

Computed tomography perfusion of ischaemic stroke patients in a rural Malaysian tertiary referral centre

Man K, Kareem A M M, Ahmad Alias N A, Shuaib I L, Tharakan J, Abdullah J M, Prasad A, Hussin A M, Naing N N

ABSTRACT

Introduction: Computed tomography (CT) perfusion is a new method to diagnose ischaemic stroke especially in developing countries. It identifies the area and is useful to predict the size of final infarction. The aim of this study was to assess cerebral ischaemia with CT perfusion (CTP) among patients with acute ischaemic stroke in Hospital Universiti Sains Malaysia, a tertiary referral centre in a rural setting.

Methods: 42 consecutive unenhanced CT and CTP examinations of the brain in adult patients were evaluated prospectively. Unenhanced CT images were divided into normal, suspicious or frank infarction. CTP images was classified as normal or ischaemic. Subgroup analysis was carried out with a limit of six hours from time of ictus.

Results: Out of 42 patients, 20 had frank infarction on unenhanced CT, 15 had suspicious CT studies, while seven were normal. There was no significant association of demographical, clinical and radiological parameters to CTP in the whole group among acute stroke patients without frank infarction. Among the subgroup of patients without frank infarction, there was no significant association between unenhanced CT and CTP in patients who were studied less than six hours after stroke (p-value is 0.063) as well as those after six hours (p-value is 0.317). The prevalence of a normal unenhanced CT and positive CTP for ischaemia was 22.7 percent (95 percent confidence interval 7.8, 45.4).

Conclusion: CTP may be a useful imaging tool for determining cerebral infarction in a rural-based community population, especially in cases where the unenhanced CT is normal. Thrombolysis is a therapeutic option, even when the history of onset of stroke is unclear.

Keywords: brain, cerebrovascular accident, computed tomography, ischaemic stroke, stroke

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INTRODUCTION

Ischaemic stroke in the Northeast coast of West Malaysia may be due to large artery atherosclerosis, cardioembolism or small vessel occlusion⁽¹⁾. Large artery occlusion typically gives rise to an infarct affecting cortical parts of the cerebrum, whereas occlusion of the small penetrating branches of cerebral arteries is thought to be the source of small deep lacunar infarcts. These small infarcts could be the consequence of hypertensive cerebral small vessel vasculopathy, but cardiac embolism, intracranial large artery disease, and carotid stenosis have also been proposed as possible aetiological factors. It has been postulated that single and multiple lacunar infarcts might form distinct entities with different pathogenesis and risk factors.

Since the establishment of the stroke services of the Department of Neurosciences, Hospital Universiti Sains Malaysia (HUSM), our pick-up rate of stroke patients qualifying for intravenous recombinant tissue plasminogen activator (rTPA) has been less than 15%. A larger group presenting after the three-hour time window but not exceeding six hours, has been documented in a prior study⁽¹⁾. The objective of this study thus was to analyse patients with a history of ischaemic stroke arriving to HUSM Stroke Services Unit in relation to their demographical, clinical and radiological parameters using the six-hour time limit.

METHODS

This prospective study consisted of adult patients with clinical signs and symptoms of ischaemic stroke that were initially evaluated with unenhanced computed tomography (CT) of the brain as well as by a CT perfusion (CTP) examination. All patients had clinical review and a follow-up magnetic

Department of
Radiology
School of Medical
Sciences
Universiti Sains
Malaysia
16150 Kubang Kerian
Kelantan
Malaysia

Man K, MD, MMed
Lecturer

Kareem A M M,
MBBS, MMed
Associate Professor

Ahmad Alias N A,
MD, MMed,
Associate Professor
and Head

Shuaib I L, MD, MMed
Associate Professor

Department of
Neurosciences
School of Medical
Sciences
Universiti Sains
Malaysia

Tharakan J, MD, DM
Associate Professor

Abdullah J M, MD,
PhD, FACS
Professor and Head

Department of
Medicine
School of Medical
Sciences
Universiti Sains
Malaysia

Prasad A, MBBS, DM
Neurologist and Lecturer

Hussin A M, MD, MMed
Neurologist and Lecturer

Unit of Biostatistics
and Research
Methodology
School of Medical
Sciences
Universiti Sains
Malaysia

Naing N N, MD, PhD
Associate Professor
and Head

Correspondence to:
Prof Jafri Malin Abdullah
Tel: (60) 9 766 4240
Fax: (60) 9 764 8613
Email: deptneuroscience
sppspusm@yahoo.com

resonance (MR) imaging of the brain to rule out other non-stroke abnormality six weeks after the CTP, followed by three-monthly follow-up for a duration of 12 months. Ethical approval was given by the Human Research and Ethical Committee of the Universiti Sains Malaysia.

History of duration of ictus was taken from both patient and relatives to ascertain that the duration of ictus to CT was noted correctly. Inclusion criteria were patients with signs and symptoms of acute stroke, up to three days of symptoms onset and no history of allergy to contrast agent. Exclusion criteria were patients less than 18 years of age, those with haemorrhagic stroke or space-occupying lesion on CT, and patients who were haemodynamically unstable. Neurological status was determined using the National Institute of Health Stroke Scale (NIHSS)⁽²⁾.

CT was acquired using a multidetector CT scanner (Light speed; General Electric Medical Systems, Milwaukee, WI, USA). Unenhanced CT with 3.75 mm thickness basal sections and 7.5 mm thickness supratentorial axial sections were obtained. The images were reviewed for evidence of old or recent infarction. CTP was performed for all 42 patients. CTP images were acquired after injecting 50 ml of iodinated contrast agent (300 mg/ml) into a peripheral vein through a 16-gauge catheter, with a power injector at flow rate of 4 ml/s and scan delay of four seconds. Total exposure time was 45 seconds. Four slices in one second with the thickness of 5 mm and image matrix of 512 x 512 were obtained immediately after the unenhanced CT study in a standardised section covering the basal ganglia, thalamus, and parts of the anterior, middle, and posterior cerebral artery territories (ACA, MCA, and PCA, respectively). Scan duration was 45 seconds with parameters of 80 kV and 240 mA⁽³⁾. A total of 180 to 200 images were obtained per examination.

Two blinded senior radiologists evaluated the unenhanced CT and CTP images separately, using the workstation monitors available in the CT scan room. They were unaware of the time duration of the ischaemic stroke. The radiologists classified the unenhanced CT images into normal, suspicious or frank infarction. Suspicious scans were defined as loss of gray-white differentiation or subtle evidence of cerebral oedema where there is a high possibility of infarction. Frank infarction was defined as focal parenchymal hypodensity, notably of the insular ribbon or deep nuclei (equivalent to a decrease of 4-10 HU) with hyperdense middle cerebral artery sign (60 HU)^(4,5). CTP

analysis and reconstruction followed similar standard published protocol⁽⁶⁾. Qualitative interpretations of the CTP images were based on published criteria⁽⁷⁾. Cerebral blood flow, cerebral blood volume and mean transit time were evaluated using software on the CT scanner in all cases. Mismatch between the cerebral blood flow and cerebral blood volume indicates the area of penumbra or ischaemia. The normal cerebral perfusion was 20 ml/100 gm/min whereas umbra has cerebral perfusion less than 16 ml/100 gm/min and penumbra between 15-20 ml/100 gm/min.

Clinical and radiological data were analysed on STATA version 7.0 for windows. The whole group analysis to determine association between demographics and CTP was done by using chi-square and Fisher's exact tests. The association between findings of unenhanced CT and CTP was analysed using McNemar's test. The level of significance was set at 0.05.

RESULTS

A total of 42 patients were included in this study within a one-year period. Of these, 54.8% of the patients were males (n=23) and 45.2% were females (n=19). The mean age was 62.5 (\pm 11.2) years old. The youngest patient was 29 years old and the oldest was 81 years old. Malays formed the majority of patients with 37 (88.1%), followed by four Chinese (4.0%) and one Indian (2.0%).

The most frequent chief complaint was weakness in one side of the body (90.5%), followed by weakness and fits (21.4%). Other chief complaints included headache, vomiting, loss of vision and slurring of speech, which constituted 7.1% of symptoms. 15 patients (35.7%) had diabetes mellitus and hypertension, ten (23.8%) had hypertension only, and four (9.5%) had diabetes mellitus only. 13 (31%) of patients were healthy prior to the current presentation. 20 patients (47.6%) had a NIHSS of between 16 and 25, 15 patients (35.7%) had a NIHSS of between 5 and 15, and 7 (16.7%) had a NIHSS of less than 5.

The mean time of presentation was 10.5 (\pm 7.4) hours. The earliest time of presentation was two hours and the latest presentation was 24 hours. When the time of presentation was categorised, five patients (11.9%) were between 2 and 3.9 hours, 11 patients (26.2%) were between 4 and 5.9 hours, and 26 patients (73.8%) were between 6 and 24 hours. Most of the patients (83.3%) were given aspirin as a mode of treatment. Five (11.9%) did not receive aspirin due to coagulation abnormalities, four (9.5%) were treated with

Table I. Associations between unenhanced CT and CTP of the brain among ischaemic stroke patients with normal or suspicious findings (n=22).

Time	CTP		p-value ^a
	Normal	Ischaemic	
Onset of symptoms (≤6 hours)			0.063
Unenhanced CT			
Normal	2	5	
Suspicious	0	9	
Onset of symptoms (>6 hours)			0.317
Unenhanced CT			
Normal	0	0	
Suspicious	1	5	

^a McNemar's test was applied
Level of significance was set at 0.05

intravenous nimodipine, and only two (4.8%) were given recombinant tissue plasminogen activator.

Of a total of 42 unenhanced CT studies that were reviewed, seven (16.7%) were normal, 15 (35.7%) were suspicious, and 20 (47.6%) had frank cerebral infarction. The middle cerebral artery territory was infarcted or suspicious in 25 patients (71.4%), the anterior cerebral artery was involved in six patients (17.1%), and the posterior cerebral artery in four patients (9.5%). Out of the 22 patients with normal or suspicious unenhanced CT, CTP detected an area of ischaemia in 19 patients (86.4%). CTP was normal in three patients (13.6%) which was attributed to transient ischaemic attack that recovered spontaneously during the CTP study. Follow-up MR imaging revealed no evidence of infarction six weeks after stroke in all patients.

There was no significant association between demographics and CTP ($p=0.547$, Fisher's exact test), as well as time to imaging ($p=0.063$). In patients with frank infarction on unenhanced CT ($n=20$), all were studied more than six hours after stroke and all of them had abnormal CTP. Subgroup analysis of 16 patients who were studied within six hours from onset of stroke showed normal unenhanced CT in seven (43.8%) and suspicious findings in nine (56.2%) patients. On CTP study, two (8%) were normal, and 14 (92%) cases showed ischaemia. Two male patients presented within 2.5 hours onset of stroke, both of whom were less than 40 years of age. Unenhanced CT showed no abnormality but CTP revealed ischaemia and they were treated with intravenous rTPA. Both patients regained full motor power with no significant residual weakness. MR imaging of the brain performed six weeks after the stroke showed no abnormality. All the patients with ischaemic CTP were male

patients and stayed within an one hour radius of this hospital.

There was no significant association between unenhanced CT and CTP among patients when the onset of symptoms was less than six hours ($p=0.063$). Five patients had normal unenhanced CT and positive CTP, giving a prevalence rate of 22.7% (95% CI 7.8,45.4). There was no association between unenhanced CT and CTP among the six patients who arrived more than six hours after the onset of symptoms ($p=0.317$) (Table I).

DISCUSSION

HUSM has capabilities to manage ischaemic stroke patients with intravenous (IV) and intra-arterial (IA) thrombolysis. So far, to our knowledge, there have not been any published studies from any developing country, especially in a rural setting like our hospital. We undertook this study over a period of one year with the intention to study the influence of time to CTP and intervention after a stroke clinical study done earlier⁽¹⁾. Three other similar Western studies with 12 to 31 patients have used CTP to evaluate stroke with various end-points⁽⁸⁻¹⁰⁾.

The majority of patients in this study were Malays, followed by those of Chinese and Indian race. This was in keeping with the distribution of races in the state of Kelantan where Malays formed the largest ethnic group, followed by Chinese and Indians. More than 90% of patients was 50 years old and above, and the majority were males. This gender distribution was quite similar to a previous study done five years ago in the same hospital, where 58% of patients were males and 42% were female⁽¹⁾. Hypertension was the most frequent risk factor associated with stroke. About 59.5% of patients had this disease, which was higher than a Western study which reported that 35% of Native Americans had hypertension as a risk factor of stroke⁽¹¹⁾. About 45% had diabetes mellitus as a risk factor, which was higher than our previous study (22%) and another Western study (6.2%)⁽¹¹⁾.

The mean time of presentation of 10.5 hours after stroke in this study was shorter compared to the earlier study (17.2 hours)⁽¹⁾ but longer compared to a Philippine study (7.5 hours)⁽¹²⁾. Factors that contributed to the increased number of patients that presented earlier include increased level of education, medical knowledge, health consciousness, and better access to medical facilities. The number of patients arriving within six hours of ictus is comparable to a previous study by Fogelholm et al who studied 349 patients, 43% of whom presented

within six hours⁽¹³⁾. A further larger study with higher numbers would determine the significance of time to treatment in our rural population.

Ischaemic stroke patients with normal unenhanced CT with no evidence to suggest infarction or haemorrhage should proceed to CTP in developing countries with these appropriate facilities. Our study showed that CTP was able to detect 22.7% of cerebral ischaemia with normal unenhanced CT in patients presenting less than six hours after ictus. This shows that CTP was superior to unenhanced CT in detecting acute ischaemia^(14,15), particularly in cases presenting within six hours when unenhanced CT would most likely be normal. Furthermore, in two patients who were treated with an intra-arterial rtPA regime, excellent results were achieved, illustrating the potential for using CTP to direct emergency treatment⁽¹⁶⁾.

Previous stroke trials have shown that thrombolysis as well as neuroprotective drugs can be used in acute stroke, with the most important predictor of clinical success being time to treatment. Our study has several implications for provision of neuroimaging services in acute stroke. Emergency neuroimaging service using CTP has the potential to be more cost-effective and efficient than using diagnostic MR imaging in our hospital, especially when the patient arrives at odd hours of the day or night when MR imaging services are non-active. Limitations of this study were delayed consent by family members and stroke patients who did not want to be involved in this study, contributing to the small population for this study.

In conclusion, our study suggests that in a developing country like Malaysia, especially a less developed state like Kelantan, improved imaging techniques such as CTP can identify ischaemia and differentiate it from irreversible infarcted tissue, thus appropriately selecting patients for emergency thrombolytic therapy.

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