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ORIGINAL RESEARCH

The Effects of Postoperative Trimetazidine Treatment on Ischemia-Reperfusion Injury after Isolated Surgical Myocardial Revascularization

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ABSTRACT

Background: Surgical revascularization is the gold standard in the management of patients with multi-vessel coronary artery disease (CAD). It is well known that increased oxidative stress during ischemia-reperfusion and post-revascularization procedures leads to the release of free radical in the circulation. This process can cause reversible or irreversible myocardial damage. **Aim:** The aim of this study was to assess the effect of trimetazidine on decreasing postoperative ischemia-reperfusion myocardial damage. **Material and methods:** This prospective single-blind randomized controlled trial included 90 patients with elective surgery, operated between March 2018 and October 2018. The patients were divided into two equal groups, a study group and a control group; those in the study group received trimetazidine 35 mg b.d., immediately after tracheal extubation, in addition to their regular therapy. Pre- and postoperative levels of specific blood biomarkers such as high-sensitivity troponin T (hs-TnT), creatine kinase-MB (CK-MB), and malondialdehyde (MDA) were evaluated. Patients were followed for a period of 6 months after surgery. **Results:** MDA levels were lower in patients who received trimetazidine, leading to a reduction in oxidative stress and improved cardiomyocyte protection by augmentation of the antioxidant status. The quality-of-life assessment with the Minnesota Living with Heart Failure Questionnaire yielded excellent results. **Conclusions:** Improvement of myocardial cell metabolism and decreasing the level of postoperative ischemia-reperfusion damage is alleviated by postoperative regular trimetazidine therapy.

Keywords: trimetazidine, malondialdehyde, oxidative stress, coronary artery bypass grafting, postoperative results

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BACKGROUND

Coronary artery disease (CAD), including myocardial infarction and its lethal mechanical complications, is associated with a 66% mortality in Bulgaria, being the most common cause of death. Energy metabolism disorders are a common pathological feature of most chronic diseases, including cardiovascular diseases.[1] Recent studies suggest that the development of atherosclerosis and CAD is accompanied by energy reduction and depletion within the main energy producers and cellular metabolism regulators, such as the mitochondria.[2,3]

Mitochondrial dysfunction can directly lead to cell death, inflammation, and oxidative stress. However, even with mitochondrial dysfunction, normal cell metabolism may also persist in a modified state.[4] These pathophysiological modifications can also be observed in the homeostasis of cardiomyocytes, especially during reperfusion

injury in various conditions such as stable or unstable angina pectoris, myocardial infarction, coronary artery bypass grafting (CABG), percutaneous coronary interventions (PCI), and others.

Myocardial reperfusion injury is caused by the generation of free radicals such as superoxide anion and hydrogen peroxide, which are removed from cardiac cells by a series of scavenger enzymes and antioxidants.[5,6] Cellular damage and its potential reversibility are determined by a variety of factors such as the duration of ischemia, the presence of coronary collaterals, early restoration to normal physiological (basal) pH level at the time of reperfusion, etc.[7,8]

Despite successful revascularization through CABG or PCI, a substantial number of patients experience recurrent angina.[9–11] Optimal drug therapy is a key component in the treatment of angina, even after surgical or interventional procedures. First-line anti-ischemic agents include beta-blockers and nitrates, whereas second-line options include medications such as nicorandil, ivabradine, ranolazine, and trimetazidine.[12–14]

Trimetazidine, or [1-(2,3,4-trimethoxy benzyl) piperazine dihydrochloride], is an anti-ischemic drug that provides cardioprotective benefits without affecting coronary blood flow and cardiac contractility. It modulates the heart's metabolism by inhibiting long-chain 3-ketoacyl CoA thiolase, which reduces free fatty acid oxidation and shifts energy substrate utilization from fatty acid to glucose without influencing hemodynamics.[15] This mechanism makes trimetazidine an excellent complementary drug for treating CAD, as it promotes coronary vasodilation and improves endothelial function.[16] An additional short- and long-term advantage of trimetazidine in diabetic patients is decreasing fasting glucose levels without affecting the lipid profile.[17]

The aim of this study was to investigate the effects of trimetazidine on reactive oxygen species generated by myocardial ischemia-reperfusion injury or systemic inflammatory response after surgical coronary revascularization. Several laboratory biomarkers for myocardial damage, including creatine kinase-MB (CK-MB) and high-sensitivity troponin T (hs-TnT), malondialdehyde (MDA) as an indicator of oxidative stress, as well as functional indicators were measured and evaluated over a 6-month follow-up period after CABG.

MATERIAL AND METHODS

We carried out a prospective single-blind randomized controlled trial between March 2018 and October 2018, involving 93 patients who underwent elective isolated CABG. Three patients were excluded because of serious complications that required prolonged treatment in the intensive care unit (acute renal failure requiring continuous vinovenous hemodiafiltration in two cases, and acute respiratory distress syndrome requiring prolonged mechanical ventilation in one case).

The final study cohort consisted of 90 patients (Table 1), who were divided into two groups, a study group and a control group. The study group (n = 45) consisted of 34 male and 11 female patients, who received regular therapy with trimetazidine 35 mg b.d., immediately after tracheal extubation. The control group consisted of 33 male and 12 female patients who received placebo. The remaining drug therapy was identical for all patients in both groups: acetylsalicylic acid 100 mg o.d., rosuvastatin 10 mg. o.d., metoprolol 50 mg b.d., perindopril 5 mg o.d., and gliclazide 60 mg o.d.

Exclusion criteria were the following: emergency or redo-operations, severe left ventricular dysfunction with

TABLE 1. Demographic and preoperative characteristics

Variable	Study group (*n* = 45)	Control group (*n* = 45)	p value
Male sex, n (%)	34 (75.6%)	33 (73.3%)	>0.05
Age (years)	62.97±9.45 (55-72)	64.18±6.54 (52-75)	>0.05
BMI	29.3 (23.1–32.4)	29.6 (24.2-31.9)	>0.05
Diabetes type 2, n (%)	45 (100%)	45 (100%)	>0.05
Arterial hypertension, n (%)	31 (68.8%)	29 (64%9)	>0.05
Hyperlipidemia, n (%)	30 (66.6%)	31 (68.8%)	>0.05
Elective surgery, n (%)	45 (100%)	45 (100%)	>0.05
Patients with implanted stents, n (%)	11 (24%)	14 (31%)	>0.05
Total number of stents deployed, n	16	19	>0.05
EuroSCORE II, mean ± s.d.	1.6 ± 0.4	1.5 ± 0.7	>0.05

TABLE 2. Intraoperative data

Variable	Study group (n = 45)	Control group (n = 45)	p value
CPB time (min), mean ± s.d. (range)	43.7 ± 3.3 (38–51)	43.5 ± 3.8 (38–55)	>0.05
Aortic cross-clamp time (min), mean ± s.d. (range)	27.4 ± 2.5 (22–31)	28.2 ± 2.7 (21–34)	>0.05
Number of bypass grafts performed, n	135	135	>0.05
Venous bypass grafts, n	90	90	>0.05
Off-pump procedures, n	nil	nil	–

TABLE 3. LVEF in the two groups

Variable	Study group (n = 45)	Control group (n = 45)	p value
12 h before surgery (%)	44.1 ± 0.2 (41–51)	45.2 ± 2.7 (41–51)	>0.05
1 h after surgery (%)	43.8 ± 5.7 (38–48)	44.6 ± 3.2 (39–51)	>0.05
On discharge (%)	47.5 ± 2.8 (43–53)	47.8 ± 2.9 (43–55)	>0.05
6 months after surgery (%)	54.4 ± 3.2 (48–62)	53.9 ± 3.0 (49–57)	>0.05

Data expressed as mean ± s.d. (range).

TABLE 4. CK-MB levels in the two groups

Variable	Study group (n = 45)	Control group (n = 45)	p value
12 h before surgery (%)	2.9 ± 0.2 (2.4–3.6)	2.9 ± 0.2 (2.4–3.5)	>0.05
12 h after surgery (%)	37.9 ± 5.7 (29–49)	37 ± 5.9 (27–49)	>0.05
6 months after surgery (%)	3.1 ± 0.4 (2.1–3.8)	3.2 ± 0.3 (2.7–3.8)	>0.05

Data expressed as mean ± s.d. (range).

TABLE 5. hs-TNT levels in the two groups

Variable	Study group (n = 45)	Control group (n = 45)	p value
12 h before surgery (%)	19.9 ± 1.1 (18.3–22.1)	20.5 ± 2.1 (18.3–31.1)	>0.05
12 h after surgery (%)	187.2 ± 8.9 (165–206)	186.8 ± 12.5 (166–221)	>0.05
6 months after surgery (%)	19.4 ± 1.1 (17.9–22)	19.6 ± 1.2 (18.1–22.3)	>0.05

Data expressed as mean ± s.d. (range).

left ventricle ejection fraction (LVEF) below 40%, permanent atrial fibrillation, renal or liver failure, pulmonary disease, and insulin-dependent diabetes.

A series of pre- and postoperative assessments were performed for all patients, including transthoracic echocardiograms 12 h before the operation, 1 h after the operation, on the day of discharge, and 6 months after the surgical myocardial revascularization (Table 2).

CK-MB (Table 3) and hs-TnT (Table 4) blood levels were examined 12 h before, 12 h after, and 6 months after the procedure. Blood samples for MDA evaluation (Table 5) were taken 12 h before, and 12 h, 1 month, and 6 months after the procedure.

To reduce variability in the results, all surgical procedures were conducted by the same surgical team.

OPERATIVE TECHNIQUE

All 90 patients were operated using a standard cardiopulmonary bypass technique with central cannulation of the aorta and he right atrial appendage. Myocardial protection was achieved using intermittent cold-blood cardioplegia, administered via retrograde (sinus venosus) and antegrade (aortic root) route. The aorta was clamped at 32 °C, and the cardioplegic solution was administered into the aortic root via the antegrade route. Distal anastomoses

TABLE 6. MDA levels in the two groups

Variable	Study group (n = 45)	Control group (n = 45)	p value
12- h before surgery (µmol/ml)	236 ± 11 (223–243)	232 ± 12 (219–244)	>0.05
12- h after surgery (µmol/ml)	287 ± 18 (269–303)	284 ± 20 (264–300)	>0.05
1- month after surgery (µmol/ml)	227 ± 9 (211–233)	270 ± 14 (260–282)	<0.05
6- months after surgery (µmol/ml)	211 ± 7 (205–216)	231 ± 13 (221–239)	<0.05

Data expressed as mean ± s.d. (range).

TABLE 7. Postoperative data

Variable	Study group (n = 45)	Control group (n = 45)	p value
Cardiac ward stay (h)	23.4 ± 2.9 (17–29)	23.3 ± 2.6 (18–28)	>0.05
In-hospital stay (days)	6.8 ± 0.8 (5–8)	7.1 ± 0.7 (5–8)	<0.05
Total blood loss (ml)	255.7 ± 60.6 (170–410)	276 ± 66.2 (180–440)	>0.05

Data expressed as mean ± s.d. (range).

were performed using saphenous vein grafts to the right coronary artery and the circumflex artery or marginal branches, while the left internal mammary artery was grafted to the left anterior descending artery.

RESULTS

The demographic and preoperative characteristics of the patients are summarized in Table 1. Mean age at the time of CABG was 62.97 ± 9.45 years in the study group and 64.18 ± 6.54 years in the control group. In total, 34 patients (75.6%) in the study group and 33 patients (73.3%) in the control group were male. All patients had three-vessel CAD. From the study group, 11 patients (24%) had a total of 16 stents implanted, whereas 14 (31%) patients from the control group had a total of 19 stents implanted previously. The European System of Cardiac Operative Risk Evaluation II score (EuroSCORE II) was low in both groups (1.6 ± 0.4 in the study group and 1.5 ± 0.7 in the control group).

Every patient received on-pump CABG. There were no significant differences between the two groups regarding age, sex, body mass index, duration of cardiopulmonary bypass (CPB) and aortic cross-clamp time, or the total number of grafts (Table 2). No in-hospital deaths were recorded. Furthermore, there were no significant differences between the two groups in the baseline values of CK-MB, hs-TnT, and MDA or the preoperative hemodynamic data (Tables 3, 4, 5 and 6). However, there was a significant difference in MDA levels between groups at 1 month and 6 months after surgery.

In summary, the data suggest that although postoperative trimetazidine treatment does not improve LVEF, it does reduce MDA production, thereby lowering oxidative stress and enhancing myocardial cell protection by augmenting antioxidant status.

Regarding overall hospital stay, there was a trend (with marginal statistical significance) for a shorter hospital stay in the study group (Table 7).

The 6-month follow-up after surgery showed no ischemic incidents in any of the patients. Additionally, the quality-of-life assessment with the Minnesota Living with Heart Failure Questionnaire yielded excellent results.

DISCUSSION

Given that the best setting to study myocardial ischemia-reperfusion injury is the cardioplegia-arrested heart during a cardiac surgical procedure, we performed the present study in patients undergoing open heart surgery. Reperfusion of an ischemic area, especially with oxygen, can lead to further tissue damage, termed reperfusion injury. Ischemia-reperfusion injury results in microvascular damage, reversible contractile dysfunction (termed myocardial stunning), and in some cases irreversible cardiomyocyte damage, leading to ischemic myocardial necrosis. Studies have confirmed that ischemia-reperfusion during cardiac surgery increases the formation of free radicals and highly reactive molecules such as O_2, OH, and H_2O_2. These free radicals have an important role in microvascular dysfunction, and the disturbances caused by ischemia-reperfusion damage following cardiac arrest may lead to organ death. Increased oxidative stress also leads to protein and lipid oxidation, leading to molecular and cellular dysfunction. Free radicals react with polyunsaturated lipids in

membranes to produce lipid peroxidation products, which can inhibit protein synthesis and alter enzyme activity. Polyunsaturated fatty acid oxidation of membrane phospholipids can lead to membrane rupture, mitochondrial dysfunction, and Ca^{2+} overload. Free radicals react with membrane-bound lipids and cause lipid peroxidation.

Cardiopulmonary bypass is associated with above-average levels of lipid peroxidation and an imbalance in antioxidant status. MDA is formed by lipid peroxidation of unsaturated fatty acids and is a marker of oxidative degradation of cell membranes. MDA has negative mechanical effects on cardiac function. Increasing antioxidant levels can make the heart more resistant to ischemia-reperfusion damage. Antioxidant administration reduces cardiomyocyte damage and dysfunction during open heart surgery and acute myocardial infarction.[7] MDA was measured preoperatively and postoperatively as a marker of oxidative stress.

Trimetazidine is an anti-ischemic agent that inhibits long-chain mitochondrial 3-ketoacyl-CoA thiolase in myocytes, thereby partially inhibiting fatty acid oxidation and increasing glucose oxidation. It can improve antioxidant capacity and prevent toxicity caused by oxygen free radicals, counteract Ca^{2+} overload, and reduce the necrotic area. Trimetazidine has traditionally been used primarily in patients with CAD or cerebrovascular disease. It has no effect on cardiac flow, contractility, or heart rate, suggesting that it acts by directly improving energy metabolism in the myocardium. Trimetazidine can bind to mitochondria, significantly increasing the rate of glucose oxidation and decreasing the rate of fatty acid oxidation. Given that it is metabolized in the liver and excreted in the urine,[6–8] patients with renal failure or liver dysfunction were not included in this study.

Postoperative trimetazidine treatment is associated with increases in major antioxidant enzyme systems but does not alter postoperative hemodynamics, thus having an important role in preventing ischemia-reperfusion injury by increasing endogenous antioxidants. Some authors found significant reductions in hs-TnT levels during CABG in the trimetazidine pretreatment group. The increase in endogenous antioxidants and the stability of MDA levels in systemic venous samples suggests regulation of oxidative stress throughout the body, which may not be directly related to the heart.[15–17]

CONCLUSIONS

In this study, there was no difference in LVEF improvement in neither group 6 months after CABG surgery; however, the group that received trimetazidine had lower MDA levels and shorter hospital stay compared with the control group. Because of its protective effect against ischemia-reperfusion injury, trimetazidine must be considered in the medical regimen after CABG.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

ETHICAL APPROVAL

The study was approved by the local medical ethics committee (approval no. 8/23.11.2017).

CONSENT TO PARTICIPATE

All study participants provided written informed consent before being enrolled in the study.

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