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Meta-analysis of randomized intra-arterial thrombolytic trials for the treatment of acute stroke due to middle cerebral artery occlusion

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Abstract

Background—Randomized clinical trials supporting the use of intra-arterial administration of thrombolytics (IAT) for the treatment of stroke due to middle cerebral artery (MCA) occlusion have been positive on some, but not all, endpoints. A meta-analysis was performed to estimate with more precision the effect of IAT on several key clinical endpoints.

Methods—All randomized trials of IAT in the treatment of MCA stroke were identified by PUBMED search and by hand search of potentially relevant references. Trial methodologies were assessed for compatibility in study protocols and statistical analysis. A meta-analysis was performed evaluating the effect of IAT on functional outcome at 90 days and symptomatic intracranial hemorrhage (SICH) within 24 h.

Results—Three trials met the criteria for the meta-analysis. IAT treated patients were significantly more likely to have a modified Rankin scale (mRS) 1 (31% vs 20%, OR 2.0, 95% CI 1.2 to 3.4, $p=0.01$); mRS 2 (43% vs 31%, OR 1.9, 95% CI 1.2 to 3.0, $p=0.01$); and NIH Stroke Scale score 0 or 1 (23% vs 12%, OR 2.4, 95% CI 1.3 to 4.4, $p=0.007$) at the 90 day follow-up. There was no effect on mortality at 90 days (20% vs 19%, OR 0.84, 95% CI 0.5 to 1.5). The risk of SICH was significantly increased in the active treatment arms (11% vs 2%, OR 4.6, 95% CI 1.3 to 16, $p=0.02$).

Conclusions—Our meta-analysis demonstrates that all standard functional endpoints for stroke trials were substantially improved in the active treatment arms. Despite an increased risk of SICH, there was no effect on mortality. These results support endovascular treatment of acute ischemic stroke due to MCA occlusion with intra-arterial thrombolytics.

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INTRODUCTION

Endovascular treatment of acute stroke with intra-arterial thrombolytics (IAT) has emerged as an important therapeutic modality. Despite increasingly widespread availability,¹ however, the evidence base for stroke interventions utilizing intra-arterial (IA) lytics is limited to a few relatively small randomized trials. The most widely cited of these, the Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial,² demonstrated an apparently substantial increase in the likelihood of a good outcome (modified Rankin Scale (mRS) 0–2) after stroke due to middle cerebral artery (MCA) occlusion (absolute risk reduction (ARR), 15%, number needed to treat, 7), but this result was never verified by a second randomized trial which would have been required for FDA approval. The lytic agent used in this trial, recombinant prourokinase, is no longer commercially available. A second randomized study of IA therapy using urokinase—the Middle Cerebral Artery Embolism Local Fibrinolytic Trial Intervention (MELT)³—was performed in Japan. This trial was stopped after enrolling 114 patients (target enrollment 200) due to the regulatory approval of intravenous recombinant tissue plasminogen activator in Japan. Although the absolute percentage of patients achieving a good outcome (based on a primary endpoint of mRS 0–2) was higher in IA treated patients compared with controls (49% in the active treatment arm; 39% in controls), this result did not reach statistical significance. In order to estimate with a greater degree of precision the potential benefit of IAT, we performed a meta-analysis of all randomized clinical trials with consideration of all potentially clinically relevant endpoints.

METHODS

Randomized, placebo controlled trials of IAT for the treatment of acute ischemic stroke due to MCA occlusion were selected for meta-analysis. Analysis was restricted to MCA occlusion to limit heterogeneity, as the location of occlusion has been shown to be an independent predictor of outcome following acute stroke due to large vessel occlusion.⁴ Studies were identified based on search of the PUBMED database, bibliographic references and the authors' knowledge of the stroke literature. Analyses were based on intention to treat populations where possible. Studies were assessed for heterogeneity and pooled ORs were computed utilizing RevMan (RevMan V.5.0; The Nordic Cochrane Centre, Cochrane Collaboration, 2008). The following endpoints were evaluated: 90 day mRS 1; 90 day mRS 2; 90 day National Institutes of Health Stroke Scale score (NIHSS) 0 or 1; 90 day mortality; and symptomatic intracranial hemorrhage (SICH) within 24 h.

RESULTS

Three studies meeting the criteria for this meta-analysis were identified: PROACT I,⁵ PROACT II² and MELT.³ All three trials enrolled patients with MCA occlusion and had a treatment window of 6 h after symptom onset.

The study design differed somewhat between the three studies (table 1). The randomization strategy employed in PROACT II differed from the other trials in that it was stratified based on three NIHSS strata: NIHSS 4–10; 11–20; 21–30. Despite intended enrollment of patients with MCA M1 or M2 occlusion only, PROACT I enrolled one patient with a tandem internal carotid artery (ICA)–MCA occlusion. The remaining patients in all trials had occlusion of the MCA only without ICA involvement. The MELT trial excluded patients with NIHSS >22 whereas the cut-off was 30 in the PROACT I and II trials. PROACT II utilized a CT exclusion criteria of hypodensity in >1/3 of the MCA territory; neither PROACT I or MELT used CT as an exclusion in this manner. Different definitions for successful revascularization were utilized in the PROACT and MELT trials. In the PROACT trials, complete revascularization was defined as complete restoration of blood

flow (TIMI 3) through the M1 and all M2 branches of the MCA; partial revascularization was defined as partial or complete restoration of blood flow (TIMI 2 or 3) through the M1 and all M2 branches *and* TIMI 2 flow in at least one branch. In MELT, successful revascularization was characterized according to the reperfusion of the affected stroke territory, including distal arterial branches, using three strata (partial reperfusion of the affected territory <50%, partial reperfusion of the affected territory 50% and complete reperfusion). Finally, SICH was defined by MELT using a unique definition that included either neurological deterioration associated with a 4 point decline in NIHSS or new 'objective signs'. PROACT I defined SICH as new intracranial hemorrhage (ICH) causing neurological deterioration (without further definition). In PROACT II, SICH was also defined as ICH causing neurologic deterioration but neurologic deterioration was specified to consist of either a 4 point increase in NIHSS or 1 point deterioration in level of consciousness.

The thrombolytic agents and the procedural details of the three trials varied also (table 1). The study drug in the PROACT trials was recombinant pro-urokinase (r-proUK, 6 mg in PROACT I and 9 mg in PROACT II). The entire dose was administered as a continuous infusion over 2 h directly into the proximal portion of the clot, and the infusion was continued irrespective of recanalization. Urokinase (maximum dose 600 000 U) was utilized in the MELT trial. The drug was administered incrementally (repeated infusions of 120 000U over 5 min) distal to the clot or in the distal portion of the clot until recanalization was achieved or 2 h had elapsed. In MELT, mechanical disruption of the clot with the microwire was permitted whereas this maneuver was forbidden in the PROACT trial protocols. Finally, procedural heparin doses varied in the three trials. In the PROACT trials, heparin was given to both IA treated patients and controls. Notably, the first 16 patients enrolled in PROACT I were treated with high dose heparin (100 U/kg bolus followed by 1000 U/h); the heparin dose was subsequently decreased (2000 U bolus followed by 500 U/h for 4 h) after rates of SICH appeared to be higher than expected. This decreased dose of heparin was used in the PROACT II trial. In the MELT trial, 5000 U of heparin were given at the start of the procedure in the IA treatment group only; the study protocol did not provide for additional heparin in the IA group or for any heparin administration in the control group.

The presenting features of patients in these studies are summarized in table 2. In comparison with the patients enrolled in the PROACT trials, patients in the MELT trial had lower NIHSS (14 vs 17–19) and were treated substantially earlier (3.8 h vs 5.3–5.5 h). The combined rate of both partial and complete revascularization and the prevalence of MCA M1 occlusion appeared to be higher in the MELT trial whereas apparently higher rates of complete revascularization were observed in the PROACT trials (19% vs 5%). As noted above, however, a different classification of revascularization was used in the PROACT trials than that used in MELT, rendering direct comparison between the two trials difficult.

Despite the differences in study design and treatment protocols, there was no significant heterogeneity of the major outcome variables in the three studies (figure 1). Functional outcomes were significantly improved by IAT administration: IAT treated patients were significantly more likely to have mRS 1 (30.8% vs 20.0%; ARR 10.9%; OR 2.0, 95% CI 1.2 to 3.4); mRS 2 (43.1% vs 30.8%; ARR 12.4%; OR 1.9, 95% CI 1.2 to 3.0); and NIHSS 0 or 1 (23.0% vs 12.3%; ARR 10.7%; OR 2.4, 95% CI 1.3 to 4.4) at the 90 day follow-up. No treatment effect was shown on mortality at 90 days (19.6% vs 18.5%; absolute risk increase 1.1%; OR 0.84, 95% CI 0.5 to 1.5). The risk of SICH was significantly increased in the active treatment arms (10.5% vs 2.4%; absolute risk increase 8.1%; OR 4.6, 95% CI 1.3 to 16).

DISCUSSION

The results of this meta-analysis provide a precise estimate of the beneficial effect of IAT when administered within 6 h of symptom onset for the treatment of acute stroke due to MCA occlusion. Despite the inclusion of only three trials enrolling a total of just 334 patients, a statistically and clinically robust increase in the odds of a favorable functional outcome was observed in the IAT treated patients in comparison with control subjects. Although the small number of trials and patients limits the degree of certainty regarding the efficacy of the intervention, formal meta-analysis may be conducted on as few as two studies⁶ and the degree of confidence is reflected in statistically significant improvements in all measures of functional outcome at 90 days at the $p < 0.05$ level.

Although similar in terms of time window and artery occluded, the three trials included in our analysis did have some significant differences in terms of patient populations, study design and methodology. Despite being more likely to have occlusion of the M1 segment of the MCA, patients in the MELT trial had a lower NIHSS and were treated substantially earlier than were patients in the PROACT trials. These factors almost certainly contributed to a greater proportion of patients in the MELT trial with mRS 1 at 90 days compared with the PROACT trials. The higher recanalization rate in the MELT trial is another potential contributor, given the strong association between recanalization and outcome.⁷ The fact that MELT patients had milder strokes and were treated earlier than PROACT patients also likely contributes to the finding that MELT was statistically positive on the endpoint of mRS 1 but not mRS 2, whereas the opposite result was seen in the PROACT II trial (statistical benefit for the endpoint of mRS 2 but not mRS 1).⁸

Variation in the interventional techniques and thrombolytic employed in the trials may also account for some differences in outcome. Infusion of additional lytic after proximal recanalization may have resulted in the higher rates of complete recanalization seen in PROACT I and II compared with MELT. On the other hand, the MELT protocol allowed for mechanical disruption with the guidewire, which was performed in 68% of cases and may, in part, have accounted for the apparently higher rate of partial or complete reperfusion in MELT compared with the PROACT trials. Recanalization after acute stroke intervention is strongly associated with improved outcomes,⁷ and complete recanalization following endovascular intervention may be associated with better outcomes than partial recanalization.⁹

Despite the differences among the trials, there was no statistically significant variation of study outcomes on any of the endpoints assessed and there was a consistent clinically and statistically significant improvement of functional outcomes at 90 days among patients treated with IAT. The odds of a good functional outcome by all commonly used metrics for stroke trials—mRS 1, mRS 2 and NIHSS 0 or 1—were increased approximately twofold. The absolute increase in the likelihood of a good outcome by these measures was 11–12%, corresponding to a number needed to treat of 8–9. Despite this overall benefit, the amelioration of functional outcomes came at the cost of increased risk of SICH, with an OR of 4.6 in the lytic treated group. There was no net effect on 90 day mortality.

It should be noted that two additional placebo controlled trials have been performed, both of which were excluded from the meta-analysis due to enrollment of patients with occlusions in locations other than the MCA. The Australian Urokinase Stroke Trial (AUST)¹⁰ evaluated the effect of IAT for patients with vertebrobasilar disease up to 24 h. This trial was excluded from the meta-analysis because we limited our search to trials of patients with MCA occlusions treated within 6 h. The results of the AUST trial, which randomized 16 patients, were in the same direction as the results of the trials that were included in this meta-analysis.

A good outcome was seen in 50% of patients in the urokinase arm compared with 12.5% in the control arm. A second trial¹¹ performed in Latvia randomized 12 patients with anterior circulation stroke (ICA or MCA) to a strategy of IA actilyse followed by intravenous actilyse infusion and 33 patients to placebo. Outcomes in the IA/intravenous arm were substantially better than controls: at 1 month a favorable outcome was seen in 67% in the active treatment arm versus 21% in the control arm; the 1 month mortality rate was 17% in the active treatment arm versus 48% in controls. Given increased rates of favorable outcome in the IA lytic treatment arms in both studies, inclusion of these trials in the meta-analysis would not have significantly altered the overall findings of improved functional outcomes at 90 days among IA lytic treated patients.

Our results are consistent with previous meta-analyses of IAT for the treatment of acute stroke.¹²⁻¹⁴ These studies differed from ours, however, in that different trials were included and different outcomes were assessed. In the analysis by Lee *et al*, the AUST¹⁰ trial and the Latvian trial¹¹ were included. We believe that the difference in outcome between MCA occlusion and ICA or posterior circulation occlusions,⁴ as well as the relatively smaller hemorrhage risk¹⁵ and increased time window for intervention¹⁰¹⁶ in the posterior circulation, justify the exclusion of the AUST and Latvian trials from the meta-analysis. More limited meta-analyses have also been performed evaluating only the odds of death and dependency but not the other endpoints in our analysis (mRS 0–1, NIHSS 0 or 1, mortality and SICH).¹³¹⁴ In addition, data for the important outcome of mRS 0–2 (corresponding to non-disabling stroke) from the PROACT trial have not been published previously. As a result, these other meta-analyses based their calculations for this endpoint on the assumption that the same number of patients had an mRS of 0–1 as an mRS of 0–2 in this trial (in other words, that no patients in the PROACT trial had an mRS of 2). In fact, four patients in the IA treated group and none in the control group had this outcome, leading to an underestimate of the beneficial effect of IA intervention.

IAT for the treatment of stroke patients initiated within 6 h after ictus has been recommended in the American Heart Association/American Stroke Association guidelines with class I, level B evidence based largely on the PROACT trials.¹⁷ This meta-analysis provides stronger evidence that IAT is likely safe and effective within 6 h of stroke due to MCA occlusion in patients ineligible for intravenous recombinant tissue plasminogen activator.

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Key points

- ▶ Randomized clinical trials supporting the use of intra-arterial administration of thrombolytics (IAT) for acute stroke due to middle cerebral artery occlusion have been positive on some, but not all, endpoints.
- ▶ We performed a meta-analysis to estimate the effect of IAT on clinical outcomes with more precision.
- ▶ We found that IAT substantially improved all standard measures of functional outcome after acute stroke; furthermore, despite an increased risk of symptomatic intracerebral hemorrhage, there was no effect on mortality.
- ▶ These results strongly support the endovascular treatment of acute stroke due to middle cerebral artery occlusion with intra-arterial thrombolysis.

Figure 1.

Forest plot comparing the effect of of intra-arterial thrombolysis (IAT) versus placebo for middle cerebral artery stroke in the 6 h window after acute ischemic stroke. The following endpoints were assessed: (A) 90 day modified Rankin Scale (mRS) 1; (B) 90 day mRS 2; (C) National Institutes of Health Stroke Scale score (NIHSS) 0 or 1 at 90 days; (D) mortality within 90 days; and (E) symptomatic intracranial hemorrhage (SICH) within 24 h. MELT, Middle Cerebral Artery Embolism Local Fibrinolytic Trial Intervention; PROACT, Prolyse in Acute Cerebral Thromboembolism trial.

Table 1

Presenting features

	PROACT ⁵	PROACT II ²	MELT ³
N	40 (26 IA)	180 (121 IA)	114 (57 IA)
Age (years) (mean)	68	64	67
Male (%)	48	59	65
NIHSSS-B (median)	17–19	17	14
Symptoms to start of infusion (h)	5.5	5.3	3.8
Clot location			
ICA/MCA (n (%))	1 (3)	0	
M1 (n (%))	21 (53)	111 (62)	81 (71)
M2 (n (%))	18 (45)	69 (38)	33 (29)
Recanalization *			
Treated			
Partial or complete (%)	58	66	74
Complete (%)	19	19	5
Controls			
Partial or complete (%)	14	18	-
Complete (%)	0	2	-

* MELT defined recanalization based on flow in the affected arterial distribution and the PROACT trials defined recanalization based on the status of only M1 and M2 vessels. ICA, internal carotid artery; MCA, middle cerebral artery; MELT, Middle Cerebral Artery Embolism Local Fibrinolytic Trial Intervention; NIHSSS, National Institutes of Health Stroke Scale score; PROACT, Prolyse in Acute Cerebral Thromboembolism trial.

Table 2

Study design and protocols

	PROACT ⁵	PROACT II ²	MELT ³
Treatment protocol			
Lytic agent	6 mg r-proUK	9 mg r-proUK	UK 600 000 U maximum
Strategy	Infusion of half total dose over 1 h in proximal one-third of clot; if clot partially lysed at 1 h, catheter advanced further into clot; remaining half dose infused regardless of recanalization. Mechanical disruption with guidewire prohibited.	Same as PROACT	Injection of one-fifth of the total dose over 5 min distal or into clot; repeat injections over maximum of 2 h until recanalization achieved. Mechanical disruption with guidewire allowed.
Heparin	High dose (first 16 patients): 100 U/kg at start, then 1000 U/kg infusion; low dose: 2000 IU at start, then 500 U/h infusion	2000 U at start; 500 U/h infusion	5000 U at start
Randomization	2:1	2:1 (by NIHSS strata, 4–10; 11–20; 21–30)	1:1
Blinding	Double blind	Single blind (no placebo IA infusion but follow-up blind)	Single blind (no placebo IA infusion but follow-up blind)
Key inclusion criteria	Treatment within 6 h NIHSS 4–30 Age 18–85	Treatment within 6 h NIHSS 4–30 Age 18–85	Treatment within 6 h NIHSS 5–22 Age 20–75
Key exclusion criteria	Clot	Occlusion of artery other than MCA	Occlusion of artery other than MCA
CT exclusion criteria	ICH or significant mass effect with midline shift	Hypodensity in 1/3 of MCA territory.	ICH only
SICH definition	New ICH causing neurological deterioration	New ICH causing neurological deterioration (4 point increase in NIHSS or 1 point deterioration in level of consciousness)	New ICH on 24h CT + either new objective neurologic signs or 4 point increase in NIHSS
Revascularization	Partial: At least TIMI 2 flow in all M1 and M2 branches AND TIMI 2 flow in at least one M1 or M2 branch. Complete: TIMI 3 flow in all M1 and M2 branches.	Same as PROACT	Stratified into: partial reperfusion <50% of affected territory; partial reperfusion 50% of affected territory; and complete reperfusion.
Primary endpoint	Recanalization at 120 min	mRS 2	mRS 2

IA, intra-arterial; ICA, internal carotid artery; ICH, intracranial hemorrhage; MCA, middle cerebral artery; MELT, Middle Cerebral Artery Embolism Local Fibrinolytic Trial Intervention; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale score; PROACT, Prolyse in Acute Cerebral Thromboembolism trial; r-proUK, recombinant pro-urokinase; SICH, symptomatic intracranial hemorrhage; UK, urokinase.