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Effect of Pentoxifylline in Ameliorating Myocardial Injury in Patients With Myocardial Infarction Undergoing Thrombolytic Therapy: A Pilot Randomized Clinical Trial

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Abstract

Cell death following acute myocardial infarction (MI) is the hallmark pathology of cardiovascular disease, leading to considerable mortality and morbidity. Platelet and neutrophil activation and inflammatory cytokines, prominently TNF-α, play an important role in the development of cell death. Because pentoxifylline inhibits platelet and neutrophil activation and reduces TNF-α, this study was performed to assess the potential benefit of pentoxifylline in the reduction of myocardial injury following acute MI. In this randomized clinical trial, 98 patients with acute MI were randomly divided into 2 groups. The intervention group received an oral dose of 1200 mg of pentoxifylline immediately before thrombolytic therapy (TLT). All patients received the same standard protocol for treatment of MI. Cardiac enzymes were checked over 48 hours. ST resolution was measured over 90 minutes. Then all patients were followed up for a 1-month period to assess major adverse cardiac effects (MACEs). There were no significant differences in peak levels of CPK ($P = .18$) and CK-MB ($P = .33$) between the 2 groups, whereas peak level of troponin I was significantly lower in the pentoxifylline group (16.8 ± 10.4 vs 21.3 ± 11.6; $P = .048$). No significant change between the groups was observed in biomarkers levels, ST segment resolution, cardiac ejection fraction, and MACEs. The results showed that pentoxifylline significantly reduced the peak value of troponin I in patients with acute MI receiving TLT. No significant change was observed in the other studied parameters. Further outcome-based studies are needed to show the clinical relevance of differences between the groups in troponin peak.

Keywords

CK-MB, ischemia injury, pentoxifylline, ST resolution, STEMI, troponin I

Acute ST-elevation myocardial infarction (STEMI) is one of the main leading causes of death and disability in the world.[1] Disruption of atherosclerotic plaque is the primary mechanism in the development of acute coronary syndrome (ACS).[2] Subsequent platelet and neutrophil aggregation is a critical step leading to acute MI. Next is accumulation of inflammatory cytokines, mainly tumor necrosis factor α (TNF-α) and interleukins (IL), releasing free oxygen radicals and oxidative stress at the site of infarction, damaging heart tissue and resulting in cell death.[3–6]

Pentoxifylline, a xanthine derivative, was approved in the United States in 1984 for treatment of intermittent claudication and peripheral vascular disease. Several clinical and experimental studies have described the potential benefits of pentoxifylline in cardiovascular disorders. Pentoxifylline primarily reduces TNF-α production and inhibits phosphodiesterase (PDE) activity and therefore increases cyclic adenosine monophosphate (cAMP) level that leads to activation of protein kinase A and inhibition of nuclear factor kappa-B.[7–9]

Many research groups have reported that pentoxifylline leads to a significant decrease in platelet aggregation and adhesion to blood vessel walls in both animal and clinical studies.[8–13] Pentoxifylline inhibits platelet aggregation by different mechanisms such as inhibiting PDE activity that converts cAMP to AMP on the platelet membrane. Furthermore, it decreases formation of pseudopodium in platelets and decreases the production of platelet factor 3.[8–13]

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Pentoxifylline also decreases neutrophil adhesion to vascular endothelium and reduces its response to platelet activating factor and cytokines such as TNF-α and IL-1.[8,9,14–17] In 1 study, Neuner et al reported downregulation of inflammatory cytokines including IL-1 β, IL-6, IL-8, and TNF-α after administration of pentoxifylline.[17]

Data also showed that intravascular administration of pentoxifylline caused an increase in prostacyclin and vasodilation.[8,9,14,18–20] This drug acts as an effective hydroxyl radical sweeper, prevents vascular endothelial damage, reduces the protein leakage from small coronary arteries, and reduces the myeloperoxidase enzyme levels as an index of tissue leukocyte aggregation.[8,9,21,22]

Several documents have also supported the potential benefit of pentoxifylline in reduction of ischemia-reperfusion cell injury in animal model studies.[8,9,23–26] To the best of our knowledge, there are no clinical studies that evaluated the effect of pentoxifylline in patients with acute myocardial infarction undergoing thrombolytic therapy to reduce cardiac cell injury.

Given the possible mechanisms of cell death after myocardial infarction and potential cardiovascular benefit of pentoxifylline, we planned to perform this study to evaluate the effect of pentoxifylline in attenuating cardiac injury in patients with STEMI undergoing thrombolytic therapy.

Methods

Study Ethic

This study was approved by the ethics committee on clinical studies of Tabriz University of Medical Sciences. Then it was registered on the WHO clinical trial registry platform with ID IRCT2015102624722N1. Informed consent was obtained from all patients. The study was done according to the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects.[27]

Study Design and Population

This single-center, randomized, controlled trial study was conducted at the Madani Heart Center of Tabriz University of Medical Sciences in northwestern Iran between April 2014 and April 2015. The inclusion criteria of the study were all consented patients aged 18 years and older with a confirmed diagnosis of anterior myocardial infarction (MI) who received thrombolytic therapy. Acute STEMI was defined by ST-segment elevation $\geq$ 2 mm in at least 2 contiguous precordial leads.

The exclusion criteria were patients with a recent history (within 3 months) of coronary artery bypass grafting or percutaneous coronary intervention (PCI) or heart attack; history of renal failure (creatinine > 2.5 mg/dL); sensitivity and contraindication to aspirin, clopidogrel, streptokinase, or pentoxifylline; with cardiogenic shock; who were pregnant or breastfeeding; unconsented; with the inability to fill out or understand the consent form; and those who wanted to discontinue the study at any time.

Study Process

In this study 98 patients were randomized in a 1:1 ratio to treatment (n = 49) and control (n = 49) groups using DatInf RandList in Clinical Trials software (version 1.2) by an independent person. Patients in the treatment group received 1200 mg oral pentoxifylline (the maximum daily dose of pentoxifylline; three 400-mg tablets, generic form) immediately before thrombolytic therapy (TLT) plus the standard treatment, whereas the control group received only the standard treatment for STEMI.

In our center, the standard treatment for STEMI in the emergency department is according to the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines and includes heparin 60 units/kg bolus followed by continues infusion of 12 units/kg/min by adjusting to an aPTT target of 50–70 seconds, a loading dose of 162–325 mg chewable non-enteric-coated aspirin, as well as 300 mg of clopidogrel plus intravenous or sublingual nitrate and morphine sulfate or pethidine.[28]

Patients with the diagnosis of acute anterior STEMI and without contraindications to thrombolytic therapy received 1 500 000 IU streptokinase diluted in 100 mL of normal saline intravenously over 30–60 minutes in both groups. All patients received TLT within 2–4 hours of the onset of acute MI.

Peak levels of cardiac troponin I (cTnI) and creatine phosphokinase MB (CK-MB) were calculated to estimate the infarct size. ST-segment resolution and left ventricular ejection fraction (LVEF) were assessed to evaluate the effect of intervention and thrombolytic therapy using the transthoracic echocardiography method before discharge. ST-segment resolution was defined as the reduction of the highest ST-segment elevation in any lead by at least 50% of the initial value in the first 60–90 minutes of treatment.

All demographic, clinical and paraclinical data were recorded including age, sex, medical history, drug history, and current medications. All patients were either visited at the hospital outpatient clinic or were contacted by phone 1 month after hospital discharge to determine their vital status and subsequent major clinical events.

Blood Sampling

A blood sample was drawn from each patient for laboratory analysis of levels of cardiac enzymes including creatine phosphokinase (CPK) and CK-MB. Cardiac enzymes were measured on emergency

department arrival as a baseline sample and every 8 hours until 48 hours after thrombolytic therapy according to ACCF/AHA recommendation.[28] Cardiac troponin I (cTnI) was measured on arrival to the emergency room and then 8, 16, and 32 hours after thrombolytic therapy.

Study End Points

The primary end point of the study (by intention to treat) was evaluation of levels of cardiac enzymes during the first 24–48 hours after initiating TLT and comparing peak and cardiac enzymes levels between groups.

The secondary end points of the study included the comparison of ST resolution after 90 minutes and LVEF in 2 groups. Patients also were evaluated for the occurrence of major adverse cardiac events including angina, repeated heart attack, hospitalization because of cardiac events, and mortality after 1 month.

Statistical Analysis

The study sample size was calculated based on a type I error probability of $\alpha = 0.05$ and a power of 80%. We calculated the number of subjects needed for the study to be 98 (49 in each group) based on previous works with pentoxifylline and inflammatory responses in patients with coronary artery disease.[29,30]

Descriptive statistics for the study population were evaluated by mean ± standard deviation. To compare the quantitative variables between the groups, chi-square and Fisher's exact tests were used. After ensuring the normal distribution of data by the Kolmogorov-Smirnov test, the independent t test and repeated-measure analysis of variance (ANOVA) were used to compare the levels of cardiac enzymes on different consecutive occasions. $P < .05$ was considered statistically significant. SPSS 16.0 software (SPSS Inc., Chicago, Illinois) was used for data storage and analysis.

Results

A total of 104 patients were eligible for the study and allocated 1:1 to the intervention (standard treatment + pentoxifylline) and control (standard treatment) groups. Six patients were excluded from the study (4 patients not meeting the inclusion criteria, 2 patients lost to follow-up because they did not continue the study). Finally, 98 patients (49 in the control group and 49 in the intervention group) were entered in the study (Figure 1). The mean age of the study population was 59.5 ± 12.8 years, with a median of 60 years. Demographic and clinical data of the study groups are shown in Tables 1 and 2.

Mean CPK peak value was 3217.5 ± 2474.7 U/L in the control group and 2602 ± 2100.4 U/L in the intervention group ($P = .18$). Mean CK-MB peak level was 368.1 ± 317.3 U/L in the control group and 309.6 ± 280.2 U/L in the intervention group ($P = .33$). Mean cTnI peak level was 21.3 ± 11.6 ng/mL in the control group and 16.8 ± 10.4 ng/mL in intervention group ($P = .048$).

Comparison of the average total cardiac enzymes in the 2 groups did not show a significant difference in cardiac enzymes between the groups (the obtained P values for CPK, CK-MB, and cTnI were .21, .42, and .054, respectively).

According to the repeated-measures ANOVA, no significant difference was seen in the trend of biomarkers during the study time ($P = .73$ for CPK, $P = .9$ for CK-MB, $P = .419$ for cTnI). The trend of biomarker changes is shown in Supplementary Figures 1, 2, and 3.

There was no significant difference in ST resolution (χ^2 [2] = 1.28, $P = .525$) and left ventricular ejection fraction in the 2 groups (t [95.9] = 1.46, $P = .14$).

The evaluation of secondary outcomes after 1 month showed 2 and 4 cases of angina in the control and intervention groups, respectively. In the control group, 2 cases of heart failure and ventricular tachycardia and 1 case of nonanginal pain that needed hospitalization were observed. In the intervention group, 1 patient experienced recurrent stroke.

One case of death was documented in the control group. Based on statistical analysis, no significant differences between the 2 groups were seen in the secondary outcomes ($P = .56$).

Discussion

To the best of our knowledge, this randomized, controlled trial is the first study that investigated the effect of pentoxifylline on the reduction of myocardial injury in patients with myocardial infarction receiving thrombolytic therapy. The results of this study showed that 1200 mg pentoxifylline immediately before thrombolytic therapy in patients with STEMI significantly reduced the mean peak level of cTnI. However, no significant change was seen in the level of cardiac biomarkers, ejection fraction, resolution of ST-segment elevation, and 1-month patient outcomes in either group.

Correlation Between Infarct Size and Peak Level of Cardiac Biomarkers

Based on data driven from imaging studies using both scintigraphy and magnetic resonance imaging (MRI) methods, peak cTnT and cTnI values in patients with STEMI correlate with infarct size, with a good correlation coefficient of 0.8 to 93.[31–34] This relationship is applicable for the peak value of CK-MB with a slightly weaker correlation than cTnI and cTnT.[35] Based on the results of this research, the peak value of cTnI in

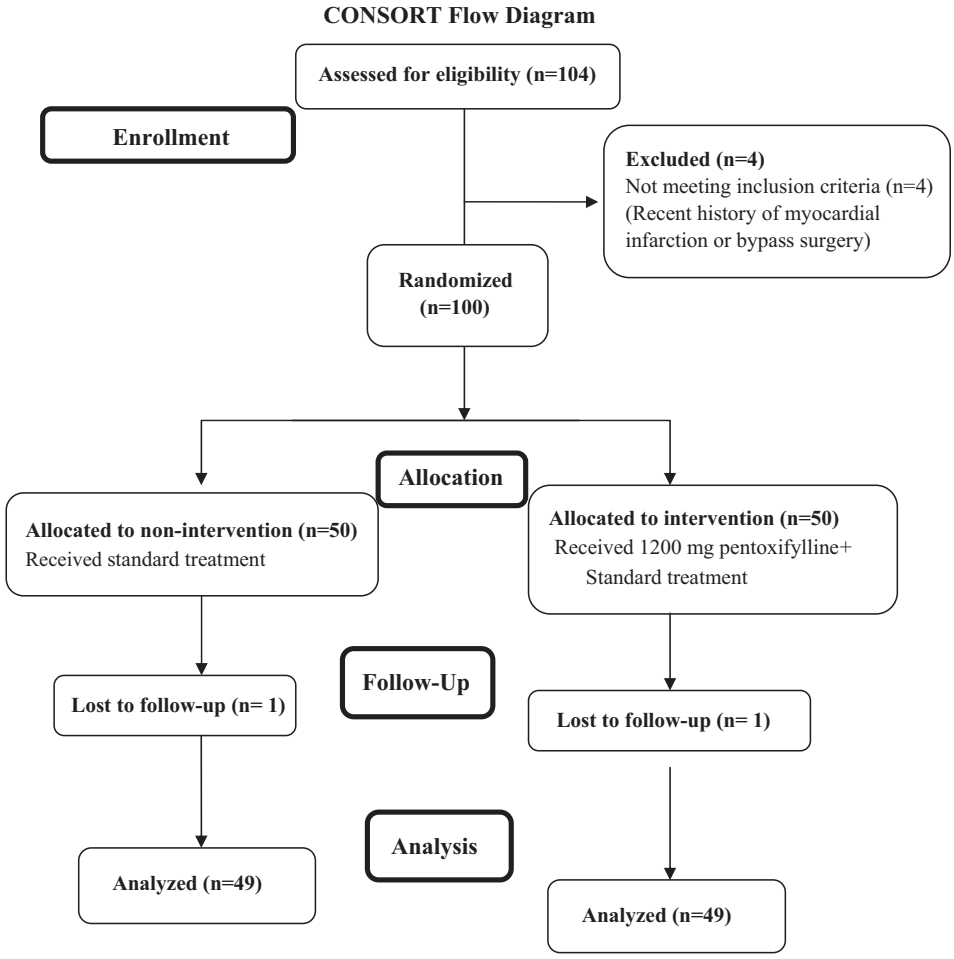

Figure 1. CONSORT flow diagram of the study.

the pentoxifylline group was significantly lower than in the control group, which can reflect a smaller infarct size in the pentoxifylline group. This finding is compatible with preliminary animal studies.[20,36] For example, Jiang et al at Emory University in Atlanta administered pentoxifylline intraperitoneally 10 minutes before reperfusion with 2 doses of 10 and 50 mg/kg in an ischemia-reperfusion model of rats. They showed that pentoxifylline significantly decreased infarct size in a dose-dependent manner compared with the control with a significant reduction in TNF-α.[36]

In another study Dauber and colleagues at the University of Colorado Health Sciences Center hypothesized that because leukocytes play an important role in ischemia-reperfusion injury of cardiac cells and because pentoxifylline reduces neutrophil activity, it might diminish coronary vascular injury.[20] To test this hypothesis, they administrated 20 mg/kg bolus plus 0.1 mg/kg/min infusion of pentoxifylline before reperfusion in an ischemia-reperfusion model of dogs using the dual radioisotope protein leak index (PLI) method to determine the burden of ischemia-reperfusion injury. They showed that pentoxifylline significantly reduced the increase in PLI, by 40% after 60 minutes of ischemia and by 25% after 90 minutes of ischemia, and concluded that pentoxifylline reduces coronary vascular injury because of ischemia-reperfusion.[20]

Prognostic Value of Cardiac Troponins Level in STEMI Patients

The prognostic value of troponins elevation has been described in STEMI patients. For example, in the GUSTO-III trial with 12 666 STEMI patients who received fibrinolytic therapy, it has been shown that elevation of troponin T at the time of acute MI is a predictor of 30-day mortality (15.7% vs 6.2% for nonelevated troponin T patients).[37] Furthermore, analysis of 21 studies on 18 982 patients with acute coronary syndrome showed that elevation of troponin I or T correlated with an increased risk of 30-day mortality or reinfarction (odds ratio, 3.44; 95%CI, 2.94–4.03).[38]

The correlation between cardiac troponin level and mortality rate has been confirmed by many studies. In the GUSTO IV ACS trial with more than 7000

Table 1. Demographic and Clinical Data of Patients at Baseline

Demographic and Clinical Data	Intervention Group	Control Group	*P*
Age (years), mean± SD	58.7 ± 13.3	60.3 ± 12.5	.53
Sex (male/female)	38/11	38/11	1
Familial history, n (%)	1 (2)	0 (0)	.31
Ischemic heart disease, n (%)	2 (4.1)	3 (6.1)	.64
Diabetes mellitus, n (%)	14 (28.6)	14 (28.6)	1
Hypertension, n (%)	21 (42.9)	27 (55.1)	.22
Smoking, n (%)	26 (53.1)	27 (55.1)	.83
Hyperlipidemia, n (%)	4 (8.2)	5 (10.2)	.72
Creatinine (mg/dL), mean ± SD	1.3 ± 1.1	1.1 ± 0.3	.32
Hemoglobin (mg/dL), mean ± SD	14.3 ± 1.6	14.2 ± 1.5	.8
Beta-blockers, n (%)	12 (24.5)	16 (32.6)	.37
ACEIs/ARBs, n (%)	22 (44.9)	25 (51)	.54
CCBs, n (%)	4 (8.2)	5 (10.2)	.72
Antilipid agents, n (%)	20 (40.8)	22 (44.9)	.68
Antidiabetes agents, n (%)	14 (28.6)	14 (28.6)	1
Other drugs	10 (20.4)	14 (28.6)	.34

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; SD, standard deviation.

Table 2. Changes in Cardiac Biomarkers During 48 Hours After Myocardial Infarction

Biomarker, Mean ± Standard Deviation	Intervention (n = 49)	Control (n = 49)	*P*
CPK_0 (U/L)	178.4 ± 18.6	182.3 ± 30.3	.73
CPK_8 (U/L)	2202.4 ± 2160.9	2694.6 ± 2389.5	
CPK_{16} (U/L)	1744 ± 1403.1	2111.6 ± 1821.3	
CPK_{24} (U/L)	1154.1 ± 988.4	1351.4 ± 1493.4	
CPK_{32} (U/L)	759.9 ± 575.2	932.8 ± 1037.2	
CPK_{40} (U/L)	544 ± 422.7	661.2 ± 610.4	
CPK_{48} (U/L)	416.6 ± 319.8	527.5 ± 696.6	
$CK\text{-}MB_0$ (U/L)	18 ± 4	18.2 ± 5	
$CK\text{-}MB_8$ (U/L)	280.8 ± 289 .1	319.2 ± 316.3	.9
$CK\text{-}MB_{16}$ (U/L)	185.6 ± 155.4	216.1 ± 208.8	
$CK\text{-}MB_{24}$ (U/L)	115.7 ± 100	129.7 ± 128.3	
$CK\text{-}MB_{32}$ (U/L)	72.2 ± 50	82.2 ± 66.3	
$CK\text{-}MB_{40}$ (U/L)	57.7 ± 39.9	61.5 ± 41.1	
$CK\text{-}MB_{48}$ (U/L)	49.7 ± 39.2	52.8 ± 34.1	
$cTnI_0$	0.7 ± 0.3	0.9 ± 0.3	
$cTnI_8$ (ng/mL)	15.2 ± 11.1	18.7 ± 11.8	.42
$cTnI_{16}$ (ng/mL)	11.6 ± 9.9	16.2± 11.5	
$cTnI_{32}$ (ng/mL)	7.3 ± 6.8	9.5 ± 9.1	

cTnI, cardiac troponin I; CPK, creatine phosphokinase; CK-MB, creatine phosphokinase type MB, the level of CPK and CK-MB.

patients, there was a significant correlation between the quartiles of cTnT level (≤0.01, 0.01 to 0.12, 0.12 to 0.47, and >0.47) and 30-day mortality. For example, 30-day mortality from the first to fourth quartiles of cTnT increased from 1.1% to 7.4 %. Furthermore, the first and second quartiles of cTnT corresponded to 2.5% to 6.7% in the 30-day rate of MI. However, no further increase occurred among the upper 3 quartiles.[39] A similar correlation between the level of troponins and mortality was shown in the FRISC study, the TIMI IIIB trial, and the GUSTO IIa trial.[40–43]

These findings are compatible with a recently published study of this research group on coronary heart disease patients undergoing elective PCI. In that randomized, controlled trial, 1200 mg of pentoxifylline before elective PCI did not result in a significant difference between the studied groups.[30]

Study Limitations and Strengths

The results of the present study should be interpreted with caution because it has some limitations. First, this was a pilot study with a limited number of studied samples that was performed at a university center. To attain an accurate result, a large sample size and multicenter studies are needed. Second, because of time and cost limitations, the follow-up period in our study was 30 days, which was a partially short period. Hence, the follow-up can be extended to 6–12 months to find an accurate outcome. Third, we did not use scintigraphy or MRI methods to estimate infarct size

in our patients because of an accessibility problem. However, as mentioned above, peak levels of cardiac biomarkers are widely used in the clinic to provide a rough estimate of infarct size. Fourth, we encountered cost limitations, and we measured CK-MB and CPK levels in 8-hour intervals and cTnI level 8, 16, and 32 hours after arrival to the emergency room; however, the pattern of enzyme measurement in our study was compatible with ACCF/AHA guideline recommendations, but measurement of cardiac biomarker in a shorter interval may cause the attainment of an accurate peak value.

The strengths of the study should also be noted. First, this is the first clinical randomized investigation of pentoxifylline in a setting of acute STEMI. Second, the potential benefit of pentoxifylline in the reduction of the cTnI peak value in STEMI patients was shown for the first time in this study. The clinical interpretation of this finding might be that pentoxifylline may decrease the infarct size in patients with STEMI. This finding is also in agreement with the previous preliminary animal model studies.[20,36] However, it needs to be confirmed by large trials using MRI and advanced imaging methods to determine the infarct size. Taken together, longer duration of administration of pentoxifylline during acute MI with a larger sample size and using the MRI method to measure infarct size is recommended to confirm the results of this study. Furthermore, outcome-based studies are needed to show the clinical relevance of the observed difference in troponin peak between the groups.

Conclusion

The results of the present study showed that 1200 mg pentoxifylline immediately before thrombolytic therapy in patients with STEMI significantly reduced cTnI peak level. However, it did not result in a significant change in the other studied parameters including the level of cardiac biomarkers, ejection fraction, resolution of ST-segment elevation, and 1-month patient outcomes. Further large studies are needed to confirm these findings.

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Declaration of Conflicting Interests

None.

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Supporting Information

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