Perspective

Being late may not be too late! Widening the horizons for stroke thrombolysis with Computed Tomographic Perfusion (CTP) and Magnetic Resonance (MR) brain imaging

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Abstract

Stroke is the leading cause of adult disability worldwide. Most strokes are ischemic in nature and amenable to cure if detected and treated early enough with reperfusion therapy. Delay in presentation and unknown onset time are key limiting factors of reperfusion therapy in current practice. Cerebral perfusion computed tomographic imaging (CTP) and magnetic resonance imaging (MRI) with special sequences aid in identifying acute stroke patients who present late or with unknown onset time, yet reperfusion treatment may have a benefit. Establishing such imaging facilities at tertiary care hospitals in Sri Lanka would strengthen acute stroke care by offering hope for a cure. It is cost-effective in long term by reducing the burden of prolonged disabilities in stroke patients.

Keywords: Ischemic stroke, Computed tomographic perfusion imaging, Wake-up strokes, Thrombolysis, diffusion-weighted imaging

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Stroke is the second commonest cause of death and the leading cause of adult disability worldwide. Every year, 15 million people throughout the world suffer a stroke, and 5 million are left significantly disabled (1). In 2019, there were 6.55 million deaths due to stroke globally (2). The prevalence of stroke in Sri Lanka is 10.4 per 1000 adults aged ≥18 years with a 2:1 male: female ratio (3). Ischemic strokes are responsible for 85% of all strokes and occur commonly due to occlusion of a cerebral artery by a thrombus which may arise in-situ or embolize from elsewhere.

The mainstay of treatment of acute ischemic stroke is to open up the blocked artery (reperfusion therapy) by either intravenous thrombolytic therapy or by catheter aided mechanical clot retrieval. The current guidelines recommend thrombolytic therapy within 4.5 hours and clot retrieval treatment within 6 hours of stroke symptom onset, respectively, based on clinical and non-contrast CT brain images-based criteria (4). A substantial proportion of patients who present more than 4·5 hours after stroke onset or who have unknown onset (e.g., wake-up stroke) are excluded from these criteria for thrombolytic treatment. Greater the delay, the poorer the prognosis with treatment as more salvageable neurons will undergo necrosis. Recombinant tissue-type plasminogen activator (r-tPA) and tenecteplase (TNKase) are the drugs used commonly for stroke thrombolysis and are widely available. Clot retrieval therapy needs special endovascular devices with trained personnel and is more expensive than thrombolytic

therapy, and availability is limited even in developed countries.

To decide on reperfusion treatment in acute ischemic stroke, the time of symptom onset is very crucial. If the time of onset of symptoms is not known, the time last-seen well (TLSW) is taken as the denominator. But if the time of symptom onset or TLSW is not known, it may not be possible to proceed with thrombolytic therapy or clot retrieval. Especially this happens when strokes happen while asleep and patients awaken with stroke symptoms. About 20-25% of acute ischemic strokes are wake-up strokes (WUS) and remains a therapeutic dilemma (5). Conventionally such patients are excluded from thrombolytic therapy due to the fear of the greater risk of hemorrhagic transformation if the 4.5-hour time window has elapsed.

However, within this subgroup of patients, there may be a reasonable number who have developed a stroke within 4.5 hours of awakening or have salvageable brain tissue (penumbra) despite late presentation beyond 4.5 hours. Reperfusion therapy could be offered to such patients if selected precisely. Evidence is emerging that thrombolysis is beneficial in acute strokes from 4.5 to 9 hours in patients with a larger penumbra and a small ischemic core (5-7). Such patients should be carefully selected for treatment and would have a favourable outcome with thrombolysis. Patients with well-demarcated infarction >1/3 of MCA territory on non-contrast CT brain are excluded from thrombolysis.

Two techniques are widely used to evaluate such patients with an unknown onset time of stroke symptoms. CT perfusion brain imaging and MRI with Diffusion-weighted MRI (DWI) and fluid-attenuated inversion recovery (FLAIR) mismatch or DWI and Perfusion Weighted Imaging (PWI) mismatch enable differentiation of the penumbra from the irrevocably damaged infarcted brain (the infarct core).

Unenhanced CT brain remains the first line of imaging in the assessment of acute stroke patients. CTP is an important adjunct to unenhanced CT brain imaging at hospitals with acute stroke services. This is more accessible and less time consuming compared to MRI in the setting of the acute ischemic stroke, where time is a crucial factor of prognosis. CTP aids identification of the ischemic core and the penumbra, and a patient with a small core and a larger penumbra is likely to benefit from reperfusion therapy.

Three parameters are typically utilized in CTP to estimate the ischemic penumbra. These include Cerebral blood flow (CBF- the volume of blood flowing in a unit of brain mass during a unit of time), Cerebral blood volume (CBV- cerebral blood volume, which is equivalent to the fraction of a voxel that contains blood vessels), Time to peak (TTP)or mean transit time (MTT-average time required for a contrast bolus to traverse the voxel) (8).

Based on the above parameters, infarct core is defined as an area with prolonged MTT or time to maximum (Tmax), markedly decreased CBF and markedly reduced CBV. Ischemic penumbra often surrounds the core and has prolonged MTT/Tmax and slightly reduced blood flow but importantly normal or increased CBV due to autoregulatory vasodilatation and collateral blood flow (8-9). Modern CT scanners are equipped with software that can automatically estimate the size of the core and penumbra.

Patients with a larger penumbra and a negligible ischemic core may benefit from thrombolysis up to 9 hours from the onset of stroke symptoms (4,6).

To perform CT perfusion brain imaging, a CT scanner of more than 128-slice is required together with the appropriate software, which may incur an additional cost. Radiographers need training on CTP protocol and handling the software. Iodinated contrast is given (around 40 ml) for CTP and needs to be cautious in patients with advanced renal diseases. Performing CTP takes a few minutes (5-10) and will be more applicable than MRI, which takes a longer time to acquire images in an acute stroke setting.

CTP increases the sensitivity and specificity of the diagnosis of acute ischemic strokes, aids in excluding stroke mimics, and informs about prognosis and treatment decisions. These important benefits of PCT must be weighed against several disadvantages of the technique. PCT necessarily results in increased radiation exposure to the patient, increased contrast administration that may result in renal injury, increased imaging time that may slightly delay treatment, and increased cost.

CTP is more useful in strokes that are due to large artery occlusion. Small infarcts (lacunar type) and infratentorial infarctions are poorly visualized on CTP imaging due to their low resolution (10).

Identification of ischemic penumbra and be done with the help of either DWI/FLAIR mismatch at 3 Tesla (3T) or PWI/DWI mismatch. DWI/FLAIR mismatch helps to identify strokes within a 4.5-hour thrombolysis window, and PDI/DWI mismatch may help from a 4.5 – 9-hour window (7,11). Limitations in using MRI based protocols for stroke thrombolysis are the prolonged time taken to complete the imaging and the cost.

CTP is more feasible and cost-effective due to the wider availability of CT scanners and the shorter time duration taken to complete the imaging protocol. It is important to acquire the necessary software if not available with

existing high-end CT scanners. The utilization of MRI in acute stroke settings is less feasible due to its limited availability, higher demand, greater cost and the longer time taken to acquire images.

It is important to establish at least one centre in every province of Sri Lanka as a stroke reference centre, with aforementioned advanced imaging capabilities together with other facilities such as clot retrieval treatment to provide better stroke care for a wider range of acute stroke patients including WUS and late presentations. This would be productive in the long term by reducing the costs of managing disabled stroke patients lifelong. More importantly, the general public should be educated on stroke symptoms and seek treatment within a 4.5-hour treatment window to have a better outcome from thrombolytic treatment.

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