Original Article
Beneficial effects of trimetazidine as a metabolic therapy on cardiac recovery and quality of life for patients with coronary heart disease after percutaneous coronary intervention

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Abstract: Objective: The retrospective study investigated the effect of trimetazidine (TMZ) as a metabolic therapy on cardiac recovery and quality of life (QOL) for patients with coronary heart disease (CHD) after percutaneous coronary intervention (PCI). Methods: We included 100 CHD patients who underwent PCI in the Affiliated Calmette Hospital of Kunming Medical University between January 2016 and June 2016. Patients were randomly assigned to control and experimental groups. Patients in the control group took secondary prevention medications and those in the experimental group were given secondary prevention medications and three-month oral administration of TMZ. The treadmill exercise test, the echocardiogram, the six-minute walking test (6MWT), the MOS 36-Item Short-Form Health Survey (SF-36), and the Seattle Angina Questionnaire (SAQ) were administered to 100 patients. Results: Patients who had taken secondary prevention medications and oral administration of TMZ in the experimental group were compared to those patients who had just taken secondary prevention medications in the control group on metabolic equivalents (METs), left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDd), the SF-36 and SAQ subscale scores: the experimental group exhibited increased METs and LVEF, and decreased LVEDd compared with the control group; there were significant differences in the SF-36 domains of general health, role physical, bodily pain and social functioning between two groups; the 6MWT distance was longer in the experimental group than in the control group; the experimental group had higher SAQ subscale scores of physical limitation, angina stability, treatment satisfaction and disease perception than the control group. Conclusion: Our study provides evidence that oral administration of TMZ as a metabolic therapy may improve cardiac recovery and QOL for CHD patients undergoing PCI.

Keywords: Trimetazidine, coronary heart disease, percutaneous coronary intervention, metabolic therapy, quality of life

Introduction

Coronary heart disease (CHD), a polyfactorial disease, is mainly manifested with atherosclerosis induced by lipid metabolism disorders [1]. CHD is one of the dominating causes of death and disease burden in developed countries and developing countries [2]. CHD mortality of Chinese population in both urban and rural districts has grown since 1980s [3, 4]. Accumulating evidence suggests that CHD has a number of risk factors, such as age, gender, body mass index (BMI), blood pressure, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), cigarette smoking, and diabetes mellitus [5-7]. Percutaneous coronary intervention (PCI) is relatively effective to achieve successful revascularization and to improve heart rate recovery (HRR) in patients with cardiovascular disease [8]. Although PCI shows short-term improvement for heart transplant patients, there is still some disagreement on long-term efficacy of PCT [9]. It is urgent to find alternative and beneficial therapies to improve quality of life (QOL) for CHD patients after PCI.
Metabolic dyslipidemia is defined by a concomitant increase in triglyceride (TG) levels and a decrease in HDL-C, and may contribute to an increased risk of CHD [10]. Interestingly, metabolic therapy would benefit patients with heart failure through modulating cardiac metabolism but not altering hemodynamics, with the use of metabolic modulators, including trimetazidine (TMZ), perhexiline, ranolazine and etomoxir [11]. CHD also induces congestive heart failure characterized by the failure of sufficient blood and oxygen supply from heart to peripheral tissues and organs [12]. TMZ is a kind of cellular anti-ischemic agent, which is a metabolic com-

Table 1. Comparison on baseline characteristics of CHD patients undergoing PCI between control and experimental group

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Control group</th>
<th>Experimental group</th>
<th>t/x²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>62.33 ± 8.08</td>
<td>61.12 ± 7.63</td>
<td>0.770</td>
<td>0.443</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30</td>
<td>23</td>
<td>1.967</td>
<td>0.161</td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration (year)</td>
<td></td>
<td></td>
<td>0.518</td>
<td>0.772</td>
</tr>
<tr>
<td>≤ 5</td>
<td>15</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-10</td>
<td>29</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 10</td>
<td>6</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td>0.271</td>
<td>0.602</td>
</tr>
<tr>
<td>18.5~23.9</td>
<td>10</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 18.5 or &gt; 23.9</td>
<td>40</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td>2.361</td>
<td>0.307</td>
</tr>
<tr>
<td>Never smokers</td>
<td>3</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former smokers</td>
<td>18</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent smokers</td>
<td>29</td>
<td>22</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: CHD, coronary heart disease; PCI, percutaneous coronary intervention; BMI, body mass index; continuous data were compared between two groups using t test; categorical data were compared between two groups using Chi-square test.

Table 2. Comparison on METs between patients with TMZ treatment in the experimental group and those without in the control group

<table>
<thead>
<tr>
<th>Group</th>
<th>METs before treatment</th>
<th>METs after treatment</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>4.91 ± 1.14</td>
<td>5.43 ± 1.06</td>
<td>2.309</td>
<td>0.044</td>
</tr>
<tr>
<td>Experimental group</td>
<td>4.97 ± 1.26</td>
<td>5.96 ± 1.03</td>
<td>4.396</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>t</td>
<td>0.266</td>
<td>2.353</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.956</td>
<td>0.039</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: METs, metabolic equivalents; TMZ, trimetazidine; continuous data were compared using t test.

Metabolic dyslipidemia is defined by a concomitant increase in triglyceride (TG) levels and a decrease in HDL-C, and may contribute to an increased risk of CHD [10]. Interestingly, metabolic therapy would benefit patients with heart failure through modulating cardiac metabolism but not altering hemodynamics, with the use of metabolic modulators, including trimetazidine (TMZ), perhexiline, ranolazine and etomoxir [11]. CHD also induces congestive heart failure characterized by the failure of sufficient blood and oxygen supply from heart to peripheral tissues and organs [12]. TMZ is a kind of cellular anti-ischemic agent, which is a metabolic com-

Materials and methods

Study subjects

A total of 100 CHD patients undergoing PCI in the Affiliated Calmette Hospital of Kunming Medical University between January 2016 and June 2016 were selected as study subjects. Patients consisted of 53 males and 47 females, with a mean age of 61.70 ± 7.88 years. These patients were assigned to a control group and an experimental group at random. Patients were diagnosed as CHD according to the criteria for diagnosis of ischemic heart disease reported by the World Health Organization [16]. Patients were included if they met the following criteria: (1) patients experienced chest discomfort due to exertion, fatigue and physical activity, the symptom was relieved by rest, and there were reversible ischemic electrocardiographic changes at onset; (2) patients had a ST-segment depression of 0.1 mV or more in the exercise electrocardiogram; (3) patients had significant coronary stenosis (greater than 70% lumen diameter) who underwent PCI within recent 6 months. Patients were excluded if they had non-cardiac chest pain caused by lesions of the chest wall, lung and esophagus, and myocardial ischemia caused by peripheral vascular disease; if they were accompanied by severe lesions in the lung, liver, kidney, blood
and gastrointestinal tract; if they had allergic reactions to medicines; if they were pregnant and lactating women. Patients in the control group took secondary prevention medications and those in the experimental group took secondary prevention medications and three-month oral administration of 20 mg tid TMZ (Vasorel, batch No.: 4J4513, France Les Laboratoires Servier). This study was performed based on the protocols approved by the commitment of our hospital (2016-7). All patients signed written informed consents prior to recruitment.

Treadmill exercise test

The treadmill exercise test was performed using the modified Bruce protocol [17]. Before test, patients were well-informed about the modified Bruce protocol. After having a rest for 15-30 min, patients were trained to run on a treadmill (Diamond pro740SB, Mitsubishi Electric Corporation, Tokyo, Japan) 1 hour before breakfast and 1 hour before dinner (19°C~22°C, 40%~50% of humidity). Metabolic equivalents (METs) of patients were recorded.

Echocardiogram

All echocardiograms were performed using a Vivid 7 cardiac ultrasound machine (GE Healthcare, Milwaukee, Wisconsin) with a 2~4 MHz transducer, following a standardized protocol. With Simpson's method, left ventricular ejection fraction (LVEF) and left ventricular end-diastolic dimension (LVEDd) were measured to reflect changes of cardiac structure of patients.

The MOS 36-Item Short-Form Health Survey (SF-36) scales

The SF-36 is a brief self-administered questionnaire that generates scores across 36 items describing 8 dimensions: general health (GH), physical functioning (PF), role physical (RP), bodily pain (BP), vitality (VT), social functioning (SF), role emotion (RE) and mental health (MH). Higher scores of the SF-36 subscales indicated better QOL.

Six minute walk test (6MWT)

The 6MWT was performed indoors, along a flat, straight, enclosed, and seldom traveled corridor that had 30 m of length and a hard surface [18]. Before testing, patients were required to adjust environment and were well-informed about the purpose of test. The distance that 100 patients walked in 6 min were measured.
TMZ as metabolic therapy for CHD

The seattle angina questionnaire (SAQ)

All patients were interviewed by the physician using the SAQ [19] to quantify the physical and emotional effects of CHD. This instrument is a 19-item self-administered questionnaire leading to five scales that measure clinically important dimensions of CHD: physical limitation (PL), angina stability (AS), angina frequency (AF), treatment satisfaction (TS) and disease perception (DP). Higher scores of the SAQ subscales indicated better QOL.

Statistical analysis

The statistical package for the social sciences (SPSS) version 21.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Continuous data were expressed as mean ± standard deviation, with t-test used to compare data between groups. Categorical data were expressed as ratio and percentage, with Chi-square test used to compare data between groups. A P valu < 0.05 indicated statistically significant differences.

Results

Baseline characteristics of CHD patients undergoing PCI

One hundred CHD patients undergoing PCI were assigned to a control group and an experimental group. Patients in the control group consisted of 30 males and 20 females, aged 37–72 years and with a mean age of 62.33 ± 8.08 years. Patients in the experimental group comprised 23 males and 27 females, aged 37–72 years and with a mean age of 61.12 ± 7.63 years. No significant difference was found in age, gender, disease duration, body mass index (BMI) and smoking history between control and experimental groups (P > 0.05) (Table 1). There was no death, case of loss to follow or withdrawal from the study.

Oral administration of TMZ increased METs of CHD patients undergoing PCI

Before any treatment to CHD patients undergoing PCI, the METs did not differ significantly between control and experimental groups (P > 0.05). After taking secondary prevention medications, patients in the control group had increased METs (P < 0.05), and after taking secondary prevention medications and oral administration of TMZ, patients in the experimental group also exhibited increased METs (P < 0.05). The METs were higher in patients taking secondary prevention medications and oral administration of TMZ compared with those patients just taking secondary prevention medications (P < 0.05) (Table 2).

Oral administration of TMZ improved cardiac function of CHD patients undergoing PCI

The echocardiogram showed that the LVEDd and LVEF exhibited no significant difference between control and experimental groups before any treatment to CHD patients undergoing PCI (P > 0.05). After taking treatments, patients in both control group and experimental group had reduced LVEDd and increased LVEF (all P < 0.05). However, LVEDd was dropped and LVEF was increased in a more intense fashion in patients of experimental group compared with those patients of control group (Figure 1). The result implied that oral administration of TMZ improved cardiac function of CHD patients undergoing PCI.

Oral administration of TMZ improved QOL of CHD patients undergoing PCI

Scores of SF-36 subscales did not differ significantly between control and experimental groups before treatment (P > 0.05). After taking secondary prevention medications, patients in the control group exhibited a remarkable increase in GH, PF, RP, BP, VT, SF and RE scores but did not in MH score (P < 0.05). After taking

Figure 2. Comparison on the 6MWT distance between patients with TMZ treatment in the experimental group and those without in the control group. *, P < 0.05 compared with the before treatment; #, P < 0.05 compared with the control group. Note: 6MWT, six minute walk test; TMZ, trimetazidine.
Table 4. Comparison on scores of SAQ subscales between patients with TMZ treatment in the experimental group and those without in the control group

<table>
<thead>
<tr>
<th>Group</th>
<th>Control group</th>
<th>Experimental group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td>PL</td>
<td>52.17 ± 12.34</td>
<td>63.56 ± 14.76*</td>
</tr>
<tr>
<td>AS</td>
<td>45.27 ± 13.65</td>
<td>73.45 ± 16.67*</td>
</tr>
<tr>
<td>AF</td>
<td>55.35 ± 21.34</td>
<td>79.34 ± 14.56</td>
</tr>
<tr>
<td>TS</td>
<td>34.77 ± 14.34</td>
<td>59.65 ± 13.34*</td>
</tr>
<tr>
<td>DP</td>
<td>32.49 ± 12.76</td>
<td>44.92 ± 13.45*</td>
</tr>
</tbody>
</table>

Note: SAQ; Seattle Angina Questionnaire; TMZ, trimetazidine; PL, physical limitation; AS, angina stability; AF, angina frequency; TS, treatment satisfaction; DP, disease perception; *P < 0.05 compared with data before treatment; *P < 0.05 compared with the control group; continuous data were compared among multiple groups using one-way analysis of variance.

secondary prevention medications and oral administration of TMZ, patients in the experimental group also had increased scores of GH, PF, RP, BP, VT, SF and RE (P < 0.05), but did not in MH score (P > 0.05). However, SF-36 subscales of GH, RP, BP and SF exhibited higher scores in patients of experimental group than in those patients of control group (P < 0.05), but PF, VT, RE, MH subscales did not (P > 0.05) (Table 3). The result suggested that oral administration of TMZ improved QOL of CHD patients undergoing PCI.

Oral administration of TMZ increased 6MWT distance of CHD patients undergoing PCI

The 6MWT indicated that no significant difference was found in the 6MWT distance between control and experimental groups before treatment (P > 0.05). After taking secondary prevention medications, patients in the control group exhibited an increased 6MWT distance (P < 0.05), and after taking secondary prevention medications and oral administration of TMZ, patients in the experimental group also showed a significant increase in 6MWT distance (P < 0.05). However, the 6MWT distance was longer in patients of experimental group than in those patients of control group (P < 0.05) (Figure 2).

Oral administration of TMZ alleviate symptoms of angina in CHD patients undergoing PCI

Before any treatment to CHD patients undergoing PCI, there was no significant difference in scores of SAQ subscales between control and experimental groups (P > 0.05). After taking secondary prevention medications, patients in the control group had higher scores of SAQ subscales (P < 0.05), and after taking secondary prevention medications and oral administration of TMZ, patients in the experimental group also showed higher scores of SAQ subscales (P < 0.05). However, SAQ subscales PL, AS, TS and DP scores were all higher in patients of experimental group in comparison to those patients of control group (P < 0.05), but the AF score was not (P > 0.05) (Table 4). The result indicated that oral administration of TMZ alleviated symptoms of angina in CHD patients undergoing PCI.

Discussion

CHD is a large and increasing burden of death in East Asia and its morbidity grew quickly over the past 20 years [2]. By evaluating METs and LVEF, 6MWT distance, SF-36 subscales, SAQ scales of patients receiving oral administration of TMZ following PCI, the study demonstrates that TMZ as a metabolism therapy improves exercise tolerance, cardiac function and QOL, and attenuates angina symptoms.

First of all, the METs and 6MWT distance were increased in patients receiving TMZ treatment compared with those patients without. A meta-analysis that investigates the effect of TMZ on METs in patients with ischemic heart disease (IHD) shows that oral administration of TMZ contributes to improvements in METs, peak oxygen uptake (pVO2), total exercise duration (TED), and 6MWT distance [20]. Vitale et al. also suggest that TMZ may improve TED in patients with stable exertional angina [21]. More importantly, TMZ, in part, attenuates myocardial energy metabolic dysfunction, inhibits oxidative stress markers, and suppresses myocardial fibrosis and ventricular remodeling [22]. Additionally, 3-month TMZ treatment improves left ventricular function through reducing whole body energy demand in patients suffering from systolic heart failure [23]. TMZ treated patients show both improved systolic and diastolic cardiac function, and
thereby left ventricular remodeling is prevented [24]. There is an increase in LVEF at 6 and 18 months after TMZ treatment by the improvement of energy production [25]. In this study, we also found the LVEDd was decreased and the LEVF was increased in CHD patients treated with TMZ. In consistent with our results, TMZ therapy reduces LVEDd and increases LVEF, thereby improving cardiac function in several studies [22, 26]. The use of TMZ exhibits a protection against glucose metabolism in cardiomyocytes [27]. TMZ improves myocardial glucose utilization during ischemia by inhibiting fatty acid oxidation, and acts as a metabolic modulator so as to improve left ventricular function [28]. Hence, the addition use of TMZ to PCI in CHD patients improves exercise tolerance and cardiac function.

In additional, this study also shows that the QOL is improved in CHD patients after TMZ treatment. GH, RP, BP and SF scores of patients with TMZ treatment are higher than that of patients without TMZ treatment. As a specific partial inhibitor of fatty acid oxidation, TMZ improves the inflammatory state, left ventricular function and QOL of patients with systolic heart failure [23, 29]. It also appears to improve muscle function with an increased muscle force in the elderly [30]. In elderly patients with ischemic heart disease, TMZ improves the QOL, reduces the occurrence of angina episodes, and also increases skeletal muscle strength [31]. Our results show that scores of PL, AS, TS and DP are significantly increased after oral administration of TMZ, suggesting the reduction in the severity of angina. Peng et al. report an anti-anginal effect of TMZ against stable angina pectoris via a metabolic mechanism, reducing the symptoms and improving functional status [32]. César et al. indicates that the effects of TMZ on episodes of angina and QOL are impressive in patients with CHD [33].

In conclusion, the overall results indicate that TMZ therapy increases exercise tolerance, improves cardiac function, and relieves angina symptoms, thereby contributing to better QOL in CHD patients undergoing PCI. This study would provide evidence for the recommendation of the adjunct of TMZ to conventional therapy for CHD patients following PCI. However, the results supporting this finding may be limited by the small size of the study population. Meanwhile, the molecular mechanism underlying TMZ functioning in CHD is wanted in future studies.

Acknowledgements

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Disclosure of conflict of interest

None.

Ethics statement

This study was conducted based on the protocols proposed by the Ethics committee of Kunming First People’s Hospital (2016-7).

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References

TMZ as metabolic therapy for CHD


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