ADVANCES IN THE MANAGEMENT OF TRANSIENT ISCHAEMIC ATTACK AND STROKE

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ABSTRACT

Among many important advances in the management of transient ischaemic attack (TIA) and stroke are: the updated definition of TIA; risk stratification scores for TIA; the urgent diagnostic and treatment process for TIA; thrombectomy treatment for large vessel occlusive ischaemic stroke; cryptogenic stroke evaluation and treatment, including long-term monitoring for paroxysmal atrial fibrillation; and strategies to improve outcomes for patients including mirror therapy for neglect and timing of mobilisation after stroke. Future research will focus on: antiplatelet strategies after TIA; selecting patients for treatment with recanalisation therapies in an extended time window; uncovering the cause of strokes previously defined as cryptogenic; and better defining the optimal timing and dose of mobilisation after stroke.

Keywords: Transient ischaemic attack (TIA), acute stroke treatment, cryptogenic stroke, stroke rehabilitation.

INTRODUCTION

Owing to the results of important research in transient ischaemic attack (TIA) and stroke, secondary stroke rates and stroke-related deaths have dropped over the last two decades. This review will focus on advancements in the areas of TIA, acute stroke, cryptogenic stroke, and rehabilitation management.

TRANSIENT ISCHAEMIC ATTACK

About 20% of ischaemic strokes are closely preceded by a TIA.[1] The classic definition of TIA, i.e. 'focal cerebral dysfunction of an ischaemic nature lasting ≤24 hours with a tendency to recur', has been largely replaced by one that emphasises tissue rather than time.[2] The American Heart Association (AHA)/American Stroke Association (ASA) definition is "a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia."[3] Inherent in this definition is the early acquisition of neuroimaging; patients with evidence of new ischaemic injury are identified as having had a stroke, while those without a new injury are defined as having a TIA. The concept of an acute ischaemic cerebrovascular event, similar to the concept of an acute coronary syndrome, has also been proposed.

The risk of stroke following TIA is highest in the first 48 hours after occurrence.[4] Risk stratification has been a topic of major interest in order to better guide the timeliness and extent of healthcare resource utilisation for suspected TIA patients. The most widely used prediction rule is the ABCD2 score;[5] however, it has been shown to have only modest predictive ability.[6,7] Additionally, the ABCD2 score has been shown to have low sensitivity when used by non-neurologists.[8] Although data do not generally support the use of the ABCD2 score until after the condition has been confirmed as

TIA by a stroke specialist, its use is supported by current AHA/ASA and National Institute for Health and Care Excellence (NICE) guidelines to aid early management decisions.[9] While some report utility of the ABCD2 score to be useful in discriminating TIAs from mimics,[10] several studies have shown that the ABCD2 score is not reliable at discriminating between high and low-risk TIAs. Dual TIA (i.e. a TIA event within 7 days before another TIA) contributes to short and long-term prediction of stroke, and also improves ABCD2 performance.[7] ABCD2 is not accurate in predicting atrial fibrillation (AF) or large vessel stenosis, both of which require prompt intervention.[11] Incorporation of brain imaging improves prediction of stroke.[7,12-14] ABCD3 and ABCD3-I are both superior in the prediction of short and long-term risk of stroke.[7] Carotid stenosis and intracranial stenosis are associated with recurrent strokes,[7] therefore the addition of vasculature imaging techniques to risk scores provides better accuracy for predicting the recurrence of stroke. Intracranial large vessel occlusion is also a predictor of decline in functional status in patients with TIA.[15]

Whether patients with a TIA should be admitted to the hospital or not is a point of spirited discussion. Current guidelines recommend urgent management for patients presenting with TIA, but it is unclear if these patients should be hospitalised.[16] The primary reason for hospitalisation is completion of TIA evaluation and secondary prevention.[3,17] Specialised TIA clinics and observation units in the emergency department may provide a safe approach to TIA while avoiding hospital admissions.[18] Reductions in hospital admissions of up to 80% can be achieved with this approach and may improve patient satisfaction. Admissions would be targeted towards patients requiring an urgent procedure, transition to anticoagulation, or for medical management of vessel-narrowing producing clinical worsening due to haemodynamic compromise. Short-term dual antiplatelet treatment of TIA and minor stroke was shown to be beneficial in the CHANCE trial. However, uncertainty about the generalisability of the results given the high event rates in both arms of the trial along with the relatively low use of statin and anti-hypertensive agents did not lead to the sudden discontinuation of the POINT trial, which is ongoing. Importantly, the event rates of 10% at 90 days seen over a decade ago now appear to be in the range of 3–4% with the urgent evaluation and management strategy.[19]

ACUTE REVASCULARISATION THERAPY IN ISCHAEMIC STROKE

Intravenous alteplase is the only US Food and Drug Administration (FDA)-approved lytic therapy for the treatment of acute ischaemic stroke.[20] The NINDS trial showed improved outcomes in acute ischaemic stroke patients treated with tissue plasminogen activator (tPA) <3 hours from symptom onset and several subsequent trials have corroborated these findings.[21-24] Although not approved by the FDA in the 3–4.5 hour window, ECASS III showed benefit of tPA administration during this period and its use during this time has been endorsed by the AHA/ASA.[25,26] The ENCHANTED study did not show non-inferiority of alteplase 0.6 mg/kg compared with 0.9 mg/kg with respect to death and disability at 90 days; however, ordinal analysis of the modified Rankin scale score did show non-inferiority. Additionally, major symptomatic haemorrhage occurred less frequently in the 0.6 mg/kg group (1.0% versus 2.1%, p=0.01).[27]

The guidelines for the use of tPA were developed according to the population enrolled in the trials and as such there were initially many contraindications to tPA, which were not based on any specific safety issues observed. Given that patients had to meet very specific criteria, tPA, although effective, was only given to a small percentage of stroke patients.[26,28] There is little evidence of how some of these contraindications affect safety in patients that receive tPA. Multiple studies show that patients may benefit from an individualised decision to give tPA.[28]

Historically, the computed tomography (CT) scan was the most widely used method for the acute evaluation of stroke since it can accurately identify hyperacute haemorrhage (0–6 hours). Gradient echo magnetic resonance imaging (MRI) has been shown to be as good in detecting acute haemorrhage as the CT scan.[29-31] Diffusion weighted imaging (DWI) is more sensitive than the CT scan for the detection of acute ischaemia.[31-33] Multimodal CT and MRI (parenchymal, perfusion, and vascular imaging) have the potential to identify patients with an ischaemic penumbra that may benefit from reperfusion therapy. MRI to identify chronic vascular injury can be useful after acute reperfusion therapies have taken place.[31] There are several ongoing trials for treating patients who wake up with stroke symptoms using thrombolytic therapies (alteplase

or tenecteplase) and/or endovascular procedures.[34] The imaging parameters are an estimation of a DWI/fluid-attenuated inversion recovery mismatch or evaluation of penumbral tissue on MRI or CT perfusion.

tPA has been shown to be better than conservative care in patients with large vessel occlusion, however it only has limited efficacy in this situation.[35] Initial endovascular therapies for stroke included intra-arterial infusion of thrombolytic agents, as well as first-generation mechanical devices, such as the Merci retriever. In 2013, however, the largest randomised trial at that time, the Interventional Management of Stroke (IMS) III trial showed no benefit to endovascular therapy above and beyond best medical therapy alone. However, there had been advances in both endovascular technique as well as in imaging which were not incorporated into the trial. The major advance in endovascular therapy was the use of stent-retrievers, which resulted in dramatically increased rates of rapid recanalisation as compared with previous-generation devices. In late 2014 and early 2015, five randomised trials, MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, and REVASCAT showed the benefit of endovascular therapy compared with the best available medical therapy.[36-40] Collectively, endovascular therapy improved functional independence on the modified Rankin scale (≥2) at 90 days by absolute difference of 20% (46% versus 26%).[41]

In spite of the dramatic changes in stroke management during the last two decades, only a small percentage (5%) of patients with acute ischaemic stroke receive tPA.[42] Endovascular therapy is safe and effective when there is a small amount of tissue that is already infarcted prior to treatment. However, many patients are ineligible because there has been too much damage prior to treatment. In these cases, neuroprotective agents may be useful in combination with reperfusion strategies.[26,43] Although hundreds of putative neuroprotective agents showed benefit in animal models, none resulted in a positive human trial.[44-46] Future studies may combine a neuroprotective strategy with recanalisation rather than neuroprotection alone.

On the endovascular side, an important question is how wide is the timeframe within which the procedure can be performed, and for whom. Treatment is relatively safe and effective within 6 hours from symptom onset. Additional imaging using CT angiography collateral score assessment, DWI, or perfusion imaging with either CT or MRI may allow better selection of patients within that time window. In addition, some patients present with large vessel occlusion and a low National Institutes of Health Stroke Score (NIHSS).

Contentious issues which should be noted include whether or not to treat stroke patients with thrombectomy, and in patients with tandem occlusion of cervical internal carotid artery and intracranial occlusion whether acute stenting or angioplasty alone should be performed.

CRYPTOGENIC STROKE

Stroke of unexplained cause or 'cryptogenic' stroke accounts for approximately 30% of all ischaemic strokes.[47,48] According to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria, cryptogenic stroke is defined when no stroke mechanism can be identified after routine, exhaustive, or incomplete evaluation.[49] One of the neuroimaging features in cryptogenic stroke patients is the presence of superficial infarcts occurring in up to 60% of cases,[50] which led investigators to use the term 'embolic stroke of undetermined source' in reference to a non-lacunar infarction occurring in the absence of a specific identifiable embolic source, such as AF, valvular heart disease, or large artery stenosis.[51] An important mechanism in cryptogenic stroke that, when identified, leads to anticoagulation therapy is paroxysmal AF. It is detected in 20–30% of patients with cryptogenic stroke by outpatient telemetry or implantable loop recorders. Less documented embolic sources include patent foramen ovale (PFO), atheroma of the aortic arch, and artery-to-artery embolism from sub-stenotic atherosclerotic plaque.[49]

Paradoxical embolism through a PFO is hypothesised to be one of the possible mechanisms leading to cryptogenic stroke. There is a weak association, however, between PFO and cryptogenic stroke.[52] Investigators designed the Risk Of Paradoxical Embolism (ROPE) score to identify patients with cryptogenic stroke and a PFO in whom the PFO is the likely stroke mechanism. In those patients, the risk of recurrent stroke was low. In addition, several clinical trials showed no significant benefit of PFO closure over medical treatment in reducing the risk of recurrent stroke in patients with cryptogenic stroke.[53] Antiplatelet therapy remains the mainstay

of treatment in most patients with cryptogenic stroke and evidence of a PFO.[54] Several studies have demonstrated increased prevalence of aortic arch atheromas >4 mm in size[55-57] and ipsilateral non-stenosing complex internal carotid plaques in patients with cryptogenic stroke. Antiplatelet therapy agents remain the mainstay of treatment in patients with cryptogenic stroke and evidence of thick aortic arch plaque.[54,58]

Atrial dysfunction or 'cardiopathy' has been introduced as a possible stroke mechanism in patients with cryptogenic stroke. Serum biomarkers of atrial dysfunction such as N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) have been shown to be associated with an increased risk of cardioembolism independent of AF.[59] Atrial arrhythmias and electrocardiogram findings such as supraventricular tachycardia[60] and increased p-wave terminal force in lead V1[61] have also been associated with ischaemic stroke risk in the absence of AF, particularly those related to embolism (cardioembolic and cryptogenic stroke subtypes).[62] Left atrial enlargement is also associated with the risk of incident ischaemic stroke in the absence of AF[63] and recurrent ischaemic stroke particularly related to embolism (cryptogenic or cardioembolic), an association independent of AF.[64]

AF, with its implied left atrial stasis in the setting of an irregular contractile function, has been used to provide a direct mechanistic explanation for embolism.[65] A *post hoc* analysis of the Asymptomatic AF and Stroke Evaluation in Pacemaker Patients and the AF Reduction Atrial Pacing Trial (ASSERT), however, showed a lack of a temporal relationship between subclinical AF detected on pacemaker interrogation and stroke, suggesting that AF signifies underlying atrial cardiopathy, which is possibly the direct cause of stroke in most of these patients. Recent randomised trials proved the efficacy of outpatient cardiac monitoring in detecting AF after cryptogenic stroke with a detecting rate of 16% at 30 days with non-invasive monitoring[66] and 30% at 3 years with implantable monitors[67] leading to anticoagulation therapy for secondary stroke prevention.

Unless AF is detected after a cryptogenic stroke, we agree with the AHA/ASA guidelines guidelines which which suggest that antiplatelet therapy be the treatment for secondary stroke prevention in this population.[54] Despite this therapeutic approach, the risk of recurrent stroke after cryptogenic stroke remains substantial, reaching up to 20% at 2 years.[68] A *post hoc* analysis of the Warfarin-Aspirin Recurrent Stroke trial showed that warfarin was superior to aspirin in reducing recurrent stroke risk in patients with NT-proBNP ≥750 ng/dL (hazard ratio: 0.30, 95% confidence interval: 0.12–0.84; p=0.021), a marker of atrial cardiopathy, in the absence of AF. This suggests the need for clinical trials comparing anticoagulation versus antiplatelet therapy in patients with cryptogenic stroke and atrial cardiopathy.

ADVANCES IN STROKE REHABILITATION

Stroke rehabilitation is an important part of the continuum of care and important studies have come out in the last few years highlighting potential methods to improve outcomes. The focus of this section will be on the results of studies focussed on mirror therapy, intensive early mobilisation, and non-invasive brain stimulation.

Spatial neglect is a disabling sequela of stroke, which can lead to difficulties with participation in rehabilitation and long-term functional outcomes. Mirror therapy has been used in an attempt to overcome these deficits. The Mirror Therapy in Unilateral Neglect After Stroke (MUST) trial was an open-label, blinded endpoint, randomised trial of patients with unilateral neglect 48 hours after stroke.[69] Patients assigned to mirror therapy looked into a mirror as they worked with the limb on the neglected side. Patients assigned to sham treatment looked at the non-reflecting side of the mirror during therapy sessions. Treatment regimen was 1–2 hours per day for 5 days per week, over 4 weeks. Twenty-six patients were treated with mirror therapy and 20 with sham. At 1, 3, and 6 months, patients assigned to mirror therapy had significantly improved spatial attention on the affected side, as measured by the star cancellation test, line bisection test, and picture identification task. In addition, the percentage of patients with a good outcome at 6 months, as defined by a modified Rankin scale score of 0–2, was 10% in the sham treatment group and 46% in the mirror therapy group (p=0.01). Further trials with the modified Rankin scale as the primary outcome measure would be very meaningful, for a treatment that is not very expensive.

The timing and amount of mobilisation following ischaemic stroke has been a subject of significant interest to those caring for patients in the post-acute setting. The efficacy and safety of very early mobilisation within 24 hours of stroke onset (AVERT) parallel group, single-blind, randomised controlled trial at 56 acute stroke units in five countries comparing usual stroke-unit care alone or very early mobilisation in addition to usual care.[70] Patients were eligible for participation if they had haemorrhagic or ischaemic stroke, including those who underwent thrombolysis. The very early mobilisation intervention included: 1) mobilisation within 24 hours of stroke onset; 2) focussing on sitting, standing, and walking (i.e. out-of-bed activity); 3) at least three additional out-of-bed sessions compared to usual care. The intensity of intervention was prescribed according to functional ability, with four levels specified, and titrated according to recovery. There were 1,054 patients who received very early mobilisation and 1,050 received usual care. The groups were well matched on baseline characteristics. Time to first mobilisation was at a mean of 18.5 hours after stroke in the very early mobilisation group and at a mean of 22.4 hours in the usual care group. The daily amount of treatment averaged 31 minutes in the very early mobilisation group and 10 minutes in the usual care group. A favourable outcome (modified Rankin scale score of 0–2) was more likely to occur in the usual care group (46% versus 50%, p=0.004). On secondary analysis, there was no significant shift in the modified Rankin scale score. Time to walking 50 metres unassisted by 3 months was virtually identical in the two groups. The rates of late and serious complications (such as pneumonia and venous thromboembolism) were not significantly different between the two groups. The researchers plan to perform a further dose–response analysis to establish the effect of dose of rehabilitation on efficacy and safety outcomes. Future research questions will include the best time to initiate rehabilitation after stroke, the type of training to be initiated, and the type of patient who might benefit most.

CONCLUSION

Among many important advances in the management of TIA and stroke are the updated definition of TIA, risk stratification scores for TIA; the urgent diagnostic and treatment process for TIA; thrombectomy treatment for large vessel occlusive ischaemic stroke, cryptogenic stroke evaluation and treatment including long-term monitoring for paroxysmal AF; and strategies to improve outcomes of patients including mirror therapy for neglect and timing of mobilisation after stroke.

Future research will focus on antiplatelet strategies after TIA; selecting patients for treatment with recanalisation therapies in an extended time window; uncovering the cause of strokes previously defined as cryptogenic; and better defining the optimal timing and dose of mobilisation after stroke.

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