Efficacy of Intra-Arterial Fibrinolysis for Acute Ischemic Stroke

Meta-Analysis of Randomized Controlled Trials

Meng Lee, MD; Keun-Sik Hong, MD, PhD; Jeffrey L. Saver, MD

Background and Purpose—Although intra-arterial (IA) fibrinolysis for acute ischemic stroke has been clinically available for many years, it is not a therapy approved by the US Food and Drug Administration. Single, randomized, clinical trials (RCTs) have suggested beneficial effects, but no single RCT has demonstrated that IA fibrinolysis yields increases in both good (modified Rankin Scale score 0 to 2) and excellent (modified Rankin Scale score 0 to 1) outcomes when compared with the control group. Relatively few participants and inadequate statistical power in single RCTs may have contributed to this difficulty.

Method—We performed a systematic literature search to identify RCTs of IA fibrinolysis in acute ischemic stroke. Multiple outcomes were analyzed, with emphasis on good and excellent outcomes at 90 days or at trial end point.

Results—The systematic search identified 5 RCTs with 395 participants comparing IA fibrinolysis and control. IA fibrinolysis was associated with increased good (odds ratio = 2.05; 95% CI, 1.33 to 3.14; \( P = 0.001 \)) and excellent (odds ratio = 1.41; 95% CI, 1.31 to 3.14; \( P = 0.003 \)) outcomes. For additional end points, IA fibrinolysis was associated with increased frequencies of minimal neurologic deficit (National Institutes of Health Stroke Scale score 0 to 1), minimal impairment of activities of daily living (Barthel Index 90 to 100 or 95 to 100), and recanalization. IA fibrinolysis was associated with increased radiological and symptomatic intracerebral hemorrhage. However, there was no difference in mortality between groups.

Conclusions—Formal meta-analysis suggests that IA fibrinolysis substantially increases recanalization rates and good and excellent clinical outcomes in acute ischemic stroke. Increased hemorrhage frequencies were not associated with any increase in mortality. \( \text{(Stroke}. \, 2010;41:00-00.) \)

Key Words: intra-arterial fibrinolysis acute ischemic stroke outcomes meta-analysis

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Materials and Methods

The study was performed according to the recommendations of the Quality of Reporting of Meta-analysis statement. We systematically searched the Cochrane Central Register of controlled trials, PubMed, the World Health Organization international clinical trials registry, the Internet Stroke Center stroke trials, and the clinical trials.gov website from 1966 to August 2009 by entering the following search phrases: “intra-arterial,” “local,” “fibrinolysis,” “thrombolysis,” “urokinase,” “turookinase,” “tissue plasminogen activator,” or “streptokinase” crossed with “stroke,” “cerebrovascular disease,” “cerebrovascular attack,” “brain attack,” or “brain infarct.” We restricted the search to human studies and clinical trials. There were no language restrictions. Manual searches of bibliographies of all
relevant trials and review articles were reviewed and identified by 2 investigators (M.L. and K.S.H.).

Studies were selected when they met the following entry criteria: (1) study was an RCT, (2) the active treatment consisted of IA fibrinolysis (with or without additional IV fibrinolysis), and (3) reported end points included good clinical outcome (mRS score 0 to 2 or nearest equivalent) and/or excellent clinical outcome (mRS score 0 to 1 or nearest equivalent) at 90 days or at trial end point. Studies were excluded when the control group was confounded by an active therapy not used in the treatment group. The methodological quality of the RCTs was assessed on a 100-point scale previously used by Liebeskind and colleagues. The scale addresses the following 5 aspects of trial design and reporting: randomization, outcome, inclusion/exclusion criteria, description of therapeutic regimen, and statistical analyses.

The leading outcomes of interest were good (mRS score 0 to 2 or nearest equivalent) and excellent (mRS score 0 to 1 or nearest equivalent) clinical functional outcomes at 90 days or at trial end point. Additional outcomes of interest were minimal neurologic deficit (National Institutes of Health Stroke Scale score 0 to 1), minimal impairment of activities of daily living (Barthel Index 90 to 100 or 95 to 100), partial or complete recanalization (Thrombolysis In Myocardial Infarction grade 2 to 3), complete recanalization (Thrombolysis In Myocardial Infarction grade 3), radiological intracranial hemorrhage, symptomatic intracranial hemorrhage, and mortality.

All data from eligible trials were independently abstracted by 2 independent investigators (M.L. and K.S.H.) according to a standard protocol. Discrepancies were resolved by discussion with a third investigator (J.L.S.) and by referencing the original report. Data were analyzed according to the intention-to-treat principle. The Cochrane Collaboration’s Review Manager Software Package (RevMan 5) was used for the meta-analysis. Odds ratio (OR) with 95% CI was used as a measure of the association between IA fibrinolysis and outcomes. All reported probability values were 2 sided, with significance set at <0.05. Heterogeneity was assessed by the probability value of χ² statistics and I², which describes the percentage of variability in the effect estimates that is due to heterogeneity rather than chance. Heterogeneity was considered significant when the probability value of χ² statistics was <0.05. We regarded an I² value of <40% as “heterogeneity might not be important” and >75% as “considerable heterogeneity” based on the suggestion of the Cochrane Handbook for Systematic Reviews of Interventions. We pooled data across trials by using the fixed-effects model based on Peto’s method and compared the results with those obtained from a random-effects model. We also performed a sensitivity analysis to further explore the robustness of our results. To identify any study that may have exerted a disproportionate influence on the summary treatment effect, we removed each individual trial from the meta-analysis 1 at a time.

Results

Of the 11 RCTs retrieved for detailed assessment, 4 were excluded owing to confounding (IV fibrinolysis in the control group in 2 trials, IA fibrinolysis in the control group in 2 trials, and 2 were excluded for no mRS scores (or nearest equivalent) in the outcome assessment (Figure 1). Our final analysis included 5 RCTs, comprising 395 individuals, with 224 (57%) participants randomly assigned to the active treatment group and 171 (43%) to the control group. Some data not provided by original articles but published in the latest Cochrane Review were also used.

The study design, quality, and baseline characteristics of these RCTs are shown in Table 1. Four trials compared pure IA fibrinolysis with controls, and 1 compared combined IV and IA fibrinolysis with controls. All but 1 trial were judged as having adequate allocation concealment during randomization. Four trials showed good to excellent scores, and 1 trial showed a lower score on a formal clinical-trial reporting quality scale. Four trials enrolled anterior circulation ischemic stroke patients with a treatment time window within 6 hours, whereas 1 trial enrolled posterior circulation ischemic stroke patients with a treatment time window within 24 hours. The number of participants ranged from 16 to 180. Baseline median or mean National Institutes of Health Stroke Scale scores ranged from 14 to 25. Among 5 trials, 3 assessed outcome at 90 days, 1 at 6 months, and 1 at 12 months.

Pooling the results from the fixed-effects model showed that IA fibrinolysis was associated with increased good clinical outcomes (42.9% vs 28.1%; OR = 2.05; 95% CI, 1.33 to 3.14; P = 0.001; number needed to treat = 6.8) and excellent clinical outcomes (31.1% vs 18.1%; OR = 2.14; 95% CI, 1.31 to 3.51; P = 0.003; number needed to treat = 7.7) (Figure 2). The estimates from the random-effects model were similar to those of the fixed-effects model. The trial of Keris et al was particularly methodologically distinctive in having the active
intervention consist of combined IA and IV fibrinolysis rather than IA fibrinolysis alone. Analysis excluding this trial, of IA fibrinolysis alone, showed similar evidence of benefit, for example, good outcome without death or dependency (OR = 1.83; 95% CI, 1.14 to 2.92; P = 0.01).

For additional end points, IA fibrinolysis also was associated with increased frequencies of minimal neurologic deficit (23.0% vs 12.3%; OR = 2.24; 95% CI, 1.27 to 3.95; P = 0.005), minimal impairment of activities of daily living (43.6% vs 33.1%; OR = 1.60; 95% CI, 1.01 to 2.51; P = 0.04), partial or complete recanalization (64.6% vs 17.8%; OR = 6.42; 95% CI, 3.67 to 11.24; P < 0.00001), and complete recanalization (19.0% vs 1.4%; OR = 4.62; 95% CI, 2.02 to 10.56; P = 0.0003). IA fibrinolysis was associated with in-

<table>
<thead>
<tr>
<th>Countries</th>
<th>PROACT, 1998&lt;sup&gt;17&lt;/sup&gt;</th>
<th>PROACT II, 1999&lt;sup&gt;18&lt;/sup&gt;</th>
<th>Keris et al, 2001&lt;sup&gt;19&lt;/sup&gt;</th>
<th>Macleod et al, 2005&lt;sup&gt;20&lt;/sup&gt;</th>
<th>MELT, 2007&lt;sup&gt;21&lt;/sup&gt;</th>
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<td>No. of participants</td>
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<td>Latvia</td>
<td>Australia and New Zealand</td>
<td>Japan</td>
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<td>64</td>
<td>61</td>
<td>64</td>
<td>67</td>
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<td>Female, %</td>
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<td>40</td>
<td>37.5</td>
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<td>17</td>
<td>25</td>
<td>19.5</td>
<td>14</td>
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<td>MCA occlusion</td>
<td>MCA occlusion</td>
<td>ICA or MCA occlusion</td>
<td>BA or VA occlusion</td>
<td>MCA occlusion</td>
</tr>
<tr>
<td>Allocation concealment</td>
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<td>Yes</td>
<td>Inadequate</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
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<td>83</td>
<td>43</td>
<td>75</td>
<td>77</td>
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<td>&lt;6 hours</td>
<td>&lt;6 hours</td>
<td>&lt;24 hours</td>
<td>&lt;6 hours</td>
</tr>
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<td>Intervention</td>
<td>IA pro-UK+IV heparin vs IV heparin</td>
<td>IA pro-UK+IV heparin vs IV heparin</td>
<td>IV t-PA t-PA+IV heparin vs IV heparin</td>
<td>IA UK+IV heparin vs IV heparin</td>
<td>IA UK+IV heparin vs IV heparin</td>
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<td>No</td>
<td>Not mentioned</td>
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<td>Outcome assessment</td>
<td>90 days</td>
<td>90 days</td>
<td>12 months</td>
<td>6 months</td>
<td>90 days</td>
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</table>

PROACT indicates PROlyse in Acute Cerebral Thromboembolism; MELT, Middle cerebral artery Embolism Local fibrinolytic intervention Trial; NIHSS, National Institutes of Health Stroke Scale; MCA, middle cerebral artery; ICA, internal carotid artery; BA, basilar artery; VA, vertebral artery; and UK, urokinase.
increased radiological (25.4% vs 6.4%; OR = 3.37; 95% CI, 1.90 to 5.95; \( P<0.0001 \)) and symptomatic (8.9% vs 2.3%; OR = 2.87; 95% CI, 1.21 to 6.83; \( P=0.02 \)) intracerebral hemorrhage. However, there was no difference in mortality between groups (20.5% vs 24.0%; OR = 0.82; 95% CI, 0.48 to 1.39; \( P=0.46 \) (Table 2). There was no significant heterogeneity among trials for all outcome estimates. In the sensitivity analysis, excluding individual trials yielded pooled results that were not significantly different from the overall pooled estimates.

### Discussion

To date, the PROlyse in Acute Cerebral Thromboembolism II study is the only formally positive trial of IA fibrinolysis,\(^18\) although other trials have shown trends favoring IA fibrinolysis in acute ischemic stroke.\(^{17,19–21} \) Inadequate statistical power, attributable in part to early study terminations because of slow recruitment and approval for IV t-PA treatment,\(^{20,21} \) may have contributed to this paucity of formally positive trials. The current meta-analysis, which pooled data from all relevant trials, provides a strong indication of efficacy of IA fibrinolysis in acute ischemic stroke. Beneficial effects of IA fibrinolysis were highly statistically significant for increased rates of both good and excellent final clinical outcomes. The odds of these outcomes were more than doubled by active treatment.

Findings for other clinical outcomes were consistent with the effects on global disability. IA fibrinolysis was associated with substantially increased rates of no or minimal neurologic deficit and no or minimal impairment of activities of daily living at the final visit. IA lysis did increase the rate of any radiological or symptomatic hemorrhage. However, there was no increased mortality associated with IA lysis, consistent with prior studies indicating that many postfibrinolysis radiological hemorrhages are confined to already-damaged tissue and do not worsen final outcome.\(^{23,24} \)

IA fibrinolysis was associated with a marked increase in recanalization rates in the meta-analysis. Recanalization and restoration of nutritive perfusion are the presumed main mechanisms of action of IA lytic intervention.\(^{25} \) However, a discrepancy was noted between the magnitude of IA fibrinolysis treatment effect on the physiological biomarker of recanalization and final clinical outcomes. IA treatment was associated with an absolute increase in the rate of partial or complete recanalization (46.8%), 3 times higher than the absolute increases in the rate of good (14.8%) or excellent (13.0%) final clinical outcome. This disjunction likely reflects 2 factors. In some patients, recanalization improves outcome at points on the global disability spectrum not captured by analysis of a single health-state transition on the 7-level mRS.\(^{26} \) In other patients, the ischemic field is already fully infarcted before intervention, with no penumbral tissue remaining that reperfusion can salvage.\(^{27} \)

There was no statistical heterogeneity among trials included in this meta-analysis. One small trial was distinctive in having the active intervention consist of combined IA and IV fibrinolysis rather than IA fibrinolysis alone.\(^{19} \) Analysis excluding this trial, of IA fibrinolysis alone, showed similar evidence of benefit, for example, mRS score 0 to 2 (OR = 1.83, 95% CI, 1.14 to 2.92, \( P=0.01 \)). Similarly, another small trial was unique in enrolling enrollment to posterior circulation stroke patients and permitting treatment up to 24 hours.\(^{20} \) Again, excluding this trial did not affect our overall findings.

Meta-analyses are only as valid as the studies selected. Trial quality was generally high in this analysis, but not uniformly so. Blinding of treatment assignment is challenging in trials of endovascular intervention versus medical therapy. Most trials\(^{17,18,20,21} \) used blinded raters for final outcome assessments, but only 1 trial (PROlyse in Acute Cerebral Thromboembolism)\(^{17} \) was fully double-blind, with all patients and treating physicians unaware of group assignment. Four trials used randomization for treatment assignment, but 1 trial alternated patients between treatment groups.\(^{19} \)

It is instructive to compare the magnitude of the IA fibrinolytic treatment effect observed in the meta-analysis with that of IV t-PA, although comparisons must be made cautiously, as IV therapy is applied to both small- and large-artery occlusion patients and IA therapy only to large-artery occlusion patients. For good clinical outcomes, the benefit per 100 patients treated is 12 within \(<3 \) hours of IV t-PA,\(^{26,28} \) 15 with IA fibrinolysis, and 5 within 3 to 4.5 hours of IV t-PA.\(^{29} \) For excellent clinical outcomes, the benefit per 100 patients treated is 17 within \(<3 \) hours of IV t-PA,\(^{28} \) 13 with IA fibrinolysis, and 7 within 3 to 4.5 hours of IV t-PA.\(^{29} \) Accordingly, indirect comparison suggests that the benefit of

<table>
<thead>
<tr>
<th>End Points</th>
<th>IA Fibrinolysis, n/N (%)</th>
<th>Control, n/N (%)</th>
<th>OR (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS 0–2(^{17–21} )</td>
<td>96/224 (42.9)</td>
<td>48/171 (28.1)</td>
<td>2.05 (1.33–3.14)</td>
<td>0.001</td>
</tr>
<tr>
<td>mRS 0–1(^{17,18,20,21} )</td>
<td>66/212 (31.1)</td>
<td>25/138 (18.1)</td>
<td>2.14 (1.31–3.51)</td>
<td>0.003</td>
</tr>
<tr>
<td>NIHSS 0–1(^{17,18,21} )</td>
<td>47/204 (23.0)</td>
<td>16/130 (12.3)</td>
<td>2.24 (1.27–3.95)</td>
<td>0.005</td>
</tr>
<tr>
<td>Barthel Index 90–100 or 95–100(^{17,18,21} )</td>
<td>89/204 (43.6)</td>
<td>43/130 (33.1)</td>
<td>1.60 (1.01–2.51)</td>
<td>0.04</td>
</tr>
<tr>
<td>TIMI grade 2–3(^{17,18} )</td>
<td>95/147 (64.6)</td>
<td>13/73 (17.8)</td>
<td>6.42 (3.67–11.24)</td>
<td>(&lt;0.0001 )</td>
</tr>
<tr>
<td>TIMI grade 3(^{17,18} )</td>
<td>28/147 (19.0)</td>
<td>1/73 (1.4)</td>
<td>4.62 (2.02–10.56)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Radiological ICH(^{17–21} )</td>
<td>57/224 (25.4)</td>
<td>11/171 (6.4)</td>
<td>3.37 (1.90–5.95)</td>
<td>(&lt;0.0001 )</td>
</tr>
<tr>
<td>Symptomatic ICH(^{17–21} )</td>
<td>20/224 (8.9)</td>
<td>4/171 (2.3)</td>
<td>2.87 (1.21–6.83)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mortality(^{17–21} )</td>
<td>46/224 (20.5)</td>
<td>41/171 (24.0)</td>
<td>0.83 (0.48–1.39)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

**Table 2. Effect of IA Fibrinolysis on Radiological and Clinical End Points**

NIHSS indicates NIHSS, National Institutes of Health Stroke Scale; TIMI, Thrombolysis In Myocardial Infarction; and ICH, intracranial hemorrhage.
IA lysis is somewhat similar to early, <3-hour IV t-PA and better than 3- to 4.5-hour IV t-PA. This finding accords with what little data are available from direct, head-to-head clinical trials and large registries. There are only 2 small RCTs with 34 participants comparing IA and IV fibrinolysis to date, and the results are inconclusive.11,12 The results from the prospective observational registries comparing IA and IV efficacy were conflicting.30,31 In the study of ischemic stroke with hyperdense middle cerebral artery sign on computed tomography, IA fibrinolysis was more beneficial than IV fibrinolysis, even though IA fibrinolysis was started later.30 On the other hand, the results from another study did not support the often-held assumption that IA fibrinolysis is superior to IV fibrinolysis in patients with an acute symptomatic basilar artery occlusion.34 In addition, combined IV-IA therapy may offer advantages over either modality alone. The safety and efficacy of combined therapy are currently under investigation.

Our study has limitations. Meta-analyses may be biased when the literature search fails to identify all relevant trials or the selection criteria for including a trial are applied in a subjective manner. To minimize these risks, we performed thorough searches across multiple literature and trial databases and used explicit criteria for study selection, data abstraction, and data analysis. Meta-analyses optimally reflect all performed trials of an intervention. The thorough literature and registry search undertaken may not have identified trials that were performed but never reported (reporting bias).

In conclusion, formal meta-analysis suggests that IA fibrinolysis substantially increases recanalization rates and good and excellent clinical outcomes in acute ischemic stroke. Increased hemorrhage frequencies are not associated with any increase in mortality.

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Disclosures
J.J.S. has received honoraria from universities as a visiting professor; is an employee of the University of California, which holds a patent on retriever devices for stroke; is a scientific consultant regarding trial design and conduct to Concentric Medical, Talecris, and Ev3; is a site investigator in multicenter trials sponsored by Lundbeck for which the University of California Regents receive payments based on the clinical trial contracts for the number of subjects enrolled; is a site investigator in the National Institutes of Health IMS 3 and CLEAR-ER multicenter clinical trials, for which the University of California Regents receive payments based on the clinical trial contracts for the number of subjects enrolled; has declined consulting/honoraria monies from Genentech since 2002; and is funded by National Institutes of Health–National Institute of Neurological Disorders and Stroke Awards P50 NS044378 and U01 NS 44364.

References


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