The frontiers of acute stroke management

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Abstract
The field of stroke has rapidly advanced in recent years with more effective reperfusion therapies (thrombolysis and endovascular thrombectomy) applied to a broader range of patients, including using imaging-based selection to treat beyond standard time windows. Recent trials have provided signals that neuroprotection and specific treatments for intracerebral haemorrhage may be achievable. The range of targeted secondary prevention strategies has also expanded, particularly with direct oral anticoagulants, more potent lipid lowering agents and patent foramen ovale closure.

Key learning points
- Endovascular thrombectomy offers improved reperfusion and revascularisation rates as well as leading to increased functional independence at 90 days compared with standard medical treatment. Patient factors and imaging findings determine the magnitude of benefit and the risk of adverse effects.
- Advanced imaging with CT perfusion or MR diffusion-perfusion can improve diagnostic confidence and inform the use of thrombolysis >4.5h and thrombectomy >6 h post-onset. CT perfusion may be more accessible compared with MRI in most stroke centres.
- Tenecteplase is a genetically engineered form of tissue plasminogen activator that has a longer half-life, higher specificity for fibrin and increased resistance to plasminogen activator inhibitor-1. It can be administered as a single bolus (without the subsequent infusion required with alteplase). This may be more convenient and effective, especially in centres that do not have endovascular thrombectomy on site.
- Short term use of combined aspirin and clopidogrel for 3 weeks reduces the risk of recurrent stroke after minor stoke and high risk transient ischaemic attack. A low density lipoprotein target <1.8mmol/L also reduces the risk of recurrent stroke.
- Percutaneous closure of patent foramen ovale is now recognised as effective in reducing recurrent stroke in younger patients with no other cause for stroke identified.

The patient journey for acute stroke patients has substantially evolved in recent years. Community recognition of stroke remains suboptimal with further education required to immediately activate emergency services.

Prehospital care
Due to the time sensitive nature of reperfusion therapy, early community recognition of stroke is crucial to rapidly activate emergency services. The FAST (Face, Arm, Speech, Time) mnemonic is used in many English-speaking countries and captures the majority of treatable stroke patients. Paramedic triage tools to identify likely large vessel occlusion (LVO) and transport to an endovascular-capable centre are increasingly used and reduce delays incurred by inter-hospital transfers.[1] In some cities, mobile stroke units equipped with computed tomography (CT) permit rapid assessment of stroke symptoms, exclusion of intracerebral haemorrhage and early thrombolysis with increasing evidence of faster treatment, improved outcomes and cost effectiveness.[2]

Emergency department care
Prehospital notification of suspected stroke patients can activate the stroke team and radiology staff to clear the CT scanner, facilitating direct transport from emergency department triage to CT.[3] These are key elements in reducing door-to-needle time which improves patient outcomes. In regional and rural centres without onsite stroke physician expertise, telestroke consultations provide cost-effective specialist advice and thrombolysis with a safety profile comparable to major metropolitan hospitals.[4] Telemedicine also allows selection of patients suitable for transfer to an endovascular-capable hospital for thrombectomy.

Brain imaging to diagnose and determine management
The non-contrast CT brain remains essential to identify intracerebral haemorrhage (ICH), hypoattenuation and more subtle signs of ischaemic stroke such as a hyperdense artery (acute thrombus in an artery) and loss of grey-white differentiation.[5,6] CT angiography (in the same imaging session) should also be routine to identify large vessel occlusion suitable for endovascular thrombectomy as clinical severity is insensitive. CT perfusion (CTP) is useful to confirm the diagnosis of ischaemic stroke versus mimics and assists clinicians to select thrombolysis and endovascular thrombectomy candidates, particularly beyond standard time windows.[7,9] The mismatch between a large area of critically delayed flow and a smaller area of severely reduced flow estimates the region of ischaemic penumbra that

is salvageable with rapid reperfusion. MRI is often not immediately available in the emergency department but is more sensitive for the diagnosis of ischaemic stroke and very useful to confirm the diagnosis.

Intravenous thrombolysis

Intravenous thrombolysis with alteplase, a recombinant tissue plasminogen activator (tPA), has been widely used as reperfusion therapy for acute ischaemic stroke presenting within 4.5 hours of symptom onset.[10] The treatment benefit is preserved across the spectrum of age and a wide range of clinical severity but reduces rapidly with elapsed time from stroke onset. Non-disabling stroke patients may not benefit[11] but this does not apply to patients with mild but potentially disabling symptoms. Recent trials have indicated benefit of thrombolysis up to 9 hours after onset (or within 9 hours of the midpoint of sleep in wake-up onset stroke) if perfusion imaging is favourable.[12] However, patients with large vessel occlusions of the internal carotid, basilar or middle cerebral artery have relatively early low recanalisation rates.[13,14]

Tenecteplase is a genetically modified tPA with a longer half-life, higher specificity to fibrin and increased resistance to plasminogen activator inhibitor-1. It is the standard thrombolytic for ST-elevation myocardial infarctions at a dose of 0.5 mg/kg. Recent trials suggest than 0.25mg/kg tenecteplase is more effective than alteplase in large vessel ischaemic stroke with similar safety profile.[14,15] Single bolus administration of tenecteplase and lower cost in many countries have practical advantages.

Endovascular thrombectomy

Multiple trials published in 2015 established endovascular thrombectomy as a highly effective treatment to reduce disability in patients with ischaemic stroke due to large vessel occlusion, across the spectrum of age and clinical severity. Trials in patients with basilar artery occlusion have been challenging to execute and results equivocal, although most guidelines recommend thrombectomy given the dire natural history.[16,17]

Endovascular thrombectomy is beneficial in a broad range of patients selected on the basis of large vessel occlusion within 6 hours of stroke onset. Patients also benefit in the 6-24h time window if there is evidence of salvageable brain tissue on more advanced imaging (CT perfusion or MRI).[8,9] However, the proportion of patients with favourable imaging profiles reduces rapidly over time so treatment should still occur as fast as possible. Ongoing trials are investigating the benefit of thrombectomy in patients with a large area of irreversibly injured brain and those with mild clinical deficits.

Secondary prevention

There is a 3-15% risk of recurrent stroke within 90 days of an acute ischaemic event or transient ischaemic attack (TIA).[18] Specialist driven management and intervention within a stroke unit has been found to reduce the rate of recurrent stroke and achieve better outcomes.[19] A combination of lifestyle modifications (smoking cessation, diet, exercise) with pharmacological secondary prevention should be used to minimise the risk of recurrent stroke.[20]

Antiplatelet therapy is key to preventing ischaemic stroke, unless the patient has atrial fibrillation in which case anticoagulation is required. The addition of clopidogrel to aspirin for the first 21 days after onset of mild stroke or high risk TIA reduces the rate of recurrent events compared with aspirin alone.[18,21] Ticagrelor and aspirin also reduces recurrent stroke versus aspirin alone.[22] Unlike clopidogrel, which is a prodrug, ticagrelor does not rely on enzymatic activation for its effect. However, it is currently more expensive than clopidogrel and there are no data comparing its effectiveness for stroke prevention and bleeding risk to clopidogrel.

In patients with atrial fibrillation, direct oral anticoagulants are now generally used in preference to warfarin unless there is renal failure, mechanical prosthetic valve or rheumatic mitral stenosis.[23] Limited data are available to inform timing of anticoagulation after stroke with the volume of stroke generally considered when attempting to balance the risk of haemorrhagic transformation against early recurrent stroke.[19] Dabigatran can be reversed using idarucizumab (including prior to thrombolysis)[24] and andexanet alfa has been approved in some countries for reversal of anti-Xa inhibitors.[25] For those with genuine contraindication to anticoagulation, left atrial appendage occlusion may be an option.[20]

Statins have long been part of guidelines to reduce the risk of cardiovascular events including stroke. Recent data indicate that an LDL target of less than 1.8 mmol/L reduces recurrent stroke.[26] The new class of proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors may have an increasing role either in combination with a statin or in statin-intolerant patients.

Paradoxical embolism via a patent foramen ovale (PFO) has been a controversial cause of cryptogenic stroke. However, recent trials have established benefit of percutaneous closure, especially in patients aged <60 with no other identifiable cause for stroke.[27]

Multiple trials published in 2015 established endovascular thrombectomy as a highly effective treatment to reduce disability in patients with ischaemic stroke due to large vessel occlusion, across the spectrum of age

Future Directions

Intracerebral haemorrhage remains a therapeutic challenge with no specific therapies other than intensive blood pressure reduction and stroke unit care. A recent minimally invasive surgery trial was neutral overall but patients who had successful removal of haematoma to <15mL appeared to benefit.[28] Further trials of haemostatic agents and minimally invasive surgery are ongoing.

Neuroprotection has been a disappointing field for decades. Although neutral overall, a recent trial of nerinetide, as an adjunct to endovascular thrombectomy, showed promise in patients who did not receive alteplase,[29] and further trials are ongoing.

Conclusion

Stroke management has dramatically evolved over recent years with high quality evidence for reperfusion with thrombolysis and endovascular thrombectomy, improved secondary prevention strategies targeted to stroke aetiology and streamlined systems of care to accelerate treatment. Ongoing systems evolution, particularly in pre-hospital care, and future strategies for intracerebral haemorrhage, neuroprotection and recovery are the frontiers for further advancement.

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