of 197 minutes from symptom onset in the 114 patients. Intra-arterial UK infusion was started at the mean of 227 minutes from symptom onset in the 56 patients in the UK group. One patient in the UK group was not treated with intra-arterial UK infusion because of technical reason. One patient in the control group underwent intra-arterial UK infusion because of human error. The UK and control groups were well matched with regard to the mean 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 endpoints at 90 days

The primary and secondary end points at 90 days are summarized in Table 2. For the primary endpoint, 28 patients (49.1%) in the UK group had mRS 0 to 2 at 90 days compared with 22 patients (38.6%) in the control group (p=0.345). Nevertheless, for the secondary endpoints, the UK group showed a 15.8% to 21.1% absolute increase in excellent functional outcome (mRS 0-1) compared to the control group at 90 days (p=0.045). There were significantly more patients with NIHSS 0 or 1 at 90 days in the UK group than the control group (p=0.017). The UK group included more patients with Barthel index of 95 or more than the control group, but the difference did not reach at the significance level (p=0.065). The 90-day cumulative mortality was 5.3% in the UK group and 3.5% in the control group (p=0.647). Death was attributed to medical complications associated with the initial stroke in 2 patients, hemorrhagic transformation in 1, recurrence in 1, and malignant tumor in 1 (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 intra-arterial UK infusion. Mechanical clot disruption was performed in 39 of the 57 patients (68%). Recanalization was complete in 3 patients, partial 50 % and more in 27, partial less than 50% in 12, and not achieved in 15.

Severe adverse events

Severe adverse events are summarized in Table 4. Intracerebral hemorrhge within 24 hours of treatment occurred in 5 patients (9%) in the UK group, including one patient with hematoma caused by perforation by the guide wire, compared with 1 patient (2%) in the control group (not significant). Severe brain edema followed by air embolism in one patient in the UK group. There was no significant difference in the frequency of severe adverse events between the UK and control groups.

Early ischemic change expanded from that of the inclusion criteria was observed on the initial CT scan in 9 of 114 patients (7.9%). Among these patients, 5 patients received intra-arterial UK therapy and 2 patients developed hemorrhagic transformation within 24 hours.

Discussion

The MELT Japan suggested beneficial effects of intra-arterial fibrinolysis in patients with acute stroke caused by MC artery occlusion of less than 6 hours' duration, although the result was negative with respect to the primary endpoint. The absolute increase of excellent neurological outcome, a secondary endpoint, was 19.3 % as mRS, which was better than other previous intra-venous rt-PA trials.[2,15] Compared with the patients receiving conventional therapy, patients treated with intra-arterial 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 intra-arterial UK (p=0.045) indicates that one in 6 patients treated with intra-arterial UK will benefit.

The MELT Japan restricted patient selection to MC artery occlusion because of the poor natural history[1] and the most frequent location in patients with severe stroke of less than 6 hours' duration.[16] In contrast to the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA trial,[2] 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 MC artery occlusion. It is debatable what is the optimal cut-off point of the functional outcome scale for dichotomization of outcomes in an acute stroke trial. The PROACT II trial defined mRS score of 2 or less (dichotomised for independency) as the favorable outcome, and showed the efficacy of intra-arterial fibrinolysis.[13] The European Cooperative Acute Stroke Study II, defining mRS of 0 and 1 (dichotomised for complete recovery or minimal deficit) as the favorable outcome, failed to show the efficacy of intra-venous fibrinolysis, although an analysis of mRS score of 2 or less as the secondary end point demonstrated the efficacy of thrombolysis.[15] On the contrary, the NINDS study demonstrated significant increase in the percentage of patients with mRS 0 and 1.[2]

Various reasons can be proposed for the failure to show efficacy as measured by mRS in this study. Firstly, 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 PROACT II trial reported that only 25% of the control group demonstrated mRS 2 or less. Administration of neuroprotective agents such as the free radical scavengers,[17] which are widely used in Japan for improving functional outcome in patients with acute ischemic stroke, may also have affected this finding. Secondly, the number of enrolled patients was too small to recognize any difference between the UK and control groups at the primary endpoint in the present study. In the PROACT II study, 13 patients allocated to the proUK group did not receive fibrinolytic therapy and 5 control patients received fibrinolytic agent. If these 18 patients are removed from the intention-to-treat analysis, the difference is not significant. Thirdly, the CT criteria of the MELT Japan are different from other trials.[2,3,13-15,18] The MELT Japan did not apply the one third rule of early ischemic CT sign which was widely used.[2,3,13-15,18-20] Instead, patients were

included with no or subtle early ischemic signs only in the insular cortex, frontal and temporal opercula, or lenticular nuclei. Such an area may cover less than one third of the MC artery distribution area, so the patients in the MELT Japan might have had less severe stroke than in other randomized acute stroke trials. Thereby, the mean NIHSS score was smaller to those in other studies[2,3,14,15]

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.[13] 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 protect fibrinolytic agents should lead to faster and more complete recanalization and potentially even better patient outcomes.

The total ICH rates were consistent with those previously reported in patients with embolic stroke.[21-23] There was no significant difference in the rates of ICH throughout the trial period, which may reflect delayed recanalization in the control group with hemorrhagic transformation, whereas the higher early rate with UK reflected drug-induced recanalization and reperfusion hemorrhage.

The NINDS study supports the use of intravenous rt-PA within 3 hours of stroke, but limited data suggest that intravenous rt-PA may be relatively ineffective in the subset of patients with MC artery occlusion. An angiography-based trial demonstrated that successful recanalization with intravenous infusion of rt-PA was significantly less likely in complete MC artery occlusion than peripheral lesions.[16] Baseline NIHSS score greater than 10 and hyperdense MC artery sign on CT (significant MC artery occlusion) both predict poor clinical outcome for patients treated with intravenous rt-PA at less than 3 hours from symptom onset.[24] Intra-arterial fibrinolysis may have greater potential in both the recanalization rate and the wider therapeutic window. Intra-arterial fibrinolysis may be feasible after intravenous rt-PA in patients with persistent MC artery occlusion.[25-27]

The therapeutic window in acute human ischemic stroke has been very controversial.[28,29] Recent diffusion and perfusion magnetic resonance studies suggest that as many as two thirds of patients with acute MC artery distribution stroke have brain tissue at risk even 24 hours after stroke onset, but the clinical relevance of these observations is uncertain.[30] The MELT Japan demonstrated that the therapeutic window may extend to at least 6 hours for a significant number of patients with major stroke due to MC artery occlusion although it was clarified by the secondary endpoint.

Conclusion

Local intra-arterial UK fibrinolysis therapy for patients with acute MC artery occlusion at less than 6 hours after onset is safe and more likely to lead to complete recovery at 90 days. This should be reserved, however, because the trial was aborted prematurely and the primary end point did not reach

at the statistical significance. Further studies with a larger number of patients are needed to confirm these results.

Appendix: The MELT Japan Study Group

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Table 1. Characteristics of Treated Patients

		UK	Control
n		57	57
Male sex		64.90%	64.90%
Age, y		66.9 ± 9.3	67.3 ± 8.5
NIHSS		14.7 ± 5.1	14.2 ± 4.2
Cardioembolic stroke		88%	83%
Time from onset to hospitalization, min		68 ± 46	79 ± 52
Time from onset to allocation, min		199 ± 61	206 ± 54
BP at hospitalization		154/88	145/82
violation of BP		14	6
Occlusion location			
	proximal M1	14 (24.6%)	18 (31.6%)
	distal M1	25 (43.9%)	24 (42.1%)
	M2	18 (31.6%)	15 (26.3%)

UK, urokinase; NIHSS, National Institutes of Health Stroke Scale; BP, blood pressure.
All values are mean ±SD or literal values.

Table 2. Clinical Outcomes at 90 days

Scores	UK (n=57)	Control (n=57)	P value
Modified Rankin Scale			
0 to 2	28 (49.1%)	22 (38.6%)	0.345
0 and 1	24 (42.1%)	13 (22.8%)	0.045
NIHSS 0 and 1	20 (35.1%)	8 (14.0%)	0.017
Barthel Index 95 or greater	28 (49.1%)	19 (33.3%)	0.087

Table 3. Mortality within 90 days

	UK (n=57)	Control (n=57)	P value
All mortality	3 (5.3%)	2 (3.5%)	0.647
intracerebral hemorrhage	1	0	
recurrence	1	0	
malignant tumor	1	0	
renal failure	0	1	
sepsis	0	1	

Table 4. Complications

	UK	Control
Intracerebral hemorrhage	5 (9%)*	1 (2%)
Brain edema	3 (5%)#	2 (4%)
Recurrence	4 (7%)	1 (2%)
Other	3 (5%)	5 (9%)

* including one patient caused by perforation by the guidewire.

including one patient followed by air embolism.

Figure legends

Fig.1

Distribution of patients for entry and randomization. UK indicates urokinase.

Fig.2

Representative computed tomography (CT) scans at baseline (left) and 24 hours after symptom onset (right) in a 72-year-old man with left hemiparesis allocated to the Control group. Baseline CT was performed 2 hours after symptom onset.

Left: Subtle early ischemic sign was seen in the right insular cortex (arrow) and lenticular nuclei (arrowhead).

Right: New infarctions are present in the insular cortex and lenticular nuclei.

Supplement

Secondary endpoint at 24 hours and 30 days

The UK group had a significantly better neurological outcome by mRS at 30 days (p=0.009), as NIHSS at 24 hours (p=0.022), and 30 days (p=0.017), and as Barthel Index at 30 days (p=0.016).

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Fig. 1

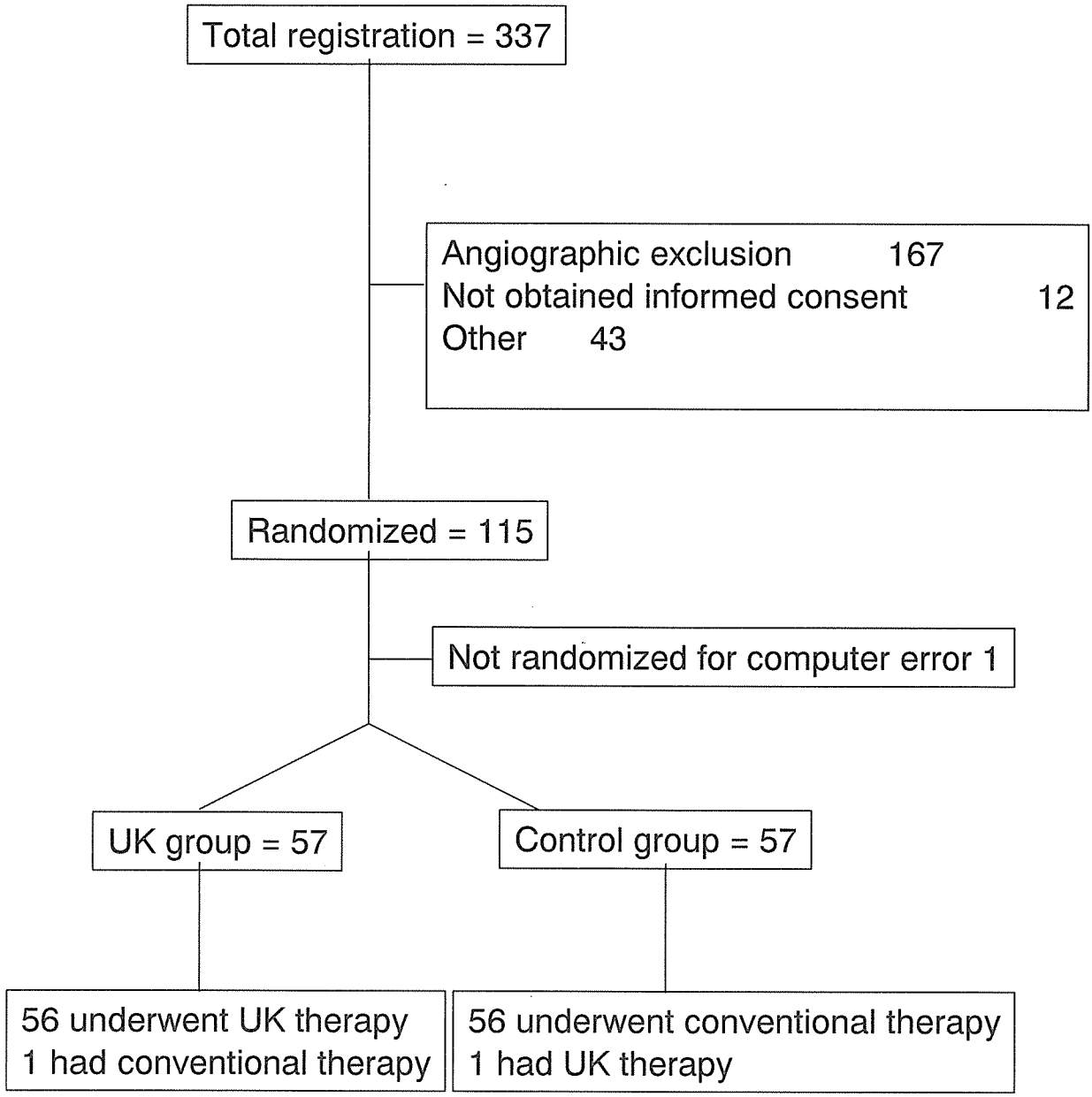
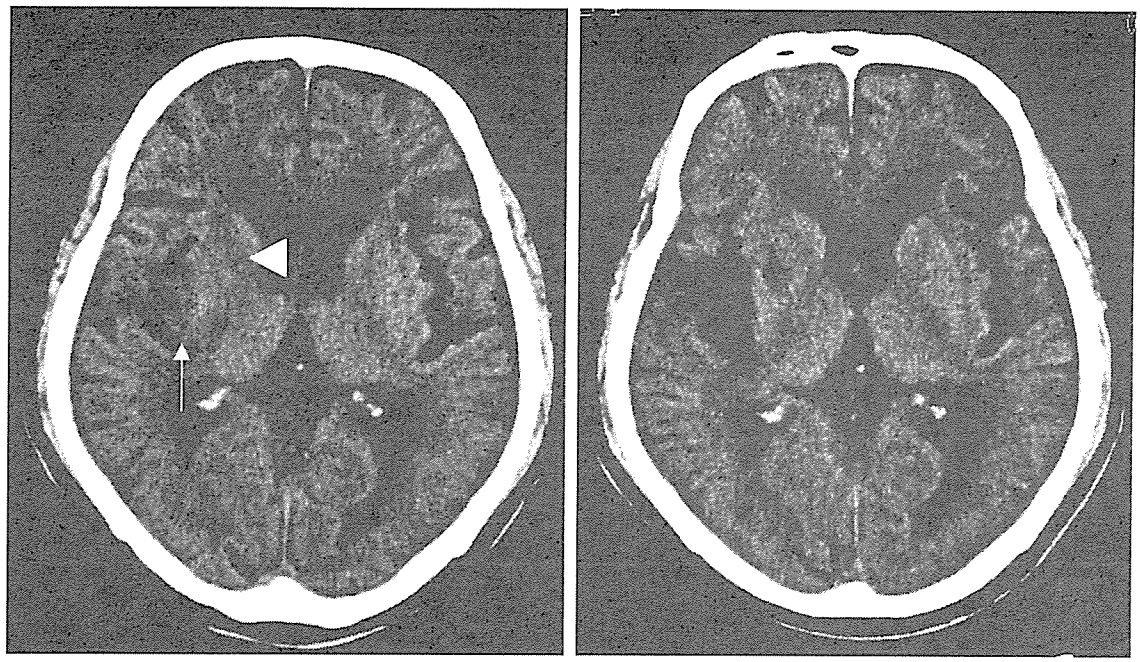

Total registration = 337
Angiographic exclusion 167
Not obtained informed consent 12
Other 43
Randomized = 115
Not randomized for computer error 1
UK group = 57
Control group = 57
56 underwent UK therapy
1 had conventional therapy
56 underwent conventional therapy
1 had UK therapy

Fig. 2



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