Case Report

Stroke Thrombolysis at 5.5 Hours Based on Computed Tomography Perfusion

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Abstract

A young man was admitted with sudden onset of right-sided weakness. He was assessed in the emergency department, and an immediate computed tomography (CT) perfusion study of the brain was arranged, which showed a left middle cerebral artery territory infarct with occlusion of the M1 segment. There was a significant penumbra measuring approximately 50% of the arterial territory. By the time his assessment was completed, it was 5.5 hours from the onset of symptoms. He was nonetheless administered intravenous recombinant tissue plasminogen activator (rtPA) based on the significant penumbra. He was discharged from the hospital after one week with significant residual deficit. At 2 months clinic follow-up, he showed almost complete recovery with a Modified Rankin Score of 1. We hope to demonstrate that a significant penumbra is an important determinant for good neurological recovery and outcome following stroke thrombolysis, even when patients present outside the 4.5 hours onset-to-treatment time window.

Keywords: *stroke, computed tomography, perfusion, rtPA, thrombolysis, developing countries*

Introduction

Stroke is a major cause of mortality and morbidity. Patients who seek treatment within 4.5 hours of the onset of symptoms may potentially benefit from intravenous recombinant tissue plasminogen activator (rtPA). The earlier the drug is administered, the better is the clinical outcome. However, evidence is now emerging that patients may be treated with intravenous rtPA for up to 6 hours following a stroke; this is counter-balanced by a higher risk of haemorrhagic transformation (1). The current standard practice remains a 4.5 hour cut-off, as extending the thrombolysis window to 6 hours has yet to be incorporated into international guidelines regarding strokes.

Non-contrasted computed tomography (NCCT) imaging remains the gold standard in many stroke centres. This is mainly because computed tomography (CT) is more easily available, accessible, and is comparatively cheaper than magnetic resonance imaging (MRI). Growing evidence suggests that computed tomography perfusion (CTP) with contrast may increase diagnostic sensitivity as it enables definite delineation of large arterial territory infarcts and the penumbra (2). In our patient, the use of CTP provided evidence of a significant area of salvageable cerebral tissue. This information was crucial in making the decision to thrombolyse the patient outside the normal time window.

Case report

A 29-year old man was brought to our centre with sudden onset of neurological deficit. The onset of symptoms was at approximately 1630 hours, and he arrived at the hospital at approximately 1900 hours. He was accompanied by two colleagues who provided a collateral history. The patient was at work when he developed sudden onset of right hemiplegia associated with right facial asymmetry. The patient was fully conscious but was not responding to questions. His colleagues were unsure of his medical history except that he was a heavy smoker (20 cigarette pack-years). The patient's wife later verified this account and confirmed that the patient was not diagnosed with any chronic disease and was not on regular medication at the time. He was a social

drinker but did not use illicit drugs.

On examination, the patient had dense right hemiplegia, an upper motor neuron VIIth cranial nerve deficit, and ipsilateral neglect. He was aphasic. His vital signs were as follows: pulse, 80 beats per minute with regular rhythm; blood pressure, 130/80 mmHg; and oxygen saturation, 97% when inspiring room air with a respiratory rate of 20 breaths per minute. The remainder of his clinical examination was unremarkable. In particular, there was no evidence of a metabolic, cardiovascular, or arteritic disorder that would explain the stroke. His National Institute of Health Stroke Scale (NIHSS) was 14. A CTP of the brain was requested, and it showed an established infarct in the right lenticulostriate territory with an occlusion of the M1 segment of the middle cerebral artery. There was significant penumbra estimated at approximately 50% of the corresponding arterial territory (Figure 1). By the time the assessment of the patient was completed, it was approximately 5.5 hours from the onset of symptoms. Nonetheless, following careful deliberation between the neurologist and the radiologist on-call, with consideration of the significant penumbra in the CTP and the patient's young age, a decision was made to administer intravenous rtPA with informed consent from the patient's wife. He received the standard dose of intravenous alteplase (0.9 mg/kg body weight). There were no complications, and an MRI brain at 24 hours showed an acute infarct in the left middle cerebral artery territory but no evidence of any haemorrhagic transformation (Figure 2). The patient showed marginal improvements clinically at 24 hours post-thrombolysis, with a reduction of the NIHSS score to 10 and weakness of the right upper and lower limb Medical Research Council (MRC) power grade 2/5. Other clinical parameters remained unchanged from admission.

There was no identifiable cause of his stroke. Investigations conducted included a full blood screen for thrombophillic, vasculitic, and connective tissue disorders; a transthoracic echocardiogram with bubble study; carotid Doppler assessment; and an MRI brain. His family history was unremarkable.

After a week, the patient was discharged with significant neurological deficit. He still had weakness over the right upper and lower limbs (power grade 3/5), required a naso-gastric tube for feeding, and was dysphasic. He was referred to physiotherapy and other allied health specialties for stroke rehabilitation. At clinic follow-up two months later, he had motor deficit involving the right hand only and was able to swallow normally.

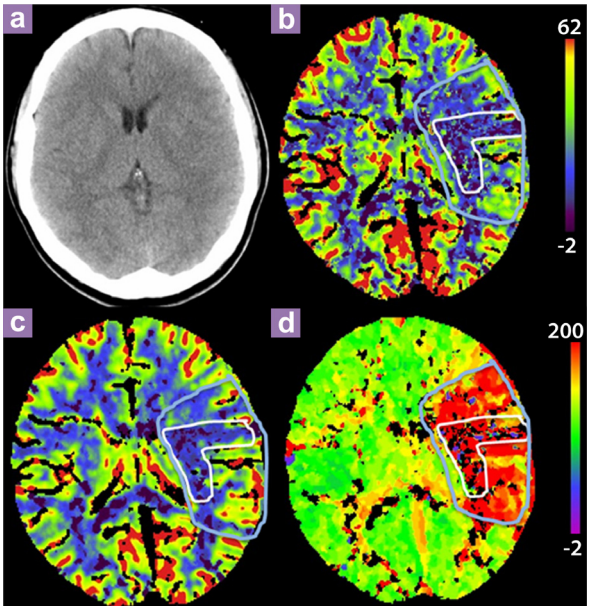

Figure 1: Non-contrasted computed tomography (NCCT) and computed tomography perfusion (CTP) were performed concurrently on admission. (a) NCCT shows subtle loss of grey white matter differentiation at the left temporo-parietal region. CT perfusion map of cerebral blood flow (b), cerebral blood volume (c), and time to peak (d) demonstrate an area of reduced cerebral blood volume and cerebral blood flow that corresponds to ischaemic core (white area). An area of penumbra in the left MCA territory is demonstrated as a larger area of reduced cerebral blood flow and increase time to peak (blue area).

His speech had improved and he was now able to communicate in his native Cantonese although speaking Malay was still a problem. His Modified Rankin score was 1 at the follow-up visit.

Discussion

Thrombolysis for acute stroke was introduced into clinical practice in 1996. The benefits of rtPA have been validated in several randomised controlled trials (3). The early trials of rtPA had strict inclusion and exclusion criteria, and these restrictions were subsequently incorporated into the guidelines for stroke thrombolysis. The restrictions included limiting use to those below 80 years of age and using a 3 hour onset-to-treatment (OTT) cut-off. These considerations

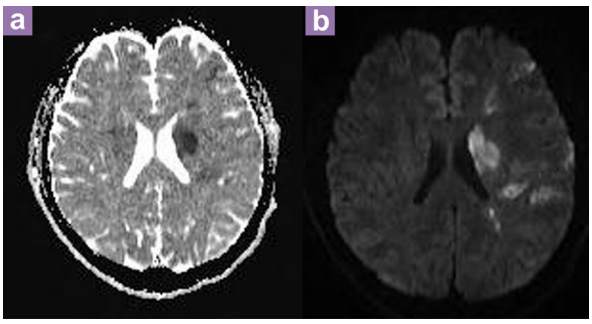

Figure 2: Magnetic Resonance Imaging brain performed 24-h post-thrombolysis. (a) Diffusion-weighted image (DWI) showing restricted diffusion in the left middle cerebral artery territory and (b) apparent diffusion coefficient (ADC) map showing corresponding hypointensity in the same area suggesting an acute infarct.

were put in place to ensure that the benefits from reperfusion therapy would be optimal whilst keeping adverse events at a minimum.

Having such strict eligibility criteria for thrombolysis has its drawbacks. It is estimated that only 2–5% of patients presenting with an acute stroke to hospital were given thrombolysis therapy (4). One of the reasons for ineligibility was presentation beyond the recommended onset-to-treatment time. This duration was therefore extended to 4.5 hours with the publication of the Third European Cooperative Acute Stroke Study (ECASS 3) trial, which showed benefit in patients presenting beyond 3 hours after the onset of neurological symptoms (5).

Of late, several more studies have investigated the benefits of thrombolysis in groups of patients with characteristics which were previously not included in early thrombolysis trials. The Third International Stroke Trial (IST 3), with approximately 50% of the subjects in the above 80 years old age group, showed benefits of thrombolysis that were similar to those found in younger patients in the National Institute of Neurological Disorders and Stroke (NINDS) trial (1). Furthermore, the trial also published results that appear to suggest that thrombolysis beyond 4.5 hours may be of benefit. The question whether further extension of the time-window is possible, although fraught with controversy, provides food for thought.

The concept of ischaemic penumbra is based on the rationale that to achieve maximal benefit from reperfusion therapy, thrombolysis should be administered to at-risk ischaemic brain tissue before cell death is established. Indeed, some studies go so far as to suggest that the penumbra is as, if not more important than the time of onset of neurological deficit in deciding the best patients who will benefit most from reperfusion therapy (6). Our case report demonstrates this very well as the patient had a significant penumbra and a small infarct core on CTP, despite having received thrombolysis beyond the recommended OTT time window, with consequent good neurological recovery. Current methods to determine penumbra include MRI with diffusion/perfusion weighted image (DWI/PWI) sequences and CTP.

By using MRI with a DWI/PWI mismatch sequence to estimate ischaemic penumbra, the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) provided some evidence that the time window for thrombolysis might be extended beyond 3 hours (7). However, the limitation for adopting this technique to determine the extent of ischaemic penumbra is the limited availability of MRI facilities in certain centres, especially in developing countries such as Malaysia.

A much more feasible alternative is a CTP scan, as a CT machine is comparatively more readily available. A study by Szithra et al. found that in the 3–6 hours time-window, using CTP to detect penumbra, the rate of adverse events and the patients functional outcome were comparable to those of the group thrombolysed at less than 3 hours using NCCT (8). An additional benefit of utilizing CTP is the ability to distinguish stroke mimics such as migraine with aura and seizure with Todd's paresis (2).

One argument put forward against incorporating the use of CTP is the longer duration required to perform the additional sequences, which would potentially delay the administration of a thrombolytic agent. This scenario was demonstrated perfectly in our patient. However, Szithra et al. showed that utilisation of CTP only added 10 minutes to the arrival-to-treatment (ATT) time (8). Furthermore, studies using multi-modal MRI selection for thrombolysis showed that in the more-than-3 hours time-window group, the OTT time was not a significant factor in patient outcome (9).

Prospective studies looking at extending the time window for thrombolysis are currently being performed, and we await the results with heightened anticipation (10).

Thrombolysis has been proven to be useful in patients presenting with acute stroke. Presently, several prerequisites are put in place to determine eligibility of patients to receive thrombolysis

therapy. This is to ensure that patients obtain maximal benefit. There are those that advocate strict adherence to label use. We hope to demonstrate that in certain cases, with the right tools, off-label use may be beneficial. However, proper large-scale trials are needed to validate our findings.

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Conflict of Interest

None.

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Authors' Contributions

Drafting of the article: RS, SA, SM, SP
Critical revision of the article for the important intellectual content: RS, THJ, NMI
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