Research about the influence of different doses of urokinase on microcirculation related indicators for patients with acute myocardial infarction

Hong-Lin Chen¹*, Wei-Dong Li²

¹Department of Cardiovascular Medicine, People’s Hospital of Rengshou, Renshou, Sichuan, 620500
²Department of Cardiovascular Medicine, Affiliated Hospital of North Sichuan Medical Hospital, Nanchong, Sichuan

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Objective: To observe the influence of different doses of urokinase on microcirculation related indicators for patients with acute myocardial infarction (AMI).

Methods: 240 cases of patients with AMI were randomly divided into three groups, these patients were treated with different doses of urokinase therapy, low dose group (0.5 million IU), middle dose group (1.5 million IU) and high-dose group (3 million IU). Then the differences of recanalization situation and microcirculation related indicators between the three groups were compared.

Results: The recanalization rate of low dose group was lower than middle dose group and high-dose group; After 2 h of treatment, the ST segment decline, PI, AUC of low dose group were lower than middle dose group and high-dose group, QTd and enzyme-peak hours were longer than middle dose group and high-dose group, LVEF, LVESV and LVEDV were lower than middle dose group and high-dose group, all P<0.05. There were no significant differences of outcome measures between the middle dose group and high dose group, P>0.05. The incidence of adverse reactions of bleeding of high-dose group was higher than middle dose group and low dose group, all P<0.05.

Conclusion: 150 IU urokinase is safe, effective dose for the treatment of AMI.

1. Introduction

Acute myocardial infarction (AMI) is a myocardial necrosis caused by acute and continuously hypoxic-ischemic of coronary artery which is the consequence of thrombus formed from agglutination of platelets on broken athermanous plaque. The broken athermanous plaque could be consequence of excessive excise, coldness or emotional changes. Therefore, recovery of blood flow in infarcted vein or myocardial perfusion in infarcted area in a fast, complete and continuously manner is essential the treatment of AMI. So does the saving of dying myocardial and the prevention of the extending of myocardial ischemia and infarction[1,2]. Early venous thrombolytic therapy of AMI have already been verified in massive multicenter clinical trials in 1980s[3,4]. Urokinase is one of the common thrombolytics in china now. AMI patients in this study are divided into groups treated with urokinase in different doses. The efficacy and safety of urokinase therapy is discussed and evaluated by observing the changes of myocardial microcirculation after treatment.

2. Materials and methods

2.1. Clinical information

AMI fit AMI diagnostic standard of ACC/AHA 2007 without fibrinolytic contraindications treated in our hospital from Sep
2012 to Mar 2014 are chosen. (1) Duration of chest pain 30 min. No relieving after in-taking of nitroglycerin. (2) Onset 6 h; (3) two or more adjacent chest lead ST elevation in ECG 0.2 mv, limb leads 0.1 mv, or new or possible new left bundle branch block; (4) age between 18-75. Exclusion criteria: (1) Major surgery or trauma within 1 month; (2) history of cerebral hemorrhage; (3) arterial aneurysm, suspected dissection of aorta; (4) sever liver or kidney function insufficiency; (5)active peptic ulcer; (6) allergic to urokinase.

240 patients are chosen. Patients are equally and randomly divided into 3 groups (low dose group: 600 000 IU; middle dose group: 1 500 000 IU; high dose group: 3 000 000 IU).52 male patients and 28 female patients with the average age of (54.32±8.33) and onset duration of (3.56±1.35) are chosen in low dose group. AMI danger factor in low-dose group is 37 cases of smoking, 49 cases of hypertension, 15 cases of diabetes and 46 pervious angina pectoris. 54 male patients and 26 female patients with average age of (55.21±8.59) and onset duration of (3.74±1.30) are chosen in middle dose group. AMI danger factor in middle-dose group is 41 cases of smoking, 45 cases of hypertension, 13 cases of diabetes and 49 pervious angina pectoris. 51 male patients and 29 female patients with average age of (55.68±8.14) and onset duration of (3.62±1.25) years are chosen in high dose group. AMI danger factor in high dose groups is 36 cases of smoking, 42 cases of hypertension, 16 cases of diabetes and 44 cases of previous angina pectoris.

2.2. Treatment method

2.2.1. Treatment

Venous thromolytic adjuvant drug is administrated for all patients. Intravenously injection of heparin (60 U/kg) following 300 mg orally administrated aspirin and clopidogrel are conducted before thrombolysis. Continuously administration of aspirin and clopidogrel orally after thrombolysis is needed. The dose of aspirin 3 d after operation is 100-300 mg/d. The dose is changed into 50-100 mg/d after that. The administration of clopidogrel (75 mg/d) should last for more than a month. Method of thrombolysis treatment: domestic urokinase (trade name: TPUK, Guangdong Techpool biochemical pharmaceutical co., LTD, 500000 U/ vial), 500 000, 1 500 000, 3 000 000 IU of urokinase is added into 100 mL of saline. Intravenously dripping is finished within 30 min.

2.2.2. Indicator

In order to observe the opening situation of artery, coronary arteriography inspection is performed 90 min after administration of thrombolytic drug. Classification is conducted according to blood perfusion situation. (TIMI classification(2)): class 0, no blood flow or perfusion on far-end of infraction area; class 1, contrast agent could be found in infraction area, relating artery is not fully filled with contrast agent; class 2, partly perfusion, clearance/fulfillment of contrast agent is slower than that of regular artery; class 3, fully perfusion. Clearance/fulfillment is normal. TIMI is classified as class 2 or class 3 is diagnosed as infraction recanalization.

Determination of microcirculation parameters: In order to record the descend range of ST segment and QTd interval, ECG is recorded both 2 h after the operation and before the operation. Interval triggering and second harmonics as well as PI and AUC are also simultaneously recorded. In order to calculate WMSI through Devereux formula, LVEF, LVESV and LVEDV are recorded by ultrasonic cardiogram. Bleeding signs in expectoration, vomits, urine and stool, skin or mucosa is observed.

2.3. Statistical analysis

In order to analysis the difference in quantitative data by t test and to analysis the difference in enumeration data by $\chi^2$ test, SPSS17.0 software is employed. The situation that $P<0.05$ is considered as significant.

3. Results

3.1. Analysis of revascularization rate and TIMI blood flow classification among three groups

The ratio that TIMI blood flow is classified as class 0 and class I in low dose group is higher than that in high dose group or middle dose group. The ratio that TIMI blood is classified as class II and class III is lower than that in high dose group and middle dose group ($\chi^2 = 5.861, \chi^2 = 5.963, P<0.05$). Revascularization rate in low dose group is significantly lower than that in high dose group and middle dose group. ($P<0.05$) No significant meaning could be found in TIMI blood flow classification and revascularization rate between middle dose group and high dose group. The details are shown in Table 1.

3.2. Analysis of microcirculation indicators in patients among three groups

Decent range of ST segment, PI and AUC in low dose group 2 h after therapy are significantly lower than that of high dose group and middle group. QTd interval and enzyme peak time is also significantly longer than that of high dose group and middle dose group ($P<0.05$). No significant difference could be found in all
microcirculation parameters between middle dose group and high dose group. \((P>0.05)\) The results are shown in Table 2.

### Table 1

Analysis of TIMI blood flow classification and revascularization rate between two groups [n (%), \(n=80\)].

<table>
<thead>
<tr>
<th>Group</th>
<th>TIMI bloodflow classification</th>
<th>Revascularization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>I</td>
</tr>
<tr>
<td>Low dose</td>
<td>20(25.00)</td>
<td>33(41.25)</td>
</tr>
<tr>
<td>Middle dose</td>
<td>11(13.75)</td>
<td>10(12.50)</td>
</tr>
<tr>
<td>High dose</td>
<td>9(11.25)</td>
<td>13(16.25)</td>
</tr>
</tbody>
</table>

Compare with middle dose group, \(*P<0.05\); Compare with high dose group, \(*P<0.05\).

### Table 2

Analysis of microcirculation parameters of patients among three groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>ST decent (%)</th>
<th>QTd interval (ms)</th>
<th>IV</th>
<th>AUC</th>
<th>Enzyme peak (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>68.35±8.17*</td>
<td>53.32±8.11*</td>
<td>2.54±0.67*</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Middle</td>
<td>87.21±7.63*</td>
<td>53.42±8.12*</td>
<td>2.54±0.67*</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>High</td>
<td>89.06±7.48*</td>
<td>53.32±8.12*</td>
<td>2.54±0.67*</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Compare with middle dose group, \(*P<0.05\); Compare with high dose group, \(*P<0.05\).

### 3.3. Analysis of results of ultrasonic cardiogram among three groups

No significant difference could be found in results of ultrasonic cardiogram among three groups before therapy \((P>0.05)\). LVEF, LVEDV, LVEDV in low dose group is significantly lower than that of high dose group and middle dose group before therapy. However, WMSI in low dose group is significantly higher than that of high dose group and middle dose group \((P<0.05)\). No significant difference could be found in LVEF, LVEDV, LVEDV and WMSI between middle dose group and high dose group \((P>0.05)\). The results are shown in Table 3.

### Table 3

Analysis of ultrasonic cardiogram results among three groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>LVEF (%)</th>
<th>LVEDV (cm)</th>
<th>LVEDV (cm)</th>
<th>WMSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>36.25±2.13*</td>
<td>48.32±1.22*</td>
<td>42.36±0.33</td>
<td>3.06±0.41*</td>
</tr>
<tr>
<td>Middle</td>
<td>35.12±1.54*</td>
<td>48.32±1.22*</td>
<td>42.36±0.33</td>
<td>3.06±0.41*</td>
</tr>
<tr>
<td>High</td>
<td>36.71±1.44*</td>
<td>48.32±1.22*</td>
<td>42.36±0.33</td>
<td>3.06±0.41*</td>
</tr>
</tbody>
</table>

Compare with middle dose group, \(*P<0.05\); Compare with high dose group, \(*P<0.05\).

### 3.4. Analysis of adverse reactions among three groups

The rate of adverse reaction in low dose group, middle dose group and high dose group is 5% (4 cases), 7.5% (6 cases) and 21.25% (17 cases), respectively. The rate of bleeding event in high dose group is significantly higher than that in low dose group and middle dose group.

### 4. Discussion

The increasing of AMI in our country is found every year recently. According to count in 2003, the number of AMI in china is 700 000 annually, 400 000 deaths are included. Health and wellbeing of middle-aged and aged people are seriously threatened by AMI[2]. It is currently considered that AMI is generally caused by the breaking of atherosclerotic plaque. The exposure of basal collagen fibers under endangulum could be caused by the breaking of unstable atherosclerotic plaque and artery skin. The adhesion, aggregation and releasing of platelets and the forming of both thrombin and fibrous protein are therefore induced. Insufficient coronary blood supply is further caused by thrombogenesis and lumen obstruction. Myocardial ischemia or myocardial necrosis is finally induced[5,6]. Therefore, recovery of blood flow in infarcted vein or myocardial perforation in infarcted area is essential the treatment of AMI. So does the saving of dying myocardial and the prevention of the extending of myocardial ischemia and infarction. Now, reperfusion therapy such as PCI and thrombolytic therapy are major therapy for myocardial infarction with acute ST elevation[7-9]. However, PCI emergency is not available in some hospital. Thrombolytic therapy is the only choice. Urokinase is the common drug used in AMI thrombolytic therapy. But there’s still disposition on safety and efficiency of it[10,11]. According to our study, revascularization rate in low dose group is significantly lower than that in high dose group and middle dose group. No significant difference could be found in TIMI blood flow classification and revascularization rate in middle dose group and high dose group \((P>0.05)\).

Coronary microcirculation disability is the only danger risk that alters the prognosis of AMI. Myocardial injury exacerbation could be caused by metabolism & energy changes induced by extending and shrinking of arteriole as well as insufficient myocardial blood flow. There are also relevance between coronary microcirculation malfunction and no-reflow after PCI according to recent research[12,13]. Myocardial perfusion could be observed through MCE inspection. Blood flow of microcirculation could be observed through strength and distribution of eco. Large PI and AUC could be features for sufficient blood flow. Degree of decline for ST segment and QTd interval in ECG parameters are common indicator for myocardial microcirculation in clinic. Large decline of ST segment and minor QTd interval means higher degree of reperfusion[14,15]. Decline of ST segment, PI and AUC 2 h after therapy in low dose group is significantly lower than that in high dose group and middle dose group. QTd interval and enzyme peak time in low dose group is significantly longer than that in high dose group and middle dose group \((P<0.05)\). Good improvement on coronary blood flow could be observed in middle dose group and high dose group. Additionally,
cardiac parameters such as LVEF, LVESV and LVEDV in middle dose group and high dose group are significant higher than that in low dose group.

150 IU of urokinase for the treatment of AMI is safe and efficient according to comprehensive adverse reaction, TIMI blood flow and revascularization ratio.

References


