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Review Article

Endovascular stroke therapy

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ABSTRACT

Background: Following the development of intravenous thrombolysis as a successful treatment for ischaemic stroke, advances in neurointerventional radiology have facilitated endovascular approaches to treatment. This article reviews the available endovascular therapeutic options and their evidence-base.
Summary: Initial studies demonstrated that endovascular treatment of ischaemic stroke with intra-arterial thrombolysis and/or the use of clot-retrieval, thrombus aspiration and stent-retriever devices produced early recanalisation and reperfusion and improved neurological outcome. More recent randomised trials, however, have failed to show translation of recanalisation into successful clinical outcome with 'time to treatment' proving crucial. In this rapidly evolving field, combined therapy incorporating intravenous and intra-arterial thrombolysis in combination with endovascular clot-retrieval has been developed and further studies are expected to yield better evidence to guide the optimal treatment of acute cerebral ischaemia.

1. Introduction

Randomised controlled trials (RCTs) have shown ischaemic stroke to benefit from intravenous thrombolysis up to 3 and 4.5 h after symptom onset, with increasingly favourable outcomes the sooner the thrombolysis is administered [1–4]. This is in accordance with the phase "time is brain" and has been borne out by thrombolysis registry data [5,6]. It has been suggested that the benefit of intravenous thrombolysis may extend beyond 4.5 to 6 h in some patients but further studies are needed [7].

Favourable clinical outcome of intravenous thrombolysis has been associated with vessel recanalisation [8]. Studies have demonstrated reperfusion to be observed much less frequently in proximal large vessel artery occlusion compared with more distal vascular occlusion and recent studies have demonstrated recanalisation in only 18–25% of patients receiving intravenous thrombolysis for internal carotid artery (ICA), M1 middle cerebral artery (MCA) or basilar artery occlusion compared with 52% in M2 MCA occlusion [9–17]. Theoretically, administering thrombolytic agents directly into an area of clot or attempting to remove thrombus mechanically may increase efficacy. Endovascular intervention also has potential for faster recanalisation with a lower dose of lytic agent, visualisation of the clot being lysed (with prognostic implications), the possibility of increasing the time window from symptom onset to treatment and providing a therapeutic strategy for patients in whom intravenous thrombolysis is contraindicated [18]. In this article, we describe the endovascular therapeutic options developed and their evidence-base.

2. Methods

In March 2013, an electronic database search was performed of MEDLINE, EMBASE, HMIC, CINAHL and the Cochrane Library using the following MeSH and keywords: ischaemic; stroke; thrombolysis; intraarterial; endovascular; clot retrieval. All relevant articles between the years 1966 and 2013 were included. The resultant information was supplemented by extensive manual searching of references. Articles were evaluated against pre-defined criteria for eligibility and relevance that incorporated the following study characteristics: acute stroke patients, interventions, comparisons, outcomes and follow-up if pertinent. Inclusion of articles was based on an agreement between two independent reviewers (Ajay Bhalla, Jonathan Birns) using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist [19].

2.1. Intra-arterial thrombolysis

Intra-arterial thrombolysis was developed as an alternative to intravenous therapy for acute ischaemic stroke, with positive results being demonstrated in preliminary investigations [20,21]. These initial observational studies were followed by seven RCTs that investigated the efficacy and safety of intra-arterial thrombolysis for acute ischaemic stroke (Table 1) [22–29]. Whilst the trials showed conflicting results, the majority of studies showed improvement in recanalisation and/or

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Table 1
Randomised controlled trials investigating the efficacy and safety of intra-arterial thrombolysis for acute ischaemic stroke.

Study	Subjects	Study design	Results	Conclusions
PROACT I [29]	n = 40 Acute MCA territory occlusion within 6 h of ictus NIHSS ≤ 30	Randomised 2:1 to receive 6 mg prourokinase plus heparin (n = 26) or heparin only (n = 14).	No significant difference in 90-day mRS ≤ 1 (31% vs 21%), mortality (27% vs 42%) or symptomatic ICH (15% vs 14%) between patients treated with prourokinase vs placebo. Recanalisation achieved in 57% patients treated with prourokinase vs 14% placebo patients (2p = 0.017). Both recanalisation and haemorrhage frequencies influenced by heparin dose.	Intra-arterial prourokinase was associated with superior recanalisation in acute ischaemic stroke compared with placebo. Heparin dose influenced haemorrhage frequency and recanalisation.
PROACT II [22]	n = 180 Acute MCA territory occlusion within 6 h of ictus NIHSS ≤ 30	Randomised to receive 9 mg of prourokinase plus heparin (n = 121) or heparin only (n = 59).	Significantly increased proportion of patients with 90 day mRS < 2 (40% vs 25%; p = 0.04), recanalisation (66% vs 18%; p < 0.001) and 24-hour symptomatic ICH (10% vs 2%; p = 0.06) in those treated with prourokinase vs placebo. No significant difference in mortality (25% vs 27%) between patients treated with prourokinase vs placebo.	Despite an increased frequency of early symptomatic ICH, intra-arterial prourokinase significantly improved clinical outcome at 90 days.
Ducrocq et al. [23]	n = 27 Acute ischaemic stroke within 6 h of ictus	Randomised to receive 900,000 units urokinase via intravenous (n = 14) or intra-arterial (n = 13) routes.	Study terminated prematurely because 7/27 patients (26%) died (4 in the intravenous group and 3 in the intra-arterial group). No significant difference in proportion of patients with mRS ≤ 2, mortality or frequency of symptomatic ICH between treatment groups. Average treatment times were significantly shorter in the intravenous (4 h 16 min) vs intra-arterial group (5 h 24 min; p = 0.007).	The trial was too small to provide any conclusions.
Macleod et al. [24]	n = 16 Acute ischaemic stroke due to occlusion of the basilar or vertebral arteries within 24 h of ictus. Glasgow Coma Scale ≥ 9	Randomised to receive intra-arterial urokinase plus heparin/warfarin anticoagulation (n = 8) or heparin/warfarin anticoagulation (n = 8).	4/8 patients who received intra-arterial urokinase compared with 1/8 patients in the control group were not dead or disabled (combined Barthel and Rankin scores and mortality) at 6 months (OR: 0.14 (0.02–1.43); p = 0.28). Among survivors, median mRS was 1 in the urokinase group and 3 in the control group.	Results supported the need for a large-scale trial to establish the efficacy of intra-arterial thrombolysis for acute basilar artery occlusion.
MELT [25]	n = 114 Acute MCA territory occlusion within 6 h of ictus NIHSS ≤ 22	Randomised to receive intra-arterial urokinase (n = 57) or placebo (n = 57).	Study terminated prematurely after approval of intravenous infusion of alteplase in Japan. Non-significant increase in proportion of patients with 90 day mRS < 2 (primary endpoint) (49% vs 39%; p = 0.44) but significant increase in 90-day mRS ≤ 1 (42% vs 23%; p = 0.045) in those treated with urokinase vs placebo. No significant difference in 90-day mortality (5% vs 4%; p = 1) and 24-hour ICH (9% vs 2%; p = 0.206) between patients treated with urokinase vs placebo.	The trial was aborted prematurely and the primary endpoint did not reach statistical significance. Nevertheless, the secondary analyses suggested that intra-arterial thrombolysis may increase the likelihood of excellent functional outcome.
SYNTHESIS pilot [26]	n = 54 Acute ischaemic stroke within 3 h of ictus for intravenous therapy and within 6 h of ictus for intra-arterial therapy NIHSS ≤ 25	Randomised to receive 0.9 mg/kg (maximum 90 mg) alteplase intravenously within 3 h (n = 29) or intra-arterially within 6 h (with additional intravenous heparin, mechanical clot disruption and/or retrieval if necessary) (n = 25).	Increased proportion of patients with 90 day mRS ≤ 1 (48% vs 28%; p = 0.067 in those treated with intra-arterial vs intravenous thrombolysis). No significant difference in mortality (20% vs 14%) or symptomatic ICH (14% vs 8%) between patients treated with intra-arterial vs intravenous thrombolysis. Median treatment times were significantly shorter in the intravenous (2 h 35 min) vs intra-arterial group (3 h 15 min; p < 0.001).	Intra-arterial thrombolysis is a safe and feasible alternative to intravenous thrombolysis in acute ischaemic stroke.
SYNTHESIS expansion [27,28]	n = 362 Acute ischaemic stroke within 4.5 h of ictus	Randomised to receive 0.9 mg/kg (maximum 90 mg) alteplase intravenously (n = 181) or intra-arterially (with additional intravenous heparin, mechanical clot disruption or retrieval or a combination of these approaches) (n = 181).	No significant difference in 90-day mRS ≤ 1 (30% vs 35%), mortality (26% vs 18%) or 7-day symptomatic ICH (6% vs 6%) between patients treated with intra-arterial vs intravenous thrombolysis. Median treatment times were significantly shorter in the intravenous (2.75 h) vs intra-arterial group (3.75 h; p < 0.001).	Endovascular therapy incorporating intra-arterial thrombolysis is not superior to standard treatment with intravenous thrombolysis for acute ischemic stroke.