Eligibility of Patients with Acute Myocardial Infarction for Thrombolytic Therapy: Retrospective Cohort Study

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Aim. To investigate the eligibility of patients with acute myocardial infarction (AMI) for thrombolytic therapy (TT) and evaluate the results of treatment.

Methods. Retrospective analysis included 366 patients with AMI, mean age 66±11 years, treated in 1999. We analyzed age, gender, previous infarction, previous TT, present TT with streptokinase and its effects on the course and outcome, pain-to-door time, and door-to-needle time. Reperfusion and reocclusion were evaluated non-invasively according to the occurrence of the reperfusion and reocclusion syndrome.

Results. One hundred patients (27%) underwent TT. It was less frequently applied in older patients, women, and patients with previous myocardial infarction. Reperfusion was achieved in 66 (66%) patients and reocclusion occurred in 9 (14%). Final outcome was successful in 57 (57%) patients. The TT group had more frequent arrhythmias (67% vs. 41%, p<0.001) and less frequent heart failure (20% vs. 39%, p<0.001) than the patients without TT. The mortality after TT was significantly lower (7% vs. 17%, p=0.015), without fatal outcome in patients with finally successful TT. Reasons against TT application were late arrival to hospital (51%) and contraindications for TT (34%). In patients without TT, the median pain-to-door time and door-to-needle time were significantly longer than in the TT group (7 vs. 2.5 hours and 55 vs. 20 min, respectively; p<0.001).

Conclusion. Older age, female gender, previous myocardial infarction, and late arrival to the CCU negatively influence the use of TT in AMI. TT should be improved by shortening pain-to-door time, broadening indications, and limiting contraindications.

Key words: age factors; coronary care units; eligibility determination; myocardial infarction; myocardial reperfusion; patient selection; streptokinase; time factors; thrombolytic therapy

Acute myocardial infarction is the leading cause of death in the developed countries, as well as in transitional countries (1,2). In about 90% of patients it is caused by the disruption of an atherosclerotic plaque, followed by acute thrombosis and complete occlusion of an epicardial coronary vessel. Myocardial necrosis begins within 15 minutes and spreads from the endocardium toward the epicardium during the next several hours (3). As severe consequences are related to the extent of necrosis, the major goal of therapy is to restore coronary blood flow as quickly as possible and save the jeopardized myocardium (4,5).

Reperfusion methods, thrombolytic therapy, and primary angioplasty have proven their effectiveness in numerous clinical investigations and are now an standard of care in appropriately selected patients (5-10). By converting plasminogen to plasmin, which lyses the fibrin within the clot, thrombolytic agents restore coronary blood flow, reduce infarct size, improve left ventricular function, and reduce complications and mortality (5-10). Regrettfully, numerous factors impede the use of thrombolytic therapy in a significant number of patients. Most often, the reasons for that are the time delay from the onset of symptoms to hospital admission or the existence of contraindications (3,5).

Despite the recent progress, thrombolytic therapy is still underutilized in acute myocardial infarction, with significant variations between and within different countries (3). Variations in the treatment affecting the outcome in certain population groups (e.g., elderly patients and women) have also been observed (3,11). Also, such data lack for transitional countries, including Croatia.

The aim of this study was to investigate the eligibility of patients with acute myocardial infarction for...
thrombolytic therapy, assess the treatment results, and reveal their influencing factors.

**Methods**

**Patients**

A retrospective analysis is included in all patients with acute myocardial infarction in whom reperfusion therapy was applied in the Coronary Care Unit (CCU) of the University Hospital Center Rijeka in 1999. Diagnosis of acute myocardial infarction was made on the basis of at least two of the following criteria: (1) typical symptoms of angina pectoris lasting >30 minutes with no relief on nitrroglycerin; (2) evolution of typical ECG changes; (3) significant elevation of serum creatine kinase (CK) and its isoenzyme CK-MB activities (at least two times the upper normal limit) (3). The clinical variables analyzed were age, gender, previous myocardial infarction, previous thrombotic therapy, and presence of thrombotic therapy and its effects on the course and outcome. Time intervals were based on the onset of symptoms to the hospital admission (pain-to-door time) and from the hospital admission to the CCU (door-to-needle time). These intervals were analyzed according to the Killip class (I–IV) (3).

**Thrombolysis**

Thrombolytic therapy was applied in patients with chest pain lasting >30 minutes, with no relief on nitrroglycerin; ST elevation ≥0.1 mV in at least two adjacent ECG leads, and hospitalization within 12 hours of the onset of symptoms. In all criteria were also extended to patients with ST depression ≥0.1 mV in V1–V3 ECG leads and ST elevation ≥0.1 mV in V1–V3 ECG leads as a sign of a strictly posterior infarction. Contraindications were recent bleeding (excluding menstural), obvious hemorrhagic diathesis, suspected aortic dissection, severe hypertension (>180/110 mmHg, >24.0/14.7 kPa), intracranial disease or previous cerebrovascular accident, severe retinopathy, bleeding in patients with six months, severe hepatic or renal insufficiency, extensive gery within one month, large athero mal within one week, pro-longed or traumatic cardiopulmonary resuscitation within two weeks, anti-coagulant therapy within 24 h, and previous streptokinase therapy within one week. Age ≥75 years was considered a contraindication (3).

Patients were treated with rapid intravenous streptokinase infusion (1.5x10^6 U during 60 min) and all other standard or necessary concomitant therapy. Reperfusion was evaluated non-invasively, based on the presence of at least four of the six signs of the "reperfusion syndrome": 1) subjective symptoms of improvement in the patient's status, 2) rapid elevation of serum CK activity (the "wash-out" phenomenon); 3) early peak of CK activity within 12 hours; 4) significant increase in ST elevation on the control ECG registered three hours after starting TT (adequate increase in the ST elevation sum of ≥20% in more than two adjacent ECG leads); 5) rapid evolution of the ECG pattern; 6) reappearance of reperfusion arrhythmias (accelerated idioventricular rhythm, late ventricular premature beats); and 6) disappearance of pre-existing conduction disturbances (3,12,13). The reappearance of early reocclusion was also evaluated on the basis of non-invasive vector teria: 1) reappearance of anginal pain; 2) recurrent ST segment elevation on the control ECG; and 3) repeated increase in serum CK activity (double CK peak) (3,12,13).

**Statistical Analysis**

Continuous variables were expressed as mean ± standard deviation and the time intervals by medians. Differences between groups were tested with the Student's t-test or the non-parametric Mann-Whitney test, and for medians with the median test. Discrete variables were shown as frequencies, and their differences were tested using the chi-squared test with Yates correction, or with the Fisher's exact test. Statistica pack age Statistics for Windows, release 4.5, StatSoft, Inc. 1993, was used. All comparisons were two-tailed and p-value <0.05 was considered statistically significant.

**Results**

During the year 1999, 366 patients with acute myocardial infarction were treated in our CCU (Table 1). Their mean age was 66±11 years (range 32–93 years); most patients (39%) were between 65 and 74 years old. About two thirds were men (250 or 68%), their mean age was significantly lower than in women (64±12 vs. 69±10, p<0.001). Female patients who did not receive thrombolytic therapy were significantly older than those treated with streptokinase (72±9 vs. 60±8 years, p<0.001). Of the 77 (21%) patients with previous myocardial infarction, seven (9%) were previously treated with thrombolytic therapy. When comparing the patients with and without thrombolytic treatment for the same vari able, analysis revealed that thrombotic therapy was less frequently used in older patients, women, and patients with previous myocardial infarction (Table 1).

Thrombolytic therapy was applied in 100 (27%) patients, more frequently in men than in women (30% vs. 21%), although this difference was not significant (p=0.07). In the group aged under 55, it was more frequent in men, in the group of 55 to 64 years of age in 38%, from 65 to 74 years of age in 21%, and in the oldest age group (≥75 years) in 4% of the patients. Reperfusion was achieved in 66 (66%) patients. Considering that early reocclusion occurred in 9 (14%) patients with reperfusion, defined success was achieved in 57 (57%) patients.

The course and in-hospital mortality in relation to the application of thrombolytic therapy are shown in Table 2. In patients with thrombolytic treatment,

<p>| Table 1. Clinical characteristics of patients with acute myocardial infarction |
|------------------|------------------|------------------|</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%) of patients</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55</td>
<td>63 (17)</td>
<td>36 (36)</td>
</tr>
<tr>
<td>55–64</td>
<td>79 (22)</td>
<td>30 (30)</td>
</tr>
<tr>
<td>65–74</td>
<td>142 (39)</td>
<td>30 (30)</td>
</tr>
<tr>
<td>≥75</td>
<td>82 (22)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>250 (68)</td>
<td>76 (76)</td>
</tr>
<tr>
<td>Women</td>
<td>116 (32)</td>
<td>24 (24)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>77 (21)</td>
<td>13 (13)</td>
</tr>
<tr>
<td>Previous thrombolysis</td>
<td>7/77</td>
<td>1/13</td>
</tr>
</tbody>
</table>

aTT – thrombolytic therapy.

bPatients with TT vs. patients without TT.
arrhythmias were more frequent, whereas heart failure and postinfarction angina were less frequent. The mortality rate in the thrombolytic group, when compared to the patients without thrombolytic treatment, was significantly lower (Table 2), with no deaths in patients with definite success of thrombolysis. The mortality rate in patients without reperfusion and in those with reocclusion was the same as in those without thrombolytic therapy (17%). The total mortality rate was 14%.

Complications of thrombolytic treatment appeared in 20% (20%) of patients. During streptokinese infusion, 13 (13%) patients had short and mild episodes of hypotension, which was in all cases successfully corrected with volume expansion, with no further negative influence on the course of illness and the final outcome. Of the 7 (7%) patients with hemophilia, 5 had minor bleeding at the site of venepuncture. Two (2%) patients with severe bleeding, due to retroperitoneal hematoma and gross hematuria, were successfully treated with blood transfusion.

Most of the ten reasons for not applying thrombolytic therapy were late arrival to hospital (51%) or existing contraindications (34%), and the less frequent cause was the non-existence of evident changes in the first ECG (10%) (Table 3). In 5% of the patients, the reasons for deciding against thrombolytic therapy remained unknown.

Table 2. Secondary cardiac events and mortality in patients with acute myocardial infarction in relation to thrombolytic therapy (TT)

<table>
<thead>
<tr>
<th>Secondary cardiac events</th>
<th>No. (%) of patients</th>
<th>with TT (n=100)</th>
<th>without TT (n=265)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmias</td>
<td>67 (67)</td>
<td>109 (41)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>20 (20)</td>
<td>104 (39)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Postinfarction angina</td>
<td>8 (8)</td>
<td>40 (15)</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>7 (7)</td>
<td>44 (17)</td>
<td>0.015</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Reasons for restraining from thrombolytic therapy (TT) in patients with acute myocardial infarction

<table>
<thead>
<tr>
<th>Reasons</th>
<th>No. (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time delay &gt;6 hours</td>
<td>135 (51)</td>
</tr>
<tr>
<td>Existence of contraindications</td>
<td>90 (34)</td>
</tr>
<tr>
<td>Absence of ECG criteria for TT</td>
<td>ST depression</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
</tr>
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</tbody>
</table>

Table 4. Time intervals relevant to the course of illness and thrombolytic therapy (TT) in patients with acute myocardial infarction

<table>
<thead>
<tr>
<th>Time intervals</th>
<th>Findings in patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>with TT</td>
</tr>
<tr>
<td>Pain-to-door time (h)</td>
<td>4.3 (0.5-72)</td>
</tr>
<tr>
<td>Door-to-needle time (min)</td>
<td>40 (5-25)</td>
</tr>
</tbody>
</table>

The median pain-to-door time in all patients was 4.3 hours; in patients with thrombolytic treatment it was significantly shorter than in patients without thrombolytic therapy (Table 4). The median door-to-needle time in all patients was 40 minutes. In patients with thrombolytic therapy, this interval was also significantly shorter than in patients with out thrombolysis (Table 4).

Discussion

Medical practice in certain fields of medicine varies significantly between various countries, reflecting to a large extent their economic and cultural development. Substantial differences may also exist between regions within the same country. Different aspects of management of patients with acute myocardial infarction were widely investigated in developed countries, revealing factors important for the patients' outcome (3). Although such data are crucial for the further improvement of patients' care, in the transitional countries they are largely missing. Our study aimed at providing such data for Croatia. The CCU of the Clinical Hospital Center Rijeka is the only such unit in three Croatian districts, with a catchment population of about 400,000 inhabitants of the western Croatia. It is one of the units with the largest number of treated patients in Croatia, considering that about 350-400 patients with acute myocardial infarction are treated each year. The mean age of our patients was relatively high (66±11 years), somewhat higher than that in large clinical trials of thrombolytic therapy (6-9). The patients' clinical characteristics, age in particular, determine not only the therapeutic approach but also affect the results of treatment and the final outcome. Old age (>70) used to be a contraindication for thrombolytic therapy due to the high risk of treatment complications, in particular intracranial hemorrhage. In elderly persons, the higher incidence of coexisting diseases also increases the risk. It was subsequently demonstrated that older patients, considering their naturally unfavorable course of illness, could benefit considerably from thrombolyis (10). Serious complications of thrombolytic therapy may be avoided by an individual approach to the patient, taking into account the biological than the chronological age and the accompanying diseases as well (14). However, many physicians hesitate to apply thrombolytic therapy in older patients, especially those over 75 years of age (11). The use of thrombolytic therapy in our study also declined with age. The less frequent use of streptokinese in female than in male patients (21% vs. 30%) can be explained by the higher age of women with AMI.

Although criteria for the evaluation of reperfusion and reocclusion used in this study are not to be readily available, our results correspond to the world-wide experience of achieved reperfusion in 50%-60% of patients, with a reocclusion incidence of 5%-30% (5-10). In most of our regional and urban hospitals only non-invasive criteria can be used, since catheterization laboratories are not available. In patients with thrombolytic therapy, the infarct course and outcome were more favorable than in patients without thrombolytic treatment. The higher incidence of arrhythmias in the group with thrombolytic therapy can be explained by a temporary electrical myocardial destabilization after reperfusion and a
more frequent appearance of mainly benign reperfusion arrhythmias. In our patients, the favorable effects of reperfusion on the reduction of the infarct size and the possibility of recurrent ischemia resulted in a substantially lower occurrence of heart failure and postinfarction angina, and a significantly lower mortality rate. Consequently, there were no serious complications of thrombolytic therapy, with the exception of two major bleedings (retroperitoneal hematoma and gross hematuria), both successfully managed with blood substitution.

Streptokinase treatment for acute myocardial infarction has been in use in our CCU since December 1984. Initially, only 10% of our patients underwent this type of treatment, which was confirmed by the low proportion of patients with previous myocardial infarction for whom thrombolytic therapy was started. However, since 1986, the use of thrombolytic therapy has been gradually increased to 40% of all patients with acute myocardial infarction, and the CCU has become useful (3,30). Croatia, with its formerly isolated and remote regions, should consider such measures in remote communities, such as islands and mountain regions, where the predicted transportation time to the hospital is longer than 90 minutes and the adequate medical equipment and staff is not available (3,30). In these cases, telemetric ECG transmission from field to the CCU is useful (3,30). Croatia, with its territory of inhabited islands, should consider such health systems organization and infrastructure.

Based on the results of this study, appropriate measures must be taken to increase the availability of thrombolytic therapy to the patients with acute myocardial infarction in the region of Rijeka. Such measures should include educational programs informing the public about the symptoms of acute myocardial infarction and the importance of early intervention, better organization of pre-hospital health services and medical education of all persons involved in the management of these patients. By these measures the proportion of patients treated with thrombolytic therapy could be increased from today’s 27% to some 35%-40%.

References


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