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Acute treatment and prevention of stroke

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Introduction

The management of patients with acute stroke is centred on urgent hospital admission and assessment, brain scanning, care in a stroke unit and rehabilitation. For patients with ischaemic stroke, alteplase (thrombolysis), decompressive surgery (for malignant cerebral oedema) and aspirin are the mainstays of treatment. Secondary prevention is centred on lifestyle changes and reducing blood pressure and, in those with ischaemic stroke or transient ischaemic attack (TIA), antithrombotics (with oral anticoagulation for cardioembolic stroke and antiplatelet drugs for others), lipid-lowering agents and carotid endarterectomy.

This review describes recent and ongoing research in stroke at the Nottingham Stroke Trials Unit, specifically the management of blood pressure in acute stroke and the early prevention of recurrence after ischaemic stroke or TIA with intensive antiplatelet therapy. A theme common to both research programmes is the use of sequential primary research (epidemiological studies, preclinical studies and clinical trials) and secondary research (systematic reviews and meta-analyses) to assess the programme repeatedly and determine whether it should continue, evolve or stop.[1] Other ongoing research in the unit, which is not discussed further in this article, includes research into anticoagulation, procoagulation, neuroprotection, prevention of cognitive decline, cerebral oedema, dysphagia and stem cells.

Reducing blood pressure in acute stroke

Blood pressure (BP) is increased (systolic BP >140 mmHg) in about 80% of patients with acute ischaemic stroke or primary intracerebral haemorrhage (PICH).[2] Both high BP and low BP (which is uncommon) are associated independently with poor outcome, assessed as early death, early recurrence and late death or dependency.[2] A longstanding clinical question from the 1980s is whether BP should be reduced. Although epidemiological data suggest that should be the case, pathophysiological considerations based on hypothesised negative effects on cerebral perfusion in the presence of dysfunctional autoregulation have inhibited research.

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Nitric oxide (NO) donors are a candidate target for lowering BP in patients with acute stroke. Nitric oxide is a key mediator as a neurotransmitter, in the regulation of cerebral blood flow (CBF) and systemic haemodynamics, and in terms of platelet and leucocyte function. It is potentially neuroprotective[3] and has peripheral vasoactive and cardioprotective properties. A series of three small, phase 2, randomised controlled trials (RCTs) assessed the safety and effects of transdermal glyceryl trinitrate (GTN), an NO donor, in acute or recent stroke.[4,5] Transdermal administration of GTN was chosen as it has the advantages that administration is easy and visible, treatment can be stopped by removal of the patch if necessary and the presence of dysphagia, a common complication of stroke, will not interfere with drug delivery. In the first trial (37 patients randomised in a ratio of 1:1 to active treatment or placebo), GTN reduced 24-hour BP, measured using ambulatory blood pressure monitoring, over the first day, although tachyphylaxis was apparent by day 7. In addition, GTN had no antiplatelet effects, assessed through aggregation and expression of surface adhesion molecules, which means that it can be given to patients with PICH. (The finding on platelet function contrasts with the results of an earlier uncontrolled study of intravenous sodium nitroprusside (SNP), in which platelet function was attenuated.)[6] In the second trial (90 patients randomised in a ratio of 2:1 to active treatment or control), GTN increased vascular compliance but had no effect on large artery blood flow determined using transcranial doppler (TCD) assessment of cerebral blood flow velocity and pulsatility index.[4]

The third trial (18 patients randomised in a ratio of 2:1 to active treatment and control) showed that GTN did not alter cerebral blood flow assessed quantitatively using xenon computed tomography (CT) despite reducing systolic BP by 23 mmHg.[5] (The above-mentioned study showed a similar finding, with SNP reducing BP but having no effect on CBF assessed semi-quantitatively using single-photon emission computed tomography (SPECT).) Indeed, a meta-analysis of the effect of hypertensive agents on CBF (six RCTs and eight before–after studies) suggested that modest reductions in BP do not alter CBF. Although the three trials of GTN were small, no safety concern or negative impact on functional outcome was found.[4,5] In a meta-analysis of the three phase 2 trials, GTN reduced systolic BP by 9 mmHg over 24 hours.

In view of the apparent safety of GTN and rationale for administering it, the large Efficacy of Nitric Oxide in Stroke (ENOS) trial was started in 2001. The aim is to compare the safety of reducing BP with GTN given for seven days with control in a single-blind design.[7] In addition, patients who are taking antihypertensive agents at the time of their stroke are also randomised in a partial factorial design to continue or stop these

temporarily for seven days. The primary outcome is death or dependency, with ordinal analysis of the seven-level modified Rankin Scale. Current recruitment exceeds 50 patients per month from more than 100 sites in 19 countries, which means that the trial should achieve its intended recruitment of 3,500 patients by the end of funding in late 2013 (www.enos.ac.uk); at the end of January 2012, 2,800 patients had been recruited, with 1,403 (50%) in the continue–stop part of the trial. In addition to a publication on the protocol,[7] other publications have shown that it is safe to reduce BP in patients with severe ipsilateral carotid stenosis and that recruitment is feasible and welcomed in Poland. Publications are also being developed on differences in PICH between countries, outcome after PICH, outcome after dysphagia, cognition after stroke, quality of life after stroke, reduction in the use of graduated compression stockings and recruitment performance in Romania.

Although ENOS is investigating the management of BP in hospital for patients recruited within 48 hours of onset (Table 1), it cannot test the safety and efficacy of lowering BP in the ultra-acute phase before hospital administration. In the single-centre, phase 2 Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial (RIGHT; www.right-trial.org), 41 patients with presumed stroke were screened, consented, randomised and treated in ambulances around Nottingham by paramedics trained in trial processes (see Table 1). Although the final results are not yet available, most recruited patients had a final diagnosis of stroke or TIA and the mean time from event to enrolment was less than 90 minutes.

Although most research worldwide has focussed on reducing BP, a small number of studies have assessed the effect of increasing BP, in part to try to improve cerebral perfusion. In a small, phase 2 trial in subacute stroke, amphetamine was assessed because of reported neuroreparative effects in preclinical stroke models in addition to its known vasopressor properties. In a subsequent meta-analysis including 11 clinical studies (329 patients), amphetamine increased BP, had no effect on subsequent functional outcome but was associated with a non-significant increase in death.

Intensive antiplatelet therapy for preventing early recurrence

According to the National Institute for Health and Clinical Excellence (NICE), long-term antiplatelet therapy for secondary prevention should comprise monotherapy with clopidogrel (after ischaemic stroke) or dual therapy with combined aspirin and dipyridamole (after TIA).[8] The Prevention Regimen For Effectively Avoiding Second Strokes (PRoFESS) mega-trial showed that these regimens were comparable in efficacy.[9] Unlike in cardiology, where aspirin and clopidogrel (or its derivatives such as prasugrel or ticagrelor), are routinely used together, their combination after stroke or TIA is associated with increased

Table 1. Inclusion and exclusion criteria for ongoing ENOS, RIGHT and TARDIS trials.

Criteria	ENOS[7]	RIGHT	TARDIS
Inclusion	• Age >18 years • Ischaemic stroke or PICH syndrome lasting >1 hour • Event <48 hours • Systolic BP 140–220 mmHg • Motor weakness • Conscious GCS score >8 • Previously independent • Meaningful/proxy consent	• Age ⩾40 years for men; ⩾55 years for women • Presumed stroke event ≤4 hours • FAST score >1 • Systolic BP ⩾140 mmHg	• Age ⩾50 years • Non-cardioembolic ischaemic stroke or TIA • Event ⩽48 hours • TIA with ABCD2 score ⩾4, crescendo TIA or already taking dual therapy • Motor weakness or dysphasia • Conscious GCS ⩾8 • Previously independent • Meaningful/proxy consent
Exclusion	• Definite need for, or contraindication to, nitrate • Definite need for pre-stroke or new antihypertensive agents • Unlikely to be available for follow up at day 90	• Definite need for, or contraindication to, nitrate • GCS score ⩽8 • Hypoglycaemia • Not ambulatory prior to onset of event • Pregnant or breastfeeding	• Definite need for, or contraindication to aspirin, clopidogrel or dipyridamole • Definite need for oral anticoagulation • TIA, with motor weakness and dysphasia <10 minutes • Pure sensory symptoms, vertigo or dizziness • Received thrombolysis within last 30 hours • PICH, SAH or other cause of event • Severely increased systolic BP >185 mmHg

ABCD2 = age/blood pressure/clinical presentation/duration of symptoms/diabetes stroke risk score; BP = blood pressure; ENOS = efficacy of nitric oxide in stroke; FAST = face, arm and speech test; GCS = Glasgow coma scale; PICH = primary intracerebral haemorrhage; RIGHT = Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial; SAH = subarachnoid haemorrhage; TARDIS = triple antiplatelets for reducing dependency after ischaemic stroke; TIA = transient ischaemic attack.

major bleeding of sufficient magnitude to negate any benefit in reducing recurrent ischaemic events, as seen in three large trials (Management of ATherothrombosis with Clopidogrel in High-risk patients (MATCH), Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) and Secondary Prevention of Small Subcortical Strokes (SPS3)). However, the situation differs for patients with acute stroke, in whom dual antiplatelet therapy is more effective at preventing recurrent events than monotherapy – an effect that is not outweighed by major bleeding (these data are summarised in a systematic review).[10] Interestingly, the composition of antiplatelet monotherapy and dual therapy does not seem to matter. This strategy is not adopted widely because none of the component trials in the meta-analysis[10] individually showed benefit, although non-significant trends were present early in many of the studies, such as PRoFESS.[11]

The contrast between these findings for acute and chronic stroke, and the well-supported observation that risk of recurrence is highest soon after stroke or TIA, raises the hypothesis that acute, short-term antiplatelet therapy based on all three agents (aspirin, clopidogrel and dipyridamole) might further reduce recurrence without being compromised by excess bleeding. In a series of *in vitro* laboratory experiments, aspirin, dipyridamole and AR-C69931 (an antagonist of the platelet P2Y12 receptor that acts directly – unlike clopidogrel, which is a prodrug and is inactive against the receptor *in vitro*) were used together or separately. The combination of all three agents was more effective than monotherapy or dual therapy in inhibiting adenosine diphosphate (ADP)- or platelet-activating factor (PAF)-induced platelet P-selectin expression, monocyte or neutrophil activation, and monocyte–platelet or neutrophil–platelet conjugation. Two crossover, phase 1 and 2 trials followed, in which volunteers and patients with previous stroke received, in random order, aspirin, clopidogrel or dipyridamole, each pairwise combination (dual therapy) and all three together (triple therapy).[12] In the presence of collagen *ex vivo*, triple therapy was superior to all antagonists and their dual combinations (except where clopidogrel was present) in reducing aggregation, monocyte activation and platelet–leucocyte conjugation in response to ADP.[12] An explanation here is that it is difficult to demonstrate activity of dipyridamole on platelet function *ex vivo* because of its mode of action as a stimulant of intraplatelet inhibitory pathways, where aspirin and clopidogrel inhibit stimulatory pathways.

In a second phase 2 trial, the safety and tolerability of chronic triple antiplatelet therapy (aspirin, clopidogrel and dipyridamole) was compared with monotherapy with aspirin, which was the standard of care at the time.[13] The trial had to be stopped early because the protocol became unethical with respect to giving aspirin alone. Specifically, a large phase 4 trial, European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT), confirmed the findings of an earlier phase 3 trial, European Stroke Prevention Study 2 (ESPS 2), showing that combined aspirin and dipyridamole was superior to aspirin alone for preventing recurrence after ischaemic stroke or TIA, which led NICE to recommend dual therapy in technology appraisal 90, published in 2005. Despite the very small sample size of 17, triple therapy was associated with an excessive number of, and more severe, adverse events and bleeding than aspirin alone; no effect on recurrent events was observed. In respect of laboratory measures, triple therapy reduced monocyte activation and the formation of platelet–monocyte conjugate formation *ex vivo*. The finding of increased bleeding was compatible with findings from the MATCH, CHARISMA and SPS-3 trials for combined aspirin and clopidogrel vs monotherapy. It also supports the hypothesis, described above, that future studies should focus on short-term treatment in high-risk individuals – ie those with a recent event.

On the basis of the preceding data, the Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke (TARDIS) trial was designed to assess the safety and efficacy of intensive (triple) antiplatelet therapy in comparison with guideline therapy based on combined aspirin and dipyridamole (www.tardistrial.org) (Table 1). The start-up phase of the trial started in 2009, with funding from the British Heart Foundation, with the aim of recruiting 350 patients with acute (within 48 hours) ischaemic stroke or high-risk TIA. Randomised treatment is given for 30 days and the primary outcome is measured at day 90. The primary outcome – stroke recurrence and its severity – is novel and is based on work showing that ordinalising the severity of events (eg fatal stroke, severe non-fatal stroke, mild stroke, TIA, and no stroke or TIA), as well as counting their frequency, gives more information on the effectiveness of the intervention and allows the trial to be smaller.[14] By the end of January 2012, 672 patients had been recruited (index event: 407 (61%) stroke and 265 (39%) TIA). Explanatory and intermediate outcomes are also measured in some patients, including assessment of embolic signals in the middle cerebral artery using TCD and of P-selectin levels as a measure of platelet function (measured using a novel test that allows remote testing).

Funding for the main phase is actively being sought, with the aim of recruiting up to 4,100 patients by 2017. However, the protocol will need to be changed to reflect the newer NICE guidance alluded to at the beginning of this section,[8] namely that patients with recent stroke should receive clopidogrel monotherapy, while those with TIA should have combined aspirin and dipyridamole (technology appraisal 210). As a result, patients will be randomised in the main phase of the trial to intensive treatment or one of two groups based on the NICE guidance depending on their hospital's preference.

Summary

The two programmes of research at the Nottingham Stroke Trials Unit exemplify the developmental approach needed to produce data to support a potential new indication for interventions with existing licences. The quoted studies used data from epidemiological analyses, laboratory studies, clinical phase 1, 2 and 3 trials, and meta-analyses of these and other data. A large number of translational experimental techniques have been used

to justify the ongoing phase 3 ENOS and TARDIS trials, including preclinical stroke models, cellular function (flow cytometry and platelet–leucocyte function), clinical haemodynamic assessments (including ambulatory BP monitoring, measurement of arterial compliance and TCD) and neuroimaging (with CT, SPECT and xenon CT). These were supported by judicious use of systematic reviews and meta-analyses. The programmes for both new interventions are very long term, lasting up to 20 years for GTN in acute stroke (1994–2014) and potentially up to 18 years for intensive antiplatelet therapy for ischaemic stroke or TIA (2000–2018).

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