Cognitive Outcomes following Thrombolysis in Acute Ischemic Stroke: A Systematic Review

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Background: Patients treated with thrombolytic therapy within 4.5 hours after stroke onset appear to have improved survival and functional outcomes. Poststroke cognitive impairment is associated with reduced quality of life and survival and needs to be reviewed in consideration of the administration of thrombolysis. This review aims to systematically evaluate literature exploring the effect of thrombolysis for ischemic stroke on cognition. *Methods:* An electronic search was conducted to identify articles and gray literature applying broad Medical Subject Heading terms. Literature was reviewed with a 2-step process against predetermined inclusion criteria. All relevant studies were included if they investigated global or individual cognitive domains. *Results:* Three studies satisfied the inclusion criteria but were diverse in outcome measures and duration, their heterogeneity limiting any possible pooled analysis. One study examined long-term treatment effects on global cognition and did not find a positive effect at 6 months. A positive treatment effect was reported in the acute phase in 1 study examining domains of visuoconstructive and perceptive abilities. One study retrospectively analyzed treatment effects on language and found improvement in the acute phase but not in the long term. *Conclusions:* The limited existing evidence on the effects of thrombolytic therapy on long- and short-term cognition is varied in both outcome measures and diagnostic classifications, making it difficult to extrapolate results to a global stroke population. This review should be used to inform future research in stroke treatment outcomes and highlights the immediate need for larger, more robust studies in this area. **Key Words:** Stroke—cerebrovascular disorder—thrombolytic therapy—recombinant tissue plasminogen activator—cognitive disorder—cognitive impairment—neurological impairment.

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Introduction

Stroke is the second primary cause of death and the most common life-threatening neurological disorder worldwide.[1] One third of patients suffer from dementia in the first year following stroke, with 60% of patients experiencing some form of cognitive decline.[2] Poststroke cognitive impairment (PSCI) can improve during follow-up in approximately 16%-20% of elderly patients[3,4] but is associated with increased risk of functional decline and mortality.[5] If deficits are categorized as global and severe enough to satisfy dementia criteria, the risk of recurrent stroke, dependency, and mortality are further increased with resulting social and economic costs.[6]

Treatment with intravenous recombinant tissue plasminogen activator (rt-PA) in the acute stage of ischemic stroke is approved worldwide[7-9] and has been seen to improve survival and functional outcomes when administered within 4.5 hours of onset.[10-12] The benefits of rt-PA are thought to be due to the early recanalization of occluded arteries, reducing the amount of tissue at risk of infarction.[13] The reduction of lesion volume resulting from increased cerebral reperfusion is considered to be one of the best predictors of a good outcome following ischemic stroke.[14] A recent systematic review examining the safety and efficacy of thrombolytic therapy for acute ischemic stroke strengthens previous evidence, and indicates that thrombolysis reduces the risk of mortality and dependency despite the risk of symptomatic intracranial hemorrhage.[15] Theoretically, thrombolytic drugs may therefore also improve cognitive outcomes and reduce neurological deficits by restoring blood flow in occluded vessels.[16] The impact of thrombolysis on PSCI warrants detailed review to improve knowledge around the treatment and management of such patients. The main objective of the current review is to evaluate the effect of thrombolytic therapy after ischemic stroke on cognitive outcomes.

Table 1. *Systematic search strategy*

Search stage	Strategies
1	Stroke/ or cerebrovascular disorders/ or brain ischemia/
2	Thrombolytic therapy/ or fibrinolysis/ or plasminogen/ or fibrinolysin/ or plasmin.mp.
3	(Blood clot lysis or alteplase or urokinase).mp.
4	Streptokinase/ or fibrinolytic agents/ or tissue plasminogen activator/ or rtpa.mp. or rt-pa.mp.
5	Plasminogen activators/ or recombinant tissue activator.mp.
6	2 or 3 or 4 or 5
7	1 and 6
8	Limit 7 to (English language and humans)
9	Cognition disorders/ or cognitive impairment.mp. or neurological impairment.mp.
10	Dementia/ or delirium/ or confusion/ or acute confusion.mp. or chronic confusion.mp.
11	Quality of life/ or qol.mp. or quality of life.mp.
12	Neuropsychological tests/ or neuropsychological behaviour.mp. or neurocognitive tests.mp.
13	9 or 10 or 11 or 12
14	8 and 13

Methods

An extensive electronic search was conducted on the Cochrane Library, PubMed and MedLine, Embase, and PsychInfo databases. The search terms were Medical Subject Heading terms covering stroke, thrombolytic treatment, and cognitive outcomes (Table 1), and literature was limited to stroke trials published in English on human subjects between 1990 and July 2015.

An electronic search was also conducted for relevant peer-reviewed journals (*Stroke*, *Journal of Neurology*, *Neurology*, *Age and Ageing*, *The Lancet*/*The Lancet Neurology*, and *Journal of Stroke & Cerebrovascular Diseases*), reference lists of appropriate papers, and international conference proceedings on stroke and thrombolysis. Conference abstracts from the International Stroke Conference, *Journal of Neurology*, and *Age and Ageing* were searched, and gray literature was examined by searching OpenGrey, which provides access to European gray literature between 1980 and 2005.

An initial search was conducted by means of a 2-step selection process in which 2 reviewers (L.B. and C.B.) independently reviewed the titles and abstracts to exclude obviously irrelevant articles, reducing the risk of selection bias. In a second review, reviewers (L.B. and C.B.) considered full papers against the inclusion and exclusion criteria shown in Table 2. Data were extracted from full papers to determine if they met the inclusion criteria. Uncertainty or a difference of opinion was resolved through discussion between the 2 reviewers (L.B. and C.B.). If no agreement could be reached, discussions were referred to a third person (M.D.). A pilot data extraction form was designed using guidelines in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and piloted on a sample of 10 articles to ensure the inclusion criteria could be applied generally and consistently. Studies were selected based on the participants, interventions, comparisons, outcomes, and study design (PICOS) formulation and hierarchical models of analysis to examine group effects and multiple observations of the same outcome (Table 3).

The primary outcome measure of the present review was cognition. Cognitive impairment could be measured by either a validated instrument of global cognitive function (such as the Mini-Mental State Examination, Montreal Cognitive Assessment, or Abbreviated Mental Test Score) or instruments examining individual cognitive domains such as executive function, memory, language, and visuospatial and constructional abilities.

Assessment of risk bias was independently assessed by the reviewers using the Cochrane Collaboration tool for assessing risk of bias.[17] Any differences of opinion between the 2 reviewers were resolved by way of discussion.

Due to methodological heterogeneity between the studies, we were unable to compare studies and perform a meta-analysis.

Results

Figure 1 indicates the process of study selection. The search yielded a paucity of randomized controlled trials