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Original Research Article

Efficacy of metoprolol succinate plus trimetazidine in the management of angina pectoris in coronary artery disease

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Abstract

Purpose: *To investigate the efficacy of metoprolol succinate (MET) plus trimetazidine (TMZ) in the management of angina pectoris in coronary artery disease.*
Methods: *A total of 94 patients with coronary angina were assigned equally to study group (received MET plus TMZ in addition to conventional symptomatic treatment) and control group (received conventional symptomatic treatment such as statins, nitrates, and aspirin). Heart rate was measured by a pulse oximeter, while angina attacks were measured by electrocardiogram (ECG). Left ventricular end-diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF), and left ventricular posterior wall end diastole (LVPWD) were measured by cardiac ultrasound. Enzyme-linked immunosorbent assay (ELISA) was used to determine the concentration of hypersensitive C-reactive protein (hs-CRP). Adverse reactions were self-reported.*
Results: *MET plus TMZ group produced significantly higher treatment responses for patients (95.74 %) than control group which received conventional medication (80.85 %, $p < 0.05$). Patients exhibited a significantly lower heart rate, fewer angina attacks, and a shorter duration of attacks after administration of MET plus TMZ compared to conventional medication ($p < 0.05$). MET plus TMZ treatment resulted in significantly higher LVEF, shorter LVEDD, and LVPWD than conventional treatment ($p < 0.05$). The study group exhibited a significantly milder inflammatory response indicated by lower serum hypersensitive C-reactive protein (hs-CRP) concentrations, and lower incidence of adverse events (4.26 %) compared to control group (17.02 %, $p < 0.05$).*
Conclusion: *MET plus TMZ provides significant treatment benefits for patients with angina pectoris in coronary artery disease, mitigates clinical symptoms and inflammatory responses, enhances cardiac function, and improves treatment safety by reducing risk of adverse events.*

Keywords: *Metoprolol succinate, Trimetazidine, Coronary artery disease, Angina pectoris, Inflammatory response, C-reactive protein (hs-CRP), Adverse events*

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INTRODUCTION

The incidence of coronary heart disease in China has increased in recent years. The complex pathogenesis of coronary heart disease and its differences result in multiple manifestations of the disease and a high risk of complications [1]. One of the most common complications of

coronary heart disease is angina pectoris [2]. Research indicates that angina pectoris is caused by myocardial ischemia and hypoxia, and the clinical manifestations are mainly chest pain and chest tightness [3]. Since coronary artery stenosis, spasm, and myocardial ischemia are the pathological features of coronary angina pectoris, amelioration of myocardial ischemia and hypoxia are essential for the effective control of angina pectoris in coronary artery disease.

MET is a β-blocker that effectively reduces myocardial contractility and oxygen consumption in patients [4]. Trimetazidine (TMZ) stabilizes the intracellular environment of patients, thereby contributing to the alleviation of their myocardial ischemic and hypoxic state [5]. The addition of TMZ to MET improved the treatment outcome of patients with angina pectoris in coronary artery disease compared to clinical conventional drug-controlled therapy [6]. However, the efficacy and safety of this combination regimen are less studied. To this end, this study was performed to evaluate the efficacy of MET plus TMZ in the management of angina pectoris in coronary artery disease.

METHODS

Participants

A total of 94 patients with coronary angina who were admitted to the Third Affiliated Hospital of Qiqihar Medical University between June 2021 and September 2022 were recruited and assigned equally to study (MET plus TMZ) and control groups. The study was approved by the ethics committee of The Third Affiliated Hospital of Qiqihar Medical University (approval no. 2021-05-2205) and was conducted in accordance with the Declaration of Helsinki [7].

Inclusion criteria

Patients with stable coronary angina by clinical-related test results, willing to cooperate with the treatment, with complete clinical data, and signed consent forms from patients and family members were included in the study.

Exclusion criteria

Patients with severe organ function disease, acute myocardial infarction, heart failure, cardiogenic shock, allergic and contraindicated reactions to drugs, operations, and devices used in this study, incomplete clinical data, psychiatric and cognitive-behavioral disorders, and unwillingness to cooperate with this study were excluded.

Treatments

The control group received symptomatic treatment with conventional drugs, including statins, nitrates, and aspirin, while the study group received MET plus TMA in addition to conventional symptomatic treatment. MET (AstraZeneca Pharmaceutical Co. Ltd, GMP J20150044) was administered orally at a dose of 23.75 mg/day for the first 7 days and increased to 47.5 mg/day on the 8th day. Subsequent doses were adjusted according to the patient's condition, with the maximum daily dose not exceeding 95 mg. Trimetazidine (TMZ) (Schweizer Pharmaceutical Co. Ltd, State Pharmacopoeia H20055465) was administered orally at a dose of 20 mg/day, thrice daily. The treatment duration was 6 months.

Evaluation of parameters/indices

Treatment outcomes

Treatment outcome was classified as markedly effective (clinical symptoms were significantly mitigated or disappeared, and the number and frequency of angina attacks were reduced by > 80 % compared with those before treatment). Effective (the clinical symptoms were relieved, and the number and frequency of angina attacks were reduced by 50 – 80 % compared with those before treatment), and ineffective (the condition showed no significant improvement or even further deterioration compared with that before treatment).

Clinical symptoms

Heart rate was measured by a pulse oximeter. The number and duration of angina attacks were measured by electrocardiogram (ECG) before and after treatment.

Cardiac function

Cardiac function parameters which include left ventricular end-diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF), and left ventricular posterior wall end diastole (LVPWD) were measured by cardiac ultrasound before and after treatment.

Inflammatory factors

Venous blood of 5 mL was collected from patients and centrifuged to obtain the serum. Enzyme-linked immunosorbent assay was used to determine the concentrations of hypersensitive C-reactive protein in the serum (hs-CRP).

Adverse reactions

Adverse reactions such as gastrointestinal symptoms, dizziness, and nausea were self-reported while reduced blood pressure and cardiac arrhythmias were evaluated using monitors and ECG.

Statistical analysis

GraphPad Prism 8 was used for graphical presentation, while SPSS 25.0 was used to analyze the data. Data are expressed as mean ± standard deviation (SD) and analyzed using independent students' *t*-test. Count data are expressed as n (%) and tested using chi-square (χ^2) test. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Baseline patient profile

In the control group, there were 26 males and 21 females, aged 42 - 77 (58.34 ± 3.26 years), with a disease duration of 2 - 8 (4.11 ± 0.87 years). There were 24 cases of grade II angina, 18 cases of grade III, 7 cases of grade IV, 11 cases of diabetes mellitus, 22 cases of hypertension, and 13 cases of hyperlipidemia. In the study group, there were 24 males and 23 females, aged 43 – 75 years (58.29 ± 3.21 years), with a disease duration of 1 - 9 years (4.24 ± 0.85 years). There were 23 cases of grade II angina, 16 cases of grade III, 8 cases of grade IV, 10 cases of diabetes mellitus, 24 cases of hypertension, and 16 cases of hyperlipidemia. The two groups had similar baseline profiles *($p > 0.05$)* (Table 1).

Treatment outcomes

MET plus TMZ produced better treatment responses for patients (95.74 %) compared to conventional medication (80.85 %) ($p < 0.05$; Table 2).

Clinical symptoms

In the control group, heart rate, number, and duration of angina attacks reduced significantly after treatment ($p < 0.05$). Likewise, in the study group, the heart rate, number, and duration of angina attacks reduced from 90.17 ± 5.15 bpm, 5.48 ± 1.54, and 23.08 ± 2.52 mins before treatment to 72.29 ± 5.08 bpm, 0.77 ± 0.18, and 7.11 ± 1.25 mins after treatment, respectively. The study group exhibited significantly lower heart rate, fewer angina attacks, and a shorter duration of attacks compared to the control group ($p < 0.05$) (Figure 1).

Table 1: Baseline patient profiles (n = 47)

Parameter	Control group	Study group	t/x²	*P*-value
Gender			0.171	0.679
Male	26	24		
Female	21	23		
Age (year)	42-77	43-75		
Mean age (year)	58.34±3.26	58.29±3.21	0.074	0.94
Duration of disease (year)	2-8	1-9		
Mean duration of disease (year)	4.11±0.87	4.24±0.85	0.732	0.465
Severity of angina pectoris				
II	24	23	0.042	0.836
III	18	16	0.184	0.667
IV	7	8	0.079	0.778
Co-morbidities				
Diabetes	11	10	0.061	0.804
Hypertension	22	24	0.17	0.679
Hyperlipidemia	13	16	0.448	0.502

Table 2: Treatment outcomes (n = 47)

Group	Markedly effective	Effective	Ineffective	Total effectiveness (%)
Control group	19	19	9	38(80.85%)
Study group	27	18	2	45(95.74%)
χ^2	-	-	-	5.044
P-value	-	-	-	0.024

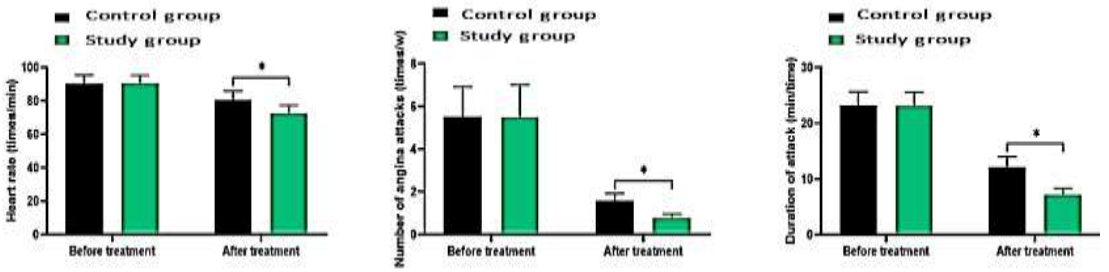

Figure 1: Clinical symptoms. *$P < 0.05$

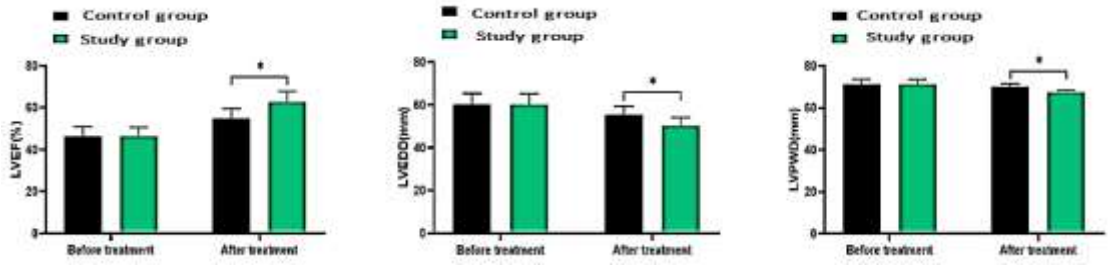

Figure 2: Cardiac function. *$P < 0.05$

Table 3: Adverse events (n = 47)

Adverse event	Control group	Study group	χ^2	*P*-value
Decreased blood pressure	2	0	-	-
Gastrointestinal symptoms	3	1	-	-
Cardiac arrhythmia	1	0	-	-
Dizziness and nausea	2	1	-	-
Total incidence (%)	8(17.02%)	2(4.26%)	4.028	0.044

Cardiac function

In the control group, LVEF, LVEDD, and LVPWD were 46.53 ± 4.28 %, 60.23 ± 5.09 mM, and 71.21 ± 2.43 mM before treatment respectively. After treatment, LVEF increased to 54.82 ± 4.76 %, and LVEDD and LVPWD reduced to 55.38 ± 4.02 mM and 55.38 ± 4.02 mM respectively. In the study group, LVEF, LVEDD, and LVPWD were 46.34 ± 4.39 %, 60.12 ± 5.18 mM, and 71.12 ± 2.37 mM before treatment respectively. After treatment, LVEF increased to 62.75 ± 5.21 %, and LVEDD and LVPWD reduced to 50.07 ± 4.06 mM, and 67.31 ± 1.01 mM respectively. MET plus TMZ resulted in significantly higher LVEF and shorter LVEDD and LVPWD than conventional medications ($p < 0.05$) (Figure 2).

Inflammatory factors

The hs-CRP before and after treatment in the control group was 5.89 ± 1.26 and 4.03 ± 0.85 mg/L respectively. The hs-CRP before and after treatment in the study group was 5.78 ± 1.32 and 2.28 ± 0.91 mg/L. A significantly milder inflammatory response was reported in the study group than in the control group as indicated by the lower serum hs-CRP concentrations ($p < 0.05$) (Figure 3).

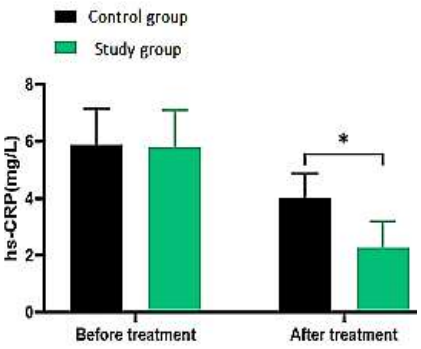

Figure 3: Inflammatory factors. *$P < 0.05$

Adverse events

The study group was associated with significantly lower incidence of adverse events than control group ($p < 0.05$) (Table 3).

DISCUSSION

Coronary artery disease refers to myocardial ischemic and hypoxic changes caused by coronary artery lumen stenosis and occlusion

due to atherosclerotic lesions [8]. The degree of coronary plaque aggregation is positively correlated with the degree of luminal stenosis in the coronary arteries [9]. Angina is triggered by excessive atherosclerosis and inadequate myocardial perfusion within the coronary arteries [10]. Angina is the most common complication of coronary artery disease and is clinically classified into stable and unstable depending on the mechanism and condition of the attack [11]. Stable angina is predictable and occurs with regularity and no significant changes in the degree, frequency, and duration of attacks over time. It normally develops after exercise or emotional excitement of the patient, and the symptoms may be rapidly relieved after rest or nitrate intervention [12]. Unstable angina is relatively dangerous [13], usually unpredictable, occurs with more severe and longer duration of pain, and responds poorly to nitrate drugs. In this study, to exclude the interference of different types of angina on the determination of efficacy, only patients with stable angina were included.

Aspirin and nitrates are conventionally recommended for the clinical treatment of angina pectoris in coronary artery disease. However, their efficacy is considered unsatisfactory in previous studies [14,15]. Research [16] has shown that inadequate blood supply to the myocardial structures is the major cause of angina pectoris. MET is a β-blocker used in clinical practice to improve myocardial oxygen metabolism with long-lasting and rapid effects [17]. Trimetazidine (TMZ) is a piperazine derivative that provides a basal energy metabolic pathway for ischemic and hypoxic cardiomyocytes, thereby stabilizing the patient's internal environment [18]. In addition, TMZ improves cardiac circulation and reduces the area of myocardial ischemia thereby increasing the degree of coronary artery dilation. A previous study [19] revealed that MET plus TMZ treatment synergistically alleviates the symptoms of coronary angina and reduces the risk of adverse reactions.

In the present study, MET plus TMZ produced significantly higher treatment responses and lower incidence of adverse events compared to conventional. These results are consistent with those of previous research [20]. This suggests that combined therapy of MET plus TMZ provides significant improvement in the treatment efficacy and lowers the risk of adverse events. Patients treated with MET plus TMZ exhibited significantly lower heart rates, less number of angina attacks, and a shorter duration of attacks when compared with conventional medication. Cardiac function parameters improved following treatment with MET plus TMZ. These results indicate that MET plus TMZ reduced disease-related symptoms and improved recovery of cardiac function in patients. The reason may be that the two drugs improve coronary blood circulation, reduce myocardial oxygen consumption, and increase the degree of coronary dilation, resulting in a synergistic effect when combined.

Currently, clinical research [21] has confirmed that chronic inflammation is an independent risk factor for cardiovascular events. Hence, the determination of the level of inflammatory factors in the patients has a predictive effect on both coronary and peripheral artery disease. Studies had revealed that the development of coronary heart disease and the formation of coronary atherosclerotic plaques are closely related to micro-inflammatory response [22,23]. In the current research, a significantly milder inflammatory response was seen in patients given MET plus TMZ than those given conventional symptomatic medication, as indicated by the lower serum hs-CRP concentrations. This result suggests that MET plus TMZ is valuable in improving the micro-inflammatory status of patients with coronary angina. It is speculated that the combined regimen may produce a protective effect on the myocardial function of patients by improving the micro-inflammatory status of patients. However, the specific mechanism remains poorly understood, and future investigations are required for further evaluations.

Limitations of this study

This study has some limitations. The results were obtained from a small sample size and in patients with stable coronary angina.

CONCLUSION

MET plus TMZ significantly provides treatment benefits for patients with angina pectoris in coronary artery disease, mitigates clinical symptoms and inflammatory responses, enhances cardiac function, and improves treatment safety by reducing the risk of adverse events. However, the results would require validation in a larger patient population with variable pathologies.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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