Should We Give Combined Antegrade-Retrograde Cardioplegia Rather Than Antegrade Alone in Patients with Left Main Coronary Disease?

[1] Nasr Hegazy , Khaled Fawzy , [2] Mostafa El-Hamamsy , [3] Abdelsalam Elhenawy

[1] Anaesthesia Dept., Faculty of Medicine, Ain Shams Univ., Egypt.
[2] Anaesthesia Dept., Faculty of Medicine, El-Fayum Univ., Egypt.
[3] Cardiac surgery Dept., Faculty of Medicine, El Azhar Univ., Egypt.

Abstract: There is still a debate about the cardioplegia administration method in patients with left main coronary disease. This prospective randomized study compared clinical, echocardiographic, markers of myocardial damage, morbidity and mortality in 103 consecutive patients with left main coronary artery disease treated with 2 different ways of giving the cardioplegic solutions. Patients were allocated into 2 groups according to the route of cardioplegia administration: combined antegrade-retrograde in 52 patients (group A) and antegrade alone in 51 patients (group B). The biochemical markers for myocardial damage showed statistically higher values in patients who underwent antegrade cardioplegia alone (group B) ($P< 0.05$) , however, its levels never fulfilled the criteria of perioperative myocardial infarction. Postoperative recovery of left ventricular ejection fraction and wall motion score index did not differ significantly between the 2 groups.It was concluded that The combined antegrade-retrograde route of giving cardioplegia reduces ischemic injury and permits early recovery of myocardial function more than giving antegrade alone in patients with left main coronary artery disease.

Key words: Coronary artery surgery, left main coronary, antegrade cardioplegia, retrograde cardioplegia.

Corresponding Author: Mostafa El-Hamamsy, Anaesthesia Dept., Faculty of Medicine, El-Fayum University, Egypt. E mail: mostafah30@hotmail.com

INTRODUCTION

The myocardium distal to complete coronary artery occlusion is not well protected by antegrade cardioplegia (Jasinski et al,.1997) and the preferential way of giving cardioplegia for myocardial protection strategy in patients with severe coronary artery disease is still under debate. Some of cardiac surgeons suggest routine use of retrograde cardioplegia administration (Jasinski et al,.1997 and Carrier et al,.1997) , and others prefer the antegrade route (Ihnken et al,.1994 and Chocron et al,.1996) . This controversy arises due to large amount of clinical, biochemical, and histological studies that have been performed during the last 2 decades. Partington and his group in 1989 argue that experimental studies on retrograde cardioplegia performed in canine model may be of questionable relevance because of the different anatomy in dogs that has predominant venous drainage through thebesian veins rather than the coronary sinus which is not the case in the human being. In human, retrograde cardioplegic solution is administered through the coronary sinus into the cardiac venous system. Most of the veins in the heart drain to the right atrium through the coronary sinus. However, a smaller part of the cardiac venous return drains directly to the cardiac chambers through the anterior cardiac veins and the thebesian veins (venae cordis minima), particularly in the right side (Ansari,2001) . Our study was designed to determine if using combined antegrade-retrograde cardioplegia is associated with better clinical outcome than usage of antegrade technique alone.

PATIENTS AND METHODS

Approval for this study was granted by our institutional review board, and all patients gave their written and informed consent before going for surgery. Between August 2005 and April 2008, a total of 103 consecutive patients had met our inclusion/exclusion criteria table (1) with left main coronary artery disease undergoing coronary artery bypass grafting were recruited into 2 groups according to the route of cardioplegic administration: combined antegrade-retrograde in 52 patients (group A) and antegrade alone in 51 patients (group B). They were randomized by drawing pieces of paper from a box. Anesthesia, perfusion and surgery were performed by the same team. In both groups we managed difficulty of weaning off cardiopulmonary bypass (CPB) primarily by dopamine 5–10 µg /kg /min. If difficulty in weaning continued, epinephrine 0.01–0.05 µg/kg /min were added to dopamine. Intra-aortic balloon pump (IABP) was used as the final strategy to wean the patients off CPB. We designed a postoperative protocol to evaluate perioperative myocardial damage after surgery. We recorded the following: the need for inotropic support and/or intra-aortic balloon pump (IABP) during coming-off cardiopulmonary bypass. Also, blood samples were collected at the beginning of the operation and 1, 4, 8, 12,

24, and 48 hours after chest closure, in order to monitor CK-MB isoenzyme and cardiac troponin I (TnI) levels. Serum CK-MB levels were studied by enzymatic immunoassay, troponin levels was assessed by electrochemiluminescence in immunoassay analysis. Electrocardiographic (ECG) tracings were obtained before surgery, upon the patient's arrival in the intensive care unit, and daily for the first 5 postoperative days. In addition to that, we did two-dimensional transthoracic echocardiography preoperatively and before hospital discharge. Diagnosis of myocardial infarction (MI) was made based on detection of peak (TnI) greater than 3.7 ng/L, TnI concentration greater than 3.1 ng/L at hour 12 as determined by (Mair et al,.1994) , an increase in CK-MB level more than 100 IU/L, newly appearing Q-wave, the disappearance of R-waves on 2 consecutive postoperative ECG tracing or new wall motion abnormality detected in echocardiography. Post-operative renal insufficiency was defined as serum creatinine level >2 mg/dl or rising in serum creatinine more than 0.5 mg/dl compared with preoperative level.

Anaesthetic technique :

All patients received premedication with sublingual lorazepam 2mg 1-2 hours before surgery. Anaesthetic technique was standardized to include fentanyl 10-20ug/kg, midazolam 0.1mg/kg, pancuronium 0.15 to 0.20mg/kg, and isoflurane 0.5% to 1.5%.

All patients received tranexamic acid 50 mg/kg intravenously after induction of anaesthesia. Each patient was monitored with intra-arterial catheter for continuous blood pressure monitoring. A pulmonary artery catheter (Swan-Ganz thermodilution catheter, Baxter International, Santa Ana,CA) was used. It provided continuous pulmonary artery pressure and central venous pressure monitoring, intermittent pulmonary capillary wedge pressure monitoring, and thermodilution cardiac output determination. Urinary catheter for monitoring urine output and serial blood gas analysis up to the discretion of the attending anaesthesiologist. After surgery, patients were transferred to the ICU for postoperative ventilation .Sedation was achieved with propofol infusion 0.5- 2 mg/kg / hour and morphine boluses. Patients were extubated according to the standard criteria.

Operative Technique and Management of CPB:

All the operations were performed via a median sternotomy and using cardiopulmonary bypass machine. The left internal mammary artery (LIMA) was used for revascularization of the left anterior descending coronary artery, and saphenous vein grafts were used for the others. After aortic cannulation followed by 2-stage atrial cannulation, a 14F retrograde coronary sinus perfusion catheter (Edwards Lifesciences Research Medical Corporation; Midvale, Utah) with a self-inflating balloon was inserted by palpation of the coronary sinus, just before restoration of (CPB). If necessary, the catheter was repositioned until the middle cardiac vein was filled, when cardioplegic solution was administered. Cardiopulmonary bypass was instituted using moderate haemodilution with a haematocrit level of 20% to 25% and mild systemic hypothermia (rectal temperature, 30–32 °C). Pump flows were 2.0 to 2.2 L/min/m^2, and the mean arterial pressure was maintained between 50 and 60 mmHg, with administration

of sodium nitroprusside or phenylephrine hydrochloride as required. In group A, the left ventricle was consistently vented through the ascending aorta. All proximal anastomoses were performed on cross-clamped aorta.

Myocardial Protection:

The delivery system for cardioplegic solution was a Y-shaped line with stop-cock on the incoming limb which used for directing the cardioplegic solution antegrade to the aortic root (in both groups) or retrograde to the coronary sinus catheter in group A only. The temperature of the blood collected for blood cardioplegia solution was 4°C s at a 4:1 blood: solution ratio.

After cross-clamping the ascending aorta, we accomplished induction of cardiac arrest in both groups by giving cardioplegic solution contained blood (1000 mL), potassium (30 mEq/L), sodium bicarbonate (10 mEq/L), and magnesium sulphate (6 mEq/L) delivered into the aortic root (the whole liter in group B) ,and half in group A, followed by coronary sinus infusion of the other half at a pressure of 70 mmHg in the aortic root and at less than 40 mmHg in the coronary sinus. The maintenance solution contained blood (500 mL), potassium (10–12 mEq/L), and sodium bicarbonate (5 mEq/L) which was given with an antegrade infusion in group B and retrogradely through the coronary sinus in group A every 20 minutes. The adequacy of cannula positioning was confirmed by observing distension of the posterior interventricular vein, maintaining coronary sinus pressure, and palpating the coronary sinus cannula.

Statistical Analysis :

All data were collected in a prospective manner and were expressed as mean ± standard deviation (SD). Analysis of continuous variables was performed with Student's t-test, and that of repeated measures was performed with the 2-way analysis of variance test. Categorical variables were expressed as percentage and were compared by χ^2 statistical analysis. All analyses were performed using SPSS software, version 9.0 (SPSS, Inc. Chicago, IL). Results were considered significant when P values < 0.05.

RESULTS

Both groups were comparable regarding the perioperative characteristics, as shown in table (2). There was no significant difference between the two study groups in gender, age, extension of the disease, pre-operative ejection fraction and comorbidities (diabetes, hypertension and recent MI). The number of patients who did not require any inotropic support was statistically significantly higher (P< 0.05) in the combined cardioplegia group table (3), furthermore, eleven patients in Group B (22%) and no patient in Group A needed IABP insertion (P< 0.05). As shown in table (3), there was only one patient demonstrating postoperative atrioventricular block in group A versus 16 patients in group B(P<0.05) . On the contrary, the prevalence of postoperative paroxysmal atrial fibrillation was higher in group B. However, all patients were

discharged with normal sinus rhythm, and no complication of atrial fibrillation was recorded during the hospital stay. The biochemical markers for MI showed no statistical difference in terms of TnI starting from postoperative hours 12 to 72. No patient had renal failure and only one patient in Group B died in the ICU on the fourth post operative day due to massive pulmonary embolism, as diagnosed by spiral CT. ICU stay, hospital stay and pre discharge ejection fraction were similar in both groups.

Table 1: Inclusion/Exclusion Criteria

Inclusion Criteria	***Exclusion criteria***
Left main coronary stenosis Proximal stenosis of coronary arteries 3 vessels disease	Redo Patients Two or single vessel disease Preoperative unstable hemodynamic state Ejection fraction < 30% Dialysis patients or Hepatic failure Cancer or Autoimmune disease

Table 2: Preoperative characteristics for both groups:

	Group A (N.52)	Group B (N.51)	P value
Age (years)	59.1 ± 1.22	58.4 ±1.25	>0.05
Sex (male/female)	35/17	33(65)	>0.05
Diabetes n(%)	31(60)	28(55)	>0.05
Hypertension n(%)	31(60)	32(62)	>0.05
Unstable angina n (%)	19(37)	16(31)	>0.05
Left main disease (50-75%) n (%)	44(85)	41(80)	>0.05
Left main disease >75% n (%)	8(15)	10(20)	>0.05
Preoperative EF	41.2±2.57	39.4±1.66	>0.05
Wall motion abnormality n(%)	4(7)	3(6)	>0.05
Indexed left ventricular mass %	29	26	>0.05

Data are presented as mean ± SD or percentage , No Statistical significant difference.
MI= myocardial infarction, EF= ejection fraction

Table 3: Intraoperative data for both groups:

	Group A (N.52)	Group B (N.51)	P value
Cardiopulmonary bypass time (min)	82.6 ±9.1	78.9±8.6	>0.05
Aortic cross clamp time (min.)	46.4±19.1	40.9±8.6	>0.05
Complete revascularization n(%)	51(98)	49(96)	>0.05
Use of Ventricular Defibrillation n(%)	0*	18(35)	<0.05

Need to Inotropes n(%)	1(2)*	19(37)	<0.05
Need to IAPB n(%)	0*	11(22)	<0.05
MI biomarkers:			
TnI at 12 hours	1.81 ± 0.61*	1.13 ± 0.24	<0.05
TnI at 24 hours	1.71 ± 1.16*	0.81 ± 0.36	<0.05
TnI at 48 hours	1.61 ± 1.88*	0.69 ± 0.42	<0.05
TnI at 72 hours	1.17 ± 1.92*	0.49 ± 0.25	<0.05
CK-MB at 12 hours	29.3 ± 66.15*	11.9 ± 69	<0.05
Perioperative Q wave n(%)	1(2)	2(4)	>0.05
Postoperative AV block n (%)	1(2)*	16(32)	<0.05
Atrial Fibrillation n (%)	8(15)*	27(53)	<0.05
ICU stay (days)	1.9±2.5	2.3±8.6	>0.05
Hospital LOS (days)	7.2±1.1	8.1±40	>0.05
Postoperative EF %	54.3±1.03	51.4±1.52	>0.05
Postoperative WM abnormalities n (%)	1(2)	2(4)	>0.05
Renal failure n (%)	0	1(2)	>0.05
Mortality n (%)	0	1(2)	>0.05

Data are presented as mean ±SD or percentage ,* P value <0.05 =Statistical significance

IABP= Intra-aortic balloon pump; MI=myocardial infarction; TnI= cardiac troponin I; AV block= atrioventricular block; EF= Ejection Fraction; WM= wall motion.

DISCUSSION

Different strategies are used to keep the myocardium alive during on-pump coronary artery bypass grafting. Indeed, myocardial protection is an art which depends largely on the surgeon's experience and skills (Mentzer et al ,.2003 and Kouchoukos,2003) . Furthermore, there is no consensus on using an optimal method for the protection of myocardium during ischemic arrest, although it has been debated since the beginning of open heart surgery (Onoratio et al ,.2003) . Myocardial protection during cardiac operations depends on adequate delivery of cardioplegia solution to all regions of the heart (Menasche et al ,. 1982) . The infusion of cardioplegic solution through the aortic root produces very quick diastolic arrest and good preservation of myocardial function. However, when advanced coronary disease is considered, it can result in an unequal distribution and consequently delayed functional recovery (Noyez et al ,.1993) . It can be overcomed by coronary sinus cardioplegia, when the unobstructed coronary venous system can be used as a route for homogenous distribution (Gundry et al ,.1990 and Menasche et al ,.1990) . Previous studies proved some advantages of retrograde blood cardioplegia perfusion which were: (1) protection in areas distal to severe occlusion and ungraftable vessels (Menasche et al ,.1990) ; (2) even protection and cooling of entire heart (Fiore et al ,.1989 and

Partington et al ,.1989) ; (3) establishment of aerobic arrest (Partington et al ,.1989) ; and (4) elevation of the heart and dissection of coronaries while giving cardioplegia (Menasche et al ,.1991) .

We noticed that, delay in cardiac arrest is a major disadvantage of retrograde cardioplegia due to prolonged initial infusion interval, and this may cause a reduction in high-energy metabolites and late ventricular dysfunction. In the present study, this problem was solved by initial aortic root cardioplegia to achieve early diastolic arrest in both groups and followed by coronary sinus infusion in group A(Fiore et al ,.1989 and Partington et al ,.1989) . The results of this study showed that combined delivery of blood cardioplegia shows a significantly lower level than the antegrade alone of postoperative TnI until the third postoperative day, which was also associated with a significantly lower release of CK-MB mass at 12 hours postoperatively. This increase in myocardial damage in the antegrade alone group coincides with (Onoratio et al ,.2003) who demonstrated that the combined route of intermittent blood cardioplegia allows better results in left main stem disease. Atrial fibrillation and ST segment changes after cross-clamp removal were more frequent when cardioplegia was given antegradely only. These can be explained by reperfusion injury due to inadequate distribution of cardioplegia, especially to the subendocardial area. These findings correspond with many investigators (Bhayana et al ,.1989 , Page et al ,.1992 , and Seitelberg et al ,.1994) . In the combined group, sinus rhythm was found more frequently. Those patients without sinus rhythm presented with nodal or bundle branch block, which again were less frequent in the combined group. One of the explanations of the development of the conduction defects is ischemic injury to the conduction system, and it is widely accepted as a complication of myocardial infarct (Seitelberg et al ,.1994, Arom et al ,.1994, and Jain 1995) . In a recent study done by (Radmehr et al ,.2008) he studied retrograde continuous infusion of cardioplegia by gravitational force combined with antegrade cardioplegia, showed satisfactory myocardial protection and eliminates the need for inotropic support compared with antegrade technique alone that coincide with this study.

Although major clinical end points such as hospital mortality, postoperative renal failure, ICU and hospital stay did not reach statistically significant differences between the 2 groups, the requirement of postoperative inotropic and intra-aortic balloon pump support were significantly lower in combined delivery group.

CONCLUSION

According to this clinical, prospective and randomized study, it was concluded that combined administration of retrograde and antegrade cardioplegia has a great protective effect on myocardial cells and would diminish both MI and the need for inotropic and mechanical support during and after CPB weaning.

Study limitations

Although our study is clinical, prospective and randomized but it still has some limitations since it is one center experience and only 103 patients. Therefore we recommend a big multicenter study.

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