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CLINICAL

Responses to acute stroke: beyond urgent imaging and systemic thrombolysis, where to now?

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CLINICAL VIGNETTE

A 72-year-old man presents with 90 minutes of sudden onset aphasia, right-sided homonymous hemianopia and ipsilateral weakness of face, arm and leg. He has no past medical history of note. A clinical diagnosis of total anterior circulation stroke is made and an urgent magnetic resonance imaging (MRI) scan of the brain is organised. This reveals an area of restricted diffusion in the left middle cerebral artery (MCA) territory, a larger perfusion deficit and an occluded proximal left MCA. He is given intravenous thrombolysis with tissue plasminogen activator (tPA). Repeat imaging the following day shows an extensive area of infarction and he subsequently requires a prolonged period of inpatient rehabilitation. His wife asks: 'could anything else have been done?'

NON-REPERFUSION BASED THERAPIES

Recent acute stroke research has been characterised by interventions with great promise in preclinical studies that failed to demonstrate benefit in clinical trials. High profile examples include the many putative neuro-protectants. It is important to recognise however that the stroke physician has a selection of evidence-based acute therapies available. Early antiplatelet therapy reduces mortality in ischaemic stroke.[1] With a number needed to treat (NNT) of 100, effects are modest for the individual patient but important at a population level. Admission to a dedicated stroke unit reduces both mortality and dependency regardless of stroke severity or aetiology. The effective components of this complex intervention are still debated, although data are emerging that protocol-driven management of fever, dysglycaemia and swallowing can have an impact on outcomes.[2]

INTRAVENOUS THROMBOLYSIS

Intravenous tPA is of proven benefit in selected patients up to 4.5 hours from symptom onset. Meta-analysis[3] of 2,775 ischaemic stroke patients treated with intravenous tPA described odds of a favourable outcome (defined as no disability and compared to placebo) as 2.8 (95% confidence interval [CI] 1.8–9.5) for treatment within 90 minutes and 1.6 (95% CI 1.1–2.2) for treatment between 91 and 180 minutes. Benefit was still apparent for patients treated between 181 and 270 minutes (odds ratio 1.4, 95% CI 1.1–1.9). This effect size has been confirmed by the third European Cooperative Acute Stroke Study (ECASS III) of 821 subjects with ischaemic stroke treated at 3–4.5 hours.[4] The rate of significant intracerebral haemorrhage was 5.9% in those treated with tPA compared to 1.1% in those treated with placebo. The corresponding NNT to achieve an excellent outcome (and avert one case of death or dependency) or achieve a reduction in disability are seven[3] and three respectively.[5] Concern that impressive randomised controlled trial results would not be realised in 'real world' settings were unfounded, with registry data showing outcomes commensurate or superior to that predicted from the trial data.[6]

As experience with intravenous tPA grows, clinicians are using tPA outside the terms of the European product licence, for example in older adults and in subjects with extremes of initial impairment. Synthesis of registry and trial data would support this approach.[7] Large prospective studies will soon establish whether treatment can be safely offered up to six hours from symptom onset and in patient groups who would not currently be treated within the terms of the licence.

In the ECASS III trial, approximately one-half of patients treated with recombinant (r)-tPA had residual disability.[4] Thus intravenous tPA is no panacea. Reperfusion rates following intravenous tPA are approximately 50% and favourable outcome is strongly associated with arterial recanalisation. Meta-analysis correlating reperfusion with functional outcome has shown that only 25% have a good outcome if reperfusion is unsuccessful, while 58% have a good outcome with successful reperfusion.[8] There are important messages contained within these data. First, we need to improve reperfusion rates as this is strongly linked with outcome, but we must also acknowledge that outcomes remain highly heterogeneous regardless of reperfusion, so novel, non-perfusion based therapies are needed.

AUGMENTING REPERFUSION STRATEGIES

Where reperfusion fails, outcomes are often poor. Other thrombolytic drugs such as tenecteplase may offer advantages over alteplase with the possibility of a longer therapeutic window and greater recanalisation rates. Results in selected patients are promising[9] but efficacy compared to tPA is yet to be established. Alternative reperfusion strategies include direct catheterisation of an occluded artery with local administration of thrombolytic agents and mechanical clot retrieval. In the Intra-arterial Prourokinase for Acute Ischaemic Stroke (PROACT) study, intra-arterial thrombolysis was shown to improve reperfusion rates and clinical outcomes in those with confirmed MCA occlusion when administered within six hours of onset.[10] This study used intra-arterial urokinase, which is not available in the UK, and it was not a direct comparison with systemic intravenous thrombolysis. Mechanical clot manipulation using percutaneous stenting and/or thrombus retrieval devices are increasingly used but there is no robust randomised trial evidence for superiority above placebo. However, a lack of level one evidence does not equate to absence of efficacy and mechanical strategies may have a role. Registry data suggest good outcomes and trial data are emerging. In the SWIFT study,[11] good outcomes were achieved in 58% of those treated with the SOLITAIRE clot retrieval device, with 83% of patients achieving reperfusion. In this randomised study, mechanical clot retrieval with the SOLITAIRE device was compared to the MERCI clot retrieval device. Participants were ineligible for, or had failed to reperfuse following intravenous tPA and had at least moderately severe stroke with onset within the past eight hours. Compared to expected outcome rates these data are impressive. Outcomes for the comparator intervention (MERCI retriever – a percutaneous mechanical thrombectomy device) were less impressive and remind us of the need for hard clinical trial data before adopting novel treatment interventions – reperfusion rates were 48%, mortality rate was 38% and good outcomes were seen in 33% of cases. These results are broadly in keeping with results of the multi-MERCI study[12] and in fact these clinical outcomes overlap with those expected from placebo and standard stroke unit care. There is clearly a place for interventional strategies but treatment decisions should be evidence-based. In this respect it is unfortunate that regulatory requirements for medical devices have allowed widespread adoption of novel devices without confirmatory phase III trial data.

IMPROVING PATIENT SELECTION FOR REPERFUSION THERAPIES

The risk/benefit ratio and the time window for reperfusion-based treatment may be extended through identification of ischaemic but salvageable brain tissue. Imaging strategies that identify brain tissue with compromised circulation (perfusion) and areas of dead tissue (diffusion) are increasingly available. In theory, patients with equivalent areas of perfusion and diffusion have little potential to benefit from reperfusion and could be spared the risks. Conversely, patients with substantial perfusion-diffusion mismatch may benefit from reperfusion even if it is outside conventional treatment time windows. Recent pooled analysis of phase II studies[13] suggest such approaches can allow the selection of patients destined to have poor or good outcome from reperfusion with intravenous thrombolytic therapy up to six hours from symptom onset.

THERAPEUTIC HYPOTHERMIA

Therapeutic hypothermia is a promising novel neuro-protectant therapy for acute stroke. Hypothermia decreases cellular metabolism,[14] limits cytotoxic and neuro-excitatory activity, reduces formation of free radicals and suppresses blood-brain barrier breakdown. Various methods for achieving hypothermia have been suggested. Basic surface cooling with icepacks and cooling pads can attain modest reduction in temperature, however tolerability is an issue and sedation or paralysis are usually needed. Intravascular cooling, infusing cooled saline via a central venous heat exchange catheter, is a more invasive strategy but allows faster cooling and greater control over rewarming. Data describing efficacy of therapeutic hypothermia in animal models of cerebral ischaemia are compelling.[15] The efficacy of therapeutic hypothermia in ischaemic stroke will be formally tested in the European Stroke Research Network for Hypothermia (EuroHYP-1) trial which should begin recruitment this year. The results of this landmark study will be eagerly awaited.

INTRACEREBRAL HAEMORRHAGE

If the MRI scan in the above case study instead revealed an area of intracerebral haemorrhage (ICH), we would have no specific proven or licensed treatment to offer beyond stroke unit care. This is a major concern. The incidence of ICH is high and expected to increase with an ageing population and greater use of anticoagulants. Mortality from ICH is substantial (approximately 40% at 30 days) and few return to independent living, particularly where the ICH is of a volume greater than 20 ml or where there is intraventricular extension of haemorrhage (IVH). Early surgical intervention (the International Surgical Trial in ICH [STICH])[16] and use of haemostatic agents to prevent haematoma growth (Factor Seven for Acute Haemorrhagic Stroke Trial)[17] have not demonstrated efficacy. However, there is reason for optimism. Post hoc analyses of STICH data demonstrated that those with superficial (≤1 cm below the cortical surface) lobar haematomas benefited from craniotomy.[16] This hypothesis will be formally tested in the STICH II trial. The Minimally Invasive stereotactic Surgery and rt-PA for ICH Extraction (MISTIE) trial programme aims to establish

whether clot size reduction in those with ICH >20 ml is safe and feasible and whether it leads to improved functional outcomes. Data from the recently presented MISTIE II study[18] show surgery can reduce ICH size and suggests those with the most reduction have the best functional outcomes. A pivotal phase III study of this approach is now needed. Further, the Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage, phase III (CLEAR III) study is now well underway and will evaluate efficacy of intraventricular thrombolytic therapy for those with a small ICH with IVH and obstruction. It seems to be a promising treatment for patients with the poorest of outcomes.[19]

FUTURE DIRECTIONS

Even when evidence-based interventions are delivered, there remains substantial heterogeneity in outcomes. Some patients rehabilitate and have good functional recovery, while others do not despite similar baseline stroke severity, similar treatment and similar response to the treatment. An understanding of the processes of recovery at the molecular level could yield novel pharmacotherapy or perhaps gene expression approaches to augment recovery.

SUMMARY

Stroke medicine has changed substantially in the last decades and there is cautious optimism in the stroke community that acute interventions will continue to improve. Our 'wish list' includes evidence-based treatments for ICH, targeted reperfusion therapy and rescue therapy for those who fail to reperfuse with conventional treatment, all of which would be augmented by potential neuroprotectant strategies, such as therapeutic hypothermia. These goals are ambitious but not unachievable and success will depend on quality clinical trials comparing novel strategies to standard care (and not other unproven strategies), along with continued major investment in stroke services. It was a challenge to introduce thrombolytic therapy across the UK and it will be orders of magnitude more difficult to routinely deliver novel imaging techniques, minimally invasive neurosurgical techniques and catheter-based thrombectomy should they prove to be effective.

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