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Review

# Management of hyper-acute Ischaemic Stroke : Current status, challenges and opportunities in Northern Sri Lanka

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**Summary:**

Stroke is one of the leading causes of chronic disability and death worldwide[1]. However, over the last two decades, this trend has been changed by twin advancement in management of acute ischeamic stroke (AIS); especially in thrombolytic therapy and multidisciplinary dedicated stroke unit[2]. AIS is distinguished by the sudden loss of neurological functions due to acute interruption of blood circulation to an area of the brain. It is commonly caused by thrombotic or embolic occlusion and less often by rupture of a cerebral artery. Stroke is the fourth commonest killer and major cause of disability among adults in Sri Lanka[3]. Annual expenditure on the management of acute stroke and neuro rehabilitation has been mounting due to increasing cardiovascular risk factors such as hypertension, smoking, diabetes mellitus, dyslipidemia, excessive alcohol intake and sedentary lifestyle concomitantly with ageing population[3]. There has been an increasing trend of all the above-mentioned non communicable diseases in recent past in North, mainly because of sudden lifestyle transformation by adopting habits introduced by visiting diaspora. Thrombolytic management at dedicated stroke unit plays a crucial part in minimizing its serious outcomes. This paper primarily reviews the indications and contraindications in choosing patients for the administration of intravenous Recombinant tissue plasminogen activator (rtPA), facilities currently available but underutilized, and the challenges faced in AIS management in Northern part of Sri Lanka.

## Introduction:

When compared to Western Countries, South Asian countries account for larger stroke burden and of the two stroke mechanisms, ischeamic stroke is more common (80%) in Sri Lanka (Fig1)[3]. Even though several studies have stated that the AIS prevalence is higher among older adults, recent studies reveal that the prevalence of AIS has been increasing among young adults as well[4].

According to the stroke registry from May 2015 to April 2017 at Teaching Hospital Jaffna, approximately 700 to 800 AIS patients have been admitted and treated. However, less than 0.1 percent of them were found to be eligible for receiving intravenous thrombolytic therapy. Further, the national survey on self-reported health in Sri Lanka 2014 states that Jaffna district has the second highest prevalence rate of chronic illnesses including stroke[3].

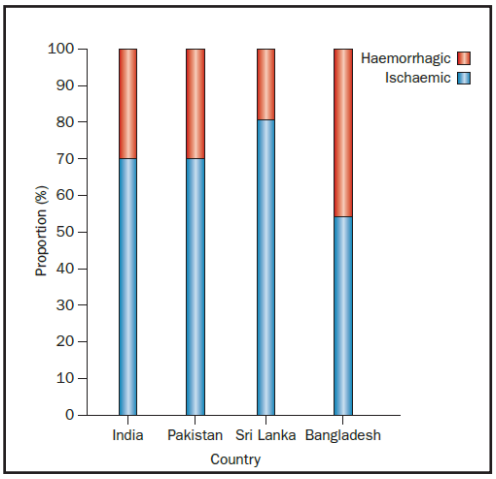


Fig 1: Distribution of ischemic and hemorrhagic stroke[3]

In addition, the prevalence of major risk factors leading to AIS, diabetes and high blood pressure, are reported to be elevated among females above 15years old while the prevalence of stroke is found to be higher among males with a male to female ratio of 3:2[3]. As a result, the health status of the population affects the productivity and efficiency of the labor force due to disability caused by chronic illnesses. Further, in South Asian countries there have been a scarcity of both human and physical resources (Trained Neurologists, Stroke specialists or well-equipped stroke unit) that are essential for Acute Ischemic Stroke Management[5,6]. In Sri Lanka, there are three well- established stroke care units functioning in Southern and North central Provinces, but no single unit has been established so far in North - East Provinces in spite of increasing trend of non-communicable diseases.

## Basis of Pharmacotherapy in AIS:

AIS management plays a crucial role in reducing the risk of severe disability or deaths due to AIS. Prior to the introduction of Recombinant tissue plasminogen activator (rtPA) for AIS management, the patients were administered with anti- platelets and statin[7]. In the current

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era, rtPA has been the most effective treatment option for acute ischeamic stroke management[8,9]. Initially, rtPA was first produced by recombinant DNA techniques in 1982 and approved as the only drug treatment for AIS in 1996 by the US food and Drug Administration (FDA)[10]. The landmark NINDS rtPA trial, carried out in 1995, showed that rtPA had a relative risk reduction of 30% compared with placebo between 0-3 hours from stroke onset[11]. However, there have been a few complications feared in the administration of rtPA in AIS patients. They are intracerebral hemorrhage (ICH), anaphylaxis or angioedema, systemic bleeding and myocardial rupture in patients receiving IV rtPA within days of an acute MI.Thus, the use of rtPA is limited to carefully selected patients[10].

## Neuro- radiological basis of rtPA management

The pharmacological target for AIS treatment is to recover the ischeamic penumbra which is the reversibly injured brain tissue around the ischeamic core[12,18]. The dynamic changes in the penumbra region and infarct expansion occur in response to regional cerebral blood flow, pathophysiological environment and treatment; it imposes an earliest intervention in AIS which is well described as "time is brain"[13]. Imaging technologies such MRI, CT, PET and SPECT can be used to identify the salvageable brain tissue. Among them, CT scan serves as the gold standard imaging technology to exclude the patients with contraindications before choosing patients to undergo IV rtPA treatment[14,18]. At the same time, diffusion-weighted image (DWI) is used to identify the reversibly injured tissue in the early hours after stroke while Perfusion Weighted Image (PWI) is to identify the area of benign oligemia[12,15]. Brain tissues that are at risk are shown by the mismatch of PWI and DWI, are targeted for recanalizational therapy. Occasionally, spontaneous recovery of the penumbra has been observed as it merges with the ischeamic core or becoming normal tissue. The treatment outcome then can be seen using CT or MRI[12,15].

## Indications and Contraindications for rtPA

In general, the indications for IV rtPA are acute neurologic dysfunction that might probably cause long-term disability, onset of AIS symptoms between 3-4.5 hours before rtPA administration and absence of hemorrhage or well-established acute infarct in the non-contrast CT[16]. Currently, three radiological units are available with 24 hours CT facilities in Northern Province. In addition, there is some improvement in the infrastructure related to transportation such as roads or highways as well as toll free ambulance services, in most part of Northern Sri Lanka. These facilities would certainly improve the delay in obtaining acute stroke care, because the accomplishment of acute stroke management is first and foremost time dependent. The necessity for the improvement in acute stroke management is demonstrated because only a minority of patients gains access to treatment, in IV rtPA within the essential window period of 4.5 hours. According to an analysis of the nationwide inpatient sample 1999 to 2004 conducted in the United States on use of thrombolysis in AIS reported that thrombolysis was used in 1.12% (95% confidence interval [CI] 0.95% to 1.32%) of ischeamic stroke hospitalizations[17]. Whereas, a survey done in year 2016 at Teaching Hospital of Jaffna, revealed only 0.13% of AIS received thrombolysis which is comparatively low in comparison with other data. In addition to the window period to carry out the treatment, the selection of the patients for IV rtPA must be done very carefully considering all the following absolute and relative contraindications.

## Absolute contraindications for rtPA

### 1. Acute intracranial hemorrhage

As suggested in AHA guidelines findings of ICH including intraparenchymal hemorrhages, subarachnoid hemorrhage, intraventricular hemorrhage, epidural hematoma, subdural hematoma or hemorrhagic conversion of infarction are considered to be one of the contraindications. Factors such as underlying cause of ICH and given treatment (Eg: Aneurysm-clipping), surgical evacuation of hematoma, volume of residual encephalomalacia, latent period since ICH determines the risk of IV rtPA treatment[19].

### 2. Severe uncontrollable hypertension*

There has been a complex relationship between blood pressure (BP),antihypertensive treatment and clinical outcomes in acute stroke[20]. Uncontrolled hypertension values exceeding a systolic (SBP) of 185mmHg or diastolic of 110mmHg were major exclusion criteria in NINDS rtPA trial[19]. Higher SBP leads to worse outcomes in AIS treatmentand increases the possibilities of ICH. The 2013 AHA guidelines also exclude the patients with the abovementioned blood pressures[11]. Thus, achieving BP control in patients by using antihypertensives prior to IV rtPA administration is recommended to be safe even though it does not improve the outcome of AIS significantly.

### 3. Serious head trauma or stroke in previous three months

If there is a post traumatic ICH due to head injury or systemic bleeding, it would be augmented by the IV rtPA. Patients with AIS which was experienced in previous three months and treated with IV rtPA are considered to have a higher risk of developing ICH, thus, were excluded in the NINDS trial as well[11]. However, such incidents are very rarely reported. Due to the short half-life of rtPA (5minutes), it is soon cleared from the systemic circulation under normal metabolic circumstances[21]. Therefore, repeating the IV rtPA could be considered in certain instances; for example, small volume of previous infarction

### 4. Thrombocytopenia and coagulopathy

According to AHA guidelines, platelet count less than 100, 000/$mm^3$ is a contraindication for giving IV rtPA for stroke[22]. However, there have not been many studies conducted on the hemorrhagic complications in patients with thrombocytopenia who receive IV rtPA. Similarly, presence of an acute bleeding diathesis/coagulopathy is also a contraindication even though there has been a paucity of data about the efficacy or safety of IV rtPA administration in AIS patients with these contraindications[11]. Potential causes for contraindication of Coagulopathy are liver cirrhosis, end stage renal disease, hematologic malignancy, vitamin K deficiency, sepsis, and antiphospholipid syndrome[11]. According to AHA guidelines, absolute contraindication to IV rtPA treatment is International Normalization Ratio (INR)>1.7 or partial thromboplastin (PT)>15 seconds[19].

### 5. Early radiographic ischeamic changes

Frank hypodensity on CT reflects most severe and irreversible brain injury that increases potential risk of hemorrhagic transformation, especially, when hypodensity on CT occupies more than 1/3 of affected cerebral hemisphere [11]. However, identification of the degree of ischemia on CT compared to infarction is challenging even by an experienced neuro-radiologist or neurologist. Signs of early ischemia, such as loss of distinction of the basal ganglia, sulcal effacement, focal swelling and mass effect, and loss of definition of gray white matter junction on CT scan are not absolute contraindications in administering IV rtPA in AIS treatment based on the 2013 AHA guidelines. In addition, it turns out to be more challenging when the onset of symptoms is unclear or diagnosed as wake-up strokes. It could be well identified or confirmed by the newer radiological imaging techniques[11] (MR Perfusion scans).

### 6. Severe hyperglycemia or hypoglycemia

Contraindication for thrombolysis is glucose levels below 50mg/dL and above 400mg.dl; these two conditions might worsen brain ischemia while hyperglycemia decreases the chances of recanalization as well as increasing the risk of ICH[19]. However, based on Virtual International Stroke Trials Registry (VITSA), there was not a convincing evidence for hyperglycemia or hypoglycemia being as contraindications of IV rtPA[22]. Once such metabolic disturbances are managed, the clinicians can consider IV rtPA in AIS patients.

### 7. Low-molecular- weight Heparin

Due to the extended activity and increased bioavailability of low molecular weight heparins, there is a high risk of hemorrhagic complications in giving IV rtPA to the patient who has had a dose within the previous 24 hours[11]. Thus, it is wise to avoid IV rtPA in such patients.

### 8. Direct Thrombin Inhibitors or Factor Xa inhibitors

Even though there have been only very few events of complications reported in the literature, clinicians should consider these as contraindications. Laboratory tests such as aPTT and INR should be done to find out if the patient is on direct thrombin of Xa inhibitors[11].

### Relative contraindications[18]

1. Advanced age (more than 80)
2. Mild or improving stroke
3. Severe stroke and coma
4. Recent major surgeries
5. Arterial puncture of non-compressible vessel
6. Recent gastrointestinal or genitourinary hemorrhage
7. Seizure at onset
8. Recent MI
9. Central nervous system
10. Structural lesions
11. Dementia

## Importance of stroke care Unit: 'sooner is better'

According to the Canadian heart and Stroke foundation, stroke care unit is a specialized, geographically defined hospital unit, dedicated for the management of all stroke patients (Evidence Level A) accomplished with an interdisciplinary team[23]. This team comprises clinicians (expertise in different aspects of medicine), nurses, occupational therapist, physiotherapist, speech-language pathologist, social workers and clinical nutritionists. Some additional medical professionals such as neuropsychologists and recreational therapists could also be included (Evidence Level: B). Such integrated stroke unit provides acute stroke care coupled with early rehabilitation. In Sri Lanka, mobile stroke unit, a rescue vehicle with an integrated CT scanner and other equipment used in essential diagnosis, would be an alternative and more effective model to reach the rural people. This helps in avoiding unnecessary delay in diagnosis or initiation of treatment. Further, telemedicine which links to a centre with experienced clinicians, would also support local services as well as increase thrombolysis rates in spite of still having to transfer some patients.

## Public stroke awareness

It has been observed that good functional outcome from acute ischeamic stroke begins with early recognition of stroke either by patients per se, caregivers or friends. The reflection from our part of region reveals poor knowledge on stroke alarming signs among the general public. Further, they adopt to use many home remedies, indigenous medicines, various blood pressure controlling medications as well as Aspirin prescribed by General Practitioners or other health assistants without proper clinical evaluation of stroke. The knowledge on intravenous rtPA for the management of hyper-acute ischeamic stroke is also found to be poor among people of North. Thus, a great difficulty is faced in obtaining informed consents since the clinicians need to provide sufficient information quickly to the patients and relatives in a way that they understand.

Apart from the poor knowledge among the public on AIS recognition and treatment options, inadequate resources in Northern Province plays a major role in increasing morbidity. Following the thirty years long brutal war in the North which ended in 2009, this region has been undergoing a huge transition in terms of its healthcare system, education system and etc. With the serious commitment of multidisciplinary team, the healthcare system has been well-improved, yet unknown to or underutilized by most of the general public. However, the government should focus more on establishing the stroke unit with all necessary facilities in addition to creating awareness among the public to utilize the current resources available in the region.

## Conclusion

Optimal acute ischeamic stroke care could be achieved by working together with the acute stroke team and other healthcare professionals. It is critical to consider absolute and relative contraindications while choosing patients for intravenous rtPA administration in AIS treatment. Clinicians should also make individualized therapeutic decisions based on the clinical presentation in the presence of indications and absence of major contraindications rather than population based therapeutic decisions. An acute stroke care protocol which outlines the major responsibilities for the urgent evaluation and treatment of acute stroke patients who present to the emergency departments published by the Ministry of Health, Sri Lanka, has to be implemented and monitored.

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