

Acute Ischemic Stroke: What is New?

ABSTRACT

Acute ischemic stroke (AIS) is the one of the leading cause of mortality and morbidity worldwide. Early management of stroke is important in reducing core size and salvaging penumbra by various re-perfusion techniques. Early identification, pre-hospital care, rapid transport, telemedicine and various apps for stroke leading to fast-paced management which subsequently prevent disability and mortality in AIS. Advances in various diagnostic modalities like automated software and treatment modalities in treatment by newer agents in intravenous(IV) thrombolysis and novel techniques mechanical thrombectomy is providing hope for better future in stroke management. Understanding of pathophysiology is utmost important in upcoming research in stroke and ultimately best patient care.

Key words: Acute ischemic stroke, Tenecteplase, New in stroke, Telestroke, Acute stroke management

INTRODUCTION

Stroke is one of the leading causes of morbidity and mortality in India. Incidence and prevalence of stroke range from 33 to 123.57/100,000 and 44.54 to 150/100,000, respectively. The 30 days case fatality rate ranges from 41.08% to 42.06% in the urban population and 18–46.3% in the rural population.^[1] Ischemic stroke comprises 85% of acute stroke and others being hemorrhagic (15%).

Males are slightly more affected than females. With the advances in thrombolysis, mechanical thrombectomy (MT), telemedicine, and better general care of patients with stroke in the past two decades there is shift from nihilism to optimism.

PATHOPHYSIOLOGY

Acute ischemic stroke (AIS) has varied etiologies such as large vessel occlusion (LVO), small vessel occlusion, cardioembolic, cryptogenic, and other etiology. Recently, embolic source of undermined source is a term introduced for non-lacunar cryptogenic stroke presumed to have embolic mechanism of stroke.^[2] Understanding the pathophysiology is very important individualizing treatment and prevent recurrence in stroke patients.

PRE-HOSPITAL MANAGEMENT

Time is the essence in treatment of stroke. Early recognition of symptoms, transportation of patient for emergency care, treatment while transportation, and informing nearest center for acute stroke management is the key for heading success in stroke. Facial drooping, Arm weakness, Speech difficulties and Time (FAST), FASTER (adding eye and react in FAST) and many others are the acronyms for the early recognition of symptoms related to stroke and to create the public awareness

Riddhi Patel¹, Rakesh singh², Satish V. Khadilkar¹

¹Department of Neurology, Bombay Hospital Institute of Sciences, Mumbai, Maharashtra, India, ²Department of Neurologist and Interventionist, Bombay Hospital Institute of Medical Sciences, Mumbai, Maharashtra, India,

Corresponding Author: Satish V. Khadilkar, Department of Neurology, Bombay Hospital Institute of Sciences, Mumbai, Maharashtra, India.
E-mail: khadilkarsatish@gmail.com

regarding it. Unfortunately, recognition of stroke symptoms among public is very poor. Activation of the emergency system (e.g. 108 in most of the states in India) by the patient or other members of the public is strongly recommended.^[3] Mobile apps to activate the emergency system and tracking the patients are the emerging tool for reducing the time and early care in stroke. Telestroke is a use of videoconferencing techniques for assisting physicians for assessment, diagnosis, management, and/or remote consultative support to patients with symptoms and signs consistent with an acute stroke syndrome.^[4] Recently, many apps have been launched for providing low-cost services of neurologist for telestroke in district hospitals. Mobile stroke units are equipped with facilities for evaluation, ruling out hemorrhage by computed tomography (CT) scan and early treatment in the acute stroke. Few centers in the India are providing this type of facility. Patients with the suspicion of stroke on early evaluation should be transported to the centers having facility of thrombolysis. On the early evaluation if patient is having LVO, then he is transferred to higher stroke centers equipped with MT treatment after starting intravenous (IV) thrombolysis (drip and ship).^[3]

HOSPITAL MANAGEMENT

All hospitals should have properly trained staff (physicians, nurses, laboratory/radiology personnel) for the early and fastest management of stroke as soon as patient arrives in emergency. All patients must be evaluated for blood sugar, blood pressure (BP), and the National Institute of Health Stroke Scale (NIHSS) before sending for imaging.

Imaging and other investigations

Primary imaging of neuroimaging is to exclude the hemorrhage, rule out mimics, to see degree of ischemic etiology, and to find out the possible etiology for the stroke. As per ASA/AHA guidelines, CT scan is effective in excluding the hemorrhage. Creatinine is not mandatory in patient requiring contrast CT angiography except in end-stage renal disease not on maintenance hemodialysis. Magnetic resonance (MR) imaging with limited sequences can be used alternatively to exclude hemorrhage. Alberta Stroke Programme Early CT Score (ASPECTS) and posterior ASPECTS are the scores for evaluation of the ischemic areas on CT. Target goal of door to needle time <20 min should be achieved in minimum 50% of stroke patients.^[3] For the patients with unknown time of stroke >4.5 h and wake up stroke, newer imaging methods such as diffusion-fluid attenuated inversion recovery (FLAIR) mismatch or diffusion perfusion mismatch are necessary to calculate penumbra. Candidates who are eligible for MT last seen well between 6 and 24 h, CT angiography with CT perfusion or MR angiography with or without MR perfusion is mandatory.^[3] In many centers, Rapid processing of perfusion and diffusion software is available to calculate core and penumbra accurately. All the patients of strokes are recommended to do head and neck vascular imaging before discharge.

Other investigations such as electrocardiography, echocardiography, baseline troponin, chest imaging, complete blood count, renal and liver function test are recommended in all patients but should not delay the IV thrombolysis. Special investigations like coagulation studies and others are required depending on clinical suspicion.

General care^[3]

Airway support and ventilatory assistance are recommended for patients with bulbar weakness and altered sensorium. Oxygen supplementation is required for patients with oxygen saturation <94%. There is no role of hyperbaric oxygen therapy in AIS except suspected air embolism. There is no evidence of benefit of induced hypothermia in patients with AIS. Cause for elevated temperature (>38°C) needs evaluation and accordingly treatment. There is a recommendation to maintain sugar levels between 140 and 180 mg/dl and treat hypoglycemia (<60 mg/dl) in AIS benefit of flat head position in AIS remains uncertain. The aim of the BP management in the stroke is to maintain adequate perfusion in the penumbra that can be accomplished

by avoiding hypotension and hypovolemia. Acute lowering of BP is required in patients with aortic dissection, preeclampsia/eclampsia, acute heart failure, concomitant coronary event, and postfibrinolysis spontaneous intracranial hemorrhage. In patients with BP >220/120 mm Hg who are not receiving IV thrombolysis or MT, BP should be lowered by 15% during first 24 h and in those with BP <220/120 mm Hg, reinstate or initiate BP-lowering agents after 48–72 h of AIS. Patients are eligible for IV thrombolysis or MT BP should be <185/110 mm Hg and should maintain ≤180/105 mm Hg 24–48 h after reperfusion. For lowering BP in AIS short and faster acting antihypertensive agents such as labetalol, nicardipine, clevidipine, enalaprilat, and hydralazine are preferred. Prophylactic seizure treatment is not recommended in AIS. For deep venous thrombolysis prophylaxis intermittent pneumatic compression and adequate hydration are recommended in immobile patients without contraindication; no well-established benefit of unfractionated heparin or low molecular weight heparin (LMWH) and elastic compression stockings should not be used. Hemodilution by volume expansion, vasodilatory agents, mechanical devices for augmenting BP, prophylactic antibiotic, transcranial near-infrared laser therapy, or high dose albumin is not recommended in AIS.

IV thrombolysis

Early reperfusion and re-canalization are the keys for reversing ischemia and reduce the infarct size. Various thrombolytic agents which convert plasminogen to plasmin are tried in various studies. IV thrombolysis should be started as early as possible as benefit of it is time-dependent. Alteplase (Recombinant Tissue Plasminogen Activator [rtPA]) is a well-known and ASA/AHA approved agent for thrombolysis which can be administered as 0.9 mg/kg of it 10% given as bolus and the remaining part as infusion. Recently, tenecteplase is another rtPA approved in the AIS with the dose of 0.25 mg/kg as bolus in most of the parts of world;^[5,6] however, in India approved dose is 0.2 mg/kg. Tenecteplase has longer half-life and greater fibrin specificity compared to alteplase.

Time window for the IV alteplase extended up-to 4.5 h to give benefit in more patients.^[7] IV thrombolysis can be administered in pregnancy, age >80 years, severe stroke (NIHSS >25) patients also but with warning if it is 3–4.5 h from onset. For the wake-up stroke and unknown time of onset if perfusion imaging and diffusion-weighted imaging-FLAIR mismatch suggests salvageable penumbra then IV thrombolysis can be given. IV thrombolysis is not indicated in patients with NIHSS <5 without disabling stroke.^[8] IV thrombolysis is indicated in the patients who are improving but still disabling stroke at the time of neurological evaluation. Patients with posterior circulation eligible for IV thrombolysis should be treated with rtPA. In latest guidelines, sickle cell anemia included as potential candidate to receive IV thrombolysis. COVID -19 is also not a contraindication for IV thrombolysis or MT. Special warnings are required in patients

with large (>10 mm) unsecured and unruptured aneurysm, untreated vascular malformation, cerebral microbleeds >10, arterial puncture at noncompressible site within 7 days; those needs careful consideration and weighing of risk to benefit. Dilemma arises when patients taking direct oral anticoagulants (DOACs) come with AIS. Patients taking dabigatran reversal of it can be done by idarucizumab (which is available in India) and after that IV thrombolysis can be given. For factor Xa inhibitor agent, reversal agent andexanet alpha is approved but availability is limited in clinical practice. DOACs related cerebral bleeding can be rapidly reversed by prothrombin concentrate complex which is available now in India.^[9,10]

Orolingual edema is a rare complication of IV rtPA having a tendency to involve hemiparetic side, most often asymmetric and more in patients taking angiotensin-converting enzyme inhibitors can be treated by combination of dexamethasone, ranitidine, and diphenhydramine. Strict BP and close neurological monitoring are required in patients receiving IV thrombolysis. If there is worsening in NIHSS then patient needs urgent imaging to exclude hemorrhage. If there is hemorrhage then Systolic BP should be kept <140–160 mm Hg, 10 units of cryoprecipitate, antifibrinolytic agents. CT scan to be recommended after 24 h of the IV thrombolysis.

Inclusion criteria for IV thrombolysis^[3] (all of the following should be “yes”)

YES

- Age ≥18 years
- Symptom onset <4.5 h
- CT without significant haemorrhage or edema
- AIS causing measurable neurodeficit.

Exclusion criteria for IV thrombolysis^[3] (all “NO” boxes must be checked before IV thrombolysis)

NO

- <3 months ago: Severe head trauma, ischemic stroke, intracranial or intraspinal surgery
- Gastrointestinal (GI) malignancy or GI hemorrhage within 21 days
- Previous ICH
- Intra-axial intracranial neoplasm
- Active internal bleeding
- Suspected aortic dissection
- Suspected infective endocarditis
- Symptom suggestive of subarachnoid hemorrhage
- Persistent elevated BP >185/110 mm Hg that can not be lowered safely
- Acute bleeding diathesis, including but not limited to
 - Platelet count <1,00,000/mm³
 - Current anticoagulant use with an international normalized ratio (INR) >1.7 or PT >15 s or a activated partial thromboplastin time (APTT) >40 s
 - Received full dose LMWH within 24 h
 - Current use of DOACs with abnormal coagulation tests^a
- Evidence of hemorrhage in CT

- Extensive regions of obvious hypo-density consistent with irreversible changes in CT
 - ^aAPTT, INR, platelet count, thrombin time, factor Xa activity assays, ecarin clotting time.

MT

Limitation of the IV thrombolysis (short window period, limited recanalization, many contraindications) can be overcome by MT. Patients suspected to have LVO who are eligible for MT should undergo noninvasive angiography. MT is indicated in patients with LVO, good pre-morbid status, and measurable neurodeficit. Rapid software is commonly used in whom time of onset >6 h before MT. Benefit of thrombectomy likely if following criteria are fulfilled- (a) Ratio of hypoperfused tissue to ischemic core >1.8, (b) Ischemic core volume <70 ml, (c) Severely delayed volume ($T_{max} >10$ s) <100 ml.^[11] Mechanical embolus removal in cerebral ischemia (MERCI) device was first FDA approved for MT. Stent retrievers are preferred than MERCI device. HERMES collaboration evaluated efficacy of MT in anterior circulation in five major trials.^[12] In anterior circulation AIS, DIFFUSE and DAWN trials extended time window for MT up-to 16 and 24 h respectively by different eligibility criteria.^[11,13] Stent retrievers (e.g. trevo, solitaire, tigertriever, embotrap, eric, and others), suction-based thrombectomy (e.g. penumbra and others), or combination (solubra) or it is used for MT. Reperfusion to be achieved mTICI grade 2b/3 for ensuring the benefit. MT in basilar artery occlusion showed benefit in earlier trials.^[14] The benefit of MT in posterior circulation compared to anterior circulation remain uncertain as shown by some new recent trials, however, patient inclusion criteria are very much crucial in deciding the outcome.^[15]

Sonothrombolysis and other agents

The use of sonothrombolysis with antifibrinolytic agents not recommended till now. IV defibrinolytic agents over rtPA are not recommended. Intraarterial fibrinolysis is not recommended over MT with stent retriever; however, it can be used in carefully selected within 6 h in whom contraindications to IV thrombolysis.

Antithrombotic and lipid-lowering agents

In patients with minor stroke (NIHSS <4) of noncardioembolic source who had not received IV thrombolysis should be started with dual anti-platelets (aspirin and clopidogrel) within 24 h of AIS.^[16] In patients who received IV thrombolysis/MT, Aspirin should be started within 24–48 h. Other antiplatelets have limited benefit compared to aspirin. Patients ≤75 years of age with clinical atherosclerotic cardiovascular disease should start high-dose statin. If intolerance or side effects to statin then ezetimibe can be given. PCSK9 inhibitors such as alirocumab and evolocumab are newer agents to lower the lipid levels. Women taking statins should use reliable method of contraception, should stop statins

1–2 months before planning pregnancy, and stop as soon as possible if become pregnant on statins.

Neuroprotective agents

Various neuroprotective agents for example magnesium and nerinetide shown promising results in animal studies but not shown benefit in real practice and are not recommended.

Neurorehabilitation

Intense and early mobilization (within 24 h) is not recommended. Active involvement of family members in physiotherapy is encouraged.^[17] The efficacy of fluoxetine and other serotonin re-uptake inhibitors in motor improvement is not well established. Activity of daily living, function mobility, depression should be assessed in all patients before discharge and should be addressed accordingly. Regular daily skin assessment, dysphagia evaluation to be recommended in all patient of stroke. Enteral food should be started within 7 days and if not possible then nasogastric tube (for short term <7 days) or percutaneous gastrostomy (in whom persistent dysphagia >2–3 weeks) can be required. Robotics^[18] and aquatic therapies showed the promising results in trials.^[19]

Referral to comprehensive stroke unit

Patients with suspected LVO, large territorial cerebral and cerebellar infarct, clinical deterioration, and brain swelling were referred to centers with available neurologists, intensivists, interventionists, neurosurgical specialists. The use of osmotic therapy and brief moderate hyperventilation (Pco₂ target 30–34 mm Hg) in patients with brain swelling as bridge to definitive treatment. There is no role of hypothermia, steroids, or barbiturate coma in these patients. Ventriculostomy in patients with obstructive hydrocephalus and decompressive suboccipital craniotomy in clinical deterioration due to brainstem compression in posterior circulation strokes is recommended.^[3] In patients with right-sided anterior circulation strokes deteriorating neurologically having malignant brain swelling despite medical therapy, decompressive craniectomy with dural expansion may be considered and with left-sided one detail discussion regarding prognosis in detail to be done with relatives.

Campaign for public awareness and stroke registries

In 2021, world stroke day theme was “Learn the signs, say it is a stroke and save precious time,” to increase the awareness of stroke signs and decrease the time for seeking medical advice. Knowledge of stroke among common parlance is the must to achieve early and fastest best treatment to reduce morbidity and mortality and can be done by providing education at social media, television, radio, camps, school and offices and so on. Training the paramedics, social workers, and volunteers to be done to manage AIS patients efficiently. Stroke registries

help in finding incidence, prevalence, epidemiology, causation and association, in particular, geographical area, and this information can be used in policymaking, research, guidelines, and better patient management. Various stroke registries are now being maintained in India.

HOW HAS MY PRACTICE CHANGED?

1. Delay in reaching to hospital in AIS is the major factor in lag of start of treatment and subsequent significant morbidity and mortality; this can be reduced using apps, mobile stroke units, and newer technology
2. Newer imaging modalities and software like RAPID can calculate penumbra and core effectively so better to guide further treatment
3. Tenecteplase is the newer approved medication for rapid use and better re-canalization compared to alteplase in LVO up-to 3 h
4. Endovascular treatment in stroke can provide better re-canalization, decrease chances of symptomatic cerebral bleed, extending the time window in LVO by newer advances
5. There is a need for starting with more and more comprehensive stroke care unit which can provide multidisciplinary approach to AIS patients
6. Public awareness regarding education-related to stroke is utmost important thing that can be done by various means of communication. Stroke registries can help in knowing stroke burden, causation or association, pathophysiology, research, and making policies for better management.

CONCLUSION

AIS is a neurological emergency that if addressed in a effective manner then can make a big difference in the lives of the patients and family members. Patient education for prevention and seeking the medical care in AIS is the equally important factor. Future research in stroke understanding pathophysiology, imaging, newer drugs, and devices in endovascular treatment is a hope for upgrading patient care.

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