An update on hyper-acute management of ischaemic stroke

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ABSTRACT

This article aims to provide a comprehensive overview of key advances on various aspects of hyper-acute management of acute ischaemic stroke. These include neuroimaging, acute stroke unit care, management of blood pressure, reperfusion therapy including intravenous thrombolysis, mechanical thrombectomy and decompressive hemicraniectomy for malignant stroke syndrome. The challenge ahead is to ensure these evidence-based treatments are now being delivered and implemented to maximise the benefits across the population.

KEYWORDS: management, ischaemic stroke, thrombolysis, thrombectomy

Introduction

Ischaemic stroke is a common emergency presentation to hospital with improving survival rates owing to access to specialist organised stroke care. There has been considerable advancement in hyper-acute stroke treatments in the last decade, which has resulted in improved outcomes and revolutionised acute stroke care from a disease with no treatment to one with multiple proven options.[1] The premise for acute stroke care is to salvage viable ischaemic brain tissue (ischaemic penumbra) surrounding the irreversibly injured core through reperfusion.[2] This article provides a comprehensive update on contemporary evidence-based management of acute stroke.

Neuroimaging for ischaemic stroke

Computed tomography (CT) of the brain using the 10-point Alberta Stroke Program Early CT Score (ASPECTS) is a useful modality in denoting early ischaemic changes.[3] Although the hyper-dense artery sign is common feature of large vessel occlusion, it cannot be identified in up to 50% of acute middle cerebral artery (MCA) occlusions using non-contrast CT (Fig 1).

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CT angiography (CTA) and CT perfusion (CTP) is important in identifying large vessel occlusion, collateral circulation and salvageable tissue for reperfusion interventions. Colour-coded CTP maps can identify brain regions with mismatch gaps by comparing reductions in cerebral blood flow (CBF) with regions of significant hypoperfusion, as reflected by delays in contrast arrival times (Tmax delays; Fig 2).[4,5] Magnetic resonance imaging (MRI), which has greater sensitivity in detecting ischaemia than CT, can also be used to assess salvageable brain tissue through magnetic resonance diffusion and perfusion maps.[7]

Acute stroke unit care

Provision of stroke unit care is the single most effective intervention for all stroke patients. Stroke units are associated
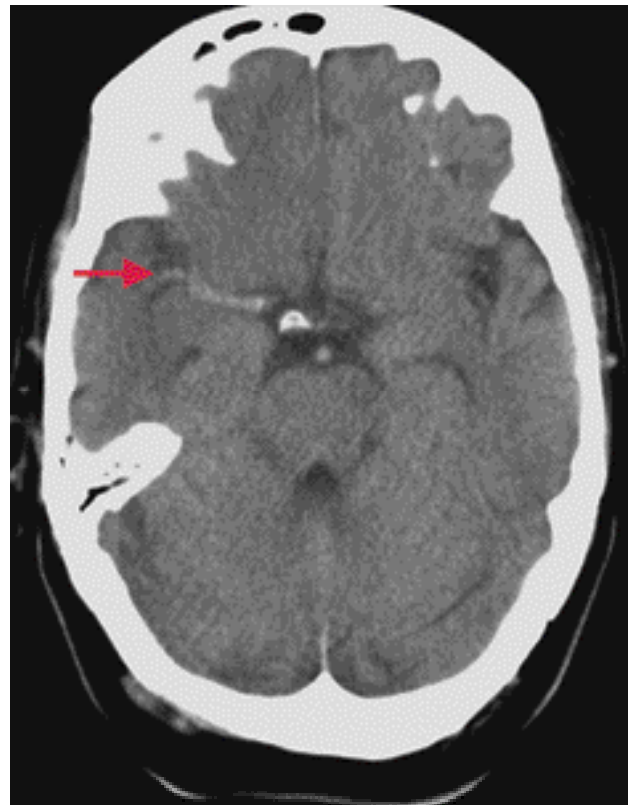

Fig 1. Computed tomography of the brain demonstrating hyper-dense middle cerebral artery sign (arrow).

Fig 2. Computed tomography perfusion demonstrating cerebral blood flow (CBF) <30% (ischaemic core) and time to maximal delay (Tmax >6 seconds) in a patient with an acute right middle cerebral artery occlusion. Difference between CBF (pink) and Tmax (green) indicating a target mismatch volume of 65 mL (46 mL – 111 mL; ratio 2.4), high-lighting indication for reperfusion with mechanical thrombectomy. Reproduced with permission from Laughlin B, Cahn A, Tai WA, Moftakhar P. RAPID automated CT perfusion in clinical practice. *Pract Neurol* 2019;2019:41–55.[6]
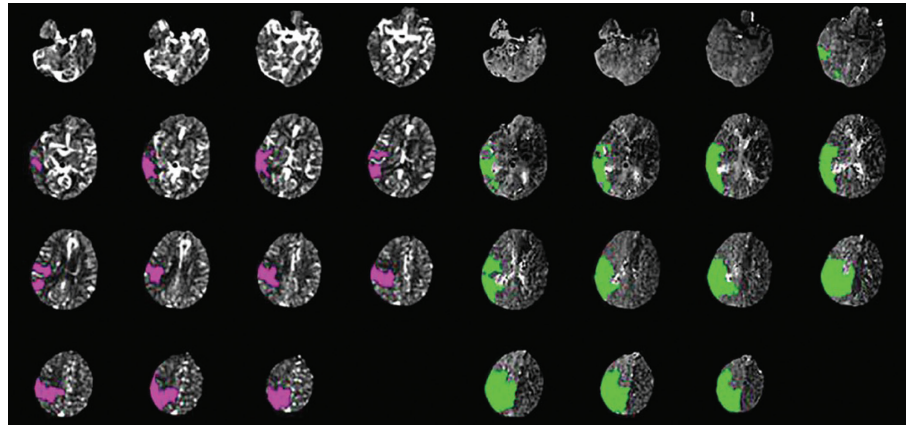
with reduced death or dependency (odds ratio (OR) 0.75; 95% confidence interval (CI) 0.66–0.85) facilitated by stroke multidisciplinary care.[8] A key function for stroke unit care is to limit neurological deterioration by monitoring for and correcting abnormal physiological parameters.[9–11] This includes strategies to correct hypotension, hypertension, hyperglycaemia, hypoxia, pyrexia, dehydration and positioning (Table 1), and to optimise management of nutrition and continence.[9,10,12,13] Training staff in the use of standardised protocols to manage physiological status can significantly improve outcomes.[13,22]

Blood pressure management

In acute stroke, there is an inherent tendency for the blood pressure (BP) to be high due to disruption of cerebral autoregulation.[23] Various strategies and agents to manage BP in acute stroke have been examined. A study examining transdermal glyceryl trinitrate (GTN) patches showed that while BP was lowered, this did not improve functional outcome.[24] An ambulance-based randomised trial examining the use of transdermal GTN in acute stroke that was then continued in hospital for 4 days showed that pre-hospital treatment with GTN did not improve functional outcome.[25] Another study also showed that immediate BP reduction in non-thrombolysed ischaemic stroke patients within 48 hours did not reduce the likelihood of death and major disability at 14 days. This study aimed at lowering systolic BP by 10–25% within the first 24 hours after randomisation, achieving BP levels of less than 140/90 mmHg within 7 days, and maintaining this level during hospitalisation.[26] For patients receiving thrombolysis with

Table 1. Specific management of physiological parameters[13,14]

Physiological parameter	Management guidance
Oxygenation	Supplemental oxygen only if oxygen saturation is below 95% and there is no contraindication[15]
	Hyperbaric oxygen is not recommended unless stroke is caused by air embolisation
Hydration	Regularly assess and ensure adequate oral/intravenous replacement so that normal hydration is maintained
Temperature	Sources of hyperthermia (temperature >38°C) should be identified and treated, and antipyretic medications should be administered to lower temperature
	Benefit of treatment with induced hypothermia is uncertain so this is not routinely recommended
Blood pressure	Patients with stroke should only receive blood-pressure-lowering treatment if there is an indication for emergency treatment, such as systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg when the patient is otherwise eligible for thrombolysis; hypertensive encephalopathy, hypertensive nephropathy, hypertensive cardiac failure or myocardial infarction; aortic dissection; pre-eclampsia or eclampsia
	Patients already on anti-hypertensive medication should resume oral treatment once they are medically stable
Blood glucose	Maintain blood glucose between 5–15 mmol/L, with close monitoring to avoid hypoglycaemia[16]
Venous thromboembolism	Immobile patients should be offered intermittent pneumatic compression within 3 days for prevention of deep vein thrombosis, continued for 30 days or until the patient is mobile or discharged, whichever is sooner[17]
	It is not advisable for stroke patients to be routinely be given low molecular weight heparin or graduated compression stockings (either full-length or below-knee) for the prevention of deep vein thrombosis[18–20]
Head positioning	An individualised approach should be adopted when comparing lying flat position or head elevation >30 degrees in the first 24 hours[21]

alteplase, the ENCHANTED trial showed that intensive BP lowering (systolic BP 130–140 mmHg within 1 hour) reduced intracranial haemorrhage (ICH), but this did not result in improved functional status at 90 days.[27] Data suggest that excessive BP lowering may worsen cerebral ischaemia and probably results in worse outcome, particularly if there is associated large vessel occlusion.[14] Evidence also exists that BP variability results in infarct growth and worsens outcome.[28] A Cochrane systematic review on interventions for altering BP in acute stroke showed insufficient evidence that lowering BP in acute stroke improves functional outcome, and suggested that further trials are needed to identify who would benefit from early treatment.[29]

Current UK guidelines therefore suggest that patients with acute ischaemic stroke should only receive BP lowering treatment if there is an indication for emergency treatment, such as systolic BP >185 mmHg or diastolic BP >110 mmHg when the patient is otherwise eligible for treatment with alteplase, or hypertensive encephalopathy, nephropathy, cardiac failure or aortic dissection.[13,14] American Heart Association guidelines suggest that a cautious BP reduction by 15% within the first 24 hours may be reasonable. Patients already on anti-hypertensive medication should resume oral treatment once they are medically stable.[13,14]

There are various parenteral options recommended in managing hypertension (BP >185/110 mmHg) in hyperacute ischaemic strokes that would otherwise be eligible for reperfusion therapy, including labetalol, nicardipine, clevidipine, hydralazine and enalaprilat; if still not controlled, sodium nitroprusside may be considered.[14] Different treatment options may be appropriate in patients with other comorbidities including acute coronary event, acute heart failure, aortic dissection or pre-eclampsia/eclampsia.[14]

Reperfusion therapy for acute ischaemic stroke

The key factors in determining whether ischaemia will lead to infarction are the presence and extent of collateral circulation and the time at which recanalisation takes place within the ischaemic penumbra. There are two modalities of reperfusion therapy available: intravenous thrombolysis (IVT) and mechanical thrombectomy (MT).

Intravenous thrombolysis

Current guidelines recommend the use of IVT with alteplase (0.9 mg/kg) if treatment is rapidly delivered within 4.5 hours of symptom onset, provided ICH has been appropriately excluded and delivery occurs within the context of an organised stroke service with skilled and trained staff to monitor for complications.[13] Meta-analysis of individual patient data (6,756 patients from nine randomised controlled trials (RCTs)) involving alteplase demonstrated that the number needed to treat (NNT) to achieve a good outcome was 10 for treatment delivered in ≤3 hours, 19 for 3–4.5 hours and 50 for >4.5 hours. The symptomatic ICH rates were 6.8% vs 1.3% in the control group, equating to the numbers needed to harm being 18.[30] There was no significant difference in mortality at 90 days (17.9% alteplase vs 16.5% control). The benefits were observed irrespective of age and stroke severity, highlighting that earlier treatment produces larger proportional benefits. It should be noted that for the 3–4.5 hour subgroup, caution needs to be applied, given that for each patient in whom treatment results in a good outcome (NNT 19), one has a symptomatic ICH; therefore the priority should be to

deliver treatment as quickly as possible. The risks of fatal ICH are not insignificant (2%) with IVT and lower doses of alteplase (0.6 mg/kg) have been shown to reduce haemorrhage risk and early mortality but do not deliver equivalent efficacy to conventional doses (0.9 mg/kg).[27] Lower doses therefore may be considered by the clinician in order to forgo the benefit of reducing disability in patients who are deemed high risk of early ICH. For patients with very mild measurable neurological deficits, although trial evidence is lacking, the use of thrombolysis may be supported in individual cases if the deficit is deemed to be disabling to the patient.[31]

Wake-up stroke

15–25% of stroke patients will not have a recognised time of onset of stroke, with patients frequently waking from sleep. Several groups have used the concept of a diffusion-weighted imaging / fluid-attenuated inversion recovery (DWI/FLAIR) mismatch (positive DWI lesion but negative FLAIR, indicating that tissue is ischaemic and salvageable rather than infarcted and non-salvageable) to guide thrombolysis. This imaging concept demonstrated a high degree of sensitivity and specificity in predicting onset of stoke within 4.5 hours.[32,33] The WAKE-UP study tested the efficacy and safety of alteplase in MRI-guided thrombolysis in patients with stroke of unknown time of onset (90% of which were wake-up stroke) using the concept of mismatch.[34] There was an 11% difference in favourable outcome in preference to the alteplase group with a non-significant difference in symptomatic ICH (2% alteplase vs 0.4% placebo). The NNT to afford favourable outcome in this trial was nine patients, highlighting potential expansion of the ischaemic stroke population eligible for recanalisation therapy.

Extending thrombolysis to 4.5–9 hours

Meta-analysis of individual patient data from three trials (EXTEND, ECASS-4 and EPITHET) has examined the merits of extending thrombolysis with alteplase to 4.5–9 hours including wake-up stroke (9 hours from mid-point of sleep) using perfusion imaging to identify salvageable tissue.[35] Two-thirds of the patients had large vessel occlusion (but did not undergo MT) and 50% of patients had wake-up stroke. The odds of excellent functional outcome at 90 days were 1.86 (95% CI 1.15–2.99) in favour of alteplase treatment and this was consistent across age, time window (4.5–6 hours, 6–9 hours and wake-up) as well as in the presence of large vessel occlusion. There were no significant differences in mortality at 90 days (alteplase 14% vs control 9%). A further recent meta-analysis of individual patient data involving alteplase for stroke with unknown time of onset guided by advanced imaging (WAKE UP, EXTEND, THAWS and ECASS 4) showed an absolute 8% improvement in functional independence despite an increase in symptomatic ICH (3% vs <1% in control arm).[36] These data suggest that IVT may be useful in bridging therapy in conjunction with MT within this specified time frame as well as being considered as stand-alone therapy in the absence of large vessel occlusion. The combination of IVT and MT in an extended time window (4.5–24 hours) is being tested in the TIMELESS trial using tenecteplase.[37]

Alternative agents

While alteplase is the only licensed thrombolytic Food and Drug Administration agent for ischaemic stroke, tenecteplase has

potential advantages over the former agent in having greater fibrin sensitivity (and hence being less haemorrhage-inducing), a longer half-life (can be given as a bolus with quicker door-to-completion time of thrombolysis) and lower costs. There have been five RCTs comparing tenecteplase with alteplase with varying results, with tenecteplase having been shown to be at least effective as alteplase for neurological improvement.[38] Campbell *et al* demonstrated that tenecteplase 0.25 mg/kg compared with standard dose of alteplase 0.9 mg/kg delivered <4.5 hours prior to MT achieved greater recanalisation and improved neurological recovery at 90 days.[39] Overall, it appeared that lower doses of tenecteplase (0.25 mg/kg) achieved a lower trend of symptomatic haemorrhage rates compared with alteplase, but higher rates of haemorrhage were observed with higher doses of tenecteplase at 0.4 mg/kg. Further studies involving tenecteplase include ATTEST 2 (tenecteplase vs. alteplase <4.5 hours), TASTE (tenecteplase vs alteplase with imaging mismatch), TWIST (tenecteplase in wake-up stroke) and TEMPO-2 (tenecteplase in minor with large vessel occlusion).[40] Therapies such as desmoteplase, argatroban, Gb IIb/IIIa inhibitors and sono-thrombolysis to augment recanalisation in conjunction with IVT have failed to improve outcomes consistently.[41]

Limitations of thrombolysis

Large vessel occlusions involving internal carotid artery and proximal MCA tend to only re-canalise between 10–25% respectively post-IVT, with evidence of residual thrombus angiographically. Several characteristics of thrombus may negate the effects of IVT, such as long thrombus length (>8 mm), greater thrombus age, the thrombus being platelet- and fibrin-rich rather than of red cell composition, and calcific thrombus material.[42]

Service delivery

Hospitals with higher volume thrombolysis activity achieve significantly shorter door-to-needle times in administering IVT.[43] Although using tele-stroke health applications and enhanced paramedic assessments are a potentially attractive model in facilitating stroke diagnosis and delivery of IVT, further developments in these models are required. Mobile stroke units (incorporating an ambulance equipped with an imaging system, a point-of-care laboratory, a telemedicine connection to hospital, and appropriate medication) have been developed with the potential to provide physicians with the necessary information and resources to screen patients safely for IVT eligibility and even initiate thrombolysis 'in the field'.

Mechanical thrombectomy

There is overwhelming evidence from RCTs for the effectiveness of MT in improving functional outcome at 90 days in patients presenting with proximal occlusion of a large vessel artery in the anterior circulation. Earlier trials failed to demonstrate efficacy due to use of older devices and not deploying uniform protocols for identifying large vessel occlusions, whereas more recent trials used modern devices such as stent retrievers and aspiration devices and placed patient selection under greater scrutiny.[44,45] The HERMES meta-analysis of individual patient data from five RCTs demonstrated benefit if MT was delivered within 12 hours of onset. The NNT to afford functional independence was between 3.2 and

7.4 patients when compared with best medical treatment.[46] There were similar rates of symptomatic ICH (4.4%) and a trend towards lower mortality (15.3%). The intra-arterial strategies examined were different in the trials to date, with subtle variations including simple imaging such as CT and CTA (MR CLEAN,[47] PISTE),[48] waiting for IVT response before proceeding (MR CLEAN)[47] and complex imaging such as CTP, MRI and multiphase collaterals with favourable imaging profile (ESCAPE,[49] EXTEND IA,[50] SWIFT PRIME,[51] THRACE,[52] THERAPY,[53] and REVASCAT).[54]

For trials delivering MT predominately within 6 hours, which included patients who also received IVT (within 4.5 hours), the rate of functional independence surpassed 60% using modern stent retriever devices.[48,50–52,55] Trials involving selective advanced imaging to identify salvageable ischaemic brain tissue also demonstrated good functional outcome ranging from 44–70% with MT.[49–52,56] Overall good functional outcome at 90 days was 20% greater (absolute benefit) with MT compared with best medical therapy.

The mantra of 'time is brain' is as important for MT as it is with IVT, with greater benefits observed if delivered within 4.5 hours of onset and with good collateral circulation. For every hour delay in MT, there is a reduction in reperfusion by 20%.[57] UK guidelines have endorsed the use of MT to be delivered as soon as possible in patients with a measurable neurological deficit (National Institutes of Health Stroke Scale (NIHSS) ≥6), with the procedure commencing within 5 hours of symptom onset in combination with IVT in confirmed occlusion of the proximal anterior circulation.[13,58] In addition to this, MT can be used within the same timeframe and criteria when IVT is also contraindicated. Patients included should only have mild disability prior to their stroke.

For those who present within 24 hours, including those with wake-up stroke, there is increasing evidence for MT using perfusion based imaging techniques, with the DAWN trial[56] looking at patients presenting at between 6–24 hours and the DEFUSE 3 trial[59] at presentations within 6–16 hours. Absolute benefits (good functional outcome) for patients in the DAWN trial compared with standard medical care equated to 36%, with DEFUSE 3 showing 28%. Accordingly, the NICE 2019 Stroke Guidelines recommends intervention within up to 24 hours if there is salvageable brain tissue ('penumbra') demonstrated by either CTP or DWI MRI sequences. There is also increasing data now supporting the use of MT in patients with M2 occlusions (first division of the MCA).[60] However, the evidence base for intervening for posterior circulation stroke, including proximal basilar artery occlusion, within <6 hours of onset is not robust, with the results of the BASICS trial demonstrating no significant benefit of thrombectomy, but intervention with MT may be considered up to 24 hours in selected cases until further trial evidence is available.[61]

Currently 1.8% of the stroke population undergoes MT in the UK, with a planned target of 10% by 2022 for England, Northern Ireland and Wales, equating to 8,000 patients per year. Current estimates suggest that 11–12% (10,000–11,500 stroke admissions) of the UK population would be potentially eligible for MT including additional support from advanced imaging, impacting those who present late (12–24 hours).[62] At present, studies have consistently demonstrated that MT is likely to be cost-effective, with net savings in lifetime analyses.[63]

Facilities for MT are not universally available and there is a need to determine how many specialist centres will be required to ensure maximum geographical provision. The choice of model will depend on local and regional service organisation,

patient characteristics and volume of admissions.[62,64] There is also a shortage of trained specialist staff to deliver MT through interventional neuroradiology, and, as such, there is an urgent need to expand this workforce as well as offering credential training for other specialties to support delivery and maintain the necessary skills and expertise for MT.[65]

There are still areas of uncertainty, which include whether patients with large vessel occlusion should forgo IVT and undergo MT directly in order to facilitate timely reperfusion. The Direct MT study suggested that MT alone was non-inferior to a combination of IVT/MT regarding functional outcome, although this needs to be replicated in future trials.[66] Other areas that require further investigation include the use of alternative thrombolytic agents to alteplase, such as tenecteplase, in combination with MT, establishing the degree of collateral blood flow with advanced imaging,[67] the optimal anaesthetic strategy (local versus general anaesthetic)[68] and which devices should be used (stent retrievers vs aspiration devices).[69]

Decompressive hemicraniectomy for malignant stroke syndrome

Large, space-occupying, hemispheric, ischaemic brain infarcts (described as malignant infarcts) are associated with the development of massive brain oedema, which may lead to herniation and early death. While conservative therapies are not supported by evidence from clinical trials, decompressive hemicraniectomy has been shown to prevent fatal internal displacement of brain tissue (and subsequent herniation) in cases of malignant MCA infarction within 48 hours of stroke, with a potential trigger for such consideration being a decline in the level of consciousness.[70] Meta-analysis of seven RCTs, involving 338 patients, demonstrated a significant 12-month 39% reduction in death (30% vs 69%) and 13% increase in the number of patients with mild to moderate disability (27% vs 14%).[71] The distribution of death and disability was similar in trials with additional 6-month and 36-month follow-up data.[71] Studies have suggested that earlier surgery is associated with lower mortality rates and better functional outcome.[72] While early trials excluded patients over the age of 60, more recently, the benefit of hemicraniectomy has been validated in older patients.[73] While decompressive hemicraniectomy has a NNT of 2 in terms of reducing mortality, treatment decisions need to focus on the acceptable quality of life after surgery.[73] In addition to surgical decompression for malignant MCA infarction, ventriculostomy and suboccipital decompressive craniectomy has been shown to be effective in the setting of hydrocephalus complicating acute cerebellar infarction.[74]

Future directions

Huge strides have been made in acute ischaemic stroke management in recent years. The challenge of how to translate improvements in cerebral perfusion from acute interventions into functional outcomes remains. Close attention to therapy assessments and interventions alongside medical treatments aligned to quality improvement strategies is an important area for the future, and uptake of technological advances, such as the use of robotic devices, may be beneficial. Imaging techniques focusing on assessments of collateral circulation and cerebral haemodynamics may help to select patients most likely to gain from IVT and MT, even beyond the timeframes investigated to date. The future may also hold promise of new thrombolytic agents and reperfusion techniques with greater efficacy and safety outcomes. Until more data are available, it is reasonable that all eligible patients should receive IVT before MT.

Minimising symptom onset to treatment time to facilitate early reperfusion is an important strategy to optimise patient outcome. Developing protocols both outside and inside stroke units is crucial in this regard. Mobile stroke units may play a role and it has been suggested that, in the future, they might also allow the use of novel diagnostic options (eg biomarkers and automated imaging evaluation) and therapies (eg neuroprotective drugs) in the prehospital setting. In rural and remote areas, the challenges of early stroke care are heightened and the use of specially designed aircrafts equipped with the ability to diagnose and treat acute stroke at remote emergency sites has been considered.[75] We anticipate further major advances in acute interventions embedded within stroke units which will hopefully improve the quality and outcomes for acute stroke patients. ∎

Conflicts of interest

Dr Mehool Patel is on the editorial board of *Clinical Medicine.*

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