Thrombolytic therapy in acute ischaemic stroke: intravenous, intra-arterial, mechanical, hybrid, and bridging

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Procedures with thrombolytic therapy

A recent meta-analysis demonstrated that recanalisation during thrombolysis in acute ischaemic stroke is strongly associated with improved functional outcomes and reduced mortality. In fact, patients treated with intravenous tissue plasminogen activator (tPA) within 3 hours of onset of cerebrovascular symptoms are 30% more likely to exhibit complete or nearly complete recovery at 3 months than a placebo-treated group. Nevertheless, approximately 50-60% of patients eligible for this therapy still show unfavourable long-term outcome. Furthermore, in angiographic controlled studies intravenous thrombolysis was associated with a recanalisation rate of 35% for M1-MCA, 54% for M2-MCA, and 66% for M3-MCA occlusions.
Patients treated with intra-arterial thrombolysis (pro-urokinase, urokinase or tPA) within a 6-hour window are also more likely to regain independence at 90 days than those assigned to placebo (40% versus 25% mRS 0-2; p=0.04); however, according to various studies, 32-60% still experience a poor outcome. Recent studies demonstrated that intra-arterial thrombolysis was more beneficial than intravenous thrombolysis in the specific group of stroke patients presenting with a hyperdense middle cerebral artery (HMCA) on CT. The hyperdense middle cerebral artery sign (HMCAS) is a marker of thrombus in the middle cerebral artery (MCA); its specificity for MCA occlusion approaches 100%, whereas its sensitivity is low. The HMCAS has been associated with severe neurological deficits, extensive brain damage, and poor clinical outcome. Although randomised studies are still lacking, these findings nevertheless suggest that for large artery occlusions, intra-arterial thrombolysis is more effective than intravenous thrombolysis. However, as shown in the PROACT II study, as well as in others, even with intra-arterial thrombolysis, 20%-40% of the vessels will not recanalise.
Bridging therapies have been advocated with administration of systemic thrombolytics followed by intra-arterial infusion of tPA to help dissolve clots. Combined intravenous and intra-arterial thrombolysis offers some advantages over either technique alone: intravenous treatment may be administered very early while the resources to deliver intra-arterial treatment are organised; furthermore intravenous thrombolysis is easy to use and widely available. On the other hand, intra-arterial thombolysis, as already mentioned, offers possible superior and earlier recanalisation. Combined intravenous (IV) and intra-arterial (IA) thrombolysis has been studied in several trials. One double-blind randomised placebo-controlled study comparing IV plus local IA tPA with IA tPA + placebo (EMS bridging trial) revealed that recanalisation was better in the IV/IA group, with complete recanalisation achieved in 6 of 11 IV/IA patients versus 1 of 10 placebo/IA patients (p=0.05). Overall, 17 patients were included in the IV/IA group and 18 in the placebo/IA group. However, despite higher recanalisation rates, the clinical outcomes were not better in the IV/IA group. Another study (IMS II) also showed that IMS subjects (81 patients) had a significantly better outcome at 3 months than NINDS (intravenous thrombolysis trial) subjects. The 3-month mortality and rate of symptomatic intracerebral haemorrhage were similar to those recorded in the tPA-treated subjects in the NINDS trial.

Procedures with mechanical thrombolysis (percutaneous transluminal angioplasty and implementation of stents)

Recent studies have also emphasised the potential role of mechanical thrombolysis, including thromboaspiration, percutaneous transluminal angioplasty (PTA) and implantation of stents, which yields recanalisation

rates of more than 75% when intra-arterial thrombolysis is added. Other studies also demonstrated a potential benefit of a multimodal approach combining mechanical disruption and platelet GPIIb/IIIa receptor antagonists, but as a rescue therapy after failure of intravenous or intra-arterial therapy. More recently, Nakano and colleagues showed in a study including 70 patients that direct PTA for acute MCA trunk occlusion resulted in a high recanalisation rate and was feasible and safe. Thirty-four patients were treated with direct PTA, and subsequent thrombolytic therapy was added if necessary for distal embolisation. The other 36 patients were treated with thrombolytic therapy alone and were used as controls. The rate of partial or complete recanalisation in the PTA group was 91.2%, whereas that in the thrombolysis-alone group was 63.9% ($p<0.01$). Furthermore, the incidence of large parenchymal haematoma with neurological deterioration in the PTA group was 2.9%, whereas it was 19.4% in the thrombolysis-alone group ($p=0.03$). Although direct PTA did not improve the rate of favourable outcome (mRS score 0 or 1; 41.7% for the thrombolysis-alone group versus 52.9% for the PTA group; $p=0.48$), outcome in terms of independence (mRS score 0, 1, 2) was significantly better in the PTA group (73.5%) than in the thrombolysis-alone group (50.0%; $p=0.04$).

Another study evaluated the efficacy and safety of intravenous tirofiban* combined with intra-arterial pharmacological and mechanical thrombolysis in patients with acute ischaemic stroke. Twenty-one consecutive patients with an acute ischaemic stroke were treated with an intravenous bolus of tirofiban and heparin followed by intra-arterial administration of urokinase coupled with mechanical thrombolysis. Thirteen patients had an anterior circulation stroke (T-siphon internal carotid artery [ICA] = 7; MCA = 6), six patients a posterior circulation stroke, and two an anterior plus posterior circulation stroke (left ICA or M1 tract of MCA plus basilar artery occlusions). Immediate recanalisation was successful in 17 of 21 patients. The following day, 14 of 19 patients improved substantially and complete vessel patency was confirmed by digital subtraction angiography. Intracranial bleeding occurred in 5 of 21 patients (3 symptomatic cerebral haemorrhages and 2 subarachnoid haemorrhages) and was fatal in three patients.

Another study evaluated self-expanding stents for recanalisation of acute cerebrovascular occlusions. Stent-assisted revascularisation increases prevailing recanalisation rates (congruent with 50%-69%) for vessel occlusions recalcitrant to thrombolytics. Eighteen patients (19 lesions) were reviewed retrospectively. Stent placement was the initial mechanical manoeuvre in 6 cases; others involved a combination of pharmacological and/or mechanical manoeuvres prestenting. GP IIb/IIIa inhibitors were administered in 10 cases intra-procedurally or immediately post-procedurally to avoid acute in-stent thrombosis. Stent deployment at the target occlusion (technical success) was achieved in all cases. An angiographic success of recanalisation was documented in 15 of 19 lesions (79%). All single-vessel lesions (n=8) were recanalised, but only 7 of 11 combination ICA and MCA lesions were recanalised. No intra-procedural complications occurred. Seven in-hospital deaths were recorded: 4 patients with stroke progression; 2 with intracranial haemorrhage and 1 with respiratory failure. The authors of this study concluded that treatment of acute symptomatic intracranial occlusions with self-expanding stents was feasible. For single-vessel lesions, stent placement with concomitant administration of IIb/IIIa inhibitors contributed to the achievement of recanalisation rates exceeding those currently reported for other means of thrombolysis.

Routine protocol for thrombolysis in our centre

All patients admitted for an acute ischaemic stroke in the MCA circulation in a 3-hour window, and meeting the criteria for eligibility for intravenous thrombolysis (0.9 mg/kg, 90 mg maximum, 10% of dose as a bolus over 1 minute, then 90% at a 1-hour perfusion rate), are first monitored with trancranial colour-coded duplex sonography (TCCD). For this a TIBI classification is used evaluating the amount of residual flow in the MCA. After 30 minutes of intravenous thrombolysis, in cases of partial or complete recanalisation observed on TCCD, a decision is made to administer intravenous thrombolysis over a total period of 60 minutes. In the absence of recanalisation, intra-arterial thrombolysis is performed with the remaining tPA dose. Our results show that patients with a dampened flow (TIBI 3), corresponding generally to a distal MCA occlusion, had the best chance of recanalising early (OR 24.7 95%CI 3.01 to 202, $p=0.003$), whereas patients with an absent residual flow (TIBI 0) corresponding to a proximal MCA or a distal internal carotid artery occlusion were significantly less likely to reperfuse (OR 0.14 95%CI 0.03-07, $p<0.02$), either with intravenous or with combined IV/IA therapy.