Imaging perfusion deficits, arterial patency and thrombolysis safety and efficacy in acute ischaemic stroke. An observational study of the effect of advanced imaging methods in The Third International Stroke Trial (IST-3), a randomised controlled trial

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Scientific summary

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Background

Intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) improves outcomes in patients treated early after a stroke but at the risk of causing intracranial haemorrhage. Restricting rt-PA use to patients with evidence of still-salvageable tissue, or with definite arterial occlusion, might help to reduce risk, increase benefit and identify patients for treatment at late time windows.

Objectives

To determine if perfusion or angiographic imaging with computed tomography (CT) or magnetic resonance (MR) help to identify patients who are more or less likely to benefit from rt-PA. We nested the study in a large multicentre randomised controlled trial of rt-PA given within 6 hours of the onset of acute ischaemic stroke: the Third International Stroke Trial (IST-3). Whether or not rt-PA use should be restricted to patients with particular imaging findings can only be tested in a randomised trial of rt-PA compared with control.

Design

The IST-3 is a prospective, multicentre, randomised controlled trial testing rt-PA (0.9 mg/kg, maximum dose 90 mg) started up to 6 hours after the onset of acute ischaemic stroke, in patients with no clear indication for, or contraindication to, rt-PA. Brain imaging (CT or MR) was mandatory pre randomisation to exclude haemorrhage. Scans were read centrally, blinded to treatment and clinical information. In centres where perfusion and/or angiography imaging were used routinely in stroke, these images were also collected centrally, processed centrally and assessed using validated visual scores and computational measures.

Setting

One hundred and fifty-six acute-care hospitals with stroke units in 12 countries for the main trial; 48 centres in eight countries performed CT perfusion and/or angiography and 37 centres in 11 countries performed MR perfusion or angiography.

Participants

Patients aged over 18 years with symptoms of acute stroke in whom brain scanning had excluded intracranial haemorrhage as the cause of stroke, with no clear indication for or contraindication to rt-PA, who could start treatment within 6 hours of symptom onset and in whom the time of onset was known. Patients with early visible infarction on plain CT scanning, and with several comorbidities, were eligible.

Interventions

Recombinant tissue plasminogen activator (0.9 mg/kg, maximum dose 90 mg) given intravenously with 10% as a bolus and the rest infused over 1 hour, started up to 6 hours after the onset of acute ischaemic stroke compared with best medical care. The first 300 patients were randomly allocated to rt-PA

or an identical-appearing placebo; thereafter, patients were randomised to rt-PA or open control. In the placebo-controlled phase, aspirin was withheld until 24 hours after trial drug administration; thereafter, aspirin was withheld until after 24 hours in the rt-PA arm and was started immediately after randomisation in the open-control arm. Otherwise, medical care was to be identical.

Main outcome measures

The primary outcome in IST-3 is alive and independent (Oxford Handicap Score 0–2) at 6 months; secondary outcomes are symptomatic and fatal intracranial haemorrhage, early and late death. The perfusion study additionally examined qualitative visually scored perfusion lesion extent [cerebral blood volume (CBV); cerebral blood flow; mean transit time (MTT); time to maximum flow (Tmax)], quantitative perfusion lesion volume for a range of parameters, the relationships between perfusion and plain scan lesions, with clinical baseline and outcome variables, and the interaction with rt-PA. Angiography images were analysed for the presence of and extent of arterial obstruction on CT or MR angiography (CTA, MRA), the density of any visible thrombus on CT (hyperdense artery sign), collateral channels, and disappearance of the occlusion on follow-up imaging. We tested associations between CTA and plain scan hyperdense artery, CTA arterial obstruction and clinical features, clinical outcome and the interaction with rt-PA. We also compared the additional effect of abnormal randomisation CTA over and above that of plain CT.

Results

Baseline characteristics of patients in IST-3 with perfusion and angiography imaging did not differ from those without. Perfusion imaging data were received on 151 patients and angiography data on 423 patients, of whom 141 and 307 were obtained pre randomisation, respectively, and the rest were obtained at follow-up. Most randomisation imaging was with CT ($n=125/141$, 89% perfusion; $n=277/307$, 90% angiography) with little MR ($n=16/141$, 11% perfusion; $n=30/307$, 10% angiography). The median age of the patients with perfusion imaging or angiographic imaging was 81 years [interquartile range (IQR) 71–86 years] and perfusion imaging and angiography was performed a median of 4 hours (IQR 1.8–4.2 hours) after stroke. The youngest patient was 18 years old and the oldest was 102 years old. Very few patients (<5%) would have met the prevailing licence criteria for rt-PA at the time of their randomisation in the trial.

Perfusion data were rateable in 120 out of 141 patients. MTT lesions were largest, with CBV lesions the smallest ($p<0.0000$). Forty-six per cent had perfusion–plain-scan mismatch on Tmax. Perfusion lesions were larger (all parameters) in patients scanned <3 hours compared with 3–6 hours, aged >80 years compared with ≤80 years and with higher National Institutes of Health Stroke Scale (NIHSS) scores. Larger perfusion lesions were associated with poor outcome [odds of good outcome decreased by ≈20% per point increase in perfusion lesion size on the Alberta Stroke Program Early CT score (ASPECT) significant for CBV and Tmax]. There was no evidence that any perfusion lesion parameter on perfusion ASPECT score or mismatch modified the rt-PA effect for the 6-month outcome. The results were the same with dichotomous or ordinal analyses.

In the angiography-imaging arm, there were 277 patients with CTA at randomisation. The randomisation plain CT scan showed a hyperdense artery or tissue ischaemia in 37% [95% confidence interval (CI) 31% to 43%]; the CTA was abnormal (arterial stenosis/occlusion) in 41% (95% CI 34% to 47%), either the randomisation plain CT or CTA were abnormal in 50% (95% CI 43% to 56%) and both were abnormal in 27% (95% CI 22% to 33%). Abnormal plain CT and plain CT+CTA had a similar association with worse stroke severity at presentation (NIHSS 7–8 points higher; $p<0.001$) with no difference in this association between plain CT and CTA. The sensitivity and specificity for predicting an infarct on follow-up CT were the same for plain CT and CTA. Plain CT and plain CT+CTA both predicted a greater likelihood of poor functional outcome ($\chi^2=20$ or 29, respectively; $p<0.001$) with no difference in predictive ability between

them. Comparison with follow-up imaging showed that rt-PA accelerated the disappearance of arterial thrombus and prevented thrombus extension but there was no evidence that patients with arterial occlusion had less benefit or more harm from rt-PA than those without arterial occlusion at presentation.

Conclusion

Larger perfusion lesions and arterial occlusion on angiography imaging identify patients with more severe stroke who have worse imaging and clinical outcomes. Perfusion lesion extent varies significantly with the perfusion parameter chosen. Perfusion–plain scan mismatch is more common in older patients and in those imaged early after stroke, suggesting that trials focusing on the use of mismatch to select patients for therapies at late times after stroke will find fewer cases with mismatch, especially in younger patients. Visual assessment is a powerful way of classifying perfusion imaging despite its apparent simplicity, and allows the use of more data (and hence achieves larger sample sizes) and is likely to be more generalisable than computational processing. Including CTA in the imaging assessment of acute stroke identifies more abnormal cases and hence may improve diagnostic confidence but does not improve prediction of prognosis either for imaging or for clinical outcomes. We found no evidence that either perfusion or angiography imaging are routinely necessary prior to treatment with rt-PA.

Future work

Individual patient data meta-analysis of comparable trials with standardised image processing should be considered in order to completely exclude the possibility that an individual perfusion threshold could identify patients who benefit more or less from rt-PA. The impact of perfusion or angiography imaging on physician confidence in the diagnosis of acute stroke, and hence the use of rt-PA, should be tested in further research to determine whether or not either should be used routinely in acute stroke. Further work is required on observer reliability of perfusion and angiography image interpretation.

Trial registration

This trial is registered as ISRCTN25765518.

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