Clinical Studies

Accelerated ST-Segment Reduction after Thrombolytic Therapy with Recombinant Tissue Plasminogen Activator (rtPA) Compared to Urokinase

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SUMMARY

Effects of therapy with urokinase (UK) and with recombinant tissue plasminogen activator (rtPA) were compared in patients with acute myocardial infarction (AMI). To achieve homogenous therapeutic conditions the comparison was restricted to patients having their first AMI and to cases of clinically successful thrombolytic therapy (defined by non-invasive criteria, such as a 50% decrease in elevated ST-segment in the worst lead of a 12 lead ECG within 300 min after onset of thrombolytic therapy, complete pain resolution during thrombolytic therapy, and later confirmed by angiography 10 days after AMI).Effects of UK and rtPA on continuous multilead ST-segment analysis and cardiac proteins (creatine kinase and its isoenzyme CK-MB, aspartate transaminase and hydroxybutyrate dehydrogenase) were analyzed during 24 hours following onset of therapy.

Continuous ST analysis showed a faster resolution of the elevated ST-segments after thrombolytic therapy with rtPA than with UK (p<0.01). Accelerated idioventricular rhythms (p<0.05) occurred sooner following rtPA than UK treatment. The wash-out of creatine kinase was increased (p<0.01) after rtPA. Although both drugs induced comparable, angiographically controlled reperfusion, the results suggest that the process of reperfusion was accelerated during thrombolysis with rtPA compared to UK. Thrombolytic therapy of AMI with rtPA may hence improve myocardial salvage. (Jpn Heart J 1996; 37: 33–41)

Key words: Urokinase rtPA Continuous ST-segment analysis Wash-out of creatine kinase

THROMBOLYTIC therapy in acute myocardial infarction (AMI) reduces mortality by approximately 27%.1,2) A recent multicenter study did not

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indicate a clear advantage of four different thrombolytic regimens with regard to mortality. However, the diversity of patients and difficulties in separating influences of additive treatments after AMI from those of thrombolytic therapy complicates the comparison of thrombolytic therapies. Hence, in contrast with foregoing studies, in the present study two different strategies of thrombolytic therapy were evaluated in a fairly homogenous group of AMI patients with prompt and successful reperfusion of the infarct-related artery. Only patients who had their first myocardial infarction were included. In this homogenous patient sample the effects of urokinase (UK) or recombinant tissue plasminogen activator (rtPA) were compared by continuous ST-segment analysis. Continuous ST-segment monitoring allows a sensitive and noninvasive estimation of reperfusion. Rapid resolution of the ST elevation precedes the changes associated with the development of acute myocardial tissue damage, with an almost 5-fold faster time course. Moreover, continuous ST-segment monitoring allows one to recognize silent ST reelevations. Thus, starting with the patients’ admittance, a computer-assisted continuous multilead ECG was monitored and the ST-segment was analyzed during the first 24 hours after thrombolytic therapy. As an additional criterion for reperfusion, cardiac serum proteins were determined before, 8 and 24 hours after thrombolytic therapy. The aim of the study was to examine whether treatments with UK and rtPA differ in their effects on ST-segment recovery and on the wash-out of cardiac proteins during the first 24 hours after therapy in patients with clinically successful thrombolysis.

**Methods**

**Patient entry criteria:** Patients with AMI admitted between March 1993 and February 1994 were examined. AMI was diagnosed by clinical symptoms, a positive 12 lead ECG, and cardiac proteins (elevated myoglobin but normal CK-MB). Only patients with their first myocardial infarction and thrombolytic therapy within the first 6 hrs after onset of pain were included in the study. Patients with angina after onset of the thrombolytic therapy were excluded from ST-segment analysis. Successful reperfusion was assessed by means of persistent pain resolution during thrombolytic therapy and a 50% decrease in elevated ST-segment in the worst lead of a 12 lead ECG within 300 min after onset of thrombolytic therapy. These criteria were fulfilled by 19 patients. Ten were treated with rtPA (age 41–78, mean 59 ± 3 yrs; mean time delay between first symptom and thrombolytic therapy, 174 ± 27 min); and 9 patients were treated with UK (age 58–78, mean 68 ± 2 yrs; mean time delay between first symptom and thrombolytic therapy, 190 ± 27 min). During the study period two of the patients treated with UK and 1 treated with rtPA had to be excluded because of
a new angina event after onset of thrombolytic therapy. None of the patients developed ventricular fibrillation or cardiac arrest during the first 24 h after onset of thrombolytic therapy and no patient succumbed to fatal arrhythmias.

**Thrombolytic therapy:** All patients were treated with heparin (1000 IU/60 kg/h i.v.), aspirin (500 mg i.v.) and nitroglycerine (2 mg/h, adapted to blood pressure, i.v.). Analgesics (morphine, FentanylR or Fortral®) were given in the prehospital phase and, if necessary, on admission. Only those patients with definite pain resolution during and after thrombolytic therapy entered the study. For thrombolytic therapy either urokinase (Ukidan®, Serono, Germany) or recombinant tissue plasminogen activator (Actilyse®, Thomae, Germany) were randomly administered according to the study protocol. UK was given as an i.v. bolus of 1.5 million IU followed by a continuous 1 hour infusion of another 1.5 million IU; rtPA was infused at a front-loaded, weight-adjusted dose (total dose per 80 kg body weight: 100 mg administered over 90 min; 15 mg as a bolus over 2 min, then 50 mg over 30 min and finally 35 mg over 60 min),3,7) with both dosages recommended by the American Heart Association. The therapies were randomly distributed in a blinded, prospective setting. The patients gave their informed consent to thrombolytic therapy. They were not aware of which of the two treatments was administered.

**Study design and continuous ST-segment analysis:** Immediately after admission to the intensive care unit a 12 lead ECG was taken, then the patients were hooked up to a continuous multi-lead ECG monitoring system with Holter ECG electrode positioning. ECG, ST-segment vectors from 3 leads (I, II, III, V, or CM5, according to the infarction), heart rate, and blood pressure were continuously recorded by the Data Management System HP78365A (Hewlett Packard, Germany). The ECG lead with the maximal ST deviation was used for evaluation of the ST vector, lead III for inferior infarctions, and CM5 (precordial) for anterior AMI. Only cases with prominent initial ST-segment elevation in recordings from these leads (more than a third of the amplitude of the QRS vector; no pacemaker) were included in the study.

For ST-segment analysis the following algorithm was applied: the isoelectric point was set to the level present 80 msec before the R peak; the ST-segment-point was allocated 120 msec after the R peak. These values were individually controlled prior to analysis and, if necessary, manually adapted. The difference between isoelectric point and ST-segment-point, representing the ST-segment vector, was measured on line and documented by a printout. ST-segment vectors were assessed before initiation of thrombolytic therapy. For further evaluation ST-segment values were normalized with the maximal ST elevation point prior to thrombolytic therapy set to 100%. The QRS duration was controlled from the 12 lead ECG on admission and 24 hours after thrombolysis.
Arrhythmias were signaled by the Arrhythmia Control System (Hewlett Packard), visually evaluated and documented. Idioventricular rhythms were marked and the time to occurrence after onset of thrombolytic therapy was recorded. The QRS duration was evaluated from the 12 lead ECG on admission and 24 h after thrombolytic therapy.

The cardiac plasma proteins creatine kinase (CK), its isoform CK-MB, aspartate transaminase (GOT), hydroxybutyrate dehydrogenase (HBDH) and hemoglobin blood levels were measured on admission, 8 and 24 hours later. Coronary angiography was performed between 10 and 15 days after AMI.

For statistical evaluation of the ST-segments an ANOVA was applied with subsequent univariate t-tests. Evaluation of CK, CK-MB, GOT, HBDH and hemoglobin were based on t-tests. A Greenhouse-Geisser corrected p-value of < 0.05 was considered significant. The text provides means ± SEM.

RESULTS

Baseline characteristics: The group treated with rtPA comprised 2 patients with anterior AMI and 8 patients with inferior AMI including 2 patients with right ventricular involvement. The UK treated group included 2 patients with anterior AMI and 7 patients with inferior AMI (one of them with right ventricular involvement). The coronary angiography 10 to 15 days after AMI confirmed patency of the infarct-related artery. A TIMI flow\(^{a}\) grade 2 or 3 was assessed in 9 of the 10 patients of the rtPA group and 8 of the 9 patients of the UK group.

<table>
<thead>
<tr>
<th>Myoglobin [mg/ml]</th>
<th>rtPA</th>
<th>Urokinase</th>
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<tbody>
<tr>
<td>300.0</td>
<td>156.0</td>
<td></td>
</tr>
<tr>
<td>120.0</td>
<td>118.0</td>
<td></td>
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<tr>
<td>118.0</td>
<td>117.0</td>
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<td>311.0</td>
<td>70.0</td>
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<td>399.0</td>
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<td>63.0</td>
<td>85.0</td>
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<td>144.0</td>
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Mean: 233.7      150.9
SEM: 56.1        28.3

Difference between groups was not significant.
Table II. Delay between Start of Therapy and Appearance of Idioventricular Rhythm

<table>
<thead>
<tr>
<th>Time until accelerated idioventricular rhythm [min]</th>
<th>rtPA</th>
<th>Urokinase</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.0</td>
<td>54.0</td>
<td></td>
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<tr>
<td>30.0</td>
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<td>10.0</td>
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<tr>
<td>15.0</td>
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<td>20.0</td>
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</table>

Mean: 20.4 43.0
SEM: 4.1 4.8

After onset of fibrinolytic therapy idioventricular rhythm occurred in 9 of 10 patients treated with rtPA and in 7 of 10 patients treated with urokinase; p < 0.05 for the difference between groups.

In one patient of each group (both with the right coronary artery affected) a TIMI grade 1 perfusion was visible. The ejection fraction was normal (> 65%) except for 1 patient after UK with 26%, and 1 patient after rtPA with 35%. The
groups did not differ significantly with respect to plasma levels of myoglobin at admittance (Table I).

**ECG:** Idioventricular rhythms occurred in 9 patients after rtPA treatment, and in 7 patients after UK treatment. After rtPA treatment idioventricular rhythms occurred earlier than after UK treatment (Table II). The QRS duration did not differ significantly between the groups (rtPA group: before therapy 96 ± 3 msec, after 24 hours 94 ± 3 msec; UK group: before therapy 94 ± 3 msec, after 24 hours 89 ± 4 msec).

**ST-segment recordings:** At the beginning of the study (baseline) the degree of ST-segment elevation did not differ between the groups. The ST-segment recordings (Figure 1) showed a prompt resolution of the ST-segment vector with a mean reduction of 54% after UK therapy and of 80% after rtPA therapy, 90 minutes after the beginning of thrombolytic therapy. During the subsequent 60 min ST-segment levels were continuously lower after rtPA than after UK treatment. In the patients treated with rtPA an almost complete ST-segment reduction (90% reduction) was achieved within 4 hours after onset of the treatment, in the patients treated with UK a 78% reduction in the ST-segment was achieved.

![Figure 2](image_url)

*Figure 2.* Mean (± SEM) concentrations of creatine kinase (CK), its isoenzyme (CK-MB), aspartate transaminase (GOT), hydroxybutyrate dehydrogenase (HBDH), and hemoglobin (Hb) in patients treated with rtPA (white bars) or urokinase (shaded bars) before, 8 and 24 hours after onset of thrombolytic therapy. *p < 0.05, for differences between the effects of rtPA and urokinase.
The individual courses of ST-segments thereafter were still more variable in patients treated with UK than with rtPA (Figure 1).

**Cardiac proteins and hemoglobin:** Measures of cardiac proteins indicated a stronger increase in the CK plasma levels after rtPA than after UK treatment. There was no significant difference in the increase in CK-MB and GOT between the two groups (Figure 2), although mean values after rtPA exceeded those after UK. HBDH plasma levels 8 and 24 hours after rtPA exceeded those after UK; actually their maxima were not reached within 24 hours. Hemoglobin values did not differ between the groups.

**DISCUSSION**

In patients after a first AMI and with clinical criteria for successful reperfusion, continuous multilead ECG monitoring showed a significantly faster ST-segment recovery following treatment with rtPA than UK. The time to 80% ST recovery after rtPA treatment averaged 150 minutes. In contrast, following UK treatment the average ST-segment reduction did not exceed 80% until 12 hours after onset of treatment. So far, continuous ST-segment analysis has been described only during thrombolytic therapy with rtPA. Myocardial salvage after successful reperfusion has been examined after treatment with rtPA, but not after UK treatment. The strict criteria of selecting only patients without previous myocardial infarction and with successful reperfusion in this study set the stage for a more sensitive comparison of the *in vivo* effects of the two pharmacodynamically different thrombolytics.

Fast resolution of the ST-segment elevation after reperfusion is known to precede changes associated with the development of myocardial tissue damage. Thus, the prolonged time to ST-segment recovery after UK therapy compared to rtPA in this study might reveal a disadvantage of UK therapy with a reduced myocardial salvage compared to rtPA treatment. In this study the earlier ST-segment recovery after rtPA treatment was accompanied by a shorter time until accelerated idioventricular rhythms occurred. Accelerated idioventricular rhythms may indicate that reperfusion occurred. In fact, here they accompanied the acceleration of ST-segment reduction, indexing reperfusion, after rtPA therapy.

Angiography performed 10 days after AMI confirmed reperfusion, except for a prominent stenotic lesion in one patient after rtPA treatment, and another significant stenosis indicated by a TIMI flow grade 1 in one patient treated with UK. Considering that angiography took place quite a long time after AMI, it is likely that in both cases silent restenotic processes developed after thrombolytic therapy.
Plasma concentrations of myoglobin (on admission), CK-MB and GOT (prior to, 8 hours and 24 hours after treatment) did not differ significantly between the groups, indicating that the area at risk was comparable in both groups. As expected after successful reperfusion, plasma levels of CK and CK-MB reached a maximum within 8 hours after thrombolytic therapy. However, the levels of CK and also of HBDH after rtPA treatment exceeded those after UK treatment (8 and 24 hours after onset of therapy). An increase in plasma CK and HBDH concentrations may be an indicator for hemolytic processes and blood cell apoptosis, but there were no signs of bleeding complications (such as hematuria or manifest bleeding) or differences in hemoglobin levels in the 19 patients. Thus, hemolysis cannot account for the finding of increased plasma concentrations of CK and HBDH after rtPA treatment.

However, though myoglobin and CK-MB did not reveal differences in the infarcted area between the two treatment groups, the wash-out of CK and HBDH was increased after rtPA. Whether this increase originated from more extended infarctional damage in the rtPA group, or was related to a local, enhanced action of rtPA on the myocardium at risk, is presently unclear. Assuming a greater infarcted area in the rtPA treated group than in the UK group, the accelerated reduction of the ST-segment elevation following rtPA treatment would be indicative of an even greater advantage of rtPA over UK in in vivo thrombolysis.

In conclusion, thrombolysis with rtPA was superior to thrombolysis with UK in accelerating ST-segment reduction in patients with successful thrombolytic therapy of a first myocardial infarction. Accelerated ST-segment regression correlates with improved myocardial salvage. Hence, beneficial effects of rtPA on myocardial salvage may be deduced from the present results.

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References


