Randomized Trial of Intraarterial Infusion of Urokinase Within 6 Hours of Middle Cerebral Artery Stroke

The Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) Japan

Akira Ogawa, MD; Etsuro Mori, MD; Kazuo Minematsu, MD; Waro Taki, MD; Akira Takahashi, MD; Shigeru Nemoto, MD; Susumu Miyamoto, MD; Makoto Sasaki, MD; Takashi Inoue, MD; for The MELT Japan Study Group

Background and Purpose—The Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) Japan was organized to determine the safety and clinical efficacy of intraarterial infusion of urokinase (UK) in patients with stroke within 6 hours of onset.

Methods—Patients with ischemic stroke presenting within 6 hours of onset and displaying occlusions of the M1 or M2 portion of the middle cerebral artery on carotid angiography were randomized to the UK or control groups. Clinical outcome was assessed by the modified Rankin Scale, National Institutes of Health Stroke Scale, and Barthel Index.

Results—The Independent Monitoring Committee recommended stopping the trial after approval of intravenous infusion of recombinant tissue plasminogen activator in Japan. A total of 114 patients underwent randomization, 57 patients in each group. Background characteristics were comparable between the 2 groups. The primary end point of favorable outcome (modified Rankin Scale 0 to 2) at 90 days was somewhat more frequent in the UK group than in the control group (49.1% and 38.6%, OR: 1.54, 95% CI: 0.73 to 3.23) but did not reach a significant level (P=0.345). However, excellent functional outcome (modified Rankin Scale 0 to 1) at 90 days, a preplanned secondary end point, was more frequent in the UK group than in the control group (42.1% and 22.8%, P=0.045, OR: 2.46, 95% CI: 1.09 to 5.54). There were significantly more patients with National Institutes of Health Stroke Scale 0 or 1 at 90 days in the UK group than the control group (P=0.017). The 90-day cumulative mortality was 5.3% in the UK group and 3.5% in the control group (P=1.000), and intracerebral hemorrhage within 24 hours of treatment occurred in 9% and 2%, respectively (P=0.206).

Conclusions—The trial was aborted prematurely and the primary end point did not reach statistical significance. Nevertheless, the secondary analyses suggested that intraarterial fibrinolysis has the potential to increase the likelihood of excellent functional outcome. (Stroke. 2007;38:2633-2639.)

Key Words: acute ■ local fibrinolysis ■ middle cerebral artery ■ stroke ■ urokinase

Embolic occlusion of the middle cerebral artery (MCA) is one of the most clinically severe types of stroke, resulting in either death or severe neurological deficit. Intravenous thrombolytic therapy may be ineffective for patients with large vessel occlusion. Intraarterial therapy has the theoretical advantage of establishing the neurovascular diagnosis and achieving high symptomatic artery recanalization rate. Direct intraarterial delivery of fibrinolytic agents is reportedly more effective to recanalize major symptomatic cerebral arterial occlusions than intravenous delivery. Combination therapy of intravenous and intraarterial infusion of recombinant tissue plasminogen activator (rtPA) has benefits in patients with acute major cerebral artery ischemia. A number of uncontrolled case series have demonstrated the benefit of local intraarterial fibrinolysis in the treatment of acute ischemic stroke, and a randomized, controlled trial, the Prolyse in Acute Cerebral Thromboembolism (PROACT) II study, demonstrated the clinical efficacy of intraarterial fibrinolysis in patients with acute stroke caused by MCA occlusion at less than 6 hours’ duration. The PROACT II study was a randomized, controlled, multicenter clinical trial in which a total of 180 patients with acute ischemic stroke of less than 6 hours’ duration caused by occlusion of the MCA were randomized. For the primary analysis, 40% of patients with fibrinolysis and 25% of control patients had a modified Rankin Scale (mRS) of 2 or less (P=0.04).
Although randomized, controlled clinical trials of rtPA (duteplase) in Japan demonstrated that intravenous administration of duteplase was beneficial for patients with acute embolic stroke within 6 hours of onset, the development of duteplase was aborted because of the patent issue. No form of thrombolytic therapy was approved in Japan until intravenous administration of rtPA was approved in October 2005 for the treatment of patients within 3 hours of onset from ischemic stroke on the basis of evidence suggesting clinical benefits.

In January 2002, we began a multicenter, randomized, controlled trial examining the safety and efficacy of intraarterial infusion of urokinase (UK) (Tokyo Mitsubishi, Tokyo, Japan) in patients with symptomatic MCA occlusion of less than 6 hours’ duration, called the MC Artery Embolism Local Fibrinolytic Intervention Trial (MELT) Japan. The MELT Japan was supported by Grants-in-Aid from the Ministry of Health, Labor and Welfare of Japan, which allowed only the use of UK for fibrinolytic therapy. When intravenous rtPA was approved for ischemic stroke in October 2005, the Independent Monitoring Committee advised discontinuation of the trial for ethical and scientific reasons. New patient enrollment was stopped on the day of the approval. We report the results of this prematurely terminated trial.

Subjects and Methods

The MELT Japan was a multicenter, randomized, controlled study conducted at 57 centers in Japan (see Supplement) between January 2002 and October 2005 under the good clinical practice regulations. The patients were randomized to the UK and control groups. The protocol was approved by all Institutional Review Boards. An independent review committee monitored the study for safety.

Inclusion and Exclusion Criteria

The inclusion criteria were: new onset of focal neurological signs in the MCA distribution allowing randomization and initiation of fibrinolysis within 6 hours from the onset of symptoms; minimum National Institutes of Health Stroke Scale (NIHSS) score of 5, except for immediate improvement before initiation of treatment; no or only subtle early ischemic signs in the insular cortex, frontal and temporal opercula, or lenticular nuclei on initial CT allowing initiation of treatment within 2 hours of CT; and age 20 to 75 years old.

The clinical exclusion criteria were: coma; NIHSS score >22; seizure at stroke onset; premorbid disability of mRS score of >2; presumed fat embolus or endocarditis; and complication of other diagnostic angiography. Patients with high risk of hemorrhagic complication were also excluded based on the following: platelet count <100 000/mm³; heparinization within 48 hours (exceeding the normal range of the local institute or >1.5 fold of the preadministration level); warfarinization with an international normalized ratio >1.7; postadministration status of other fibrinolytic agents, sodium ozagrel, argatroban, or UK; surgery or parturition within 30 days; history of intracranial hemorrhage or serious head trauma at any time; history of serious trauma except to the head within 30 days; history of intracranial hemorrhage or serious head trauma at any time; no specific treatments were indicated for the control group. Osmotic diuretics were used in patients manifesting high intracranial pressure. Intravenous infusion of fibrinolytic agents was prohibited in both UK and control groups. Any approved medical or rehabilitation treatment was allowed in all patients except for antithrombotic therapies, including heparin, warfarin, aspirin, and ticoprinid, for 24 hours after fibrinolysis in the UK group.

Evaluation

All patients in the UK group underwent repeated angiography to assess recanalization after UK infusion. All angiograms were evaluated by the Film Reading Committee, who were unaware of the clinical information, into the following treatment outcomes: no recanalization; partial recanalization <50% in the affected territory; complete recanalization 50% and over in the affected territory; and complete recanalization. No follow-up angiography was performed in the control group.

Clinical outcome was assessed by physicians unaware of the treatment allocation with the NIHSS, mRS, and Barthel Index at 7, 30, and 90 days after treatment. The physicians unaware of treatment allocation assessed outcomes from direct patient contact.

Follow-up CT scans were scheduled at 24 hours, 7 days, and 90 days after symptom onset. Symptomatic intracranial hemorrhage was defined as CT evidence of new intracranial hemorrhage with apparent neurological deterioration manifesting as objective signs or an increase of >4 points from the most recent NIHSS score. Patients with an increase of <4 points of NIHSS but who had apparent objective signs were considered as “symptomatic.” The study pro-
tocol required CT and NIHSS evaluations whenever neurological deterioration was identified.

**Primary End Point**
The primary end point was the proportion of patients with favorable outcomes (mRS scores of 0 to 2) at 90 days.

**Secondary End Points**
The secondary end points were: the incidence of symptomatic intracranial hemorrhage within 24 hours after starting treatment; any death within 90 days; the rate of the recanalization of the MCA; the proportion of patients achieving a NIHSS score of 0 and 1 at 24 hours, 30 days, and 90 days; the proportion of patients achieving a NIHSS score of 0 and 1 at 24 hours, 30 days, and 90 days; the proportion of patients achieving a Barthel Index score of 95 or greater at 30 and 90 days; the proportion of patients achieving an mRS score of 0 and 1 at 30 and 90 days; and any hemorrhagic finding on CT.

**Statistical Analysis**
The primary and secondary clinical efficacy analyses were performed on an intention-to-treat basis. We calculated that 200 patients were required for the study to have a statistical power of 80% to detect the difference of 20% in favorable outcome between the 2 groups at the 2-sided 0.05 level. Attributes and outcomes were compared between the 2 groups with the 2-tailed Fisher exact test, when appropriate.

**Results**

**Patients**
The Independent Monitoring Committee recommended stopping the inclusion of any new patients presenting at less than 3 hours after onset who were eligible for intravenous rtPA and requested that the inclusion criteria be modified in accordance or the trial be terminated. The modification of the inclusion criteria would have seriously affected the selection of the study subjects, because 77% of patients had actually arrived at the hospital within 2.5 hours. Therefore, the Steering Committee decided to stop new patient enrollment to the trial on the day of approval and to terminate the trial prematurely.

During the trial, 337 patients who fulfilled all clinical and CT inclusion criteria were preregistered for entry, of whom 115 patients (34.1%) satisfied the angiographic criteria and underwent randomization (Figure 1). One hundred sixty-seven patients (49.6%) did not fulfill the angiographic criteria, 17 patients (5.0%) were excluded for the appearance of early ischemic sings on second CT, 12 patients (3.6%) had improved NIHSS (<5) during angiography, 12 patients (3.6%) did not give consent, 2 patients (0.6%) had failed placement of the diagnostic catheter in the carotid artery, 2 patients (0.6%) were passed 6 hours from the symptom onset during angiography, and 10 patients (3.0%) were excluded for other reasons. One of the 115 patients was not randomized because of a computer system error. Of the 114 randomized patients, 57 patients were allocated to the UK group and 57 patients to the control group.

CT was performed at a mean of 105 minutes from symptom onset, and randomization was made at a mean of 197 minutes from symptom onset in the 114 patients. Intracranial UK infusion was started at a mean of 227 minutes from symptom onset in the 56 patients in the UK group. One patient in the UK group did not receive UK because of...
Table 1. Characteristics of Treated Patients

<table>
<thead>
<tr>
<th></th>
<th>UK</th>
<th>Control</th>
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<tbody>
<tr>
<td>n</td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td>Male sex</td>
<td>64.90%</td>
<td>64.90%</td>
</tr>
<tr>
<td>Age, years</td>
<td>66.9±9.3</td>
<td>67.3±8.5</td>
</tr>
<tr>
<td>NIHSS*</td>
<td>14.0 (8.0)</td>
<td>14.0 (6.8)</td>
</tr>
<tr>
<td>Cardioembolic stroke</td>
<td>88%</td>
<td>83%</td>
</tr>
<tr>
<td>Time from onset to hospitalization, minutes</td>
<td>68±46</td>
<td>79±52</td>
</tr>
<tr>
<td>Time from onset to allocation, minutes</td>
<td>199±61</td>
<td>206±54</td>
</tr>
<tr>
<td>Blood pressure at hospitalization</td>
<td>154/88</td>
<td>145/82</td>
</tr>
<tr>
<td>Left hemisphere stroke</td>
<td>56%</td>
<td>51%</td>
</tr>
<tr>
<td>Positive early CT signs</td>
<td>47%</td>
<td>47%</td>
</tr>
<tr>
<td>Occlusion location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>39 (68.4%)</td>
<td>42 (73.7%)</td>
</tr>
<tr>
<td>M2</td>
<td>18 (31.6%)</td>
<td>15 (26.3%)</td>
</tr>
</tbody>
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*Median (interquartile range). All other values are mean±SD or literal values.

Technical difficulty. One patient in the control group underwent intraarterial UK infusion because of human error. The UK and control groups were well matched with regard to the median entry NIHSS score, presumed source of embolus, sex, and age (Table 1). Early ischemic change, defined as subtle sulcal effacement or loss of gray–white matter distinction in the insular cortex, frontal and temporal opercula, or lenticular nuclei, was observed on the initial CT scan in 27 patients in both UK and control groups.

Primary and Secondary End Points at 90 Days

The primary and secondary end points at 90 days are summarized in Table 2 and Figure 2. For the primary end point, 28 patients (49.1%) in the UK group had NIHSS 0 to 2 at 90 days compared with 22 patients (38.6%) in the control group (P=0.345, OR: 1.54, 95% CI: 0.73 to 3.23). Nevertheless, for the secondary end points, the UK group included more patients with NIHSS 0 or 1 at 90 days compared with the control group (24/13, P=0.045, OR: 2.46, 95% CI: 1.09 to 5.54). There were significantly more patients with NIHSS 0 or 1 at 90 days in the UK group than the control group (20/8, P=0.010, OR: 3.311, 95% CI: 1.334 to 8.183). The UK group included more patients with Barthe Index of 95 or more than the control group, but the difference did not reach the significance level (P=0.128). The 90-day cumulative mortality was 3 patients (5.3%) in the UK group and 2 patients (3.5%) in the control group (P=1.000). Death was attributed to medical complications associated with the initial stroke in 2 patients, hemorrhagic transformation in one, stroke recurrence in one, and malignant tumor in one (Table 3). There was no significant difference between the groups.

Forty patients received the full dose of UK (600,000 IU) and 16 patients received UK less than 600,000 IU. Partial or complete recanalization was archived in 42 of 57 patients (73.7%) treated with intraarterial UK infusion. Mechanical clot disruption was performed in 39 of the 57 patients (68%). Recanalization was complete in 3 patients, partial ≥50% in 27, partial < 50% in 12, and not achieved in 15.

Table 2. Clinical Outcomes at 90 Days

<table>
<thead>
<tr>
<th></th>
<th>UK (n=57)</th>
<th>Control (n=57)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to 2</td>
<td>28 (49.1%)</td>
<td>22 (38.6%)</td>
<td>0.345</td>
</tr>
<tr>
<td>0 and 1</td>
<td>24 (42.1%)</td>
<td>13 (22.8%)</td>
<td>0.045</td>
</tr>
<tr>
<td>NIHSS 0 and 1</td>
<td>20 (35.1%)</td>
<td>8 (14.0%)</td>
<td>0.017</td>
</tr>
<tr>
<td>Barthel Index ≥95</td>
<td>28 (49.1%)</td>
<td>19 (33.3%)</td>
<td>0.087</td>
</tr>
</tbody>
</table>

Severe Adverse Events

Severe adverse events are summarized in Table 4. Intracerebral hemorrhage within 24 hours of treatment occurred in 5 patients (9%) in the UK group, including one patient with hematoma caused by guidewire perforation, compared with one patient (2%) in the control group (P=0.206). Severe brain edema followed by air embolism occurred in one patient in the UK group. Neurological deterioration related to hypotension after antipyretic suppository administration occurred in one patient in the UK group. One patient died of a metastatic brain tumor, which was not recognized at randomization. One patient died of pulmonary embolism. There was no significant difference in the frequency of severe adverse events between the UK and control groups.

Early ischemic changes greater than those permitted by the inclusion criteria were found at the central reading in 9 of 114 patients (7.9%). Among these patients, 5 patients received intraarterial UK therapy and 2 patients developed hemorrhagic transformation within 24 hours.

Discussion

The MELT Japan was aborted prematurely and the primary end point did not reach statistical significance (P=0.345). Nevertheless, compared with the patients receiving conventional therapy, patients treated with intraarterial UK infusion at a mean of 227 minutes from symptom onset were 86% more likely to achieve complete recovery at 90 days. The 19% absolute increase in favorable outcome with intraarterial UK (P=0.045) indicates that one in 6 patients treated with intraarterial UK will benefit. The absolute increase of no or slight neurological deficit (NIHSS 0 or 1), a secondary end point, was 21.1% (35.1% in the UK group and 14.0% in the control group, P=0.010). The difference in the proportion of Barthel Index ≥95 did not reach significance (49.1% in the UK group and 33.3% in the control group, P=0.128). Despite the efficacy of intraarterial fibrinolysis demonstrated at the secondary end points, and the higher absolute increase of excellent global functional outcome (mRS 0 and 1) than previous intravenous rt-PA trials,16,19 the open-labeled design of this trial would cause a significant source of biases, which are needed to be addressed. First, patients may know whether they received fibrinolysis therapy. Second, detection bias may occur, although assessors were unaware of treatment allocation. Third, the choice of poststroke therapy may have caused performance bias.

The MELT Japan restricted patient selection to MCA occlusion because of the poor natural history1 and the most frequent location in patients with severe stroke of less than 6 hours’ duration.20 In contrast to the National Institute of
Neurological Disorders and Stroke (NINDS) rtPA trial, the MELT Japan used slight or no neurological disability (mRS score 0 to 2) as the primary outcome measure and complete recovery (mRS score 0 and 1) as the secondary outcome measure because of the anticipated baseline of high severity of stroke in patients with MCA occlusion. It is debatable what is the optimal cutoff point of the functional outcome scale for dichotomization of outcomes in an acute stroke trial. The PROACT II trial defined mRS score of ≤2 (dichotomized for independence) as the favorable outcome and showed the efficacy of intraarterial fibrinolysis. The European Cooperative Acute Stroke Study II, defining mRS of 0 and 1 (dichotomized for complete recovery or minimal deficit) as the favorable outcome, failed to show the efficacy of thrombolysis. On the contrary, the NINDS study demonstrated a significant increase in the percentage of patients with mRS 0 and 1.

Various reasons can be proposed for the failure to show efficacy as measured by mRS in this study. First, because the present trial was terminated prematurely, the number of patients was obviously too few to detect any difference between the UK and control groups at the primary end point. Second, the 38.6% of patients with mRS score 0 to 2 in the control group was relatively higher than the percentage expected in the present trial. The MELT Japan did not apply the one third rule of early ischemic CT sign, which is widely used. The patients in the MELT Japan might have had less severe stroke than in other randomized acute stroke trials. Therefore, the median NIHSS score was smaller than in the PROACT studies. The rate of patients who were excluded because of the presence of early ischemic CT signs at study entry should have been collected to estimate the proportion of candidates in the population in this study.

To demonstrate the pharmacological effect of UK, the MELT Japan prohibited mechanical clot disruption except for the guidewire technique. The recanalization rate of 73.7% in the present study was better than that of 66% reported previously. The PROACT II study prohibited any mechanical procedure. Therefore, mechanical fibrinolysis may be one of the reasons for the present favorable recanalization rate. Advances in catheter technology, imaging techniques, mechanical clot removal, and more protective fibrinolytic agents should lead to faster and more complete recanalization and potentially even better patient outcomes.

The total intracranial hemorrhage rates were consistent with those previously reported in patients with embolic stroke. However, intracranial hemorrhage was 5 times more common, although not significantly, in the UK group than in the control group (5 versus one patient). Because the present trial was too small to detect any difference, a type II error is highly likely, and intraarterial fibrinolysis therapy certainly carries increased risk of hemorrhagic complication or air embolism.

Conversion of the dose of UK to the corresponding dose of rtPA is not easy, because the safety and efficacy profiles are different, but this exercise would be useful for practice in countries where UK is not available as well as now in Japan. We would like to mention only very practical comparisons. Bleeding rate is not higher in patients treated with UK than those with rtPA. Dose ranges for fibrinolysis therapy were 25 to 160 mg (mean dose, 73.5) for rtPA and 150 000 to 1 700 000 IU (mean dose, 694 000) for UK. The administration of the dose of UK was determined by the total weight of the patient according to the calculated body weight and the expected weight of the UK solution. The maximum dose was 160 mg. The dose of the UK was 25 mg for the first 56 kg, 30 mg for 57 to 80 kg, 35 mg for 81 to 100 kg, 40 mg for 101 to 135 kg, and 45 mg for 136 kg or more.

Table 3. Mortality Within 90 Days

<table>
<thead>
<tr>
<th></th>
<th>UK (n=57)</th>
<th>Control (n=57)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All mortality</td>
<td>3 (5.3%)</td>
<td>2 (3.5%)</td>
<td>0.647</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Malignant tumor</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>0</td>
<td>1</td>
<td></td>
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Table 4. Complications

<table>
<thead>
<tr>
<th></th>
<th>UK</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracerebral hemorrhage</td>
<td>5 (9%)*</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Brain edema</td>
<td>3 (5%)†</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Recurrence</td>
<td>4 (7%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (5%)</td>
<td>5 (9%)</td>
</tr>
</tbody>
</table>

*Including one case caused by perforation by the guidewire.
†Including one case followed by air embolism.
tion of rtPA in a dose of more than 80 mg causes a significantly higher bleeding rate than UK.28 On the other hand, complete recanalization was considered to be 64% or 49% in the rtPA and UK groups, respectively (P<0.05).28

The NINDS study supports the use of intravenous rtPA within 3 hours of stroke, but limited data suggest that intravenous rtPA may be relatively ineffective in the subset of patients with MCA occlusion. An angiography-based trial demonstrated that successful recanalization with intravenous infusion of rtPA was significantly less likely in complete MCA occlusion than peripheral lesions.20 Baseline NIHSS score >10 and hyperdense MCA sign on CT (significant MCA occlusion) both predict poor clinical outcome for patients treated with intravenous rtPA at less than 3 hours from symptom onset.29 Intraarterial fibrinolysis may have greater potential in both the recanalization rate and the wider therapeutic window. Thrombolytic recanalization is associated with reduction of neurological deficits and lower infarction volume on CT.8 The reductions of infarction volume and therapeutic window. Thrombolytic recanalization is associated with reduction of neurological deficits and lower infarction volume on CT.8 The reductions of infarction volume and functional outcome are highly correlated with the degree of reflow.8 Intraarterial fibrinolysis may be feasible after intravenous rtPA in patients with persistent MCA occlusion.30–32

Conclusion
The present trial was aborted prematurely and the primary end point did not reach statistical significance. Nevertheless, secondary analyses of the results suggest that local intraarterial UK fibrinolysis therapy for patients with acute MCA occlusion at <6 hours after onset may have the potential to increase the likelihood of excellent functional outcome at 90 days. Meta-analyses and more recent studies suggest a benefit for a subset of patients beyond 3 hours.33–35 The present trial also supports the clinical potential of fibrinolysis therapy at more than 3 hours after onset. Further studies with a larger number of patients are needed to confirm these results.

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Disclosures
None.

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