REVIEW ARTICLE

Meta-Analysis of Local Endovascular Therapy for Acute Ischemic Stroke

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ABSTRACT

A meta-analysis was performed to assess randomized controlled trials comparing local endovascular therapy (with and without intravenous thrombolysis) versus standard care (intravenous thrombolysis alone when appropriate) for acute ischemic stroke. Local endovascular therapy showed a significant improvement in functional independence versus standard care (odds ratio, 1.779; 95% confidence interval, 1.262–2.507; $P < .001$). This benefit strengthened further on subgroup analyses of trials in which a majority of cases used stent retrievers, trials with intravenous thrombolysis use in both arms when appropriate, and trials that required preprocedural imaging of all patients. There were no significant differences between arms in terms of mortality, hemicraniectomy, intracranial hemorrhage, and cerebral edema rates ($P > .05$). In conclusion, in the treatment of acute ischemic stroke, local endovascular therapy leads to improved functional independence compared with standard care.

ABBREVIATIONS

CI = confidence interval, GRADE = Grading of Recommendations, Assessment, Development, and Evaluations, IV = intravenous, MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in The Netherlands, OR = odds ratio, RCT = randomized controlled trial

Local mechanical and pharmacologic endovascular therapies have been extensively investigated for the treatment of acute ischemic stroke (1–7). Such therapies have been investigated as targeted, effective, and safe means of achieving arterial recanalization with the goal of improving clinical outcomes.

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After initial observational trials demonstrated benefit for endovascular approaches, randomized controlled trials (RCTs) were performed to assess these outcomes (1). The first RCT, Prolyse in Acute Cerebral Thromboembolism II (2), found a statistically significant benefit from endovascular treatment of middle cerebral artery occlusion with the use of prourokinase, but the new drug required a second trial for approval by the US Food and Drug Administration. A second RCT, the Middle cerebral artery Embolism Local fibrinolytic intervention Trial (3), again demonstrated benefit from thrombolytic therapy with urokinase, but the trial was stopped prematurely in Japan when intravenous (IV) tissue plasminogen activator (TPA) was approved and statistical significance was not yet achieved. A series of RCTs published in 2013 (4–6) demonstrated no benefit to endovascular therapy. These trials were criticized for heterogeneous patient populations, poor patient selection, inconsistent times to intervention, and low rates of stent-retriever use (7,8). In the past year, several large RCTs have been released that included carefully selected patient populations (9–13). These trials have demonstrated positive findings in terms of benefit for functional independence for patients.

Given the discordance of results among trials, a meta-analysis was performed of all RCTs of local endovascular therapy (mechanical and/or pharmacologic) with and without IV thrombolysis compared with a standard-care control that included IV thrombolysis when appropriate.

MATERIALS AND METHODS

Systematic Search and Data Abstraction

Systematic searches for RCTs of local endovascular therapy for acute ischemic stroke in humans were performed of the MEDLINE database (1946 to March week 5 2015), Ovid HealthSTAR (1966 to February 2014), Embase (1980 to 2014 week 17), AMED (1985 to March 2015), and CAB Abstracts (1973 to 2015 week 13) on March 15, 2015. The search was repeated June 17, 2015, before manuscript submission, to find any additional trials published since the original search. The search strategy is provided in the **Appendix** (available online at *www.jvir.org*).

Secondary searches were conducted by three reviewers by reviewing citations from primary studies and review papers including previously published meta-analyses and systematic reviews.

Abstracts found in the primary and secondary literature searches were independently screened for potential studies of interest by two reviewers. Studies were limited to RCTs performed on humans of any age group and published in the English language. Inclusion criteria were decided a priori to include only RCTs that compared local endovascular therapy (mechanical and/or pharmacologic) with or without IV thrombolysis versus a standard-care control that included IV thrombolysis when appropriate. Appropriate IV thrombolysis in the standard-care arm was defined as patients being permitted to receive IV thrombolysis, if no contraindications were present, within 4.5 hours of stroke symptom onset. Trials comparing local endovascular therapy versus a placebo/sham control arm were excluded, as IV thrombolysis was considered to be the current standard of care (14).

Following the initial abstract screen, the full texts of the remaining trials were independently reviewed. Inter-reviewer disagreement regarding study inclusion was resolved by discussion with the remaining study authors to reach consensus. Data were extracted into a standardized spreadsheet in duplicate independently by two reviewers.

Quality and Strength of Recommendation Assessment

Individual study bias was assessed by using the Cochrane risk of bias tool (15). This assessed the appropriate use of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete reporting of outcome data, selective reporting, and "other" (eg, industry funding). The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology was used to rate the confidence in each reported outcome as high, moderate, low, or very low on the basis of five domains: overall risk of bias, imprecision, inconsistency, indirectness, and publication bias (16). These were independently assessed by two reviewers. Disagreement was again resolved by the remaining study authors.

Statistical Analyses

Outcomes of interest were established a priori and included the percentage of patients with a modified Rankin scale (mRS) score at 90 days of 0–2, 90-day mortality rate, hemicraniectomy rate, symptomatic and fatal intracranial hemorrhage rates, and symptomatic or fatal cerebral edema rates. A 90-day mRS score of 0–2 was selected because this outcome represents functional independence for patients and has been the standard in all trials (2–6,9–13). Meta-analysis was performed when at least two RCTs existed that compared a similar treatment and control group and measured one of these prespecified outcomes. Several subgroup analyses were performed in addition to the primary meta-analysis for each outcome. The primary meta-analysis assessed all RCTs that met the aforementioned inclusion criteria. The following subgroup analyses were then performed: (*i*) meta-analysis of only RCTs that stated they had used preprocedural imaging selection (computed tomography [CT], magnetic resonance [MR] imaging, or catheter angiography) in both arms to identify target vessel occlusion before intervention, (*ii*) meta-analysis of only RCTs that reported a greater than 50% stent-retriever use rate in the endovascular arm, (*iii*) meta-analysis of only RCTs with isolated intraarterial TPA and/or mechanical thrombectomy without IV TPA in the endovascular arm, and (*iv*) meta-analysis of only RCTs that had IV TPA administered when appropriate in addition to endovascular intervention.

Meta-analyses were performed by using Comprehensive Meta Analysis software, version 2.0 (www.meta-analysis.com). Results were expressed as odds ratios (ORs), using numbers of events per number of treated and control patients. Fixed-effects and random-effects models were applied (17). To evaluate heterogeneity, the Cochran test statistic Q was evaluated. As this test has low power at small sample sizes and excessive power when there are many studies, the quantity I^2 was also calculated (17), which measures the percentage of total variation caused by heterogeneity rather than chance. Higgins et al (18) suggested values of 25%, 50%, and 75% for low, moderate, and high heterogeneity. Additionally, the τ^2 statistic is reported; this value was used to assign study weights under the random-effects model. To account for multiple comparisons, P values were adjusted by the global and sequential Bonferroni procedure and by false discovery rate (19,20).