Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial

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Summary

Background Intravenous thrombolysis with alteplase alone cannot reperfuse most large-artery strokes. We aimed to determine whether mechanical thrombectomy in addition to intravenous thrombolysis improves clinical outcome in patients with acute ischaemic stroke.

Methods THRACE is a randomised controlled trial done in 26 centres in France. Patients aged 18–80 years with acute ischaemic stroke and proximal cerebral artery occlusion were randomly assigned to receive either intravenous thrombolysis alone (IVT group) or intravenous thrombolysis plus mechanical thrombectomy (IVTMT group). Intravenous thrombolysis (alteplase 0·9 mg/kg [maximum 90 mg], with an initial bolus of 10% of the total dose followed by infusion of the remaining dose over 60 min) had to be started within 4 h and thrombectomy within 5 h of symptom onset. Occlusions had to be confirmed by CT or magnetic resonance angiography. Randomisation was done centrally with a computer-generated sequential minimisation method and was stratified by centre. The primary outcome was the proportion of patients achieving functional independence at 3 months, defined by a score of 0–2 on the modified Rankin scale, assessed in the modified intention-to-treat population (ie, patients lost to follow-up and those with missing data were excluded). Safety outcomes were analysed in the per-protocol population (ie, all patients who did not follow the protocol of their randomisation group precisely were excluded from the analysis). THRACE is registered with ClinicalTrials.gov, NCT01062698.

Findings Between June 1, 2010, and Feb 22, 2015, 414 patients were randomly assigned to the IVT group (n=208) or the IVTMT group (n=204). Four patients (two in each group) lost to follow-up and six (four in the IVT group and two in the IVTMT group) with missing data were excluded. 85 (42%) of 202 patients in the IVT group and 106 (53%) of 200 patients in the IVTMT group achieved functional independence at 3 months (odds ratio 1·55, 95% CI 1·05–2·30; p=0·028). The two groups had no significant differences in mortality at 3 months (24 [12%] deaths of 202 patients *vs* 27 [13%] of 206; p=0·70) or symptomatic intracranial haemorrhage at 24 h (four [2%] of 185 *vs* three [2%] of 192; p=0·71). Common adverse events related to thrombectomy were vasospasm (33 [23%] patients) and embolisation in a new territory (nine [6%]).

Interpretation Mechanical thrombectomy combined with standard intravenous thrombolysis improves functional independence in patients with acute cerebral ischaemia, with no evidence of increased mortality. Bridging therapy should be considered for patients with large-vessel occlusions of the anterior circulation.

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Introduction

Intravenous administration of alteplase, a tissue plasminogen activator, within 4·5 h of stroke onset improves the chance of a good outcome, and early treatment is associated with proportionally larger benefits.[1–4] However, revascularisation rates are reduced in occlusions of large proximal vessels, and the prognosis for patients with these occlusions remains poor.[5,6] Endovascular treatments increase the chance of successful and rapid recanalisation. Therefore, the use of intravenous alteplase with mechanical thrombectomy should, in theory, combine their respective advantages: quick administration and improved recanalisation.

Several randomised clinical trials have assessed this combined approach. The results of initial trials[7–9] did not show a benefit of this approach, which might be explained by the fact that imaging was not used for diagnosis and localisation of occlusion for some patients and by the low rate of reperfusion. Moreover, these studies did not use the most recent devices (eg, stent retrievers Solitaire and Trevo) that have greatly improved the speed and efficacy of recanalisation. The results of subsequent randomised trials[10–15] have consistently shown that, in patients who receive standard care, mechanical thrombectomy significantly improves revascularisation and functional independence at 3 months with no increase in mortality. Some of these trials selected patients who were most likely to benefit from a combined approach by using imaging characteristics such as ischaemia-associated abnormalities in the Alberta Stroke Program Early CT

Research in context

Evidence before this study

We searched PubMed with the terms "stroke + thrombectomy" for articles published in English before Dec 31, 2015. Our search returned numerous single-centre or multicentre studies or registry studies in which endovascular treatment improved recanalisation, and eight randomised clinical trials that investigated the effect of endovascular treatment on functional outcomes. The results of the three trials published in 2013 were negative, whereas those of the five trials published in 2015 showed that, in patients receiving standard care, complementary mechanical thrombectomy led to an increased proportion of patients achieving functional independence at 3 months with no increase in mortality.

Added value of this study

The THRACE trial also assessed functional outcomes after treatment with intravenous alteplase for thrombolysis plus mechanical thrombectomy versus intravenous thrombolysis alone in patients with acute cerebral ischaemia. To our knowledge, it is the largest study to show that mechanical thrombectomy is better than standard care alone. Although our results are consistent with those of other recent studies, the THRACE trial is unique because of its wide patient selection, with no imaging-based criteria beyond the requirement for large-vessel occlusion, and its rapid randomisation (<20 min after intravenous thrombolysis initiation), so that fast responders to intravenous alteplase were not excluded. Thus, results of the THRACE trial showed a benefit in functional outcome for the combined approach in a broad population of patients similar to that encountered in routine clinical practice.

Implications of all the available evidence

Mechanical thrombectomy seems to be beneficial and should be considered for a wide range of patients with large-vessel occlusions of the anterior circulation, regardless of age, sex, clinical severity, or intracranial location of the occlusion.

score (ASPECTS) or cerebral perfusion data to distinguish between permanent lesions and hypoperfused but potentially rescuable penumbra.[11–14] The use of imaging criteria might increase the effect of treatment but might also exclude many patients who could benefit from intra-arterial treatment.

The THRACE (THRombectomie des Artères CErebrales) trial was designed in 2009, before the results of the IMS III trial[7] became available, and has a similar protocol.[7] In THRACE, we aimed to compare standard treatment—intravenous thrombolysis alone—with intravenous thrombolysis plus mechanical thrombectomy by use of the newest devices to determine their effect on functional independence at 3 months in patients with moderate-to-severe stroke due to an occlusion of a proximal cerebral artery within 4 h of symptom onset.

Methods

Study design and participants

THRACE was a randomised controlled trial done in 26 centres in France. Patients with acute ischaemic stroke were eligible for inclusion if they were aged 18–80 years; had a US National Institutes of Health Stroke Scale (NIHSS) score of 10–25; had an occlusion of the intracranial internal carotid artery, the M1 segment of the middle cerebral artery, or the superior third of the basilar artery confirmed by CT or magnetic resonance angiography; could be administered intravenous thrombolysis within 4 h of symptom onset; and if thrombectomy could be initiated within 5 h of symptom onset. The time limit for intravenous thrombolysis initiation was initially within 3 h of symptom onset; on May 14, 2011, after enrolment of 80 patients, the trial steering committee decided to extend the time limit for intravenous thrombolysis initiation to 4 h, but the time limit for thrombectomy initiation was not changed. Patients who had cervical internal carotid artery occlusion and subocclusive stenosis were excluded (see the appendix for complete inclusion and exclusion criteria).

See Online for appendix

The study protocol was approved by the CPP (Comité de Protection des Personnes) III Nord Est Ethics Committee and the research boards of the participating centres. All patients or their legal representatives provided written informed consent.

Randomisation and masking

Patients were randomised (1:1) as soon as possible during intravenous thrombolysis to receive intravenous thrombolysis and mechanical thrombectomy (IVTMT group) or intravenous thrombolysis alone (IVT group). Randomisation was done at the coordination centre by a computer analyst who was masked to the investigation centres and to the patients. Randomisation was done with a computer-generated sequence and was stratified by centre, and sequential minimisation with a factor of 85% was used to avoid imbalance in treatment.[16] Participants were enrolled by local investigators and assigned to the trial group according to the random number. Masking of investigators and patients was not feasible because of the nature of the intervention.

Procedures

All patients received intravenous thrombolysis as per standard care—ie, 0·9 mg/kg of alteplase (maximum 90 mg), with an initial bolus of 10% of the total dose, and then infusion of the remaining dose over 60 min, irrespective of group assignment. Initially, patients allocated to the IVTMT group were to be clinically assessed after the completion of intravenous thrombolysis but before angiography. From Oct 12, 2012,