Review: Thrombolysis increases short-term death and intracranial hemorrhage but decreases long-term death or dependence

Wardlaw JM. **Overview of Cochrane thrombolysis meta-analysis.** Neurology. 2001 Sep;57 (Suppl 2):S69-76.

Wardlaw JM, del Zoppo G, Yamaguchi T. **Thrombolysis for acute ischaemic stroke.** Cochrane Database Syst Rev. 2001;(4):CD000213 (latest version 24 Jul 2001).

QUESTION

In patients with acute ischemic stroke, is thrombolytic therapy safe and effective for reducing mortality and intracranial hemorrhage and for improving functional outcome?

DATA SOURCES

Studies were identified by searching 2 databases, hand-searching journals, pharmaceutical companies, and reviewing meeting abstracts.

STUDY SELECTION

Studies were selected if they were randomized controlled trials that compared thrombolytic drugs with placebo or control treatment in patients with definite acute ischemic stroke. Trials were excluded if the treatment or control group received another active therapy not factored into the randomization.

DATA EXTRACTION

Data were extracted on patients, drug dose, administration route, duration of treatment, stroke type, results of computed tomography, and duration of follow-up. Outcomes were all-cause mortality 7 to 10 days after treatment, symptomatic or fatal intracranial hemorrhage, all-cause mortality at long-term follow-up, and poor functional outcome. Study quality was assessed on randomization method, blinding of drug administration, and blinding of outcome assessment.

MAIN RESULTS

17 trials (5144 patients) were included. Thrombolysis comprised intravenous (IV) streptokinase (4 trials), IV recombinant tissue plasminogen activator (rt-PA) (8 trials), IV urokinase (3 trials), and intra-arterial recombinant pro-urokinase (2 trials). About half the trials studied rt-PA. Most patients were treated within 6 hours of stroke. Thrombolysis increased all-cause mortality ($P < 0.001$) and symptomatic or fatal intracranial hemorrhage ($P < 0.001$) within 7 to 10 days of therapy (Table). Heterogeneity existed among trials of all-cause mortality at the end of follow-up (1 to 6 mo), even when the analysis was restricted to trials of rt-PA and showed a nonstatistically significant increase in death in patients receiving thrombolysis (Table). Death or dependence was decreased at the end of follow-up in patients who received thrombolysis ($P = 0.003$) (Table).

CONCLUSION

In patients with acute ischemic stroke, thrombolytic therapy increases short-term mortality and symptomatic or fatal intracranial hemorrhage but decreases longer-term death or dependence.

Source of funding: No external funding.

For correspondence: Professor J.M. Wardlaw, Western General Hospital, Edinburgh, Scotland, UK. E-mail jmw@skull.dcn.ed.ac.uk.

Thrombolysis vs placebo or open control for acute ischemic stroke*

Outcomes	Number of trials	Weighted event rates		RRI (95% CI)	NNH (CI)
		Thrombolysis	Control		
Death at 7 to 10 d	7	16.6%	9.8%	69% (39 to 106)	15 (11 to 25)
SIH or FIH at 7 to 10 d	17	9.4%	2.5%	273%(186 to 388)	15 (13 to 18)
Death at 1 to 6 mo†	17	19.0%	15.9%	19% (–3 to 45)	Not significant
				RRR (CI)	NNT (CI)
Death or dependence at 1 to 6 mo	12	55%	70%	7% (3 to 12)	23 (14 to 67)

*FIH = fatal intracranial hemorrhage; SIH = symptomatic intracranial hemorrhage. Other abbreviations defined in Glossary; RRI, RRR, NNH, NNT, and CI calculated from data in article.
†Random-effects model used because heterogeneity existed.

COMMENTARY

The review by Wardlaw is an update of the Cochrane review of thrombolysis for acute ischemic stroke. Like all meta-analyses, it necessarily includes different forms, administration rates, and doses of therapy. While the overview analysis is important, the real interest is in the subanalyses.

t-PA is the most commonly used thrombolytic agent for ischemic stroke and is usually given intravenously within 3 hours of stroke onset. For this subanalysis, the number of patients saved from death or dependence per 1000 treated patients was 140 (95% CI 77 to 203) and from death alone was 12 (CI 61 fewer to 38 more). In biological terms, this medicine is powerful, and one would surmise that it should have a substantial effect on the burden of stroke. Unfortunately, it has not. Despite encouraging phase-IV data, the number of patients to whom this therapy has become available is small, probably 1% to 2% of those with ischemic strokes.

The meta-analysis gives us some reason to hope that this level of penetration may be improved. When time windows of up to 6 hours after stroke were considered in patients given IV t-PA, 57 (CI 20 to 93) fewer patients died or were dependent per 1000 treated. Fortunately, only a modest trend existed toward increased death alone (18 per 1000 treated). Why then is t-PA not licensed for a 6-hour time window?

Only 1 pivotal trial exists in which t-PA has been unequivocally beneficial (1). The time window used was 3 hours. All other trials have shown trends toward a beneficial outcome, but they did not satisfy the 0.05 judge. Furthermore, even the modest increase in mortality, naturally, concerns many.

More patients need to be entered into randomized trials, particularly with treatment after 3 hours or including other circumstances in which risk and benefit are uncertain. Magnetic resonance imaging may also be useful in selecting appropriate patients (2).

Geoffrey A. Donnan, MD
National Stroke Research Institute
Heidelberg West, Victoria, Australia

References

1. **National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group**. N Engl J Med. 1995;333:1581-7.
2. **Warach S.** Neurology. 2001;57:S48-52.