Management of acute stroke

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This talk will focus on new research and changes in clinical practice that of interest to anaesthetists or which impact your practice.

1. Tenecteplase to replace alteplase as stroke thrombolytic agent of choice

Alteplase has been the stroke thrombolytic agent of choice since the publication of the NINDS trials in the mid-1990s. Alteplase is used in ischemic stroke patients out to 4.5 hours from symptom onset, or 9 hours in patients who wake up with stroke and have salvageable tissue on perfusion imaging. However, alteplase has to be given as a 10% bolus with the remainder as an infusion over an hour. This need for an infusion ties up nursing time and can slow transfer patients for thrombectomy.

Tenecteplase is a genetically engineered tissue plasminogen activator that has a longer half-life and slower plasma clearance than alteplase, which can be given as an intravenous push. Studies have confirmed that tenecteplase is;

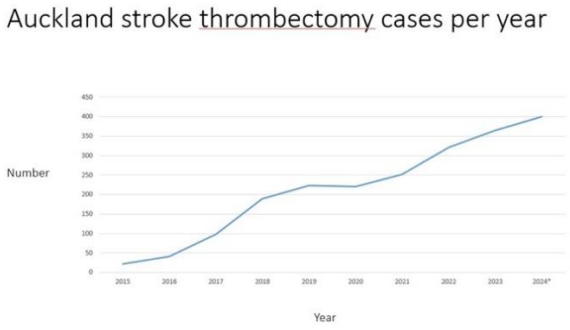
- Non-inferior to alteplase in ischemic stroke patients up to 4.5 hours from onset
- Superior to alteplase in stroke patients with large vessel occlusion
- Can be given out to 24 hours in patients with large vessel occlusion

This means that tenecteplase will replace alteplase when world-wide production problems are resolved in the next six months. This will reduce the need for nursing and ICU transfer teams, and delays for stroke thrombectomy.

2. Expanding indications for stroke thrombectomy

Since 2015 when the pivotal stroke thrombectomy trials were published, there has been a significant increase in the number of patients treated per year. In Auckland, our thrombectomy cases have increased from 22 in 2015 to a projected 400 plus this year, with similar increases in Wellington and Christchurch, the two other thrombectomy centres. In the first years, this was due to expansion of the treatment catchment area from metropolitan Auckland in 2015, to Northland, Waikato and Bay of Plenty in 2017.

However, in the last few years, this increase in numbers has also been due to an expansion of indications for thrombectomy. In 2018, the DAWN and DEFUSE studies showed that CT perfusion imaging, could identify patients with salvageable penumbral brain tissue, and that these patients clearly benefit from thrombectomy out to 24 hours from symptom onset. These patients are 'slow progressors' with good collateral blood flow keeping the penumbra alive for longer.



Then in 2023, three large randomized-controlled trials showed that patients with extensive infarction on baseline CT scans in emergency departments but who have larger areas of hypoperfused tissue at risk of infarction (penumbra) also benefit from thrombectomy. The numbers of patients with an independent outcome is smaller than those with smaller infarct cores but the benefit is real and significant. For every 100 patients with a large infarct core treated with thrombectomy, there are 16 who more achieve functional independence and 16 fewer who require hospital level care.

We're still coming to terms with the implications of these large core studies. Patients are more likely to have complications, require ICU admission, and a quarter will still die. But the bottom line is that the numbers of patients we're treating continues to increase and since an anaesthetic team is required for all thrombectomy cases (almost all of whom are treated with general anaesthesia in New Zealand) this has significant implications for anaesthetic services.

3. Pre-hospital blood pressure management

In acute stroke patients, physicians take a permissive view of blood pressure in those with ischemic stroke but tightly control blood pressure in the 15% who present with intracerebral haemorrhage. The evidence base for this practice is surprisingly scant.

The INTERACT 4 study was a pre-hospital (ambulance) study that randomized 2404 suspected stroke patients within two hours of symptom onset to with intensive BP lowering to a systolic 130-140 mmHg

with urapidil, or standard care. The baseline blood pressure was 178/98, and by hospital arrival this had reduced to 159 mmHg in the intervention group and 170 mmHg in the standard care group.

There was no difference in outcome between the early intensive blood pressure lowering and usual care patients in the group as a whole. However, there were differences depending on stroke type with better outcomes in patients with hemorrhagic stroke, and worse outcomes in patients with ischemic stroke with a number needed to harm of 25.

This study has significant implications. The practice of acutely lowering blood pressure with intracerebral haemorrhage patients, and being more permissive with ischemic stroke patients is confirmed. For anaesthetists, the study emphasizes the importance of not dropping blood pressure acutely in patients undergoing thrombectomy.

4. **Research update**

MASTERSTROKE

We'll have further guidance of exactly what blood pressure to aim for during thrombectomy when the MASTERSTROKE study, run by Doug Campbell in Auckland, is published. This multicentre randomized-controlled trial aims to test if patients treated with endovascular thrombectomy will benefit from induced hypertension. Thrombectomy patients treated with general anaesthesia are randomized to a systolic blood pressure target of 140mmHg or 170mmHg from procedure initiation until recanalization. Methods to maintain the blood pressure are at the discretion of the procedural anaesthetist. The primary efficacy outcome is improvement in disability measured by modified Rankin Scale score at 90 days. The primary safety outcome is all-cause mortality at 90 days. We've currently randomized around 450 of the planned 500 patients so the results shouldn't be too far off.

COOLHEAD 2 study

Almost all thrombectomy centres around the world work on a hub and spoke model, with most patients transferred for treatment from other hospitals. This is certainly the case in New Zealand with 80% of patients treated in Auckland transferred from another hospital, 30% via air ambulance. This leads to inevitable delays that in turn lead to an expansion of the infarct core before blood flow can be restored.

The aim of COOLHEAD-2 is to determine the feasibility of using a cooling cap as a potential neuroprotective strategy in patients undergoing thrombectomy for ischaemic stroke. We have already published a pilot study, COOLHEAD-1, where we demonstrated that head cooling is well-tolerated in awake healthy volunteers and patients with chronic stroke. With advanced MRI techniques, we showed that head cooling reduces brain temperature by approximately 1 degree celsius within 80 minutes.

COOLHEAD 2 is a feasibility and safety study that tests adherence to the intervention, complications, and recruitment rates. A cooling cap is placed on arrival to the emergency department and kept on until recanalization occurs. In the first two weeks of the study we've recruited six of a planned 40 acute stroke

patients. All going well, this is the next step in the program before carrying out a phase III randomized controlled trials in patients presenting to spoke hospitals.

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