Clinical Research

Treatment of unstable angina with trimetazidine

Xiexing Chen, Mingfang Ye

Cardiology Department 1 Affiliated Union Hospital 1 Fujian Medical University, Fuzhou 350001, China

Objective To evaluate the clinical therapeutic effects of trimetazidine on the treatment of unstable angina (UA) as well as its effects on endothelin-1 level and complications of patients. Methods One hundred and twenty patients with UA were randomized into the trimetazidine group (n = 60) and the control group (n = 60), the trimetazidine group was subjected to treatment with 60 mg trimetazidine everyday for six months plus conventional treatment, and the clinical symptoms, changes in electrocardiogram, changes in the number of plasma circulating endothelial cells (CEC) and endothelin-1 level of the two groups were observed after treatment for four weeks; and the incidence rates of cardiac arrhythmias, cardiac failure, hospitalization due to angina, myocardial infarction and sudden death were also observed after treatment for six months. Results 1) The total effective rate of integrative clinical therapeutic effects in the trimetazidine group and the control group after treatment for four weeks were 86.7% and 68.3%, respectively (P < 0.05), and the excellence rates were 36.7% and 15% (P < 0.01), respectively; the total effective rates for the therapeutic effects in electrocardiogram were 66.7% and 46.7%, respectively (P < 0.05), and the excellence rates were 30.0% and 11.7%, respectively (P < 0.01). 2) The number of plasma CEC and endothelin-1 level of the two groups after treatment for four weeks significantly decreased (P < 0.05), but the decreases in the trimetazidine group were even significant (P < 0.01). 3) The incidence rates for cardiac arrhythmia in the trimetazidine group and the control group after treatment for six months were 10% and 20% (P < 0.05), respectively, and the incidence rates for cardiac failure were 8.3% and 18.3%, respectively (P < 0.05), and the incidence rates for hospitalization due to angina were 10% and 15%, and the incident rates for myocardial infarction were 3.3% and 13.3% respectively (P < 0.05). Conclusion Trimetazidine can significantly improve the symptoms of UA and myocardial ischemia, reduce the damages to blood vessel endothelium and complications, and improve the prognosis. (J Geriatr Cardiol 2009; 6:82-86)

Key words Coronary heart disease; trimetazidine; angina, unstable

Introduction

Trimetazidine is the only definitely recommended metabolic drug by ACC/AHA/ACP-ASIM “Guideline on the treatment of stable angina” and “Guideline on the treatment of stable angina pectoris of effort” from the Branch of Angiocardiology of Chinese Medical Association, and it was strongly recommended by the latest “Guideline on the treatment of stable angina” of ESC in 2006. The latest seventh edition of “Braunwald’s Heart Disease” also definitely recommended trimetazidine as a metabolic drug to be used in the treatment of coronary heart disease. However, its effects on unstable angina still need further investigation. This study observed the clinical therapeutic effects and the adverse effects of the application of trimetazidine in the treatment of UA as well as the dynamic changes in the number of plasma circulating endothelial cells (CEC) and endothelin-1 (ET-1) which were sensitive and specific indexes for damages in blood vessel endothelium before and after the treatment, and the incidence rates of newly occurred cardiac arrhythmia, cardiac failure, hospitalization due to angina, myocardial infarction and sudden death after treatment for six months were also observed to evaluate the effects of trimetazidine on the prognosis of UA.

Patients and methods

Patients

One hundred and twenty patients with UA that were confirmed in the clinic and hospitalized patients in the department of internal medicine of our hospital were selected, which conformed to the criteria of “Recommendation for the diagnosis and treatment of UA” by the Branch of Angiocardiology of Chinese Medical Association and Editorial Committee of “Chinese Journal of Cardiology”, among them 72 cases were male and 48 cases were female, their age ranged from 53 to 82, and the average age was 60.6±9.5. There were two cases of complicated hypertension, 52 cases of complicated hyperlipemia, 38 cases of complicated type 2 diabetes, among them 72 cases were confirmed by coronary arteriography and 30 cases were old myocardial infarction. Angina broke out at least twice in one week in the selected cases, and the blood pressure was no higher than 21.3/
12.7 kPa (160/95 mmHg), and serious heart, liver, renal inadequacy, serious cardiac arrhythmias, acute cerebral accident, neurosis, climacteric syndrome, cholecystitis and cholelithiasis were excluded.

**Study protocol**

**Methods of the treatment**

All patients were subjected to fundamental treatment according to the drug medication that was recommended by “Recommendation for the diagnosis and treatment of UA” by the Branch of Angiocardiology of Chinese Medical Association. They were categorized by using random, single blind control method into the trimetazidine group and the control group. 60 cases were included in each group. The trimetazidine group was subjected to treatment with 60 mg trimetazidine everyday for six months on the basis of conventional treatment (trade name: Vasorel, which was provided by Les Laboratoires servier, France. 20 mg, it should be taken at three meals); the control group was not administered with trimetazidine and other treatments were the same to those of the trimetazidine group. If the symptoms of angina were still obvious during the course of drug medication, the patients should be administered with glycerol trinitrate tablet under their tongues to alleviate the symptoms. Patients that suffered from complicated diabetes and hyperlipemia should go on taking their original sugar-reducing drugs and fat-regulating drugs. The age, gender, blood fat, smoking history, blood sugar, grade of heart functions, course of disease, times, duration and degree of angina pectoris attacks, control electrocardiogram and other general conditions did not show any significant difference, and they were comparable.

**Clinical data collection**

The medical record and physical examination were carefully inquired before and after drug medication, and changes in clinical symptoms, heart functions and adverse effects of the drug, times and duration of angina pectoris attacks, dosage of glycerol trinitrate tablet, heart rate, cardiac rhythm and blood pressure should be documented in detail, and resting control 12-lead surface electrocardiogram was traced, and the clotting time, blood, urine and stool routine, liver and renal functions, blood fat, chest X-ray and ultrasound cardiology should be examined. Follow-up should be carried out in the clinic at least once every week. The clinical therapeutic effects and electrocardiogram therapeutic effects should be evaluated after treatment for four weeks, and the number of plasma CEC should be examined before treatment and four weeks after treatment, and the incidence rates for newly occurred cardiac arrhythmia, cardiac failure, hospitalization due to angina, myocardial infarction, sudden death and the conditions of complication occurrence were evaluated after six months.

**The determination of plasma CEC number**

The separation and counting were carried out according to Percoll density gradient centrifugation with small modification. Blood samples of 3 ml were collected from ulnar vein on an empty stomach in the morning and then transferred into anticoagulation tubes, and then Percoll with a density of 1.060 were added. The mixture was then centrifugated and the solution on the surface of Percoll solution was taken, and the supernatant was discarded after one centrifugation, then 0.5 ml physiological saline was added. The solution was shaken to suspend the cells for examination. Small amount of the above-mentioned suspension was dropped in the counting cell for blood cells and the cells were counted under a light microscope, four countings should be performed for the same sample and the average value was taken, and the unit was cells/0.9 μl. CEC were subjected to von Willebrand factor positive identification after labeled by immunocytochemical staining.

**Determination of ET-1 level in the plasma**

Radio immunoassay was used. Blood samples of 2ml were collected from ulnar vein on an empty stomach in the morning and then transferred into and fully mixed in the anticoagulation tubes, it contained 30 μl 10% EDTA disodium and 400 IU aprotinin, and then it was centrifuged at 4°C at 3 000 r/min for 15 minutes, and the plasma was collected and stored at -20°C for examination. The kits were purchased from Beijing East Asia Institute of Immunological Technology, and the operations were carried out strictly according to the instruction for use.

**Classification of clinical treatment effect**

Excellent: it did not induce angina or the times of angina were reduced by more than 80% under the same labor intensity, and the consumption of glycerol trinitrate reduced by more than 80%. Effective: the times of angina pectoris attacks and the consumption of glycerol trinitrate both decreased by 50-80%. Ineffective: the times of angina pectoris attacks and the consumption of glycerol trinitrate both decreased by less than 50%. Aggravated: the times, degree and duration of angina pectoris attacks were aggravated, and the consumption of glycerol trinitrate increased.

**Classification of electrocardiogram improvement**

Excellent: ischemic changes in the resting electrocardiogram recovered, and the submaximal exercise test turned from positive to negative. Improved: the ischemic ST segment in the electrocardiogram decreased and it returned to 1.5 mm or even higher after the treatment, but it was still abnormal; or the main leading inverted T wave became shallow by more than 50%, or T wave turned from flat to rear; or the exercise tolerance went up one grade. Ineffective: it did not reach the above-mentioned criteria. Aggravated: the ST segment in the resting electrocardiogram decreased 1.5 mm in comparison with that before the treatment, and the in-
verted T wave was deepened by no less than 50%, and the rear T wave became flat or flat T wave became inverted.

**Statistical analysis**

The measurement data were represented by the mean ±standard deviation, and the measurement data were subjected to t-test; and the numeration data were subjected to chi square test. \( P<0.05 \) indicated that the difference was statistically significant.

**Results**

**General data**

The heart functions (NYHA grading) of all of the 120 cases of UA patients were all grade I - II when they were included, and they were all subjected to treatment for six months and no case of sudden death occurred. All patients took aspirin (Ascenterine) and nitrate drugs with prolonged action, among the, 95 cases took a -receptor blocker (79.2%), 80 cases took calcium antagonist (66.7%), 78 cases took angiotensin converting enzyme inhibitor or angiotensin converting enzyme receptor antagonist (65%), 70 cases took statins (58.3%), 60 cases took antithrombosis treatment (50%), 38 cases took sugar reducing treatment (31.7%), and 21 cases took diuretic agents (17.5%), there was no significant difference in the fundamental drug medication received by both groups and they were comparable. Eight cases in the trimetazidine group and 10 cases in the control group were subjected to interventional therapy during the observation period in the treatment.

**Evaluation for the end point**

Clinical therapeutic effects: the therapeutic effects in the trimetazidine group were significantly higher than those of the control group after treatment for four weeks (Table 1).

The therapeutic effects from electrocardiogram: the therapeutic effects from electrocardiogram in the trimetazidine group were significantly higher than those of the control group after treatment for four weeks (Table 2).

Changes in the plasma CEC number and ET-a level before and after the treatment: the plasma CEC number and ET-a level of the two groups significantly decreased after treatment for four weeks, but the decreases in the trimetazidine group were more significant. The plasma CEC number and ET-a level of the trimetazidine group were significantly lower than those of the control group after the treatment (Table 3).

The conditions of complication occurrence in UA: the incidence rates of newly occurred cardiac arrhythmia, cardiac failure, hospitalization due to angina, myocardial infarction and sudden death in the trimetazidine group after treatment for six months were significantly lower than those of the control group (Table 4).

**Adverse effects**

No obvious adverse effects were found during the drug medication in the trimetazidine group and the control group. All of the patients can tolerate 60 mg trimetazidine everyday and no adverse incidents occurred. The blood pressure, heart rate and their multiplication did not show significant changes before and after the treatment \( (P>0.05) \). No abnormal changes were found in the laboratory examinations.

**Discussion**

UA is liable to develop into acute myocardial infarction and sudden death, and its main pathological bases are atheromatous plaque disruption, bleeding and formation of secondary internal clot in the coronary artery. Since serious stenosis or obstruction in the lumens lead to ischemia and anoxemia, the energy metabolism of cardiac muscle is blocked, and this is the main reason for the occurrence of serious cardiac arrhythmias, cardiac failure and sudden death. It has become the crucial step that how to reduce the oxygen consumption of cardiac muscle, increase oxygen supply and improve the energy metabolism of cardiac muscle. Traditional anti-angina drugs include nitrate preparations, \( \beta \) receptor blockers, calcium antagonists and others, which show hemodynamic effects, these drugs can increase coronary blood flow, reduce myocardial consumption of oxygen and bring the anti-angina functions into full play by expanding coronary artery, reducing heart rate and blood pressure. Previous investigations from all over the world have suggested that trimetazidine can improve myocardial metabolism and it is a kind of effective anti-angina drug, which can increase coronary reserve, reduce the serious degree of angina and increase the exercise tolerance of patients, and no hemodynamic changes were found. It can transfer the energy metabolism from fatty acid oxidation to glucose oxidation, promote the glucose oxidation pathway of cardiac muscle, inhibit \( \alpha \) oxidation process of free fatty acid and the intake of fatty acid by cardiac muscle, and thus protect cardiac muscle cells under ischemic and anoxic conditions as well as reduce ischemic damages, and it can significantly reduce the mortality by long term treatment. CEC refers to the vascular endothelial cells that are measured from the peripheral blood under physiological or pathological conditions. CEC is the unique indicator that can specifically and directly reflect the damages in blood vessel endothelium in vivo at present, and it can reflect the abnormal changes in endothelial cells, and it is simple and direct-viewing, which has reference values for the clinical judgment on blood vessel diseases and the guidance on the treatment. ET is one of the most representative serological indexes during endothelial function disorder, which can be used for indirect evaluation on endothelial functions. ET synthesis in the blood circulation under normal conditions is very low, and the damages in vascular endothelial cells can promote the increase in ET secretion when the organism is in ischemic and anoxic conditions, and then the blood
Table 1  The comparison in the integrative clinical therapeutic effects in the two groups  n(%)  

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Excellent</th>
<th>Effective</th>
<th>Ineffective</th>
<th>Totally effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimetazidine</td>
<td>60</td>
<td>22(36.7)*</td>
<td>30(50.0)</td>
<td>8(13.3)</td>
<td>5(86.7)*</td>
</tr>
<tr>
<td>Control</td>
<td>60</td>
<td>9(15)</td>
<td>32(53.3)</td>
<td>19(31.7)</td>
<td>27(68.3)</td>
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</tbody>
</table>

Note: in comparison with the control group  * P<0.01, * P<0.05

Table 2  The comparison in the therapeutic effects from electrocardiogram in the two groups  n(%)  

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Excellent</th>
<th>Effective</th>
<th>Ineffective</th>
<th>Totally effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimetazidine group</td>
<td>60</td>
<td>18(30)*</td>
<td>22(36.7)</td>
<td>20(33.3)</td>
<td>40(66.7)*</td>
</tr>
<tr>
<td>Control</td>
<td>60</td>
<td>7(11.7)</td>
<td>21(35)</td>
<td>32(53.3)</td>
<td>19(46.7)</td>
</tr>
</tbody>
</table>

Note: in comparison with the control group  * P<0.01, * P<0.05

Table 3  Comparison in the plasma CEC number and ET-1a level before and after treatment from the two groups

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>CEC(cells/0.9 μl)</th>
<th>ET-1(pg/ml)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td>Trimetazidine</td>
<td>60</td>
<td>13.3±4.3</td>
<td>7.6±3.5</td>
</tr>
<tr>
<td>Control</td>
<td>60</td>
<td>13.5±5.2</td>
<td>8.9±3.2</td>
</tr>
</tbody>
</table>

Note: in comparison with the same group before the treatment  * P<0.01, * P<0.05; comparison with the control group after the treatment  * P<0.05

Table 4  Comparisons in the conditions of complication occurrence in UA from the two groups after treatment for six months n(%)  

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Cardiac arrhythmia</th>
<th>Cardiac failure</th>
<th>Myocardial infarction</th>
<th>Hospitalization due to angina</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimetazidine</td>
<td>60</td>
<td>6(10)*</td>
<td>5(8.3)*</td>
<td>2(3.3)*</td>
<td>6(10)*</td>
</tr>
<tr>
<td>Control</td>
<td>60</td>
<td>12(20)</td>
<td>11(18.3)</td>
<td>8(13.3)</td>
<td>15(15)</td>
</tr>
</tbody>
</table>

Note: in comparison with the control group  * P<0.05

vessels can contract forcefully and persistently, and the burden of cardiac muscle is then aggravated, and subsequently coronary artery contract and then the myocardial damages are aggravated. Previous investigations all over the world in recent years have confirmed that the number of CEC in the patients that suffer from coronary heart disease and angina increased and ET secretion also increased. Overdose release of ET can induce the intense convulsion and contraction of coronary artery, and induce myocardial ischemia damages and cellular necrosis, then aggravate the damages in blood vessel endothelium. However, damages in vascular endothelial cells are one of the important mechanisms to increase ET release. Investigations by animal experiments indicated that trimetazidine can inhibit the secretion of ET-1 and promote the release of nitrate substance, and then play functions in the level of endothelial cells. Some clinical reports also suggested that trimetazidine can improve the functions of endothelial cells in patients that suffered from coronary heart disease. This study showed that the combined application of trimetazidine with traditional anti-angina drugs can significantly improve the clinical symptoms and the electrocardiogram of UA, and the number of plasma CEC and ET-1 level significantly decreased, and the incidence rates of newly occurred cardiac arrhythmia, cardiac failure, hospitalization due to angina, myocardial infarction and sudden death significantly decreased, it was statistically significant in comparison to the control group, the therapeutic effects were accurate, and it was safe and reliable, which was in accordance with the results in the references all over the world.

In general, trimetazidine can improve myocardial ischemia, alleviate angina, protect vascular endothelial cells and promote the remedial functions on damages in vascular endothelial cells, and treatment for long term can reduce the
occurrence of newly occurred cardiac arrhythmia, cardiac failure, hospitalization due to angina, myocardial infarction and sudden death and improve the prognosis. It is an effective and ideal drug for the treatment of UA and deserves to be generalized in clinical applications.

References