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Trimetazidine May Protect the Myocardium during Cardiac Surgery

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ABSTRACT

Background: Trimetazidine is an anti-ischemic agent with cardioprotective effects. The purpose of this double-blind, controlled, prospective randomized study was to investigate the possible effects of the preoperative use of trimetazidine on the biochemical markers of myocardial injury during open heart surgery and to determine if it has any myocardial protective effects.

Methods: Thirty patients undergoing coronary artery bypass grafting surgery, received either trimetazidine (study group, n = 15) or not (control group, n = 15). Pretreatment began 2 weeks before the operation with trimetazidine (60 mg/day orally), and the control group received no medication. We measured the levels of serum creatine kinase (CK), CK isoenzyme MB (CK-MB), myoglobin, and troponin T in venous blood samples obtained before and after the operation to evaluate the effect of this drug against myocardial damage. We also took serial blood samples from the radial artery and the coronary sinus before the institution of cardiopulmonary bypass (CPB) and at 2 and 15 minutes after the removal of the cross-clamp to measure lactate levels and calculate the lactate extraction of the myocardium.

Results: Postoperative levels of myoglobin, troponin T, CK, and CK-MB were significantly lower in the trimetazidine group than in the control group ($P < .05$). There was also a significant difference in the values for the lactate extraction calculation between the groups at minute 2 after the removal of the cross-clamp ($P < .05$).

Conclusion: We conclude that pretreatment with trimetazidine has some beneficial effects in protecting the myocardium and decreasing myocardial injury during the cardioplegic arrest period in open heart surgery without affecting postoperative hemodynamics.

INTRODUCTION

Numerous studies of myocardial protection during cardioplegic arrest have been published in the literature. The main purpose of these investigations was to preserve myocardial metabolism and thereby protect myocardial contractility. Some drugs provide additional myocardial protection when added to the cardioplegic solutions. In this prospective study, however, we planned to investigate a drug that is used preoperatively. The purpose of this double-blind, controlled, prospective randomized study was to investigate the possible effects of the preoperative use of trimetazidine on the biochemical markers of myocardial injury during open heart surgery and to determine if it has any myocardial protective effects.

1-(2,3,4-Trimethoxybenzyl)piperazine dihydrochloride (trimetazidine) is an anti-ischemic agent that inhibits the long-chain mitochondrial 3-ketoacyl coenzyme A thiolase in the myocyte. This drug can improve cardiac mitochondrial metabolism and is used to treat angina; it has cardioprotective effects without inducing any significant hemodynamic changes [Lopaschuk 2003; Sellier 2003; Kara 2004].

Several biochemical markers can be used to detect myocardial injury and therefore the degree of myocardial protection. Some of these markers are the enzymes creatine kinase (CK) and CK isoenzyme MB (CK-MB), myoglobin, troponin T, and the lactate extraction calculation. These protective effects of the drug in myocardial ischemia suggested that it could be used as additional cardiac protection during cardiac surgery [Stanley 2003]. Therefore, we planned this study to determine the effects of trimetazidine pretreatment on the serum activities and concentrations of biochemical markers of myocardial injury during open heart surgery.

METHODS

Thirty patients undergoing elective coronary artery surgery were enrolled in this study. The study was approved by the local medical ethics committee. All patients gave their informed consent. The patients were randomly divided into 2 groups preoperatively. The study group (group TR, n = 15) received 20 mg trimetazidine 3 times per day (60 mg/day, orally) for 2 weeks preoperatively. This drug regimen was administered as we have previously described [Iskesen 2006]. Patients in group TR received their last dose on the morning of the operation. The control group (group C, n = 15) did not receive this medication preoperatively. Preoperative values did not differ statistically between the groups (Table).

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Pre- and Postoperative Values of the 2 Groups*

Characteristic	Trimetazidine Group (n = 15)	Control Group (n = 15)
Mean age, y	57.5 ± 2.6	60.2 ± 2.1 (*P* = .15)
Men/women, n	12/3	11/4
Monovascular disease, n	2	1
Bivascular disease, n	3	6
Trivascular disease, n	10	8
Mean grafts/patient, n	2.53	2.06
Preoperative EF, %	43.3 ± 3.1	42.1 ± 2.6
Cross-clamp time, min	37 ± 9.2	35 ± 6.4
Perioperative MI, n	0	0
Preoperative CI, L/min per m^2	2.23 ± 0.5	248 ± 0.1

*Data are presented as the mean ± SEM where indicated. There was no statistically significant differences between the clinical characteristics of the trimetazidine group and the control group. EF indicates ejection fraction; MI, myocardial infarction; CI, cardiac index.

Exclusion criteria were severe left ventricular dysfunction (defined as a left ventricular ejection fraction <30% or an end-diastolic pressure of the left ventricle >16 mm Hg); emergency or redo operation; recent myocardial infarction (in the previous 4 weeks); the presence of valvular heart disease, pulmonary disease, renal or hepatic dysfunction, or insulin-dependent diabetes; and an age older than 80 years. The drug is metabolized in the liver and excreted via the urine, and because of its possible effect on the results, patients with renal failure or liver dysfunction were not included in the study. Patients using beta-blockers were also not included in the study because of possible interference with myocardial performance. Patients with hypertension continued to receive their medication until the operation. All operations were performed by the same surgical team. The surgical team and biochemical analysts were blinded with respect to the study medication.

All patient samples and measurements of variables were obtained according to the following schedule. Venous blood samples were collected to determine the serum concentrations of CK and CK-MB preoperatively (T0), at the second postoperative hour (T1), and at the 18th postoperative hour (T2).

Serial venous blood samples for the measurement of serum myoglobin and troponin T levels were collected just before cardiopulmonary bypass (CPB) (T0), at the second postoperative hour (T1), at the 18th postoperative hour (T2), and at the 48th postoperative hour (T3).

To calculate the lactate extraction, we collected blood samples from the radial artery and the coronary sinus just before the initiation of CPB (T0), at the second postoperative hour (T1), and at 15 minutes after removal of the cross-clamp (T2); therefore, we calculated 3 lactate extraction values for each patient. Lactate extraction was calculated with the following equation: Lactate Extraction = (Radial Artery Lactate – Coronary Sinus Lactate)/(Radial Artery Lactate) × 100, where the lactate concentrations are in millimoles per liter.

Standard radial arterial, central venous, and Swan–Ganz catheters were inserted preoperatively. Hemodynamic parameters such as the heart rate, the mean arterial pressure, the central venous pressure, and pulmonary capillary wedge pressure were measured just before the CPB (H0), 10 minutes after removal of the aortic cannula (H1), at the second hour in the intensive care unit (H2), and at the 18th postoperative hour (H3). We also calculated the following hemodynamic values from these findings: cardiac output, cardiac index, systemic vascular resistance index, and left ventricle stroke work index.

CK, CK-MB, myoglobin, and troponin T analyses were performed with an immunoassay kit (Elecsys Systems 2010; Roche Diagnostics, Indianapolis, IN, USA), and the Cobas Integra 400 (Roche Diagnostics) was used for measuring lactate levels. Hemodynamic parameters were measured with the thermodilution technique (cardiac monitors from Datex-Ohmeda/GE Healthcare, Chalfont St. Giles, UK; Datascope/Maquet Cardiovascular, Fairfield, NJ, USA).

Operation

The patients were anesthetized with sufentanil. All operations were done through a median sternotomy under moderate hypothermia. Aortic cannulae and 2-stage venous cannulae were used for perfusion. The retrograde cardioplegia cannula was placed into the coronary sinus via the right atrium. The same anesthetic and cardioplegic protocols were used in all patients. The combination of antegrade and retrograde blood cardioplegia was used in all patients. Our cardioplegic protocol is administered by using cardioplegia solution in a dose of 10 mg/patient weight at first and by repeating its half volume at 20-minute intervals. Our cardioplegic solution is prepared by adding of 40 mEq potassium, 10 mEq magnesium, 10 mEq sodium bicarbonate, and 10 cm^3 20% dextrose into 300 mL of an isotonic saline solution. This solution is mixed with the patient's own blood in a ratio of 1:4 and perfused. CPB was performed with a membrane oxygenator and a roller pump. Heparin was given before cannulation of the aorta (3 mg/kg). The activated clotting time was >400 seconds in all patients. The patient's temperature was reduced to 30°C-32°C. The mean flow rate was nearly 2.4 L/min per m^2. The left internal thoracic artery was used as a graft for the left anterior descending artery, and the greater saphenous vein was used for the other coronary vessels.

Statistical Analysis

Results are expressed as the mean ± SEM. The significance of differences in results between the 2 groups was determined with the unpaired Student *t* test. A difference was considered statistically significant if the *P* value was <.05.

RESULTS

Serum myoglobin and troponin T levels were significantly lower in the trimetazidine-treated patients than in the control

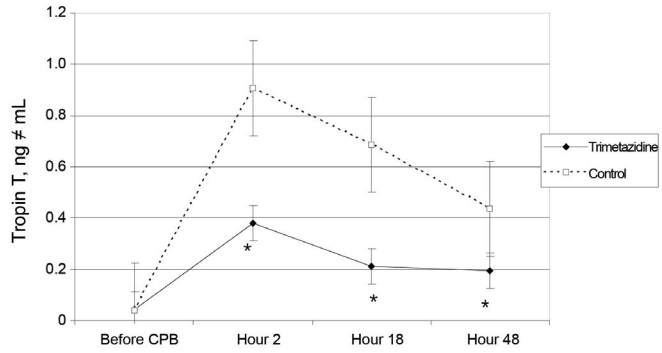

Figure 1. Plasma troponin T levels in the trimetazidine and control groups. CPB indicates cardiopulmonary bypass. *P < .05.

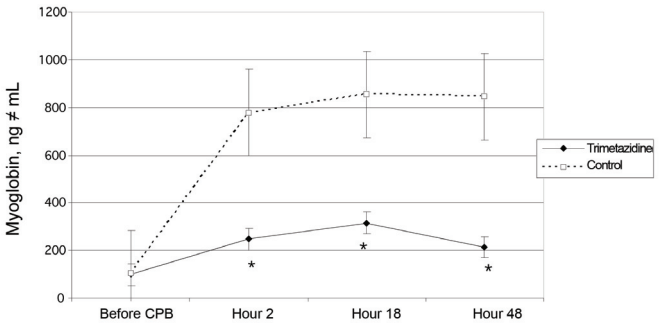

Figure 2. Plasma myoglobin levels in the trimetazidine and control groups. CPB indicates cardiopulmonary bypass. *P < .05.

group. The calculations of lactate extraction also were significantly lower in the trimetazidine-treated group.

Preoperative values were 57.1 ± 4.6 U/L versus 60.2 ± 6.3 U/L (P > .05) for CK and 15.4 ± 1.5 U/L versus 16.5 ± 0.5 U/L (P > .05) for CK-MB in groups TR and C, respectively. Serum CK activity was lower at the second postoperative hour in group TR (345.6 ± 11.4 U/L) than in group C (427.5 ± 29.1 U/L) (P > .05). At the 18th postoperative hour, CK values were significantly lower in group TR (457.5 ± 37.7 U/L) than in group C (874.4 ± 95.5 U/L) (P < .05). Serum CK-MB values were significantly lower in group TR (27.1 ± 3.7 U/L) than in group C (45.7 ± 5.5 U/L) at the second postoperative hour (P < .05). At the 18th hour, CK-MB values in group TR (17.6 ± 4.1 U/L) were also significantly lower than those in group C (49.5 ± 11 U/L) (P < .05).

Preoperative values for troponin T were 0.045 ± 0.01 ng/mL versus 0.040 ± 0.01 ng/mL (P > .05) in groups TR and C, respectively. Preoperative measurements of myoglobin were 99.2 ± 32.4 ng/mL versus 103.4 ± 39.5 ng/mL (P > .05) in groups TR and C, respectively. The serum troponin T value at the second postoperative hour was significantly lower in group TR than in group C (0.38 ± 0.05 ng/mL versus 0.905 ± 0.4 ng/mL; P < .05). At the 18th postoperative hour, the mean troponin T value was also lower in group TR than in group C (0.211 ± 0.05 ng/mL versus 0.685 ± 0.2 ng/mL; P < .05). Measurements of troponin T at the 48th hour were also significantly lower in group TR (0.195 ± 0.03 ng/mL versus 0.435 ± 0.2 ng/mL; P < .05; Figure 1). Myoglobin levels at the 2nd postoperative hour were significantly lower in group TR than in group C (247.6 ± 51.58 ng/mL versus 778.5 ± 175.45 ng/mL; P < .05). The mean serum myoglobin concentration at the 18th hour was also lower in group TR (315.2 ± 35.6 ng/mL versus 854.3 ± 153.5 ng/mL; P < .05). Likewise, myoglobin values at the 48th postoperative hour were also lower in group TR than in group C (213.7 ± 22.4 ng/mL versus 845.8 ± 175.4 ng/mL; P < .05; Figure 2).

Three lactate extraction values were calculated. The 2 groups were not significantly different at T0, which was performed just before starting CPB (5.56 ± 3.5 mmol/L versus 1.41 ± 3.1 mmol/L), but there was a significant difference between the groups for the second lactate extraction calculation at T1, which was performed at the second postoperative minute after removal of the cross-clamp (2.4 ± 1.6 mmol/L versus –2.3 ± 1.6 mmol/L; P < .05). Thus, less myocardial lactate was produced in group TR at the beginning of reperfusion; however, the 2 groups were not significantly different with respect to last lactate extraction calculation performed at T2, which was performed at minute 15 after removal of the cross-clamp (1.56 ± 0.2 mmol/L versus 2.1 ± 0.1 mmol/L); P > .05).

We found no significant differences between the 2 groups with respect to serial measurements of any of the hemodynamic variables. Cardiac index values were 1.7 ± 0.1, 2.35 ± 0.2, 2.5 ± 0.3, and 2.5 ± 0.3 L/min per m^2 for group TR at the H0, H1, H2, and H3 time points, respectively. The cardiac index values for the corresponding time points for group C were 1.6 ± 0.2, 2.2 ± 0.3, 2.3 ± 0.2, and 2.6 ± 0.2 L/min per m^2 (P > .05).

No adverse effect of the drug was detected in any patient. There were no electrocardiographic changes due to myocardial infarction, and there were no deaths in the perioperative period. There were no significant differences between the groups in the requirement for inotropic agents and the use of defibrillation after removal of the cross-clamp. Groups TR and C showed no significant differences in clinical outcomes.

DISCUSSION

The major problem in cardiac surgery is to protect the myocardium against ischemia-reperfusion injury during the period of cardiac arrest. The main purpose of cardioplegia during open heart surgery is to protect myocardial function and metabolism, but there may be some injury to the myocardial tissue that can be detected biochemically. Inefficient and inadequate myocardial protection can lead to myocardial dysfunction and even death despite good revascularization. CK-MB, myoglobin, troponin T, and lactate extraction values are important indicators of myocardial injury. We performed this study in patients undergoing open heart surgery because the best model of myocardial ischemia and reperfusion is the cardioplegia-arrested heart during open heart operation. We have shown that trimetazidine reduces the levels of increments in biochemical markers of myocardial injury during cardioplegic arrest.

We organized this study by administering trimetazidine preoperatively without addition into the cardioplegia solution, because adding this drug into cardioplegia without pretreatment has been demonstrated in animal studies to produce no hemodynamic or metabolic improvement [Silveira 2008].

Regarding the levels of the calculated lactate extraction, we have shown that the production of myocardial lactate was significantly lower in group TR than in group C during early reperfusion. High lactate levels in coronary sinus blood demonstrate that anaerobic metabolism is ongoing. A high value in coronary sinus blood produces a negative value for the equation. A low lactate level in coronary blood in the trimetazidine group at T1 (ie, the second minute) indicates that anaerobic metabolism was controlled and that acidosis in myocardial cells therefore was not increased during the early reperfusion period. We therefore can conclude that trimetazidine is beneficial for suppressing anaerobic metabolism during cardiac arrest and during the early reperfusion period; however, the groups were not significantly different with respect to values at the 15th minute (T2). We therefore can assume the 2 groups were similar with respect to aerobic metabolism during late reperfusion. Similar to our findings, some reports have described an anti-ischemic efficacy for trimetazidine [Stanley 2003].

Trimetazidine is an anti-ischemic agent that functions by partially inhibiting fatty acid β-oxidation and increasing glucose oxidation. It increases the antioxidant capacity and protects against oxygen free radical–induced toxicity [Singh 2004], and it counteracts calcium overload and reduces the area of necrosis [Barsotti 2004]. Trimetazidine has conventionally been used primarily for patients with coronary or cerebrovascular disease and has no effects on coronary flow, contractility, or heart rate, suggesting that it acts by directly improving myocardial energy metabolism. This drug can also bind to mitochondria; it significantly increases the rate of glucose oxidation and reduces the rate of fatty acid oxidation [Stanley 2003].

We investigated the serum concentrations of some selected biochemical markers of myocardial injury in our study. It is known that determinations of serum myoglobin, troponin T, CK, and CK-MB can be used with high sensitivity in patients with acute myocardial infarction injury [Penttila 2002]. In cases of perioperative myocardial infarction, increments of these values may persist during the first 48-hour period. In our study, these biochemical parameters decreased to basal values during this period; however, the values for parameters of myocardial injury in group TR were significantly lower in this period than those in group C. Some studies found that serum CK levels were significantly lower in patients with myocardial infarction who were treated with trimetazidine [Labrou 2007]. Similarly, we found CK, CK-MB, myoglobin, and troponin-T concentrations to be lower in group TR after CPB in our study. Our findings demonstrate the protective effect of trimetazidine pretreatment against myocardial injury during cardioplegic arrest in cardiac surgery. Chronic treatment with trimetazidine has also been shown in animal studies to protect the heart against ischemia-induced arrhythmias and to reduce myocardial infarct size and plasma lactate levels [Kara 2006]. The myocardial protecting effect of the drug may be due to its functioning as a free radical scavenger, which we demonstrated in another study [Iskesen 2006].

There were no statistically significant differences between the groups with respect to the hemodynamic measurements during early postoperative period, in contrast to the results of some previous studies [Belardinelli 2008]. According to these findings, we can say that trimetazidine has a cardioprotective effect and that it can limit or reduce myocardial ischemic damage without any significant hemodynamic effects [Banach 2008].

STUDY LIMITATIONS

Although the number of patients investigated in this study was small, some information could be obtained about the effects of trimetazidine on myocardial reperfusion injury. This study was planned to investigate whether this drug is beneficial for preventing myocardial injury in cardiac surgery patients. The main purpose of this study was to find a useful adjunct therapy for preventing myocardial injury during cardiac arrest. Indeed, we have shown some protective effect of this drug for reducing myocardial injury.

We failed to demonstrate its beneficial hemodynamic effect, possibly because we did not include patients with "poor ventricles" in the study. Some detailed hemodynamic studies may be necessary with a larger group of patients to evaluate this effect.

CONCLUSION

We conclude that preoperative use of trimetazidine has some beneficial effects in protecting the myocardium and decreasing myocardial injury during cardioplegic arrest in open heart surgery. Because of the protective effect of trimetazidine against ischemia-reperfusion injury, we suggest that it can be part of a patient's medical treatment protocol before open heart surgery.

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