

Successful stroke thrombolysis beyond guidelines: A case series

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ABSTRACT

Intravenous (IV) thrombolysis is a safe and effective treatment for acute ischemic stroke. The therapeutic benefit is not extended to more than 4.5 hours in many patients due to the protocol's time window restriction. Here, we reported two acute stroke cases with a moderate National Institutes of Health Stroke Scale (NIHSS) and onset greater than 4.5 hours that were successfully thrombolysed with intravenous recombinant tissue plasminogen activator (tPA) - low-dose Tenecteplase (TNK). The decision to thrombolysed both patients were based on Magnetic Resonance Imaging (MRI) Diffusion-weighted imaging (DWI)-Fluid Attenuation Inversion Recovery (FLAIR) mismatch – tissue basis rather than a time window, and this resulted in a good neurological recovery with a significant improvement in functional Modified Rankin Score (MRS) to zero at 90 days post stroke regardless of the stroke aetiology. In summary, Intravenous thrombolysis in acute ischemic stroke outside the therapeutic window but with significant penumbra based on MRI DWI-FLAIR tissue mismatch resulted in a remarkable neurological recovery after 90 days.

Keywords: stroke, thrombolysis, tissue window, tenecteplase

INTRODUCTION

Intravenous (IV) thrombolysis is a safe and effective treatment for acute ischemic stroke. The therapeutic benefit is not extended to more than 4.5 hours in many patients due to the protocol's time window restriction [1].

CASE PRESENTATION

Case 1

Forty-year-old young gentleman who has underlying hypertension, dyslipidaemia, and previous stroke with functional Modified Rankin Score (MRS) of zero, presented to us with sudden onset left-sided weakness, facial asymmetry, and slurring of speech.

The symptoms began in the morning, but it was not a wake-up stroke. On clinical findings, his vital signs were as follows; blood pressure of 140/90, pulse rate of 74 beats per minute with normal body temperature and oxygenation. The neurological examination revealed that he has left upper motor neuron 7th nerve palsy, 3/5 motor power in the left upper and lower limbs, and aphasia. His NIHSS (National Institute of Health Stroke Scale) score was 5/42. We then proceed with Magnetic Resonance Imaging (MRI) which was performed within 5.5 hours of the symptom's onset. The MRI revealed a hyperintense signal on diffusion weighted imaging (DWI) at right corona radiata, which corresponded to a vague hyperintense FLAIR signal, indicating an early infarct with a DWI-FLAIR partial mismatch (Figure 1A and

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1B). Following that, we performed T1-weighted black blood vessel wall imaging (Figure 1C), which demonstrates atherosclerotic plaque enhancement consistent with underlying intracranial atherosclerotic disease and explains the mechanism of artery-to-artery embolus cause of stroke. Intravenous thrombolysis was then commenced with Tenecteplase 0.25 milligram per kilogram (mg/kg), administered at 6.3 hours of stroke. Improvement of NIHSS was seen as early as 12 hours, where his NIHSS score reduced from 5/42 to 0/42. The risk factors assessment, including electrocardiogram, echocardiogram, Holter, chest X-ray, carotid and transcranial

doppler ultrasound, full blood counts and routine chemistry were all unremarkable. Twenty-four hours post thrombolysis, he was started on single antiplatelet- aspirin and subsequently was discharged home. On clinic follow up, at 90 days post stroke, his MRS score remains zero and he was able to meet his own needs without assistance.

Case 2

Sixty-three-year-old with premorbid functional MRS of zero, diabetes mellitus, hypertension and ischaemic heart disease with previous coronary ar-

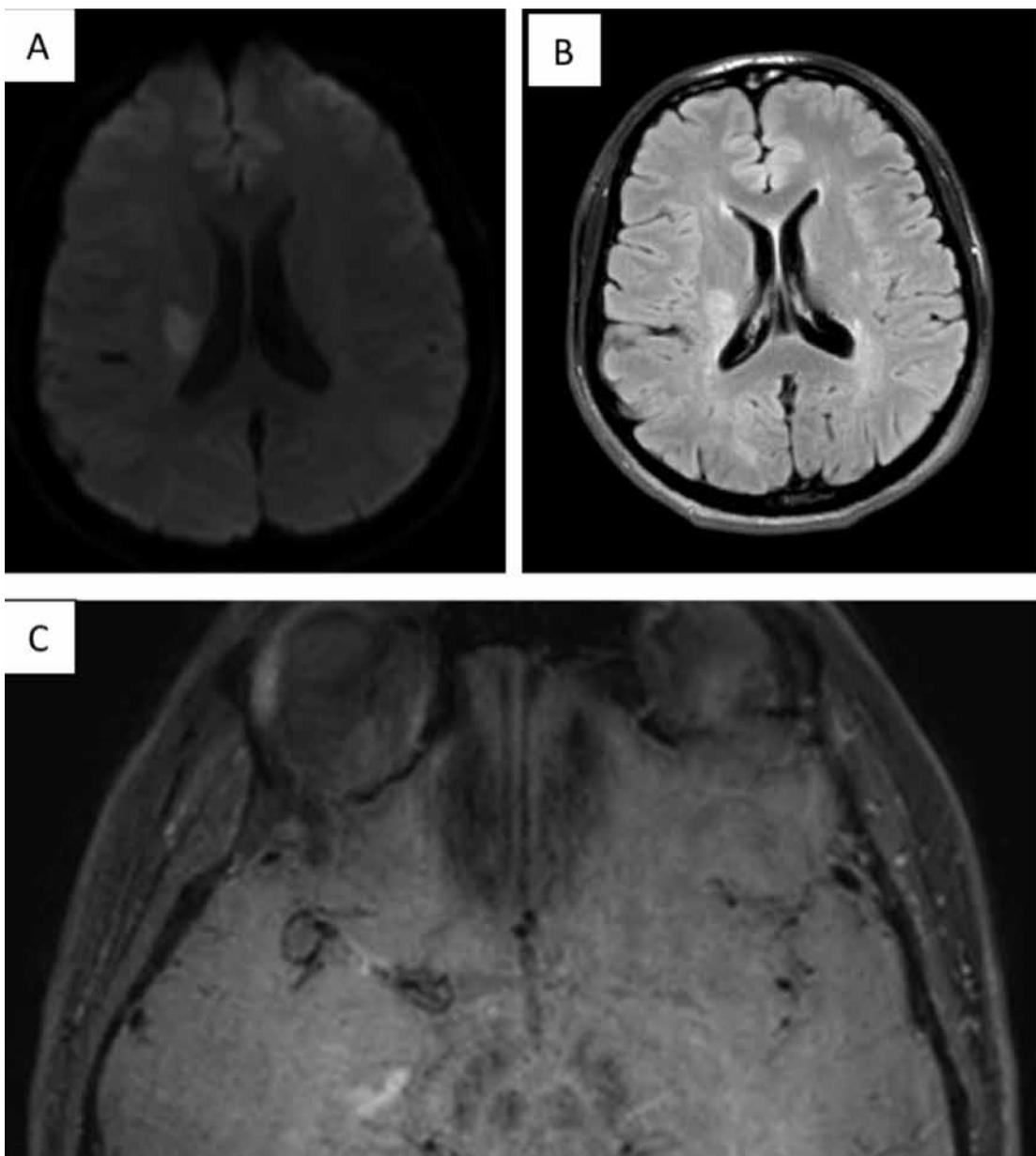


FIGURE 1. Hyper intense signal on diffusion weighted imaging (DWI) at right corona radiata (A) and corresponding vague hyper intense FLAIR signal (B) indicating early infarct with DWI-FLAIR partial mismatch. T1-weighted black blood vessel wall imaging (C) shows atherosclerotic plaque enhancement in keeping with underlying intracranial atherosclerotic disease and explain the mechanism of artery-to-artery embolus causing stroke

tery bypass graft presented with right sided body weakness associated with slurred speech. Rapid assessment of his NIHSS was 14/ 42. Clinically, he has right upper and lower limb hemiparesis with right distal hand hemichorea, right upper motor neuron 7th nerve palsy and severe dysarthria. Magnetic Resonance Imaging (MRI) was performed immediately following the clinical assessment, and during the procedure, he developed fast atrial fibrillation (AF), with a heart rate of 140bpm. He was then loaded with intravenous digoxin which successfully reverted the fast AF. The MRI brain showed presence of hyper intense signal on DWI at left middle cerebral artery (MCA) territory with normal FLAIR signal (Figure 2A and 2B) indicating hyperacute infarct with DWI-FLAIR mismatch. The Magnetic Resonance Angiography (MRA) showed no evidence of large vessel occlusion, however there was reduced opacification at M3 segment of left MCA indicating distal vessel occlusion (Figure 2C). He was subsequently thrombolysed with intravenous Tenecteplase (TNK) 0.25 mg/kg, which was given at 5.5 hours of stroke. His NIHSS score reduced from 14/42 to 8/42 at 5 hours post thrombolysis with significant improvement in motor component. Throughout his hospitalisation, he showed a steady improvement, where his NIHSS score further reduced to 0/42 at day 4 post thrombolysis. Repeated non-contrasted -computed tomography (NCCT) brain at 24 hours post thrombolysis revealed no intracranial haemorrhage. On the assessment of stroke risk, he had atrial fibrillation on electrocardiogram, but the echocardiogram was normal. Other imaging studies including carotid and transcranial doppler ultrasound were normal. His blood profile showed elevated Triglyceride (TG) and Low-Density Lipoprotein (LDL), but his haemoglobin A1c (Hba1c) was normal. He was discharged at day 6 post stroke, and he was started on anticoagulant - apixaban 5mg twice daily for lifelong. His MRS score was zero at 90 days post-stroke, and he was able to perform daily activities.

FIGURE 2. Hyperacute infarct at left parietal lobe showing hyper intense signal on diffusion weighted imaging (DWI) (A) and normal FLAIR signal (B) indicating early infarct with DWI-FLAIR mismatch. Magnetic Resonance Angiography (MRA) shows no evidence of large vessel occlusion(C), however reduced opacification at M3 segment of left MCA indicating distal vessel occlusion.

DISCUSSION

Intravenous recombinant tissue plasminogen activator (tPA) is an internationally recognised evidence-based effective treatment for patients with acute ischaemic stroke (AIS) [2,3]. Recent guidelines

recommended tPA administration in AIS patients who meet the criteria and within the therapeutic time of less than 4.5 hours of stroke onset. Initial treatment time window of 3 hours is expanded to 4.5 hours based on the European Cooperative Acute Stroke Study III [4, 5]. The thrombolysis in AIS is based on the rationale to salvage the ischaemic brain tissue before cell death established. However, everyone's penumbra differs, owing primarily to collaterals, cortical blood volume and flow reserve, and resistance to ischaemic insults. In view of the various potentially salvageable penumbra, it is feasible that certain numbers of patients could still benefit from delayed intravenous tPA beyond the therapeutic window [6-9] with the use of MRI multimodal imaging to define the tissue penumbra and core infarct. In this case series, we have demonstrated that rapid MRI sequence diffusion-weighted imaging (DWI)-Fluid attenuated inversion recovery (FLAIR) guided intravenous tPA in patients with AIS beyond 4.5 hours resulted in a good neurological recovery regardless of the stroke aetiology and severity. DWI-FLAIR mismatch was defined as the presence of a visible ischaemic lesion on DWI but absence of any corresponding parenchymal hyperintense lesion on the FLAIR. It has a relatively high specificity (71–93%) and moderate sensitivity (48–62%) for identifying stroke lesions within 4.5 h of onset [10-14]. To the best of our knowledge, the earlier trial known as the WAKE-UP TRIAL found that patients with wake-up stroke who received intravenous tPA based on a substantial MRI DWI-FLAIR mismatch had a significantly better functional outcome than placebo after 90 days [15]. Similarly, MR WITNESS trial demonstrated that Intravenous thrombolysis within 4.5 hours of symptom discovery in patients with unwitnessed stroke selected by quantitative mismatch of MRI DWI- FLAIR who are beyond the recommended time windows, is safe. This was a phase 2a multicenter trial that used alteplase (0.9 mg/kg) in patients with unknown stroke onset and DWI-FLAIR mismatch 4.5–24 h from last known well, and the results revealed that 39 percent of patients who were treated with intravenous tPA had a modified Rankin Scale (mRS) between 0 and 1 at 90 days [16]. Another phase 3 study, the EXTEND trial showed that the used of alteplase between 4.5 and 9 hours or awoke in ischaemic stroke with salvageable brain tissue resulted in a higher percentage of patients with no or minor neurologic deficits compared to placebo. To the best of our understanding, the current recommendation of 4.5 hours therapeutic window is based on a meta-analysis of trials that used a NCCT for the selection of patients [17]. In comparison, we chose to provide intravenous tPa to our patients based on an MRI DWI-FLAIR mismatch – tissue basis rather than a time window, and this

resulted in good neurological recovery regardless of the aetiology of large or small vessel occlusion or cardioembolic events. This implies that the penumbra is almost as significant, if not more so, than the time of onset of neurological deficit in determining which patients will benefit most from reperfusion therapy [18]. The use of MRI DWI/Perfusion weighted imaging (PWI) mismatch is another method that support the use of penumbral tissue-based selection for intravenous thrombolysis reperfusion therapy beyond 3 hours in AIS patients [19]. This concept is supported by evidence from the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) where alteplase significantly attenuate the infarct growth when using co-registration technique to determine the mismatch PWI and DWI. On the other hand, computed tomography perfusion (CTP) with contrast is a more feasible alternative to MRI DWI/PWI in detecting penumbra and widely available in most of the stroke centres particularly in middle- or lower-income country such as in Malaysia. A previous study on CTP guided intravenous thrombolysis in patients with wake-up stroke (WUS), stroke with unknown onset (SUKO) or stroke beyond 4.5 hours from last seen normal, seems to be safe and have similar functional outcomes and similar rates of symptomatic intracranial cerebral haemorrhage (SICH) to patients treated with standard therapeutic window – less than 4.5 hours [20]. Furthermore, despite being outside of the therapeutic window, both of our patients received intravenous Tenecteplase (TNK) 0.25mg/kg as a reperfusion therapy, which resulted in a robust clinical recovery. This is interest-

ing as to our understanding, TNK is a non-Food and Drug Administration (FDA) -approved intravenous (IV) thrombolytic, used as an off-label treatment for AIS. However, few recent trials comparing Tenecteplase and alteplase suggested that Tenecteplase is at least as efficacious as alteplase with regards to neurological improvement. Tenecteplase has a potential advantage over alteplase in that it has higher fibrin specificity and a longer half-life [21]. Study conducted by Parsons et al showed that AIS patients who had symptoms for 6 hours or less who received Tenecteplase had better reperfusion on imaging studies and clinical neurologic outcomes at 24 hours, and Tenecteplase 0.25 mg/kg had superior outcomes than those who received alteplase for all efficacy effects, including severe disability at 90 days [22]. Another recent study by Campbell et al found that Tenecteplase before thrombectomy was associated with a higher incidence of reperfusion and better functional outcome than alteplase among patients with ischemic stroke treated within 4.5 hours after symptom onset [23].

In conclusion, our case study demonstrates that thrombolysis in late-time window stroke patients using penumbra-based imaging is both safe and effective, resulting in significant neurological recovery, particularly at 90 days after stroke. Extensive research on penumbra-based thrombolysis should be conducted, including the benefit of using the Tenecteplase as a thrombolytic agent in acute ischemic stroke patients who presented beyond the 4.5-hour time window.

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