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Myocardial Protection Using Antegrade Cardioplegia Alone Compared to Antegrade Combined with Vein Cardioplegia in On-Pump Coronary Artery Bypass Graft Surgery

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Abstract **Original Research Article**

Cardioplegia is an integral component of myocardial protection. Standard delivery of cardioplegia includes antegrade and retrograde method. Retrograde technique may cause injury to the coronary sinus and inadequate right ventricular protection while antegrade alone may be inadequate especially delivery of cardioplegia through very stenotic vessels. Therefore, in this study we compare myocardial protection using antegrade cardioplegia alone compared to combination of antegrade and vein cardioplegia in on pump coronary artery bypass graft surgery. This is a cross sectional retrospective study. Two groups of patients (antegrade combined with vein cardioplegia-study group and antegrade cardioplegia alone- control group) were studied. The study group consists of 42 patients while the control group consists of 39 patients. Study population are patients aged between 30-80 years old between 1 January 2019 and 30 April 2023. Intraoperative characteristics such as cardiopulmonary bypass time, aortic cross clamp time, cardioplegia volume, number of post-operative inotropes, ventricular tachycardia and fibrillation after aortic unclamping and postoperative characteristics such as hospital stay, ICU stay, mortality, intra-aortic balloon pump insertion, chest reopen for bleeding and postoperative atrial fibrillation were compared. The results of this study showed that cardiopulmonary bypass time, hospital stay, mortality, postoperative IABP insertion and postoperative arrhythmia rate for both groups were similar, however not statistically significant. The study group required less inotropes before transfer to ICU. (2.83 VS 3.10, P=0.04). The primary finding of this study shows that there is no difference in terms of myocardial protection with antegrade combined with vein cardioplegia as compared antegrade cardioplegia alone.

Keywords: Myocardial Protection, Antegrade Cardioplegia, Vein Cardioplegia, On-Pump Coronary Artery Bypass Graft Surgery, Comparison.

INTRODUCTION

Cardioplegia is a form of pharmacological method to arrest the heart intentionally and temporarily during cardiac surgery. It is a well-known fact that high levels of potassium citrate given during cardiopulmonary bypass causes reversible cardiac arrest. The way by which potassium leads to diastolic arrest is that an influx of potassium leads to myocardial membrane depolarization and subsequently sequestration of calcium ions resulting in diastolic arrest. The persistence of potassium lowers the membrane potential and does not allow adequate repolarization [1].

Cardioplegia is key for adequate myocardial protection. Myocardial protection refers to the methods to increase the ability of the heart to withstand an ischemic insult. By arresting the heart in diastole and selective hypothermia, the primary goal is to reduce myocardial oxygen demand and the ischemic effects of being on bypass. Furthermore, the usage of cardioplegia provides a relatively motionless and bloodless surgical field [2].

Cardioplegia can be delivered via several methods. Conventionally, it is delivered via antegrade, retrograde or both. Antegrade delivery means that the solution is delivered to the right and left coronary arteries and thus supplying the myocardial in the same way that blood would normally do [3]. It is delivered via a catheter that is inserted into the proximal aorta which contains two lumens, one to deliver cardioplegia and the other to vent blood out from the heart. In other instances, such as an incompetent aortic valve, diffusely stenosed coronary vessels and previous coronary artery bypass graft surgery (CABG), a retrograde delivery of cardioplegia is deemed

necessary. For this, a retrograde cannula is inserted via an atriotomy in the right atrium into the coronary sinus and thus delivery of cardioplegia in a retrograde fashion.

Usage of retrograde cardioplegia may impose certain problems. Due to the drainage of veins of the right ventricle directly to the right atrium, the delivery to cardioplegia may be jeopardized [4]. Besides, coronary sinus injury is a potentially lethal, although rare complication. Occasionally, the presence of a membrane that is closing the orifice of the coronary sinus may lead to difficult introduction of the cardioplegia cannula, therefore leading to injury.[5]. Moreover, retrograde cardioplegia alone does not protect the heart completely, particularly the anterior aspect of the right ventricle. The delivery of cardioplegia via the antegrade alone is effective, however we may encounter problems of adequate delivery through very stenotic vessels. It is a proven fact that antegrade combined with retrograde provides effective myocardial recovery post open heart surgery [6]. However, whether or not to use the retrograde cardioplegia together with antegrade still remains an institutional decision.

There are quite a number of studies done pertaining this topic. Gokhan Onem *et al*., conducted a study in 2006 where twenty patients were divided into two groups. The first group (n=10) received only antegrade cardioplegia while the study group (n=10) received antegrade supplemented with perfusion via vein grafts. Data on enzyme release (creatinine phsophokinase-isoenzyme MB, myoglobin and cardiac troponin I) were obtained periodically. The study concluded that the supplementation of cardioplegia through the vein grafts provided no added advantage to the study patients [7]. Another study done by Mehrzad Sharifi *et al*., in 2018 where 223 patients were divided into two groups. This study yielded better postoperative cardiac performance in the study group [8]. A similar study was also done by Ali Can Hatemi *et al*., in 2011 which concluded that myocardial protection with combination antegrade and vein cardioplegia is inferior as compared to antegrade alone [9]. MT Goncu *et al*., study in 2010 performed with both these groups on the other hand showed that delivering cardioplegia through the vein provides better myocardial protection [10].

These four studies that are mentioned have various conclusions as to the potential benefit of vein combined with antegrade cardioplegia versus antegrade cardioplegia alone therefore, we would like to conduct a study in our center to determine the outcomes of both methods. The primary objective of this study is to compare both the intraoperative and postoperative outcomes using antegrade cardioplegia alone versus antegrade combined with vein cardioplegia in on-pump coronary artery bypass graft surgery. The primary outcome of this study is to look at the mortality rate between the two groups. Secondary outcome includes the hospital stay, ICU stay, IABP requirements after surgery, post-operative atrial fibrillation, number of inotropes before coming to ICU and VT/VF after aortic-unclamping.

METHODOLOGY

This is a cross-sectional retrospective study. Patients who meet the inclusion criteria were randomized into two groups who are the control group (antegrade cardioplegia alone, n=39) and study group (antegrade combined with vein cardioplegia, n=42). Patients of the control group received cardioplegia via the aortic root while patients of the study group received cardioplegia via the aortic root supplemented by antegrade perfusion via vein grafts after each distal anastomosis. None of these patients received retrograde cardioplegia. The reason retrograde was not given is because our institution routinely only infuses cardioplegia via the aortic root only. These operations were performed by two different teams.

Study population includes patients with the age group of 30 to 80 years old of Hospital Sultanah Aminah, Johor Bahru who underwent on-pump open CABG from 1 January 2019 to 30 April 2023. Sample size calculated using the two mean hypothesis testing for each variable for each variable referring to two previous journals yielded a minimal sample size of 36 patients per group which includes a 10% dropout rate [9-11].

Inclusion criteria include patients that underwent on-pump open coronary artery bypass graft surgery, patients with severe triple vessel disease (occlusion in the coronary artery more or equal to 70%, LMS more than 50%), ejection fraction of less than/equal to 35% via trans-thoracic echocardiography (TTE), and cooling temperature of 28 degrees Celsius.

Exclusion criteria are patients that underwent off-pump coronary artery bypass graft surgery, single vessel and double vessel coronary artery disease, patients without left internal mammary artery (LIMA) as a conduit/ all saphenous vein graft, coronary artery disease with concomitant valvular heart disease, patients that underwent minimally invasive coronary artery surgery, cardiac surgeries apart from coronary artery bypass graft (CABG), ejection fraction (EF) more than 35%, Patients with cooling temperatures other than 28 degrees Celsius and patients with redo sternotomy. The purpose of these exclusion criteria is mainly to reduce the confounding effects that may alter the outcome.

RESULTS

Table 1: Preoperative variables

Characteristics	Study group (n=42)	Control group (n=39)	p-value
Age	54± 8.12	58± 8.13	0.01
Sex (Male/Female)	38/4	34/5	0.73
Euroscore 1 score	2.13 ±0.31	3.23 ±0.57	0.08
LMS Disease (n/%)	9 (21)	11 (28)	0.48
BSA	1.82± 0.19	1.74± 0.20	0.06
Pre-operative Ejection Fraction (%)	31.5 ±4.57	31.4 ±3.42	0.94
Diabetes Mellitus (n/%)	29 (69)	27 (69)	0.99
Hypertension (n/%)	40 (95)	37 (95)	1.00
Smoking(n/%)	28 (67)	29 (74)	0.45
Cerebrovascular Accident(n/%)	1(2.3)	0 (0)	1.00
NYHA (1/2/3/4)	12/26/4/0	12/25/2/0	NS

Table 2: Intra operative variables

Characteristics	Study group (n=42)	Control group (n=39)	P-value
Mean number of Proximal anastomosis (n)	1.86	1.74	0.20
mean CPB time (mins)	152.95 (29.05)	150.82 (26.38)	0.73
mean Aortic cross-clamp time (mins)	97.19 (20.05)	97.85 (17.94)	0.87
mean cardioplegia volume (mls)	1852.14 (195.04)	1779.49 (261.00)	0.16
Number of inotropes upon transfer to ICU (n)	2.83 (0.62)	3.10 (0.55)	0.04
VT/VF after aortic unclamping (n/%)	2(4.8)	4(10.3)	0.42

Table 3: Postoperative variables

Characteristics	Study group (n=42)	Control group (n=39)	P-value
In hospital mortality (n/%)	2 (4.8)	3(7.7)	0.69
Mean hospital stay (days)	7.98 (2.61)	8.41 (2.84)	0.48
Mean ICU stay (days)	3.43 (2.81)	4.26 (3.51)	0.24
Postoperative atrial fibrillation (n/%)	12(28.6)	14 (35.9)	0.63
Reoperation for hemorrhage (n/%)	2(4.8)	3(7.7)	0.67
Post-operative IABP insertion (n/%)	6 (14.3)	7 (17.9)	0.77

A total of 81 patients who meet the inclusion criteria were analyzed. These patients were further divided into two groups. The first group (n=42) is the study group by which patients in this group were given cardioplegia via both the antegrade and through the vein. The second group is the control group. Patients in this group (n=39) were given cardioplegia only via the antegrade group which is the traditional method. As shown in Table 1, the demographics and pre-operative attributes were similarly distributed.

Table 2 shows the intra-operative characteristics between both groups. Both groups of patients received left internal mammary artery to left anterior descending artery anastomosis. The mean number of proximal anastomosis between both groups is somewhat similar (1.86 and 1.74). Our centre generally attempts to perform a total of three grafts for complete revascularization with two proximal anastomosis. However, occasionally as some vessels are surgically not graftable intra-operatively (too small, diffuse disease), that accounts for the lower number of proximal anastomosis. The mean cardiopulmonary bypass (CPB time) of both groups are similar albeit not statistically significant with a p-value of 0.73. Same goes to the aortic cross-clamp time where the mean time between both groups are similar although not statistically significant. Mean cardioplegia volume in the study group is 1849 milliliters ls while the mean volume infused in the control group is 1779 milliliters (p=0.16). Average number of inotropes used in the study group was 2.83 as compared to the control group of 3.10. Double the number of patients in the control group had ventricular tachycardia/ventricular fibrillation after aortic unclamping as compared to the study group.

Table 3 summarized the post-operative variables between the control and study group. The mean hospital stay between both groups are similar (7.98 vs 8.41 days, p=0.48). Mean hospital stay is 3.43 versus 4.26 days in the control group. 3 mortality was noticed in the control group compared to the two in the study group, however this did not reach statistical significance. Post-operative atrial fibrillation occurred more in the

control group compared to the study group (14 versus 12 patients). The re-operation of hemorrhage and post-operative IABP requirements were also similar in terms of numbers between these two groups.

DISCUSSION

Perioperative myocardial damage remains one of the most common causes of postoperative cardiovascular events including mortality despite a successful on pump CABG (12) Therefore, effective myocardial protection is crucial in ensuring positive postoperative outcomes. Important components of myocardial protection include optimal cardioplegia delivery and hypothermia. Researchers around the world have been looking into various aspects of the solution as well as the best routes of administration for example (warm versus tepid, blood versus crystalloid, continuous versus intermittent and retrograde versus antegrade). Despite all this, the antegrade approach is the most commonly used method in many centres.

In patients with significant coronary artery disease, delivery of antegrade cardioplegia alone can impose a problem as inadequate cardioplegia is able to pass through the stenotic vessels. Retrograde can be used, although risk of injuring the coronary sinus during introduction of the retrograde cannula is there. Apart from this retrograde cardioplegia delivery offers poor protection to the anterior aspect of the right ventricle and posterior septal regions, thus hindering the process of adequate myocardial protection. Although there are papers suggesting that simultaneous antegrade and retrograde cardioplegia offers better myocardial protection as compared to antegrade alone, this is something not routinely practiced at our centre [13].

Therefore, we believe that simultaneous infusion of cardioplegia both via the aortic root and vein could be a potential solution for better myocardial protection, especially for the group of patients in this study (EF of less or equal to 35%). Theoretically, delivery of cardioplegia through the vein after completion of each distal anastomosis should be superior as compared to antegrade alone due to the ability of the solution to be delivered beyond the stenosis as proven by a study by Lu *et al*., mentioned that passive graft perfusion (PGF) increases flow to the myocardium and therefore, shortens ischemia time [14].

In this study, myocardial protection is reflected through certain parameters which includes intra-operative variables such as hospital stay after surgery, ICU stay, number of inotropes before coming back to the ICU, VT/VF on aortic unclamping, post-operative mortality, post-operative atrial fibrillation and IABP insertion during the post-operative phase.

We notice that the mean number of inotropes before reaching the ICU was higher in the control group as compared to the study group. This could imply post-operative low cardiac output syndrome needing a higher number of inotropes; however this may not be the sole cause. Other factors such as post-operative vasodilation, poor surgical revascularization and various degrees of stenosis involving coronary vessels may be the confounding factor for this. Difference in surgical technique in both groups can also be a contributing factor. Variation in speed of surgery between two different surgical teams can lead to difference in CPB time as well as aortic cross clamp time, which can correlate to outcomes other than expected.

The higher mean volume of cardioplegia solution seen in the study group may be due to the fact that cardioplegia is infused both via the antegrade route as well as through the vein as compared to the control group. The rate of VT/VF in the control is double if compared to the study group (4 versus 2, p=0.42). Again, no statistical significance is shown here and clinically, VT/VF after aortic unclamping may have various causes such as air in the coronaries and poor surgical revascularization which not necessarily implies poor myocardial protection and this is usually a temporary phenomenon. Nevertheless, the lower rate seen in the study group may imply better myocardial protection.

The length of hospital stay and ICU stay is numerically higher in the control group versus the study group although no statistical significance is obtained. This may indicate a slightly stormier post-operative period in patients receiving antegrade cardioplegia alone due to the inadequacy of myocardial protection. However, as the difference is not profound, other factors may play a role in extending the hospital and ICU stay such as post-operative sepsis, lung pathology delaying extubation, post-operative stroke, bleeding, etc. Therefore, it is difficult to confidently conclude that the prolonged hospital and ICU stay in the control group is solely due to impaired myocardial protection. The mortality rate between both the groups were fairly similar, implying that one method is not superior to the other. The same implies the post-operative IABP requirement, re-operation for bleeding and atrial fibrillation which produced similar results between groups.

Enzyme measurement complemented with clinical findings could be a more objective way to analyze the degree of myocardial protection. The measurement of peak troponin levels at various times during the intra- and post operative phase have been used in various other studies. Gonku *et al*., Gokhan Onam *et al*., and Ali Can Hatemi *et al*., in their study included preoperative, intraoperative and postoperative cardiac enzyme levels to measure degree of myocardial injury. The higher the levels of troponins released indicate higher degree of myocardial trauma which indirectly reflects higher myocardial damage. That may also translate to inadequate cardioplegia delivery. However, as no biochemical markers are taken in this study, we

believe it may be one of the limitations of this study and perhaps in future studies, these biochemical markers would help us deduce a more definite conclusion.

Gokhan Onem *et al*., in their study concluded that simultaneous antegrade and vein cardioplegia is better than antegrade alone. The difference with our study is that the ejection fraction of patients in our study is 35% and below as compared to Gokhan Onem *et al*., which included patients of various ejection fractions. We believe that the lower ejection fraction to start off with may be a factor of difference in myocardial recovery during the post-operative phase. Merzhad Sharifi *et al*., demonstrated that patients with an ejection fraction if less or equal to 30% showed a higher ICU stay as compared to those with above 30%, showing that impaired ejection fraction is an independent risk factor for delayed myocardial recovery and similar results were demonstrated in our study.

In terms of study limitations, we believe that our study had two main limitations which we will look into in the coming future. First of all, we believe that the power of the study may be a factor to the observed outcome. By increasing the number of sample sizes, perhaps the outcome may be different. Although the sample size obtained in this study is calculated using the sample size calculator which includes ten percent of dropout rate, increasing the study subjects will definitely increase the power of the study. Secondly, by incorporating biochemical values to this study, we believe that the results obtained can provide a more objective insight as to the degree of myocardial protection. The measurements of troponin I to measure the degree of reperfusion injury adds value to the data. As these are the limitations of the study, we are confident that in the future, these factors will be looked into.

CONCLUSION

This study shows no difference in myocardial protection between patients that received antegrade combined with vein cardioplegia compared to those who received antegrade alone. As most of the study outcomes, both intra and post-operative showed no statistical significance, we accept the null hypothesis. Troponin I measurements as well as increasing the study power in the future will surely be the way to go in objectively determining the degree of myocardial protection between these two groups.

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