Emerging evidence in the delivery of stroke thrombolysis

The last decade has seen a significant refinement in the delivery of cerebral reperfusion therapy. Despite the advent of mechanical thrombectomy (Goyal et al, 2016; Royal College of Physicians Intercollegiate Stroke Working Party, 2016), intravenous thrombolysis is likely to remain the mainstay of therapeutic reperfusion for the majority of acute ischaemic stroke patients worldwide. The number needed to treat for best functional outcome is 5 for intravenous thrombolysis within 90 minutes of acute ischaemic stroke onset, underlining the 'time is brain' hypothesis (Emberson et al, 2014). This progress is largely driven by advances in our understanding of approaches to managing large vessel occlusion through better radiological imaging, randomized controlled trial data, and improvement in pre-hospital and early hospital pathways with a focus on onset- and door-to-needle times.

The importance of consideration of service delivery on intravenous thrombolysis rates should not be downplayed, as it can maximize intravenous thrombolysis rates to 20% based on current guidelines (Morris et al, 2000). Nonetheless, several clinically important research questions remain unanswered, including minimizing the risk of symptomatic intracerebral haemorrhage through improved patient selection, managing 'wake-up' stroke, peri-thrombolysis blood pressure management, and efficacy and safety of emerging thrombolytic agents (e.g. tenecteplase). This editorial expands on current guidelines and highlights emerging evidence supporting these areas of current uncertainty.

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National clinical guidelines

The most recent UK stroke national clinical guidelines provide an important summary of the evidence behind current stroke management recommendations (Royal College of Physicians Intercollegiate Stroke Working Party, 2016). These guidelines emphasize key aspects of thrombolysis delivery including licensing of alteplase, time to alteplase delivery, patient selection, dosage of alteplase, as well as considerations for symptomatic intracerebral haemorrhage risk (Royal College of Physicians Intercollegiate Stroke Working Party, 2016).

Key developments for intravenous thrombolysis in this guideline based on updated Cochrane meta-analyses (Wardlaw et al, 2012) and new randomized controlled trial evidence (Anderson et al, 2016) were the consideration of alteplase delivery for over 80-year-olds and consideration for usage of low dose alteplase respectively. First, the Cochrane review and meta-analysis showed that older patients (>80 years) benefit as much as those <80 years particularly if alteplase is delivered within the first 3 hours, highlighting the redundancy of an upper age limit (Wardlaw et al, 2012; Emberson et al, 2014).

Second, the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) randomized controlled trial comparing low- (0.6 mg/kg body weight) *vs* standard-dose (0.9 mg/kg body weight; 10% as bolus injection over 2 minutes, the remainder administered as an infusion over an hour) alteplase demonstrated significantly lower symptomatic intracerebral haemorrhage rates and 7-day mortality with low-dose therapy, but overall did not demonstrate non-inferiority with respect to a 90-day dichotomised functional outcome (Anderson et al, 2016). Nonetheless, standard-dose alteplase remains the mainstay of intravenous thrombolysis therapy, delivered as soon as possible within a 4.5-hour time window for patients under 80 years old, and within a 3-hour time window for over 80 year olds. For those over 80 years old, alteplase should be considered in the 3–4.5-hour time window on an individual basis. There may be circumstances where low-dose could be considered by the treating physician and/or patient although further research is required to define this group, potentially on the basis of comorbidities and extent of pre-existing radiologically evident burden of cerebrovascular disease.

Tenecteplase

Tenecteplase is a modified tissue plasminogen activator with preferential pharmacokinetics over its comparator alteplase. An individual patient data meta-analysis of 291 participants with acute ischaemic stroke (phase II trial) recommended further studies of 0.25 mg/kg tenecteplase, as there was no significant difference between tenecteplase and alteplase for efficacy or safety (Huang et al, 2016). The Norwegian NOR-TEST trial failed to show superiority (and was not pre-specified as 'non-inferiority') of 0.4 mg/kg tenecteplase over alteplase in 1100 patients with acute ischaemic stroke, in part related to low disability outcome from having a high number of patients with transient ischaemic attack, minor acute ischaemic stroke, and 'stroke mimics' (Logallo et al, 2017).

However, the recently completed Australian EXTEND-IA-TNK trial showed superiority of tenecteplase 0.25 mg/kg over alteplase for a radiological (early recanalisation) and not clinical outcome, in 202 highly selected thrombectomy-eligible patients with acute ischaemic stroke (Campbell et al, 2018). Accordingly, several studies are ongoing to assess tenecteplase *vs* alteplase in thrombolysis-eligible acute ischaemic stroke patients (ClinicalTrials.gov identifier NCT02814409), as well as in highly selected patients groups, including minor ischaemic stroke with large

vessel occlusion (ClinicalTrials.gov identifier NCT02398656), evidence of ischaemic penumbra on perfusion imaging (ANZCTR identifier ACTRN12613000243718), and in wake-up stroke (ClinicalTrials.gov identifier NCT03181360).

Wake-up stroke

In the absence of a defined onset time for acute ischaemic stroke, intravenous thrombolysis is contraindicated. However, radiological advancement has provided a culture shift away from duration of symptoms predicting reversibility of ischaemic burden to image-guided assessment of volume of ischaemic and infarcted cerebral matter. A 'mis-match' between diffusion weighted magnetic resonance imaging and fluid-attenuated inversion recovery sequences (FLAIR) suggests a salvageable penumbra perhaps benefiting from intravenous thrombolysis therapy. This was tested in the Efficacy and Safety of MRI-based Thrombolysis in Wake-up Stroke (WAKE-UP), where patients with acute ischaemic stroke treated with alteplase compared to placebo had a significantly better 90-day functional outcome (Thomalla et al, 2018). A potential rate-limiting factor for implementing these findings into clinical practice is the availability of 'front-door' magnetic resonance imaging. The ongoing computed tomography-based wake-up stroke trial, TWIST, may help answer this.

Blood pressure

There is ongoing controversy with respect to the management of many physiological perturbations in acute stroke, including blood pressure (Appiah et al, 2018). In particular, very little data exist to support intensive blood pressure lowering in the intravenous thrombolysis eligible population, although systolic hypertension seems to be associated with an increased risk of symptomatic intracerebral haemorrhage (Ahmed et al, 2009). The ENCHANTED study also included a blood pressure arm to compare intensive (130–140 mmHg systolic target) *vs* current guideline (180 mmHg systolic target) in patients receiving intravenous thrombolysis, and is anticipated to present its results in 2019. Furthermore, collaborative approaches using individual patient data meta-analyses are underway to better understand the position of equipoise that exists when considering lowering blood pressure in patients with acute ischaemic stroke (Sandset et al, 2018).

Conclusions

Intravenous thrombolysis significantly increases the chance of functional independence post-stroke, and an improved understanding of delivery has ensured better safety and clinical outcomes. Despite this, several aspects of intravenous thrombolysis delivery remain to be clarified including the role of new thrombolytic agents, treatment strategies for stroke with unknown onset time, including wake-up stroke, and the role of an intensive peri-thrombolysis blood pressure target. The results of ongoing trials are awaited to further refine optimal delivery of intravenous thrombolysis. **BJHM**

KEY POINTS

- Despite significant advances in delivery of intravenous thrombolysis for acute ischaemic stroke, several unanswered questions remain.
- There is no upper age limit for delivery of intravenous thrombolysis in acute ischaemic stroke but consideration of individualized patient factors is crucial when comorbidity exists.
- Randomized controlled trials of blood pressure lowering in acute ischaemic stroke are soon to report, specifically in an intravenous thrombolysis population.
- Magnetic resonance imaging-guided delivery of intravenous thrombolysis in 'wake-up' acute ischaemic stroke marks a significant step forward, although concern about resource allocation may hinder wider usage.
- Although alteplase remains the mainstay of intravenous thrombolysis therapy worldwide for acute ischaemic stroke, tenecteplase is an emerging agent with advantageous pharmacokinetic properties, which had in a higher incidence of reperfusion before thrombectomy in a small trial.
- Trials are underway to compare efficacy of tenecteplase and alteplase in larger groups of patients with acute ischaemic stroke and in specific sub-groups.

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