

What is the Efficacy and Safety of Intravenous Thrombolysis and Thrombectomy Among Patients With a Wake-Up Stroke?



TAKE-HOME MESSAGE

Among patients with a stroke occurring during sleep (wake-up stroke), endovascular therapy increases the likelihood of having a good functional outcome. Intravenous thrombolytic therapy may improve the likelihood of a good functional outcome, but the potential for an increased risk of symptomatic intracranial hemorrhage cannot be ruled out.

METHODS

DATA SOURCES

Cochrane Central Register of Controlled Trials, MEDLINE, and Embase were searched from inception to May 24, 2021 for relevant studies. In addition, the US National Institutes of Health Ongoing Trials Register, World Health Organization International Clinical Trials Registry, and Stroke Trials Registry were searched for ongoing trials. There were no language restrictions. The authors also screened reference lists of relevant trials, contacted principal investigators of the identified studies, performed forward tracking of relevant references using the Science Citation Index Cited Reference search, and contacted manufacturers of relevant equipment and devices.

STUDY SELECTION

Two authors independently screened articles for inclusion, with any discrepancies resolved by a third reviewer. Eligible studies compared all types of thrombolytic

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Editor's Note: This is a clinical synopsis, a regular feature of the *Annals'* Systematic Review Snapshot (SRS) series. The source for this systematic review snapshot is: **Roaldsen MB, Lindeklev H, Mathiesen EB. Intravenous thrombolytic treatment and endovascular thrombectomy for ischaemic wake-up stroke. *Cochrane Database Syst Rev.* 2021;12:CD010995.**

Results

Comparison of treatments for wake-up stroke.

| Outcome | No. of Studies (No. of Participants) | Total | Total | RR (95% CI) | Heterogeneity (I ²) (%) |
|--|--|--|---|-------------------|--|
| | | Events/Total Participants (%) Intervention Group | Events/Total Participants (%) Control Group | | |
| Intravenous Thrombolytics | | | | | |
| Independent functional outcome (mRS ≤ 2) | 5 (763) | 258/390 (66.2%) | 218/373 (58.4%) | 1.13 (1.01-1.26) | 0% |
| Symptomatic intracranial hemorrhage | 4 (754) | 10/386 (2.6%) | 2/368 (0.5%) | 3.47 (0.98-12.26) | 0% |
| Mortality | 5 (763) | 28/390 (7.2%) | 37/373 (9.9%) | 0.68 (0.43-1.07) | 87% |
| Endovascular Thrombectomy | | | | | |
| Independent functional outcome (mRS score ≤ 2) | 2 (205) | 54/116 (46.6%) | 8/89 (9.0%) | 5.12 (2.57-10.17) | 0% |
| Mortality | 2 (205) | 26/116 (22.4%) | 29/89 (32.6%) | 0.68 (0.43-1.07) | 0% |

CI, Confidence interval; mRS, modified Rankin Scale; RR, risk ratio.

drugs given in any dose by the intravenous route or all types of intra-arterial treatments to standard medical care or placebo for patients with wake-up acute ischemic strokes (with neuroimaging demonstrating no intracranial hemorrhage before randomization). In articles that included trials with both wake-up strokes and strokes occurring among awake patients, only the data for wake-up strokes were included.

DATA EXTRACTION AND SYNTHESIS

Two review authors independently extracted data for each trial. The primary outcome was participants who had a good functional outcome (defined by a modified Rankin Scale score of ≤ 2) at the end of the follow-up period. The secondary outcomes included death from all causes within 7 to 14 days and at the end of follow-up, symptomatic intracranial hemorrhage at the end of follow-up, quality of life at the end of follow-up, and neurologic status at 7 to 14 days and at the end of follow-up. The risk of bias was determined using the Cochrane Handbook for Systematic Reviews of Interventions.¹ For dichotomous outcomes, the authors reported risk ratios with 95% confidence intervals. Heterogeneity was measured using the I^2 statistic. Pooled data were evaluated using a fixed-effects model. The authors used the GRADE approach to determine the certainty of evidence. Publication bias was not performed due to the limited number of studies.

The initial search yielded 1,709 unique records, of which 7 trials ($n = 980$ participants) were used in the meta-analysis. Five of the trials examined intravenous thrombolytic treatment versus control and 2 examined endovascular thrombectomy versus control. The trials were published between 2012 and 2020. All 5 of the thrombolytic studies used alteplase as the thrombolytic, and all but 1 of these studies used a 0.9 mg/kg dose (exception using 0.6 mg/kg dose). Two studies used magnetic resonance imaging (MRI) DWI/FLAIR mismatch criteria for selection, 1 study used MRI or computed tomography perfusion core/penumbra mismatch criteria, 1 study used only MRI perfusion core/penumbra mismatch criteria, and 1 study selected patients with signs of ischemic tissue at risk of infarction on perfusion computed tomography. The 2 thrombectomy studies selected patients with occlusion of the internal carotid artery or proximal middle cerebral artery. Overall, endovascular therapy and intravenous thrombolytic therapy were associated with a statistically significant difference in rates of independent functional outcome (Table). There was no statistically significant difference in mortality or intracranial hemorrhage. All outcomes were deemed high certainty as per the GRADE criteria. All 7 studies were assessed as low risk of selection bias, blinding bias, and reporting bias. Two studies were deemed to have an unclear risk of attrition bias; the other studies were assessed as low risk. There was an unclear risk of other biases in 6 of the studies.

Commentary

Acute ischemic stroke is a major cause of death and disability both in the United States and worldwide.^{2,3} Intravenous thrombolytic therapy and mechanical thrombectomy are commonly recommended for eligible patients who are within the treatment period.⁴ However, approximately one-fifth of strokes occur during sleep (referred to as “wake-up strokes”).⁵ Among patients with wake-up strokes, the time of onset is often unknown and the benefits of these interventions are less clear.

This systematic review and meta-analysis found an improved functional outcome among patients with wake-up stroke who were treated with endovascular therapy.⁶ The authors also reported a small statistically significant benefit for intravenous thrombolytics.

However, it is important to consider several limitations with respect to the present review. There were only a limited number of studies, and the sample sizes were small. As such, the review

may have been underpowered for some clinically important outcomes (eg, symptomatic intracranial hemorrhage). Of note, 6 of the trials were prematurely terminated, which can be a potential source of bias. There were also different types of advanced imaging techniques used between studies. Moreover, patients in the intravenous thrombolysis group received advanced imaging assessments for evidence of threatened tissue or an ischemia penumbra. Consequently, this may not reflect all patients with ischemic wake-up stroke. Finally, although there was a moderate effect seen for endovascular therapy, the benefit for thrombolysis was much smaller, with the 95% confidence interval barely exceeding 1.

Based on the present data, we believe that endovascular therapy should be considered in appropriately selected patients with a wake-up stroke. This would be consistent with recommendations from awake large vessel occlusion stroke trials.⁷⁻⁹ Intravenous thrombolytics may be considered in appropriately selected patients,

but clinicians must weigh the potential risks of intracranial hemorrhage with the potential benefits to the neurologic outcome.

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IMAGES IN EMERGENCY MEDICINE

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DIAGNOSIS:

Endometrial cast (membranous dysmenorrhea). Ultrasound suggested air in the endometrium; this rare finding is typically associated with endometritis, which generally occurs postpartum or after surgery or instrumentation. However, in this case, the pathology was an endometrial cast (membranous dysmenorrhea) associated with exogenous progesterone (eg, oral contraceptives or injectable progesterone). This promotes the development of the decidual lining of the endometrium, and rarely, the entire mass is shed at once to create a cast of the uterine cavity.^{1,2} While there is a potential association with ectopic pregnancy, the condition—although painful—is not severe, and symptoms typically resolve with the passage of tissue.^{1,2}

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