Neurology Asia 2013; 18(4) : 355 – 360

Evaluation of time-dependent pathways in an acute ischemic stroke protocol that incorporates CT perfusion: A tertiary referral center experience

[1]Hilwati HASHIM, [2]Radhiana HASSAN, [3]Syazarina SHARIS, [4]Shahrul AZMIN, [4]Rabani REMLI, [3]Shahizon Azura MUKARI, [4]Nafisah YAHYA, [4]Hui Jan TAN, [4]Norlinah MOHAMED IBRAHIM, [5]Mohd Saiboon ISMAIL, [3]Sobri MUDA, [4]Ramesh SAHATHEVAN
on behalf of Kuala Lumpur Regionalised Intergrated Stroke Intervention Strategy (KRISIS)

[1]Imaging Unit, Faculty of Medicine, Universiti Teknologi MARA; [2]Department of Radiology, Kulliyah of Medicine, International Islamic University; [3]Department of Radiology, [4]Department of Medicine, and [5]Department of Emergency Medicine, Universiti Kebangsaan Malaysia Medical Centre, Malaysia

Abstract

Background and Objective: Intravenous thrombolysis service for stroke was introduced at the Universiti Kebangsaan Malaysia Medical Centre (UKMMC) in 2009, based on the recommendations of a multidisciplinary team of clinicians. We report the experience at our center in establishing a stroke protocol incorporating computed tomography perfusion (CTP) of the brain, to assess the feasibility of incorporating CTP in the stroke protocol.
Methods: A retrospective review of all patients who had a CTP between January 2010 and December 2011 was performed. *Results:* Of 272 patients who were admitted with acute ischemic stroke, 44 (16.2%) arrived within 4.5 hours from symptom onset and had a CTP performed with the intention to treat. The median time for symptom-to-door, symptom-to-scan and door-to-scan was 90.0 minutes (62.5 – 146.3), 211.0 minutes (165.5 – 273.5) and 85.0 minutes (48.0 – 144.8) respectively. Eight patients (2.9%) were thrombolysed of whom five received IV thrombolysis and three underwent mechanical thrombolysis. The median symptom-to-needle and door-to-needle times were 290.5 minutes (261.3 – 405.0) and 225.0 minutes (172.5 – 316.8) respectively. Four patients were thrombolysed despite being outside the window of treatment based on the CTP findings. Six of the thrombolysed patients had a Modified Rankin Score (MRS) of 1-2 at 5 months post procedure.
Conclusions: CTP provides a benefit to management decisions and subsequent patient outcome. It is feasible to incorporate CTP as a standard imaging modality in a stroke protocol. The delays in the time-dependent pathways are due to our work flow and organisational process rather than performing the CTP *per se*.

INTRODUCTION

Acute ischemic stroke (IS) remains a leading cause of mortality and morbidity worldwide.[1] In Malaysia, stroke incidence and the resulting rates of mortality and morbidity reflect the escalating trend seen in most developing countries.[2] This means that better stroke management initiatives are required by the healthcare system here.

Reperfusion using pharmacological thrombolysis leads to an improved clinical outcome in IS.[3] However, the therapeutic window for treatment is narrow and the benefit of thrombolysis is time-dependent.[4] The most recent guidelines on stroke treatment recommend the use of intravenous (IV) thrombolysis using alteplase for up to 4.5 hours from the onset of symptoms.[5] Similarly, the recommended time frame for intra-arterial (IA) thrombolysis and mechanical thrombectomy are 6 hours and 8 hours, respectively.[6] Due to the challenges of meeting these time recommendations, most stroke centers report that less than 5% of patients are eligible for thrombolysis, with higher rates (13.2%) reported by more experienced centers.[7-8] This narrow

Address correspondence to: Ramesh Sahathevan, Department of Medicine, UKM Medical Center, jalan yaacob Latiff, Bandar Tun Razak, 56000 Kuala Lumpur, MALAYSIA. Tel: 00-60-3-91456106, Email; ramesh@ppukm.edu.my

time window means that IS patients have to get to a hospital quickly where assessment must be immediately in order to prevent unwarranted delays in therapy. Imaging studies play a crucial role in the early assessment of stroke. The current guidelines and practices for thrombolysis utilize non contrast CT of the brain to exclude hemorrhage and large infarct.[6] However, recent evidence indicates that CT perfusion (CTP) of the brain can provide added clinical value in the assessment of stroke and identifying penumbra and core infarct.[9-11] In addition, the CT angiography (CTA) performed as part of the CTP protocol may delineate the site of vessel stenosis and provide the clinician with the option of mechanical thrombectomy as part of the treatment.[10]

Universiti Kebangsaan Malaysia Medical Centre (UKMMC) is a tertiary referral hospital situated in the southern part of the Malaysian capital city of Kuala Lumpur. We began a stroke thrombolysis service for IS in late 2009. This involved a restructuring of the existing hospital stroke management pathway and incorporated CTP as a part of our routine stroke protocol. The rationale was to include an imaging modality that would provide information about vessel occlusion and differentiation between infarct core and penumbra in large vessel strokes. No patient was excluded from receiving thrombolysis on the basis of a normal CTP since these patients may have had either lacunar infarcts or large territory infarcts that were outside the imaging area covered by the CTP. Patients with normal CTP were thrombolysed if they fulfilled the standard inclusion criteria for acute stroke therapy.

The aim of this audit was to assess the existing critical pathway for patients presenting with IS intended for thrombolytic therapy. Based on the data collected, we analyzed the time-dependent components of the pathway among patients who were potential candidates for thrombolysis. We sought to identify possible delays between initial evaluation at the Emergency Department (ED) and subsequent image acquisition and analysis. In addition, we sought to identify interventions aimed at correcting these delays.

METHODS

This was a retrospective review of all IS patients admitted to the UKMMC Emergency Department who had a CTP of the brain from January 2010 to December 2011. All patients who underwent a CTP were considered potential candidates for thrombolysis. In each patient, we identified the 1) time of symptom onset; 2) time of initial evaluation at the ED triage; 3) time of CTP and 4) time of thrombolysis (intravenous (IV) as well as mechanical), if it was administered. The patients' clinical histories were recalled from medical notes if data was missing from the registry. The time of CTP would be based on the time recorded on the calibration image. Time of reporting the scan was taken as the time of scan itself. We report the data in this manner because staff radiologists at UKMMC are either present during the scan or are able to remotely view the scans and provide immediate feedback.

From the data, we calculated the time from onset of symptom to arrival at the hospital (symptom-to-door), time from symptom onset to CTP (symptom-to-scan), time from symptom onset to thrombolysis (symptom-to-needle), arrival at hospital to CTP (door-to-scan), and time from arrival at hospital to receiving treatment (door-to-needle). Strictly speaking, the term 'needle' is not accurate as patients who received mechanical thrombolysis were also included in this analysis. We nevertheless refer to this set of patients as "door-to-needle" following the convention used in the literature.[12]

Results were analyzed using IBM SPSS software, version 20. Data was presented as descriptive statistics including the median and 50% confidence interval. For group comparisons, the Mann-Whitney test was used. A p-value of <0.05 was considered significant.

RESULTS

A total of 272 patients were admitted with acute ischemic stroke between January 2010 and December 2011. Of these patients, 44 (16.2%) arrived within 4.5 hours of the onset of symptoms and 37 (13.6%) arrived in less than 3 hours. Patients arriving within 4.5 hours had a CTP done with the intention to treat. Following the CTP findings, 8 patients (2.9%) were thrombolysed, of whom 5 received IV thrombolysis and 3 underwent mechanical thrombolysis (Table 1). The other patients were not given IV thrombolysis for a variety of reasons. Approximately a third each of patients were excluded due to resolving symptoms, stroke severity scores below the thrombolysis threshold and uncontrolled blood pressure or blood sugar levels respectively. No patient was excluded on basis of a normal CTP.

The median age of the CTP cohort was 61 (50.0 - 68.5) years. Thirty-one of these patients (70.5%) were male.

Table 1: Timeline of patients who went through the stroke pathway

All patients who had CTP, N=44	
Time from symptom onset to hospital arrival (symptom-to-door)	90.0 (62.5 – 146.3) minutes
Time from symptom onset to CTP (symptom-to-scan)	211.0 (165.5 – 273.5) minutes
Time from hospital arrival to CTP (door-to-scan)	85.0 (48.0 – 144.8) minutes
All patients who received thrombolysis, N=8	
Time from symptom onset to thrombolysis (symptom-to-needle)	290.5 (261.3 – 405.0) minutes
Time from hospital arrival to thrombolysis (door to needle)	225.0 (172.5 – 316.8) minutes
• IV alteplase (n = 5)	180.0 (140.0 – 225.0) minutes
• Mechanical thrombolysis (n = 3)	322.0 (301.0 – 370.0) minute

CTP: CT perfusion

DISCUSSION

Late presentation is a major factor limiting the widespread use of thrombolysis in stroke. Analysis of the data from stroke patients admitted to our hospital from 2010-2011 demonstrated that 16.2% of patients arrive within the recommended therapeutic window of 4.5 hours. Thus, nearly 20% of our IS patients fulfill the time eligibility criteria for thrombolysis. This data is encouraging and is supportive of our initiative to improve stroke care at UKMMC. Our findings parallel recently published reports from neighboring countries of Vietnam and Thailand. In these studies, 8.7% and 18.75% of stroke patients, respectively, arrived at the ED within 3 hours of experiencing symptoms.[13,14]

Imaging plays a key role in acute stroke therapy. The guidelines by the American Heart Association/American Stroke Association (AHA/ASA) propose that patients with IS should be scanned within 25 minutes, and the results of the scan should be available within 45 minutes of the patient's arrival to the hospital.[15] In terms of imaging modality, CTP of the brain has been shown to add clinical value in selecting patients who would potentially benefit from this extended window of treatment.[9,11] CTP enables the determination of the ischemic penumbra or cerebral tissue at risk. CTP of the brain has been adopted as a routine procedure in our center for all potential thrombolysis candidates. CTA performed as part of the CTP protocol can also reveal the presence of a large clot, thus making mechanical thrombectomy an option for treatment. Based on the UKMMC protocol, a normal CTP does not exclude a patient who has clinical stroke from thrombolysis. Such patients probably have lacunar infarcts with perfusion defects too small to be picked up on CTP. MRI can also be a useful tool in the analysis of ischemic penumbra, particularly in patients who arrive at the ED 3 hours after the onset of symptoms.[16] However, at this point, incorporating MRI as a standard protocol in our stroke pathway is not feasible due to limited availability of trained staff.

The door-to-scan time reported in this study was 85 (48 - 144.8) minutes, which falls short of the recommended time of 25 minutes. It can be argued that performing a CTP instead of a non contrast CT delayed the door-to-scan time. We do not have data that allow us to compare the door-to-scan times between CTP and non contrast CT. Importantly, the recommended time of 25 minutes is based on obtaining a non contrast CT. Despite the delay associated with performing a CTP, 37 (72.7%) were scanned within the window of treatment which is a promising figure. We anticipate that our research findings will enable us to further optimize our treatment of stroke patients, thus resulting in reduced delays in patient treatment. Our study shows that CTP provides a benefit to management decisions and subsequent patient outcome. The delays that may have contributed to the lag-time in performing a CTP do not warrant its removal from the routine stroke treatment protocol.

Interestingly, there was a trend towards shorter door-to-scan times when patients arrived 3 hours after experiencing symptoms. Patients who arrived after 3 hours had a median door-to-scan time of 68.0 minutes (48.0 – 150.0), compared to 92.0 minutes (47.5 – 144.5) seen in those who arrived before 3 hours. Although there were no statistically significant differences between the two groups (p=0.8), this trend suggests that the medical staff at our center tend to respond more urgently when patients are closer to the end of the treatment window. This may be due to the involvement of more senior staff in such cases. In addition, it is likely that staff members are aware of the critical

position that these patients are in and thus assign them the highest priority.

Studies in our region have demonstrated that delays in acute stroke care may be attributed to lack of communication and team-work. These results have been attributed to disorganized work flow and organizational processes, amongst others.[14,17-18] Based on this audit, we have identified some of the factors that have contributed to the delays in our treatment process.

One observation based on our analysis is that there was inadequate communication and teamwork at the prehospital stage. Unlike in many major cities in developed countries, the majority of patients at UKMMC come to the ED themselves. Only a small fraction uses the ambulance services. To compound matters, the prehospital service in Klang Valley (where the hospital is located) is provided by several different agencies, which has led to poor pre-arrival communication between the agencies and the receiving ED. In order to improve the situation, we have instructed our pre-hospital care personnel to alert the ED while *en route* to the hospital. This will activate the stroke team and put them on alert while waiting for the patient to arrive. Through joint education sessions, the stroke team has emphasized and educated the ED medical staff on the importance in recognizing IS signs and taking prompt action to ensure that these patients are attended to immediately.

In addition, we found that a small subset of medical staff working in the ED, radiology, and medical departments were not fully aware of the urgency of acute IS management including early thrombolysis. Several factors could have contributed to this, including the high turn-over rate of medical staff in these departments and the possibility that the existence of the program was not effectively communicated to all levels of staff. These factors at times hampered the effective communication between units when it came to activating the response to stroke patients, in requesting CTP and making prompt referrals to the neurologist or medical registrar. To overcome these problems, we now conduct joint education sessions for members of these three relevant departments to increase awareness regarding the service and to facilitate open discussions regarding procedural inefficiencies. Attendees are encouraged to give their opinions on how the service could be improved.

Miscommunication between the medical staff in the ED, neurology department and radiology department was also a major concern. In the initial stages of setting up thrombolysis for the treatment of stroke, the indications for requesting the CTP were not clearly defined. This resulted in delays in obtaining patient scans and, subsequently, treatment. In response, we have vastly simplified the patient admission process. All patients with suspected stroke and onset within 8 hours will have CTP imaging performed. The decision to extend the time window to 8 hours was made to accommodate patients who may benefit from mechanical thrombectomy, especially in the case of posterior circulation strokes or if IV thrombolysis was contraindicated or had failed.[6] A second research study would be useful to monitor whether these changes resulted in a clinically improved outcome.

Of our 8 thrombolysed patients, only 4 (50%) received their treatment within the recommended 4.5 hour therapeutic window. No patient was thrombolysed within the 60 minute door-to-needle time recommended by the AHA/ASA (Table 2). The outcome of our thrombolysed patients was very good; 6/8 (75%) had an MRS of 1-2 at a second follow-up 5 months after treatment. Of note, 4 (50%) of our patients were treated beyond 4.5 hours of symptom onset. The decision to proceed despite being outside the window of

Table 2: The percentage of patients who were thrombolysed within the recommended time of 1 hour and whether or not they were treated within the recommended therapeutic window of 4.5 hours

Time	n (%), total = 8	Reason for thrombolysis
Less than 1 hour	0 (0%)	
1 - 4.5 hours	4 (50%) with IV alteplase	Significant penumbra seen on CTP
More than 4.5 hours	4 (50%)	
	With IV alteplase = 1	Significant penumbra seen on CTP
	With mechanical thrombectomy = 3	MCA* stenosis seen on CTA

CTP: CT perfusion

Table 3: Frequency of symptom-to-needle time for our thrombolysis patients and the outcome of patients receiving thrombolysis according to Modified Rankin Scale

Symptom to needle time	Method	Modified Rankin Scale (MRS)	
		First follow up 36.5 (0 - 76.8) days	Second follow up 140.0 (27.0 – 321.8) days
1 - 4.5 hours	IV alteplase	1	1
	IV alteplase	2	2
	IV alteplase	2	2
	IV alteplase	Lost to follow up	
More than 4.5 hours	Mechanical thrombectomy	1	1
	Mechanical thrombectomy	Passed away 3 days post procedure	
	Mechanical thrombectomy	Lost to follow up	1
	IV alteplase	1	1

treatment was due to the promising CTP results, which showed significant penumbra in one patient and middle cerebral artery (MCA) stenosis in the other 3 patients. The patient with a significant penumbra was given IV thrombolysis and the other 3 patients underwent mechanical thrombectomy. The decision to opt for mechanical intervention in these 3 patients was made following discussions between the radiologist and neurologist. In all 3 patients, the clot burden as seen on CTP was considered significant and unlikely to respond to IV thrombolysis. Since these patients were already beyond the 4.5-hour treatment window there was also a risk of haemorrhagic transformation due to the infarct size. Two of these patients had a good outcome with an MRS of 1 during the second follow-up examination. One patient who underwent mechanical thrombectomy passed away 3 days post procedure. Despite attempts at right M1 segment MCA thrombectomy, we were unsuccessful in adequately restoring perfusion to the ischemic region and this patient suffered a complete right MCA territory infarct (Table 3).

In summary, we believe that this study highlights the advantage of performing a CTP in cases of IS. We await the outcome of the CRISP study by the Stanford Hospital group for additional data. Although the therapeutic window for IV thrombolysis in IS has been extended to 4.5 hours, additional time is needed to mobilize the stroke team, perform and interpret the CTP and prepare the drugs. Patients actually need to arrive well within the recommended timeline of 3 hours to benefit from thrombolysis.[19-20] Educating the public on stroke symptoms and availability of treatment is important to maximize the benefits of acute stroke therapy. Proper organization and management of an acute stroke service is essential to providing a comprehensive, integrated stroke treatment system that is consistent with the recommendations of leading international health advisory panels. The results of this audit of our initial acute stroke thrombolysis experience indicate that there is room for improvement. Based on our analysis we have been able to identify and successfully rectify most of these inefficiencies. Future audits will likely reflect the benefit of the changes that we have implemented.

DISCLOSURE

Conflict of interest: None

REFERENCES

1. Feigin VL, Lawes CMM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol* 2009; 8(4):355-69.
2. The World Health Report. Geneva, Switzerland: World Health Organisation2004.
3. Hacke W, Kaste M, Fieschi C, *et al*. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA* 1995; 274(13):1017-25.
4. Lees KR, Bluhmki E, von Kummer R, *et al*. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet* 2010; 375(9727):1695-703.

5. Hacke W, Kaste M, Bluhmki E, *et al*. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Eng J Med* 2008; 359(13):1317-29.
6. Clinical practice guidelines: Management of ischaemic stroke. Malaysian Society of Neuroscience, Ministry of Health Malaysia, 2012.
7. The Paul Coverdell Prototype Registries Writing Group. Acute stroke care in the US: Results from 4 Pilot Prototypes of the Paul Coverdell National Acute Stroke Registry. *Stroke* 2005; 36(6):1232-40.
8. Sattin JAMD, Olson SEMD, Liu LP, Raman RP, Lyden PDMD. An expedited code stroke protocol is feasible and safe. *Stroke* 2006; 37(12):2935-9.
9. Ezzeddine MA, Lev MH, McDonald CT, *et al*. CT angiography with whole brain perfused blood volume imaging. *Stroke* 2002; 33(4):959-66.
10. Latchaw RE, Alberts MJ, Lev MH, *et al*. Recommendations for imaging of acute ischemic stroke. *Stroke* 2009; 40(11):3646-78.
11. Schaefer PW, Roccatagliata L, Ledezma C, *et al*. First-pass quantitative CT perfusion identifies thresholds for salvageable penumbra in acute stroke patients treated with intra-arterial therapy. *Am J Neuroradiol* 2006; 27(1):20-5.
12. Casanova P, Garg N, Victor T, *et al*. Predictors of poor outcomes among ischemic stroke patients who received revascularization therapy in an inner city minority population. *Chest* 2012;142(4_MeetingAbstracts):373A-A.
13. Nguyen TH, Truong ALT, Ngo MB, *et al*. Patients with thrombolysed stroke in Vietnam have an excellent outcome: results from the Vietnam Thrombolysis Registry. *Eur J Neurol* 2010; 17(9):1188-92.
14. Disya DR, Jesada JK, Yuwares YS, Jiraporn JL, Charles HCHT. Stroke fast track reduces time delay to neuroimaging and increases use of thrombolysis in an academic medical center in Thailand. *J Neuroimaging* 2012; 22(1):53-7.
15. Target: Stroke time lost is brain lost. Target: Stroke Campaign Manual 2010:1-8.
16. Nagakane Y, Christensen S, Brekenfeld C, *et al*. EPITHET. Stroke 2011; 42(1):59-64.
17. Olson DM, Constable M, Britz GW, Lin CB, Zimmer LO, Schwamm LH. A qualitative assessment of practices associated with shorted door to needle time for thrombolytic therapy in acute ischaemic stroke. *J Neurosc Nursing* 2011; 43(6):329-35.
18. Sharma VK, Tsivgoulis G, Tan JH, *et al*. Feasibility and safety of intravenous thrombolysis in multiethnic Asian stroke patients in Singapore. *J Stroke and cerebrovascular Dis* 2010; 19(6):424-30.
19. De Silva D, Ong S, Elumbra D, Wong M, Chen C, Chang H. Timing of Hospital Presentation after Acute Cerebral Infarction and Patients' Acceptance of Intravenous Thrombolysis. *Ann Acad Med Singapore* 2007; 36(4):244-6.
20. Stemer A, Lyden PD. Evolution of the thrombolytic treatment window for acute ischaemic stroke. *Curr Neurol Neurosci Rep* 2010; 10:29-33.