Is there any benefit of preoperative oral trimetazidine in Coronary Artery Bypass Graft?

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Abstract

Objective: To evaluate the impact of preoperative oral trimetazidine on myocardial protection in coronary bypass surgery.

Methods: We conducted a prospective double blind randomized study in the Department of Cardiac Surgery, Chaudhry Pervaiz Elahi (CPE) Institute of Cardiology, Multan, Pakistan. One hundred and seventy (170) patients of isolated CABG were included in the study. All operations were done by conventional technique of CABG using cardiopulmonary bypass, moderate systemic hypothermia and cold antegrade blood cardioplegia. The patients were randomized into 2 groups i.e. Group 1 (n=85), who received and Group 2 (n=85), who did not receive Trimetazidine. Trimetazidine (20mg) was given orally, at 10:00 pm the night before operation and also at 7.00 am on the day of surgery. The CPK and CK-MB levels were determined before operation, immediately after shifting to the ICU, 12 hours and 36 hours after the operation. The comparison of CPK and CK-MB levels was carried out using analysis of variance with repeated measures. The peri-operative clinical and laboratory data were compared using Student's t-test for numeric variables and Chi-square test for categoric varaibles. The difference was considered statistically significant if the p-value was < 0.05.

Results: The pre-operative variables i.e. age, gender, Canadian Cardiovascular Society (CCS) class, ejection fraction, diabetes, history of smoking, haemoglobin level, serum creatinine etc had no differences in both group. Both groups showed no significant difference in Cardiopulmonary Bypass time (BPT), Aortic cross Clamp Time (CxT), prevalence of intra-operative arrhythmia and need for inotropic support. The analysis did not show any within group or between groups differences in the CPK and CKMB levels.

Conclusion: This study showed that oral Trimetazidine given before coronary bypass grafting did not provide any benefit in myocardial protection.

Keywords: Trimetazidine, CABG, Myocardial protection. (JPMA 62: 1271; 2012)

Introduction

Ischaemic-reperfusion injury during conventional open heart surgery is an entity widely discussed and elaborated in literature.[1,2] The strategies of myocardial protections are primarily based on the concepts of minimizing the impact of Ischaemic- reperfusion injury by enriching the cardioplegia solutions with agents that can block the effects of free radicals.

Trimetazidine has recently emerged as a drug with anti Ischaemic potential.[3,4] It is claimed to reduce intracellular influx of calcium, intracellular acidosis, inflammation, and generation of oxygen-derived free radicals after reperfusion[5,6] without any significant haemodynamic effects.[7] The cytoprotective properties of trimetazidine makes it a favourable candidate for mitigating the effects of Ischaemic-reperfusion injury during open heart surgery. However, till now the beneficial effects of trimetazidine in coronary bypass surgery have failed to reach a consensus. The present study was designed to evaluate the potential benefits of oral trimetazidine in myocardial protection during coronary bypass surgery.

Patients and Methods

A prospective randomized, placebo controlled study was conducted between February-2010 and January-2011, in the Department of Cardiac Surgery, Chaudary Pervaiz Elahi Institute of cardiology (CPEIC) Multan, Pakistan. The CPEIC is a tertiary care center of cardiology and cardiac surgery and is presently performing over 1000 open heart surgeries annually. The patients were explained the details and informed consent was taken. The study was conducted in strict compliance of the rules established by the revised Helsinki convention and had approval from the clinical audit and research committee of the institute.

In order to calculate the sample size we reviewed our electronic data base which had the records of over 1200 CABG operations. This data showed that the mean±standard deviation of the peak CKMB level reached within 24 hours of CABG was 48±22 IU/l. Assuming that

a meaningful beneficial effect of trimetazidine should reduce the CKMB level by at least 30% of this value, the anticipated CKMB level in the study group was 36 IU/l. This value was nearly 50% above the cut-off value given by the manufacturer of the CKMB test kit for diagnosing myocardial injury in non-surgical cases. It was therefore well within desirable range of good myocardial protection. At α-value of 5% and 80% power of study (1-β) the sample size was calculated as 53 patients in each group. To make our results more robust we decided to include at least 85 patients in each group i.e. 30% more than the calculated sample size.

Patients undergoing elective, isolated CABG were included in the study. Following exclusion criteria, were, observed in order to achieve matching epidemiological and clinical profiles of patients across the study groups:

The redo operations; those who required more than 4 grafts or less than 2 grafts; patients already taking trimetazidine as anti-Ischaemic drug; presence of serious co-morbidities like carotid artery disease, renal failure and previous stroke; patient who underwent coronary endarterectomy during the operation; off-pump or on- pump beating CABG; patients who were started as beating heart surgery and then converted to conventional on-pump CABG; patients who had postoperative neurological complications like stroke or acute confusional states; intra-operative injury to atrium or ventricles; those who needed peri-operative open or closed cardiac massage.

These exclusion criteria were designed to effectively exclude as many reasons as possible of CPK/CKMB rise or fall other than Ischaemic-reperfusion injury of the heart.

The patients were randomized into the following two groups by using block randomization technique because block randomization is helpful in keeping similar number of subjects in both groups i.e. Group 1: Patients who received trimetazidine and Group 2: Patients who did not receive trimetazidine.

At the outset of study, we defined 25 blocks of 4-patients in each block. Each block had a randomized sequence of two patients who received trimetazidine and two who did not receive it. The patients were then enrolled in the study according to these sequences from Block-1 to 25. This made a total of 100 patients in each group. Those patients who exhibited exclusion criteria during the study were removed from the list. After this first 85 patients in each group were finally included in the analysis.

Patients in Group-1 were given 20 mg of Trimetazidine orally, at 10:00 pm the night before the day of operation and also at 7.00 am i.e. one hour before surgery. Trimetazidine and the placebo tablets were coded by one of the authors and were given to the nurses who handed out preoperative medicines to the patients. The nurses and the patients were blinded to the drugs. The surgeons who operated upon the patients and the authors who analyzed the data also remained blinded of the this information. The code was disclosed after the results of analysis were produced.

The CK-MB and CPK levels were determined at four points of time i.e. before operation, immediately after shifting to ICU, at 12 hours and after 36 hours. The reagent used for determining the serum CPK/CK-MB levels was the product of Merck (Merck, France) and the designated reference value for detection of myocardial damage were >25 units/liter for CK-MB. While, the reference value of CPK for the same purpose was >171 units/liter for men and >145 units/liter for women.

The operations were carried out by four teams with independent consultants, at our institution, who are certified cardiac surgeons with sufficient experience. The operating surgeon remained unaware of the information regarding which of their patients had received preoperative trimetazidine.

Patients were premedicated with oral dose of 3mg bromazepam the night before surgery. Anaesthesia was induced with intra-venous morphine (0.1mg/kg), midazolam (0.05-0.1 mg /kg), and propofol (1.0-2.5 mg/kg titrated according to the response. They were given atracuronium (1mg/kg) before endotracheal intubation. The anaesthesia was maintained with sevoflorane/isoflurane. Further, supplementation of analgesia and paralyzing agent were given as needed. In all patients the standard cardiopulmonary bypass (CPB) was established with aortic and 2 stage right atrial cannulae.The CPB circuit was primed with crystalloid Ringer's solution. Heparin was administered in a dose of 300 U/Kg. The body temperature was lowered to 30-32°C. The local cooling was achieved with ice cold saline. Cold blood cardioplegia was given through cardioplegia cannula in the ascending aorta and was repeated every 20 minutes. The first dose of cardioplegia was 10-15ml/kg and further doses were given as 5-7ml/kg repeated every 20 minutes.

During ICU stay all patients had invasive and non-invasive haemodynamic monitoring. All patients underwent elective mechanical ventilation until they were ready for extubation after surgery in the ICU. They were shifted to a high dependency unit in the morning of the first postoperative day unless they required an extended ICU stay because of either respiratory support or intense ICU monitoring.

Over 200 patient characteristics were prospectively entered in our electronic database (CASCADE DATABASES, Lahore, Pakistan). The study specific data not included in the database were separately entered in a

Microsoft Excel spreadsheet (MS Excel, version 2007, Microsoft Co USA). The statistical analysis was carried out using SPSS (SPSS version 15, SPSS Inc, Chicago, IL).

The preoperative, operative and postoperative characteristics were summarized using means and standard deviation for the numeric variables. The groups were compared using Student's t-test for numeric variables and Chi-square test for categoric variables. The analysis of variance with repeated measures were used to compare the trends in rise and fall of CPK and CK-MB levels. The significance of difference between the groups was expressed as p-value and a value of <0.05 was considered significant.

Results

Preoperative, operative and postoperative characteristics of patients are summarized in Table 1 and 2. A total of 170 patients were included in the study i.e. 85 in each group. There were no significant differences between the two groups regarding their preoperative characteristics i.e. age, pre-operative body mass index, body surface area, haemoglobin, serum creatinine and ejection fraction. Majority of patients in both groups were in Canadian Cardiovascular Society (CCS) class III. Mortality risk estimation scoring systems revealed that patients in both groups had no statistically significant difference in operative risk of mortality. Moreover, there was no difference in the risk factors of coronary heart disease in both groups.

Table-1 and 2 also show that both groups were similar with respect to number of vessels revascularized, cardiopulmonary bypass time and aortic cross clamp time. Four patients in each group developed ventricular fibrillation after removal of cross clamp. There were no differences between groups in post operative outcome in terms of need for inotropic support, intra aortic balloon pump (IABP), ventilation time, ICU stay, post-operative chest drainage, pulmonary complications and hospital stay. The difference in mortality was not statistically significant in both groups.

The peak CK-MB level in 24 hours was

Table-1: Summary Statistics: Categoric Variables.

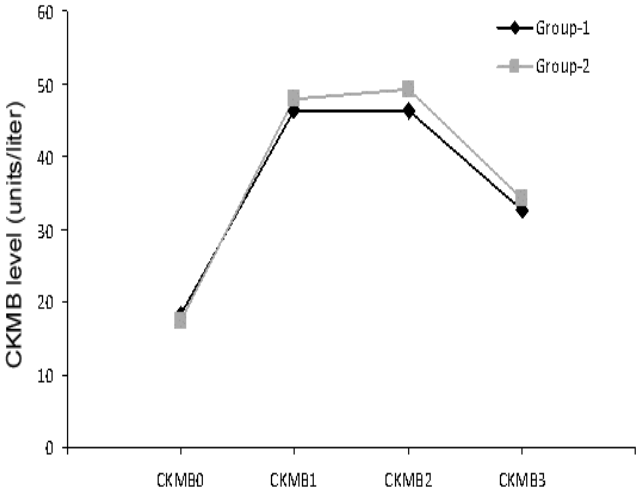
Variable		Group 1	Group 2	P-value
Gender	Male	69	79	0.02
	Female	16	6	
CCS Class	Asymptomatic	1	4	0.26
	I	0	2	
	II	12	6	
	III	67	67	
	IV	5	6	
Hypertension	Yes	34	35	0.88
	No	51	50	
Diabetes	No	48	56	0.33
	Controlled on insulin	10	10	
	Controlled on tablets	27	18	
	Diet controlled	0	1	
Hypercholestrolaemia	No	72	69	0.42
	Controlled on statins	8	5	
	Controlled on diet	0	2	
	Uncontrolled	1	2	
	Unknown	4	7	
Smoking	Non-smoker	45	42	0.81
	Ex-smoker	35	39	
	Smoker	5	4	
Family History of CAD	No	56	63	0.63
	Yes	27	21	
	Unknown	2	1	
History of COAD	No	82	80	0.47
	Yes	3	5	
No. of Grafts	2	6	14	0.15
	3	30	38	
	4	39	33	
Pulmonary Complications	Yes	8	9	0.76
	No	77	76	
Death	No	85	84	0.31
	Yes	0	1	

(CAD= Coronary Artery Disease; COAD= Chronic Obstructive Airway Disease). CCS= Canadian Cardiovascular Society.
Legend: group 1: patients received trimetazidine, while group 2; did not receive trimetazidine. The pre-operative chrematistics have been described.

Table-2: Summary Statistics: continuous variables.

Variable	Group 1 (n=85) Mean S.D	Group 2 (n=85) Mean S.D	P
Age (years)	54.41±8.76	54.8±10.79	0.79
Pre-Op Creatinine (mg/dl)	0.94±0.19	0.94±0.18	0.85
Pre-op Haemoglobin (g/dl)	12.31±1.8433	12.556±1.82	0.38
Height (cm)	165.51±8.642	165.22±8.73	0.83
Weight (cm)	72.79±14.12	71.79±12.37	0.62
BMI (kg/m2)	26.63±4.95	26.35±4.36	0.69
BSA (m2)	1.82±0.19	1.81±0.18	0.67
EF %	51.59±11.39	50.47±10.14	0.5
Parsonnet Score	4.2±3.25	4.05±3.8	0.78
Additive EuroScore	1.16±1.22	1.28±1.368	0.56
Logistic EuroScore	1.37±0.66	1.45±0.75	0.47
Bypass Time (min)	106.79±26.83	101.22±25.61	0.17
Cross Clamp Time (min)	59.44±15.22	58.47±15.17	0.68
No of grafts	3.39±0.62	3.22±0.71	0.11
Ventilation Time (hours)	5.89±7.61	5.47±2.42	0.63
Inotrops (hours)	10.8±15.15	12.86±15.29	0.39
ICU Stay (hours)	42±18.99	36.24±14.5	0.03
Chest Drainage (ml)	756.99±446.68	744.8±418.37	0.86
CK-MB0 (units/liter)	18.13±10.62	17.33±5.91	0.54
CK-MB1 (units/liter)	46.36±22.68	47.95±33.98	0.72
CK-MB2 (units/liter)	46.29±65.99	49.25±40.14	0.72
CK-MB3 (units/liter)	32.64±19.85	34.24±16.34	0.57
Peak CKMB in 24 (hours)	41.84±22.20	52.99±46.36	0.05
CPK0 (units/liter)	154.67±217.58	128.65±192.00	0.41
CPK1 (units/liter)	604.99±364.11	573.52±335.68	0.56
CPK2 (units/liter)	868.94±728.86	938.62±642.62	0.66
CPK3 (units/liter)	678.58±547.09	645.74±475.07	0.63

BMI: Body mass index, BSA: Body surface area.



Legend: group 1: received trimetazidine and group 2 did not receive trimetazidine, night before surgery and at 7am on day of surgery (CABG: Coronary Artery Bypass Graft).

Figure: Serial CKMB Levels (units/liter) after CABG Operation.

significantly higher (p value=0.05) in control group (Table-2). Table-2 also shows comparison of serial CK-MB and CPK levels between both groups. The ANOVA with repeated measures confirms that there was no significant difference in the trend of serial postoperative CPK and CK-MB in both groups. Greenhouse Geisser test was used as test of Sphericity which showed an Epsilon value of 0.55 for CKMB and 0.7 for CPK. The test of between subjects effect had a P value of 0.69 for CKMB and 0.92 for CPK. These results confirm that the serial values of CKMB and CPK in both groups have no statistically significant differences. The Figure is the graphic presentation of trend in CKMB levels. It is visually quite obvious that both groups had very similar rise and fall in CKMB levels over 24 hours.

Discussion

In normal conditions, the human heart produces energy in the form of ATP molecules mainly from the fatty acid metabolism. According to Stanley[7,8] the number of moles of the ATP produced from glucose oxidation is 12% higher than that produced from fatty acids with less oxygen consumption which may be desirable in ischaemia.[9] During ischaemia, the blood supply to the heart is either reduced or stopped completely resulting in inadequate supply of oxygen, glucose, and fatty acids to the heart.[10] Ischaemia inactivates oxidative phosphorylation, leading to a loss of adenine nucleotides and cytochrome-C, resulting in accumulation of free phosphate, fatty acids, lactic acid, and increased cellular calcium, intracellular acidosis.[11] Upon reperfusion, oxygen interacts with the damaged mitochondrial respiratory chain to produce a burst of free oxygen radicals leading to I/R injury.[12]

Trimetazidine, [1-(2, 3, 4-trimethoxybenzyl) piperazine dihydrochloride (TMZ)] is a metabolic anti-Ischaemic drug that exerts its beneficial effects without altering the haemodynamic function of the heart.[13] TMZ acts by optimizing cardiac metabolism by reducing fatty acid oxidation through the selective inhibition of mitochondrial 3-ketoacyl CoA thiolase. As a result, TMZ decreases Ischaemic stress and improves cardiac performance during ischaemia. At the cellular level, TMZ preserves ATP production and reduces intracellular acidosis and calcium overload and therefore maintains cellular homeostasis.[14] TMZ decreases oxidative damage to mitochondria and protects the heart from I/R-induced damage to mitochondrial respiration.[15] Trimetazidine, acting as an agent of metabolic manipulation, may deflect the energy production from fatty acids to promote glucose and lactate consumption in ischaemia, hence producing

high-energy phosphate with lower oxygen consumption.[16] This mechanism may be able to minimize the Ischaemic dysfunction and improve the heart performance. It has also been shown that TMZ protected post Ischaemic hearts by inhibiting the activation of neutrophils.[17]

The multicenter randomized study conducted by the European Myocardial Infarction Project-Free Radicals Group (EMIP-FR) between 1993 and 1999 studied more than 19,000 patients undergoing thrombolysis for acute myocardial infarction. The study showed that intravenous trimetazidine failed to provide any significant benefit in short- or long-term survival in these patients.[18]

Our study results are contradictory to those reported by Tünerir et al[19] who did a randomized trial on 30 patients. They obtained statistically significant ($p< 0.001$) lower levels of troponin-T and CKMB with Trimetazidine but without any statistically significant difference in haemodynamic functions. The total number of defibrillations were lower in the Trimetazidine group, but without statistical significance. However, they used a different study protocol by giving 60mg of Trimetazidine over three weeks before CABG. In another study reported by Iseken et al,[20] pretreatment with trimetazidine showed some beneficial effects in decreasing myocardial injury during the cardioplegic arrest period in open heart surgery. It showed that postoperative levels of myoglobin, troponin T, CK, and CK-MB were significantly lower in the trimetazidine group than in the control group.

The studies reported in literature have differences in their protocols of TMZ administration.[19,21] Some have given TMZ through oral route while others intravenously. There are also significant differences in dose and time of administration. We gave 2 doses of trimetazidine 20 mg in preoperative period, one at midnight before surgery and second, one hour before going to operating room. This was based on the knowledge that the peak level of trimetazidine was achieved at 3-4 hrs and half life was about 6 hrs and bioavailability of drug after oral intake was upto 90%. Hence we assumed that adequate blood levels of trimetazidine would be available at the time of operation and during operative work on the heart.

Measuring the degree of myocardial insult at cellular level is also a difficult task. The cell injury or death results in leakage of intracellular enzymes. Measuring their levels in blood is an indirect evidence of severity of cellular injury. We recorded preoperative level of CPK and CK-MB in both groups and measured postoperative level of CPK and CK-MB in a serial fashion i.e. immediate after shifting to ICU, after 12 hours and after 36 hours. There can be a criticism about the choice of CKMB as marker of myocardial injury in the presence of more specific markers like troponin-T and troponin-I. Nevertheless one must realize that the study is about comparing the effect in two groups. Since in both groups same marker was detected at similar timings, it should provide reliable comparison.

Our study showed significantly lower level of peak CKMB over 24 hours in Trimetazidine group. But the difference was not statistically significant when serial postoperative CPK and CKMB levels were compared at exact points of time for both groups. The plausible explanation of this discrepancy is that each patient probably reached the maximum value at different point of time. Our results were very similar to the double blind placebo control study done by Vedrine J and colleagues; they gave 40 mg of trimetazidine as an intravenous bolus just before skin incision and then continuous infusion at a rate of 2.5 mg/hour up to the sixth postoperative hour. Moreover, trimetazidine was also added to the cardioplegia solution. They compared fractional area change (FAC), systolic wall thickening (SWT) and left ventricular systolic work index by echocardiography. They also compared serial blood level of malondialdehyde (MDA), CPK and and CKMB. Their study concluded that in patients with a good preoperative ejection fraction undergoing CABG with standard myocardial protection, failed to show any benefit of trimetazidime.[21]

In our study there was no difference in immediate arrhythmias after removal of cross clamp in both groups. The inotropic support needed was similar in both groups and duration of need for inotropic support was not statistically significant. The whole analysis of laboratory and clinical data, suggests that there is no role of trimetazidine in myocardial protection from Ischaemic-reperfusion injury.

Conclusion

This study showed that oral Trimetazidine given before coronary bypass grafting did not provide any benefit in myocardial protection. The incidental finding of lesser increase in peak CKMB level in trimetazidine groups may reflect some benefit, which needs further evaluation.

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