

COMPARISON OF THE EFFECT OF ANTEGRADE AND ANTEGRADE/RETROGRADE CARDIOPLEGIA ON THE OUTCOME OF CORONARY ARTERY BYPASS GRAFT SURGERY FOR SEVERE CORONARY ARTERY DISEASE

Ali Gohar Zamir, Asif Mahmood Janjua, Musfireh Siddiqeh*, Farrah Pervaiz, Noor Shah, Muhammad Afsheen Iqbal, Muhammad Ashfaq

Armed Forces Institute of Cardiology/National Institute of Heart Disease (AFIC/NIHD)/National University of Medical Sciences (NUMS) Rawalpindi Pakistan, *Rawalpindi Institute of Cardiology, Rawalpindi Pakistan

ABSTRACT

Objective: To compare the early outcome of Coronary Artery Bypass Graft surgery using a combination of antegrade and retrograde cardioplegia with that utilizing antegrade cardioplegia alone in triple vessel coronary artery disease.

Study Design: Comparative cross-sectional study.

Place and Duration of Study: Department of Adult Cardiac Surgery of Armed Forces Institute of Cardiology and National Institute of Heart Diseases, Rawalpindi, from Sep 2013 to Apr 2019.

Methodology: A total of 160 patients with triple vessel coronary artery disease who underwent CABG surgery for 90% or greater stenosis in at least one major vessel in each of the three territories, namely the left anterior descending, the circumflex and the right coronary artery were investigated retrospectively. These were divided into 2 equal groups on the basis of the technique of administration of cardioplegia: in group-1 only ante grade blood cardioplegia was administered for myocardial protection and group-2 was given ante grade and retrograde cardioplegia. Clinical outcomes like peri-operative mortality and morbidity were recorded, and serum creatine kinase MB, lactate, and mixed venous oxygen saturation levels were monitored. Two dimensional echocardiogram was performed on the 6th post-operative day and follow-up visits were planned 1 week and 4 weeks after discharge from hospital.

Results: There were 2 (2.5%) early deaths in group-1 and no peri-operative mortality in group-2. Five patients in group-1 (6.25%) and 2 (2.5%) in group-2 had non-fatal peri-operative myocardial infarction. However, significant differences included increased incidence of intra-operative ventricular dysrhythmias, higher CK-MB levels at 24 hours after surgery, and increased requirement of intra-aortic balloon pump and inotropic support in Group-1.

Conclusion: We conclude from this study that the combined delivery of ante grade and retrograde cardioplegia during CABG surgery for triple vessel coronary artery disease provides better myocardial protection and hence better outcome than antegrade cardioplegia alone.

Keywords: Cardioplegia techniques, Coronary artery bypass graft surgery, Myocardial protection, Outcome.

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INTRODUCTION

One of the most important aspects of cardiac operations which has a direct impact on the outcome is the protection of myocardium during surgery. In coronary artery disease (CAD), the myocardium has low reserves of high-energy phosphates and these are further depleted during the ischaemia that entails application of aortic cross-clamp. Ninety percent of the myocardial oxygen utilization can be eliminated simply by arresting the heart, and only another 10% of

myocardial protection is added by cooling the myocardium. High-potassium cardioplegia was therefore developed to stop the heart in diastole and blood was later added to transport the cardioplegia to the myocardium^{1,2}.

The antegrade flow of cardioplegia in the coronary tree is limited by the presence of atherosclerotic obstructions rendering some degree of ischaemia which is further exacerbated by the transient interruption of coronary flow during the cross-clamp time, even when there is electromechanical silence following cardioplegic arrest. This may lead to "reperfusion-injury" caused by

Correspondence: Dr Ali Gohar Zamir, Department of Adult Cardiac, AFIC/NIHD Rawalpindi Pakistan

the sudden resumption of blood flow to the ischemic myocardium, after completion of the grafting^{3,4}, resulting in reduced cardiac contractility and impaired function after surgery^{5,6}.

The satisfactory distribution of cardioplegia to all parts of the heart is the hallmark of adequate myocardial protection and this can be aided by administering cardioplegia retrogradely into the venous system of the heart which is free of atheromas and valves, providing better sub-endocardial perfusion and uniform cooling^{7,8}.

However, in practice, the use of retrograde pathway as the sole mode of delivery of cardioplegia is limited by its failure to provide complete perfusion and hence protection of the right ventricle (RV) due to certain anatomical and technical aspects. The solution, apparently lies therefore, in combining both the antegrade and retrograde techniques^{9,10}.

Our study aims to determine that the combined approach to cardioplegia delivery provides better myocardial protection than the traditional antegrade technique in patients undergoing CABG for severe three-vessel coronary artery disease (TVCAD).

METHODOLOGY

Study Population and Clinical Outcomes

The comparative cross-sectional study was conducted from September 2013 to April 2019 at the Armed Forces Institute of Cardiology and National Institute of Heart Diseases. One hundred and sixty patients who had undergone CABG surgery for severe TVCAD, with 90% or greater stenosis in the left anterior descending artery (LAD), a sizeable obtuse marginal (OM) branch of the circumflex and a dominant right coronary artery (RCA) or its posterior descending branch (PDA) were selected so as to form 2 equal groups with comparable demographic features. We used a bolus of tepid, high potassium blood cardioplegia administered antegradely into the aortic root to achieve the initial diastolic arrest (induction) in both groups. Group-1 (80 patients) was then administered antegrade cardioplegia intermittently at approximately 20-minute intervals via the

same route throughout the duration of the application of the aortic cross-clamp. Patients in group-2 (80 patients) received two-third of the induction cardioplegia antegradely and the remaining one-third in a retrograde manner into the coronary sinus. There after retrograde cardioplegia was given almost continuously during the performance of the distal anastomoses.

Excluded from the study were emergent cases, patients having poor left ventricular function with a left ventricular ejection fraction of equal to or less than 30% (LVEF \leq 30%), patients operated within 2 weeks of a myocardial infarction (MI) and those with raised baseline creatine kinase (CK)-MB isoenzyme before surgery. Critical left main stem (LMS) disease, diffuse CAD requiring endarterectomies or long segmental reconstructions, reoperations, patients with severe multi-organ dysfunction, and those requiring intervention for associated LV aneurysmal or valvular pathology were also excluded.

Baseline electrocardiogram (ECG), 2 dimensional echocardiogram (2-D Echo) and serum CK-MB levels of each patient were documented pre-operatively. Arterial blood gas samples (ABGs) were taken after induction of anaesthesia, at 30-minute intervals during CPB, and at regular intervals in the post-operative ICU. Mixed venous blood samples were also sent for mixed venous oxygen saturation, post-operatively. ECG and CK-MB levels were recorded 1, 24 and 48 hours after surgery. 2-D Echo was done on the 6th postoperative day.

The data reviewed included pre (table-I) and intra-operative (table-II) characteristics, operative mortality and post-operative morbidity (table-III). The peri and post-operative CK-MB, lactate, and mixed venous oxygen saturation levels were also recorded. These, together with the postoperative 2-D Echo helped assess the effect of each technique of myocardial protection on the postoperative outcome including cardiac function.

Surgical Technique

All patients were counseled about the surgery and informed consent was obtained. All

CABG operations were performed employing cardiopulmonary bypass (CPB), mild systemic hypothermia and tepid blood cardioplegic arrest. Cardioplegia was prepared by diluting 1 part of the crystalloid cardioplegia solution with 4 parts of blood. Patients in group-1 received an induction dose of antegradecardioplegia into the aortic root cannula, and thereafter, cardioplegia was administered at 20 minutes intervals through the same route. Group-2 patients received two-third of the initial induction dose antegradely and the remaining one-third was given retrogradely into the coronary sinus via a self-inflating retrograde cannula keeping infusion pressure less than 40 mmHg. Subsequently these patients were administered cardioplegia by the retrograde route almost continuously, stopping transiently to facilitate visualization of the coronary targets and during manipulation of the heart for the distal anastomoses.

A mean arterial pressure of 60-70 mmHg was maintained during CPB. Saphenous vein grafts were used to bypass the RCA and OMs, while the left internal mammary artery (LIMA) was grafted to the LAD. After completion of the LIMA anastomosis, about 600 ml of warm blood without cardioplegia was given antegradely in group-1 and retrogradely in group-2, the aortic cross-clamp was removed and proximal anastomoses to the aorta were performed using a partial occlusion clamp.

All surgeries were done by the same surgeon ensuring uniformity of procedure. Soluble aspirin was given to all patients within 6 hours of surgery.

Operational Definitions

Perioperative mortality and morbidity were recorded as events occurring within 30 days of surgery; peri-operative MI was defined as the appearance of new wall-motion abnormalities on echo, new Q waves in ECG or a rise in serum CK-MB levels five-fold or greater than the upper limit; respiratory failure denoted the advent of pneumonia or the requirement of mechanical ventilatory support for more than 48 hours.

Review of Clinical Data and Statistical Analysis

The study was approved by the Institutional Ethics Review Board of the documented medical institution. Informed Consent was taken prior to the surgery from patients. T-test was applied to determine any significant association between groups. Mean \pm SD was calculated for continuous variables while categorical variables are expressed in frequency/percentages.

RESULTS

Table-I shows similar demographics in both groups. Table-II & III show intra-and-post operative data, respectively. Patients in group-1 received antegrade cardioplegia while group-2 comprised of patients who received both antegrade and retrograde cardioplegia. The mean age of patients in group-1 was 61.72 ± 10.6 and that of patients in group-2 was 60.14 ± 11.2 .

Table-I: Demographic characteristics (n=160).

Characteristics	Number of Patients	
	Group 1 (n=80)	Group 2 (n=80)
Age in Years		
Mean	61.72 \pm 10.6	60.14 \pm 11.2
Gender		
Male	59 (73.75%)	58 (72.5%)
Female	21 (26.25%)	22 (27.5%)
Obesity	23 (28.75%)	25 (31.25%)
Hypertension	67 (83.75%)	63 (78.75%)
Diabetes Mellitus	52 (65%)	55 (68.75%)
Dyslipidemia	41 (51.25%)	43 (53.75%)
Smoking	21 (26.25%)	23 (28.75%)
Previous MI	34 (42.5%)	36 (45%)
History of congestive cardiac failure (CCF)	7 (8.75%)	9 (11.25%)
Unstable Angina	21 (26.25%)	23 (28.75%)
LVEF %		
>50	57 (71.25%)	54 (67.5%)
40-50	13 (16.25%)	15 (18.75%)
30-40	10 (12.5%)	11 (13.75%)

The CPB and cross-clamp times were similar in both groups. The contents of cardioplegia was same but the volume was greater in group-2. There were 2 early deaths (2.5%) in group-1 and none in group-2. Both patients were diabetic males with total occlusion in 2 major vessels and

had intra-aortic balloon pump (IABP) inserted for difficulty in weaning from CPB. They developed sepsis and multi-organ dysfunction, postoperatively. Five patients (6.25%) in group-1, and 2

raised to levels indicating infarct, were higher in group-1. The serum lactate levels were higher in group-1 while mixed venous oxygen saturation was higher in group-2 in the early postoperative

Table-II: Intra-operative characteristics (n=160).

Characteristics	Group 1 (n=80)	Group 2 (n=80)	p-value
CPB time (minutes)			
Mean	92.14 ± 28.32	94.37 ± 25.28	
Cross-clamp time (minutes)			
Mean	61.18 ± 24.63	58.43 ± 17.38	
No. of Anastomoses			
3	42 (52.5%)	44 (55%)	
4	38 (47.5%)	36 (45%)	
No. of totally occluded coronaries			
1	11 (13.75%)	13 (16.25%)	
2	5 (6.25%)	(8.75%)	
Volume of Cardioplegia used (ml)			
Mean	2780 ± 730	3845 ± 1550	
Ventricular dysrhythmias on cross-clamp removal	8 (10%)	1 (1.25%)	0.004
No. of patients requiring defibrillation	12 (15%)	3 (3.75%)	
No. of patients requiring Inotropes	34 (42.5%)	18 (22.5%)	0.003
No. of patients requiring IABP	8 (10%)	1 (1.25%)	0.004

Table-III: Post-operative outcome (n=160).

Characteristics	Group 1 (n=80)	Group 2 (n=80)	p-value
Cratine K-MB (IU/L) Mean ± SD			
1 hour	32.7 ± 21.4	20.3 ± 12.6	0.004
24 hours	30.4 ± 18.8	18.2 ± 11.3	
48 hours	22.3 ± 11.4	13.8 ± 7.2	
Arterial lactate (mmol/l)			
hour	5.4 ± 4.1	2.7 ± 1.6	
hours	2.6 ± 0.8	2.7 ± 0.5	
8hours	2.3 ± 0.6	2.1 ± 0.4	
Mixed venous saturation %			
3 hours	65.8 ± 6.4	72.6 ± 7.5	
8 hours	69.6 ± 4.9	71.4 ± 3.2	
ICU stay (hours)	8.3 ± 6.7	9.1 ± 8.4	
Hospital Stay (days)	7.2 ± 1.7	7.7 ± 4.3	
Atrial fibrillation	5 (6.25%)	4 (5%)	
Re-exploration for hemorrhage	1 (1.25%)	2 (2.5%)	
Non-fatal MI	5 (6.25%)	2 (2.5%)	
Ventilatory support >48 hours	2 (2.5%)	1 (1.25%)	
Stroke			
Sternal wound infection	-	1 (1.25%)	
Mortality	2 (2.5%)	-	
LV Ejection Fraction % Mean ± SD	48.3 ± 7.4	53.8 ± 6.2	

(2.5%) in group-2 suffered peri-operative MI; all recovered but 1 patient from group-1 had a low LVEF of 30% on discharge from hospital. The mean CK-MB, in rest of the patients, though not

period.

Eight patients (10%) in group-1 and 1 (1.25%) in group-2 required insertion of IABP due to

difficult weaning from CPB, while 34 patients (42.5%) in group-1 and 18 (22.5%) in group-2 needed inotropic support during the early post-operative period. These differences were found to be statistically significant. In most cases the inotropes were stopped within 6 hours of surgery. Also significant were the raised CK-MB levels at 24 hours after surgery in group-1. The incidence of ventricular dysrhythmias on removal of the cross-clamp was significantly greater in group-1 (10%), and more patients required cardioversion to achieve sinus rhythm. Pre-discharge 2-D Echo showed lower LVEF in group-1, however the difference was not significant.

DISCUSSION

Before May 2017, we employed the traditional method of administering cardioplegia antegradely into the aortic root in all cases of CABG for TVCAD. We used retrograde cardioplegia only selectively in relatively high-risk CABG cases like critical LMS or LMS equivalent, emergent surgeries, and those requiring complex coronary interventions such as endarterectomies and long segmental reconstructions of diffusely diseased coronaries. Group-1 patients, who received only antegrade cardioplegia, are entirely from this time period. Since May 2017 our team is using retrograde cardioplegia in addition to antegrade cardioplegia in all cases requiring CABG surgery for TVCAD, with 90% or greater stenosis in the LAD, at least one major OM and in the dominant RCA or its PDA branch. Therefore, patients included in group-2 are those who were operated after May 2017.

We, like the majority, utilize blood rather than crystalloid cardioplegia, because of its capacity to carry oxygen to the heart during the ischaemic arrest, its buffering capacity, as well as lesser tendency to cause haemodilution and oedema¹¹. Though some studies¹², show similar clinical results with blood and crystalloid cardioplegia, the majority^{13,14,15}, indicate better protection of the myocardium using blood cardioplegia, with decreased CK-MB levels and decreased incidence of low cardiac output syndrome (LCOS) after

surgery. We used tepid cardioplegia (29°C) for myocardial protection because it avoids the delayed recovery of cardiac function and metabolism associated with cold cardioplegia ($\leq 15^\circ\text{C}$)^{16,17,18}, and reduces the anaerobic metabolism seen with warm (37°C) cardioplegia^{19,20}. Our practice of administering antegrade cardioplegia for induction achieves rapid asystole²¹, in comparison to the retrograde route. Injecting warm blood into the coronaries, before removal of the cross-clamp (hot-shot) has shown to reduce myocardial injury²².

Although, some studies have demonstrated certain degree of anaerobic metabolism in the right ventricle, following exclusively retrograde delivery of cardioplegia, myocardial high energy phosphates are rather well preserved in myocardial biopsies, which explains why myocardial functional recovery is quite satisfactory, postoperatively²³. Electron microscopic examination of such biopsies, has also shown far less cellular swelling and mitochondrial and myofibrillar degeneration with retrograde cardioplegia than with antegrade. It appears that combining the 2 techniques offsets the limitations of each, providing better clinical, biochemical and structural outcome.

Our study shows a higher incidence of peri-operative death and MI in patients who received only antegrade cardioplegia into the aortic root (group-1) in comparison to patients who received both ante- and retrograde cardioplegia for myocardial protection (group-2). Similar results have been quoted by others. Amongst the survivors who did not suffer an MI, in our study, the magnitude of elevation of CK-MB levels above baseline was higher in group-1, especially, 24 hours after surgery. Other studies have shown similar findings, suggesting less myocardial injury and hence better myocardial protection^{24,25} in the combined group. Cardioplegia as opposed to the one receiving antegrade cardioplegia.

We did not find any significant difference in the CPB and cross-clamp times, duration of ventilatory support and the average ICU and

hospital stay between the 2 groups. However, others, report shorter cross-clamp time and duration of ventilatory support and shorter ICU and hospital stay in the combined group.

There are a few studies, however, which have not identified any significant differences in the postoperative outcomes with the 2 modes of delivery of the cardioplegia.

The volume of cardioplegia in group-2 was greater because of the almost uninterrupted retrograde delivery of cardioplegia during the cross-clamp time. We believe that this provides uniform and sustained myocardial protection, minimizing the ischaemic period and hence the possibility of developing reperfusion injury. The haematocrit and electrolyte levels were monitored regularly, and changes associated with the larger volumes of cardioplegia were corrected promptly. The mean lactate levels were lower and mixed venous oxygen saturation was higher in the early postoperative samples in Group-2, indicating better haemodynamics. Others have also demonstrated lower myocardial lactate levels in the combined group, as well.^{24,25}

LIMITATION OF STUDY

This was a retrospective observational study with limited number of patients, due mainly to selection of comparable characteristics in the 2 groups. The results are mainly restricted to the peri-operative outcomes as the main impact of myocardial protection during surgery is on the events of the immediate and early post-operative period. Though the 2 groups were operated at different times, the management protocols were unchanged. Moreover, since all surgeries were performed by the same surgeon, the uniformity of procedures was ensured. The measurement of Troponin as marker of myocardial damage was introduced in the latter half of the study and therefore was not included in this study.

CONCLUSION

Research is underway in the search of the ideal cardioplegia, and the jury is still out to determine the best techniques of its delivery and the contents, and temperature, of the solution.

Whereas, the advantage of combining ante- and retrograde cardioplegia is well recognized in critical LMS and valvular heart disease, our study suggests that the combination also tends to provide better myocardial protection and hence better outcome in patients undergoing CABG surgery for severe TVCAD, when compared with the traditional antegrade approach.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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