegia group demonstrating that inflammation associated with ischemia and reperfusion damage appeared less in the hearts in which combined cardioplegia were applied.

Cardiac markers can be detected to be higher than normal levels if a complication occurs following open heart surgery [12,13]. CK-MB and troponin I as surrogate cardiac markers of myocardial ischemia were increased in both groups compared to basal levels after the cardioplegia despite there was no perioperative MI observed in our patients. However, when the magnitude of the changes were compared there was no statistically significant difference between the groups (p=0.112 and p=0.394, respectively). Albeit troponin I and CK-MB are sensitive cardiac biomarkers demonstrating myocardial injury; some other factors such as myocardial manipulation, dissection of the myocardium to detect the coronary arteries, placement of purse-string sutures may also increase the markers, so the difference between the groups was non-significant.

Chello et al. [14] reported in preoperative patients that there was an inverse relationship between the levels of BNP values and left ventricular systolic and diastolic functions. In some studies, it has been also reported that pre-operative high BNP values may be an indicator of high risk for patients who are undergoing CABG [15-19]. There was a statistically significant rise in BNP levels in both groups. If we compare the BNP changes in two groups, the increase in BNP levels was higher in Group 2. This situation was also supported by statistically significant difference between the groups in regarding the changes of EF values. Lesser decrease in EF values in combined cardioplegia group was a substantial factor demonstrating that the superiority of combined cardioplegia compared to antegrade cardioplegia alone from the point of view of myocardial protection.

As a conclusion, according to results of our clinical trial, we demonstrate that co-administration of retrograde and antegrade cardioplegia is more advantageous compared to antegrade one in terms of myocardial protection.

Declaration of conflict of interest

There is no conflict of interest.

Funding

This study was supported by the Selçuk University, Scientific Research Projects Fund (Project No: BAP-11102037).

References

1. Bolling SE, Flaherty JT, Bulkley BH, Gott VL, Gardner TJ. Improved myocardial preservation during global ischemia by continuous retrograde coronary sinus perfusion. J Thorac Cardiovasc Surg 1983; 86: 659-66.
2. Casthely PA, Shah C, Mekhjian H et al. Left ventricular diastolic function after coronary artery bypass grafting: a correlative study with three different myocardial protection techniques. J Thorac Cardiovasc Surg 1997; 114: 254-60.
3. Fabian JR, Deloche A, Swanson J, Carpentier A. Retrograde cardioplegia through the right atrium. Ann Thorac Surg 1986; 41: 101-2.
4. Bhyana J, Kalmbach T, Booth FV, Mentzer M, Schimert G. Combined antegrade/retrograde cardioplegia for myocardial protection: a clinical study. J Thorac Cardiovasc Surg 1989; 98: 956-60.
5. Bar-Or D, Lau E, Winkler JV. A novel assay for cobalt-albumin binding and its potential as a marker for myocardial ischemia-a preliminary report. J Emerg Med 2000; 19: 311-15.
6. Fiore AC, Naunheime KS, Kaiser GC et al. Coronary sinus versus aortic root perfusion with blood cardioplegia in elective myocardial revascularization. Ann Thorac Surg 1989; 47: 684-88.
7. Kulshrestha P, Rousou JA, Emgelman RM et al. Does warm blood retrograde cardioplegia preserve right ventricular function? Ann Thorac Surg 2001; 72: 1572-75.
8. Flack JE 3rd, Cook JR, May SJ et al. Does cardioplegia type affect outcome and survival in patients with advanced left ventricular dysfunction? Results from the CABG Patch Trial. Circulation 2000; 102: 84–89.
9. Rao V, Cohen G, Weisel RD et al. Optimal flow rates for integrated cardioplegia. J Thorac Cardiovasc Surg 1998; 115: 226-35.
10. Arom KV, Emery RW, Petersen RJ, Bero JW. Evaluation of 7,000+ patients with two different routes of cardioplegia. Ann Thorac Surg 1997; 63: 1619-24.
11. Aldea GS, Hou D, Fonger JD, Shemin RJ. Inhomogeneous and complementary antegrade and retrograde delivery of cardioplegic solution in the absence of coronary artery obstruction. J Thorac Cardiovasc Surg 1994; 107: 499-504.
12. Jacquet L, Noirhomme P, El Khoury G et al. Cardiac troponin I as an early marker of myocardial damage after coronary bypass surgery. Eur J Cardiothorac Surg 1998; 13: 378-84.
13. Kutsal A, Saydam GS, Yucel D, Balk M. Changes in serum levels of CKMB, LDH, LDH1, SGOT and myoglobin due to cardiac surgery. J Cardiovasc Surg 1991; 32: 516-21.
14. Chello M, Mastroroberto P, Perticone F et al. Plasma levels of atrial and brain natriuretic peptides as indicators of recovery of left ventricular systolic function after coronary artery bypass. Eur J Cardiathorac Surg 2001; 20: 140-46.
15. Wei CM, Heublein DM, Perrella MA et al. Natriuretic peptide system in human heart failure. Circulation 1993; 88: 1004-9.
16. Saribulbul O, Alat I, Coskun S et al. The role of brain natriuretic peptide in the prediction of cardiac performance in coronary artery bypass grafting. Tex Heart Inst J 2003; 30: 298-304.
17. Song MH, Kobayashi Y, Michi H. Clinical implication of atrial and brain natriuretic peptide in coronary artery bypass grafting. Asian Cardiovasc Thorac Ann 2004; 12: 41-46.
18. Matsumoto A, Hirata Y, Momomura S et al. Effects of exercise on plasma level of brain natriuretic peptide in congestive heart failure with and without left ventricular dysfunction. Am Heart J 1995; 129: 139-45.
19. Yasue H, Yoshimura M, Sumida H et al. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. Circulation 1994; 90: 195-203.