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The impact of metformin on cardiac troponin-I and ST resolution in patients with ST elevation myocardial infarction undergoing thrombolytic therapy

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Abstract

Background: Thrombolytic therapy is a key in the management of ST elevated myocardial infarction (STEMI). Metformin implies a series of cardioprotective effects. We aimed to investigate how pretreatment with metformin could affect cardiac troponin I (cTnI) levels following reteplase therapy amid STEMI patients.

Methods: A pilot randomized clinical trial was carried out in 80STEMI patients undergoing thrombolytic therapy with reteplase. The metformin group (n = 40) received a single dose of 1000 mg metformin orally before receiving reteplase, while the control group (n = 40) received only reteplase. The serum level of cTnI was measured at baseline, 8, 16, 24, and 32 hours after the admission to assess myocardial damage.

Results: There was no significant difference in cTnI levels at baseline (p = 0.657), 8 (p = 0.93), 16 (p = 0.690), 24 (p = 0.217), and 32 (p = 0.517) hours after STEMI diagnosis between two groups. The mean differences were also not significant for changes of cTnI at baseline and other time frames.

Conclusion: The results of the present study demonstrated that early use of 1000 mg metformin prior to reteplase could not reduce the level of cTnI in STEMI patients.

Keywords: cardiac troponin I, metformin, STEMI, thrombolytic therapy

Introduction

ST elevated myocardial infarction (STEMI) is a life-threatening disease with a high rate of morbidity and mortality that urges for a prompt management. Urgent percutaneous coronary intervention (PCI) with stent implantation is the best therapeutic approach in STEMI patients.[1] Although PCI is considered as the best treatment, thrombolytic therapy still remains as a pivotal therapeutic choice in reperfusion therapy of STEMI patients.[2] The key role of thrombolytic therapy is even more highlighted when door-to-needle time rises up to 120 minutes.[2]

Reteplase is a recombinant tissue plasminogen activator (t-PA), a serin protease which prevents thrombolysis via conversion of plasminogen to plasmin.[2] The ease of use, decreased time of management, and efficacy of reteplase has turned it to a valuable thrombolytic agent in clinic.[2] Reteplase is suggested in presence of STEMI who experienced the symptoms within 12 hours.[2]

Cardiac troponin (cTn) is an ideal cardiac biomarker for acute coronary syndrome (ACS) and MI; the concentration of cTn is correlated with the extension of the cardiac damage.[3] CTn is the biomarker of choice in diagnosis of MI compared to the other biomarkers such as myoglobin and creatine kinase-MB (CK-MB) due to the higher sensitivity and cardiac specificity.[3] Not only cTn helps diagnosing MI regardless of reason, but also it predicts the risk of acute thrombotic events in these patients.[4] CTnI as one of the isoforms of cTn, is only detectable in myocardium of adults.[3]

Metformin is an oral hypoglycemic agent with desirable efficacy and tolerability; which is known as first-line treatment of type 2 diabetes mellitus (T2DM).[5] The suggested mechanism for metformin is activating AMP-activated protein kinase (AMPK), which is a cellular regulator in stress conditions.[6]

Long-term treatment of metformin in T2DM patients is associated with improvement of insulin resistance and reduction of cholesterol and LDL levels.[7]

Based on the recent evidence metformin exerts cardioprotective effects beside antihyperglycemic properties; however, the mechanism is not fully understood.[8] Metformin prevents cardiac fibrosis through inhibiting the overproduction of type β transforming growth factors (TGF-βs) and reducing collagen synthesis.[8] Kewalramani et al. demonstrated that metformin could improve survival of cardiomyocytes via phosphorylating AMPK.[9] Importantly, AMPK has pivotal role in both energy supply and utilization in myocardial metabolism.[10]

Moreover, Huang et al. has explained cardioprotective effect of metformin on acute myocardial injury by inhibiting autophagy in both in-vivo and in-vitro studies via anti-inflammatory and anti-apoptotic properties.[11]

The efficacy of metformin in reducing the risk of cardiovascular diseases in T2DM patients has been established so far.[12]

Based on UK Prospective Diabetes study (UKPDS), the cardiovascular morbidity and mortality benefit of metformin in patients with T2DM is more than that in other antidiabetic agents, in long term use.[12, 13]

Based on the promising effects of metformin on cardiovascular events, this study aimed to evaluate the effectiveness of metformin on cTnI in STEMI patients who underwent thrombolytic therapy with reteplase.

Methods

Ethics

The protocol of this trial was registered in the Iranian Registry of Clinical Trials (registry number: IRCT29111206008307N84). All patients were informed about the trial and gave a written informed consent before the study initiation.

Study design

This study was a prospective, pilot, randomized clinical trial that was conducted in patients with treatment decision of thrombolytic therapy with reteplase in Shahid Madani Heart Center, Tabriz, Iran. The study was carried out between March 2020 to April 2021.

Study population

Patients aged between 18 and 80 years old who were diagnosed with STEMI and planned for thrombolytic therapy with reteplase, enrolled in this study. The exclusion criteria included history of cardiac bypass surgery 3 months prior to the study, history of heart attack, patients with renal failure (clearance creatinine [ClCr] < 30 ml/min) or end stage renal disease (ESRD), patients with contraindication and/or a history of allergy to aspirin or clopidogrel and reteplase and metformin, patients with cardiogenic shock, , patients who refuse to continue the study or had disability to fill and understand the consent form.

Study protocol

All of the consented patients diagnosed with STEMI who were planned for thrombolytic therapy with reteplase were randomized into metformin group (n=40) and the control group (n=40). Sample randomization was conducted by using computer-generated random sequence in this trial.

Patients in the metformin group received 1000 mg of metformin given orally in a single dose prior to receiving reteplase. Patients in both groups received 10 U stat reteplase followed by 10 U after 30 minutes. All of the patients were treated based on AHA/ACC guideline and received chewable tablet of ASA 325 mg, clopidogrel 300 mg (4 tablets of 75 mg), heparin 60 IU/kg as loading dose followed by 12 IU/kg/hours, and 40 mg atorvastatin. The method of treatment and doses of medications were similar.

Patients' demographic data including sex, age, weight, height, body mass index (BMI), and clinical data such as drug history (DH), past medical history (PMH), laboratory data, and positive family history of CVD were listed.

Blood sampling

The levels of cTnI serially were measured at five time points at baseline and 8, 16, 24, and 32 hours after thrombolytic therapy in both groups. The detection limit of cTnI level in the blood was 0.1 ng/mL. The upper limit normal for cTnI was 1-1.4 ng/mL. The blood cTnI levels were measured by ELISA kits.

Power and sample size calculation

The power of the study was calculated by G-Power (version 3.1.9.2) considering type I error probability $\alpha = 0.05$, confidence interval = 95%, n = 80, two groups, and 5 times serial measurements of cTnI. The power ($1 - \beta_{error}$) for cTnI test with partial eta-squared (η^2) = 0.491 and the estimated effect size (F) = 0.982 was calculated 100%.

Statistical analysis

Continuous variables were described as the mean ± standard deviation (SD). The Kolmogorov-Smirnov was used to assess normality. The repeated measure analysis of variance (rANOVA) was used to compare the difference in means of both groups. The Bonferroni test was performed as post-hoc analysis. In within group analysis, paired t-test and Wilcoxon tests were performed. Chi-square and/or Fisher's exact tests were used for categorical data. Data were analyzed using SPSS-21 (SPSS Inc., Chicago, IL) and P-value less than 0.05 was considered to be statistically significant.

Results

Totally 84 patients were included in the study. Of whom, four patients were excluded due to Clcr under 30 mL/min in one patient, and history of coronary artery bypass graft (CABG) preceding last 3 months in 3 patients. Finally, 80 patients were allocated in 1:1 ration to the intervention (n = 40) and the control (n = 40) groups (Fig. 1). Baseline demographic and clinical characteristics of the patients in two groups are demonstrated in table 1. Most of the patients were male (85% [n=34 patients] in both groups).

The mean age of patients was 57.3 ± 11.5 and 60.4 ± 11.8 years in metformin and the control group, respectively.

No significant difference was observed between groups in demographic variables. It should be mentioned that there was no significant difference between patients' risk factors and related medications in both groups, which were presented in table 1.

At baseline, the cTnI levels were the same in both groups (p = 0.657). There was no significant change in the mean level of cTnI after 8 (p = 0.93), 16 (p = 0.690), 24 (p = 0.217), and 32 (p =

0.517) hours after receiving reteplase between two groups. The mean difference for changes of cTnI at baseline and 8 hours after receiving reteplase (p =1.0), baseline and 16 hours after (p = 1.0), baseline and 24 hours after (p = 1.0), baseline and 32 hours after (p = 1.0), 8 and 16 hours after (p = 1.0), 8 and 24 hours after (p = 1.0), 8 and 32 hours after (p = 1.0), 16 and 24 hours after (p = 1.0), 16 and 32 hours after (p = 1.0), 24 and 32 hours after (p = 1.0) was not significant between the groups. The changes of cTnI levels during the study were presented in table 2 and 3. Based on results, 45% (n = 18) and 57.5% (n = 23) of the patients had ST resolution after reteplase therapy in the intervention and control group, respectively (p = 0.263).

Discussion

To the best of our knowledge, this randomized controlled trial was the first investigation that assessed the cardioprotective effect of metformin in patients who underwent thrombolytic therapy with reteplase. This study did not demonstrate the beneficial effect of metformin in preventing myocardial injury in the setting of thrombolytic therapy with reteplase.

The beneficial effect of metformin in cardiovascular disease has been demonstrated by several studies. It is believed that the mechanism of metformin in reducing cardiovascular events differs from its mechanism in reducing blood glucose level; which is activating AMPK. Calvert et al. studied the cardioprotective property of low-dose metformin in mice with MI. The results of this in-vivo study showed the beneficial cardiac effect of metformin in both diabetic and non-diabetic mice with MI.[14] The suggested mechanism for cardioprotective property of metformin was increasing phosphorylation of endothelial nitric oxide (eNOS) besides AMPK activation.[14]

Li et al. had performed a clinical trial to evaluate the cardioprotective effect of metformin on MI in patients with metabolic syndrome prior to PCI.[15] A total number of 152 patients were

randomized to metformin (250 mg, three times in day) or control group seven days prior to elective coronary intervention. The levels of CK-MB and cTnI were measured at baseline, 8, and 24 hours after the procedure; furthermore, these levels were measured one year afterward. Patients had no history of metformin treatment. After PCI, patients in metformin group had lower CK-MB elevation (14.5 vs. 32.9%, p = 0.008) and cTnI elevation (14.5 vs. 34.2%, p = 0.005) compared to control group. Based on results of the study, pretreatment with metformin significantly reduced myocardial injury after PCI and improved one-year clinical outcome in patients with metabolic syndrome after PCI.[15]

The results of our study are in contrary to the mentioned studies, which could be explained by few reasons. First, the administered dose of metformin could not be adequate enough to exhibit cardioprotection in the studies. Second, the accurate effect of metformin may not be shown since the study population is limited. Therefore, further studies with large study populations are necessitated to show the exact dose, time, and duration of metformin therapy for preventing myocardial injury following STEMI in patients who received reteplase.

The findings of our study are consistent with the findings of a clinical trial carried out by Lexis et al; in which, metformin therapy for 4 months did not improve the left ventricular function of non-diabetic patients with STEMI undergoing PCI.[16] In the mentioned study 191 patients with STEMI who underwent PCI started to receive metformin (500 mg twice daily) immediately after PCI for 4 months. the results of the study did not confirm the beneficial effect of metformin in improving cardiac outcome in patients with STEMI undergoing PCI. Furthermore, the complementary studies on the same patients demonstrated that metformin failed to improve diastolic function.[17]

A metanalysis of 35 clinical trials revealed that metformin is not associated with any additional reduction in cardiovascular events other than its effect in lowering the glucose level.[18] However,

long-term monotherapy with metformin reduced the cardiovascular events in diabetic individuals.[18]

Based on a meta-analysis of 40 studies, metformin reduced the all-cause mortality and cardiovascular events in diabetic patients (aHR=0.83); yet, failed to reduce the cardiovascular events in non-diabetic patients (aHR=0.92) [19].

There are controversial data about cardioprotective effects of metformin in non-diabetic patients. For example, Nesti el. al. study showed that metformin has no cardioprotection in non-diabetic patients who experience ischemic events, whether used prior to or at the time of ischemic events.[20] However, metformin has beneficial effects in patients with T2DM and metabolic syndrome via providing anti-ischemic effects, improving survival rate, and reducing the size of infract and the serum concentration of cardiac biomarkers such as cTn and CK-MB.[20] In the study of Li et al. metformin with dose of 250 mg, three times in day had the cardioprotective effect on MI in patients with metabolic syndrome prior to PCI [15]. Pretreatment of the patients with metformin significantly reduced myocardial injury after PCI and improved one-year clinical outcome in patients with metabolic syndrome after PCI.

Limitations

Due to some limitations, the results of the present study should be interpreted with caution. First, this study has limited sample size; therefore, the exact effect of metformin on cTnI may not be seen in this limited population. Therefore, studies with more sample sizes are needed to reveal the exact effect of metformin on myocardial injury. Nevertheless, our study has a pilot nature; therefore, this sample size may be logical for a pilot study. Second, dose, time of administering of metformin may not be suitable and need more data to identify precise doses of metformin. Third,

in this study patients received 1000 mg of metformin prior to the thrombolytic therapy; however, the use of metformin could be extended until 2-3 days after thrombolytic therapy in order for obtaining more accurate results. Fourth, it is recommended to measure both of the cardiac biomarkers including cTnI and CK-MB levels following thrombolytic therapy with reteplase. We recommend high-sensitivity troponin I (hs-cTnI) assay for future studies, which we could not use it because of cost limitations.

Conclusion

Baesed on results of the present study, the single dose of metformin 1000 mg prior to reteplase was not associated with decrease in the level of cTnI in STEMI patients. Moreover, pre-treatment of metformin did not result in a significant difference in ST resolution after reteplase therapy. Larger randomized clinical trials are required to confirm the study hypothesis.

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Conflict of interests

None to declare.

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Table 1. Demographic and clinical data of the study groups

Demographic/Clinical data	Intervention group (n = 40)	Control group (n = 40)	P-value
Age (year), mean ± SD	57.3±11.5	60.4±11.8	0.244
Weight (kg), mean ± SD	74.3±12.2	76.2±13.7	0.532
BMI (kg/m²), mean ± SD	26.5±6.5	26.4±3.5	0.944
Serum creatinine (mg/dl), mean ± SD	1.19±0.2	1.2±0.3	0.825
BUN (mg/dl), mean ± SD	18±6.3	19.7±7.3	0.279
FBS (mg/dl), mean ± SD	165.6±90	131.1±28.5	0.221
EF (%), mean ± SD	35.8±9.5	36.6±8.4	0.702
Smoking, n (%)	21 (52.5%)	22 (55%)	0.823
Opium, n (%)	0 (0%)	1 (2.5%)	1.00
Alcohol, n (%)	1 (2.5%)	3 (7.5%)	0.615
Diabetes mellitus, n (%)	9 (22.5%)	10 (25%)	0.793
Hypertension, n (%)	27 (67.5%)	19 (47.5%)	0.07
Dyslipidemia, n (%)	10 (25%)	9 (22.5%)	0.793
Other disease, n (%)	13 (32.5%)	19 (47.5%)	0.254
Familial cardiovascular history, n (%)	13 (32.5%)	12 (30%)	0.809
History of angioplasty, n (%)	8 (20%)	6 (15%)	0.556
Angioplasty after reteplase, n (%)	25 (62.5%)	23 (57.5%)	0.647
Stroke, n (%)	2 (5%)	0 (0%)	0.494
History of surgery, n (%)	4 (10%)	9 (22.5%)	0.13
Beta-blocker, n (%)	15 (37.5%)	13 (32.5%)	0.639
ARB, n (%)	9 (22.5%)	12 (30%)	0.446
CCB, n (%)	4 (10%)	1 (2.5%)	0.359
Anti-diabetes mellitus agents, n (%)	8 (20%)	10 (25%)	0.592
Anti-hyperlipidemic agents, n (%)	10 (25%)	9 (22.5%)	0.793
Nitrate, n (%)	0 (0%)	2 (5%)	0.494
Thiazides, n (%)	2 (5%)	2 (5%)	1.00

Table 2. Mean troponin I levels at baseline, 8, 16, 24, and 32 hours after receiving reteplase in STEMI patients of both study groups

Troponin I level	Intervention group (n = 40)	Control group (n = 40)	P-value
Baseline	6.6±10.8	7 ± 10.9	0.657
At 8 hours	11.7±13	8 ± 13.4	0.93
At 16 hours	10.1 ± 11.6	6.4 ± 12.8	0.69
At 24 hours	7.8 ± 8.1	11.3 ± 12.5	0.217
At 32 hours	7 ± 9.5	9.8 ± 11.3	0.517

Data were described as mean±SD

Table 3. Mean differences of troponin I levels at different time frames

Time frame	Mean difference	P-value
Baseline-8 hours		
Intervention	3.2 ± 6.4	0.465
Control	3.1 ± 7	0.260
Baseline-16 hours		
Intervention	0.36 ± 5.3	1.00
Control	3.1 ± 6.5	0.389
Baseline-24 hours		
Intervention	0.55 ± 1.29	1.00
Control	2.9 ± 6.1	0.417
Baseline-32 hours		
Intervention	0.49 ± 0.8	1.00
Control	2.7± 3.4	1.00

Data were described as mean±SD