

Management of Acute Ischemic Stroke: Status of The New And The Old Therapies

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Introduction

Stroke as most of us know is a sudden loss of brain function because of interference with blood supply to the brain. It is divided into two basic subtypes as ischemic stroke because of blockage of blood vessel and hemorrhagic stroke due to rupture of blood vessel and bleeding in brain. Out of the two ischemic stroke contributes a major burden.

Stroke is one of the major causes of human morbidity and mortality. The helplessness one experiences while treating a stroke patient is experienced by most of us who are handling the stroke patients in day to day practice and one eagerly awaits a drug which can reverse the stroke at the earliest.

Stroke In India

A review of information available on stroke was conducted by Anand K et al to estimate the morbidity due to stroke in India (1). The prevalence of stroke in India was estimated as 203 per 100,000 populations above 20 years, amounting to a total of about 1 million cases. The male to female ratio was 1.7. Around 12% of all strokes occurred in population below 40 years. The best estimate of death derived was 102,000 deaths; which represented 1.2 % of total deaths in the country.

Thus stroke forms a sizable chunk of our health problems and one therefore needs to manage it in the best possible way. There is lot of confusion with respect to use or non use of many of the available treatment modalities in acute management of stroke but everyone agrees on the fact that if a stroke patient is managed properly in the first few hours of onset, then that significantly makes a difference to the ultimate outcome in terms of mortality and morbidity. This particular article focuses attention on acute management of ischemic stroke or infarct which accounts for almost 80% of all stroke patients.

Evaluation And Management Of Ischaemic Stroke

The key in appropriate acute ischemic stroke

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management lies in quick identification of stroke and that it is an ischemic stroke. Therefore actual diagnostic process starts at the level of relatives and paramedics and primary care physicians so that patient reaches an appropriate centre at the earliest and a quick CT scan can be done at the earliest to diagnose that stroke is ischemic (Infarct). So awareness at the primary level and public level about stroke symptoms is the best thing that can help better the ischemic stroke management. Unfortunately as of today, the degree of awareness about stroke is far less one compares it with heart attack. All of us need to take up the work of making the public aware on this issue.

Emergency Evaluation And Diagnosis Of Acute Ischemic Stroke

In case of stroke, time lost is the brain lost. When blood supply to brain is compromised, billions of neurons start dying every minute. So, earlier you treat, better are the chances of saving maximum brain tissue at risk of infarction. The newer ischemic stroke modalities of thrombolysis work on this theory of time saved is brain saved as they are most useful when they are used in some stipulated time window. Given the narrow therapeutic window for treatment, all patients with suspected acute stroke should be treated with the same priority as patients with acute myocardial infarction or serious trauma, regardless of the severity of the deficits.

Immediate Evaluation

The initial evaluation of a potential stroke patient is similar to that of other critically ill patients: stabilization of the ABCs, followed by an assessment of neurological deficits and co morbidities.

1. History

The single most important piece of historical information is the time of symptom onset. This is because the newer modalities in ischemic stroke treatment like intravenous and intra-arterial thrombolysis are recommended only within three and six hours of stroke onset respectively. The current definition of the time of stroke onset is when patients were at their previous baseline or symptom-free state. For patients unable to provide this information or who awaken with stroke symptoms, the time of onset is defined as when the patient was last awake (2). Other

important things to be asked are related to risk factors for arteriosclerosis and cardiac disease and data related to eligibility of the patient for therapeutic interventions in acute ischemic stroke.

2. Physical Examination

The general physical examination includes assessment of the ABCs, examination for signs of trauma or seizure activity (eg, contusions etc). The cardiac examination focuses on identifying concurrent myocardial ischemia, valvular conditions, irregular rhythm etc. Similarly, the respiratory and abdominal examinations seek to identify other co morbidities.

3. Neurological Examination and Stroke Scale

Scores

The emergency physician's neurological examination should be brief but thorough. The American National institute of health (NIH) advocates a neurologic scale which can be administered in 10 to 15 minutes called as the NIH Stroke Scale (NIHSS) for quick assessment of stroke severity. The scale has score for each element of neurodeficiete and the total score is referred as NIHSS Score. A score of 1 to 4 indicates minor stroke, 5 to 15 indicates moderate stroke, 16 to 20 is moderately severe stroke and more than 20 is the severe stroke. The idea here is to get best assessment of neurologic status without wasting too much time. Patents that have their NIHSS score of more than 4 and less than 20 are the ones who are the best candidates for thrombolysis. The following table shows NIHSS scale.

Table 1: NIH-SSS summary (Categories and Point Assignments)

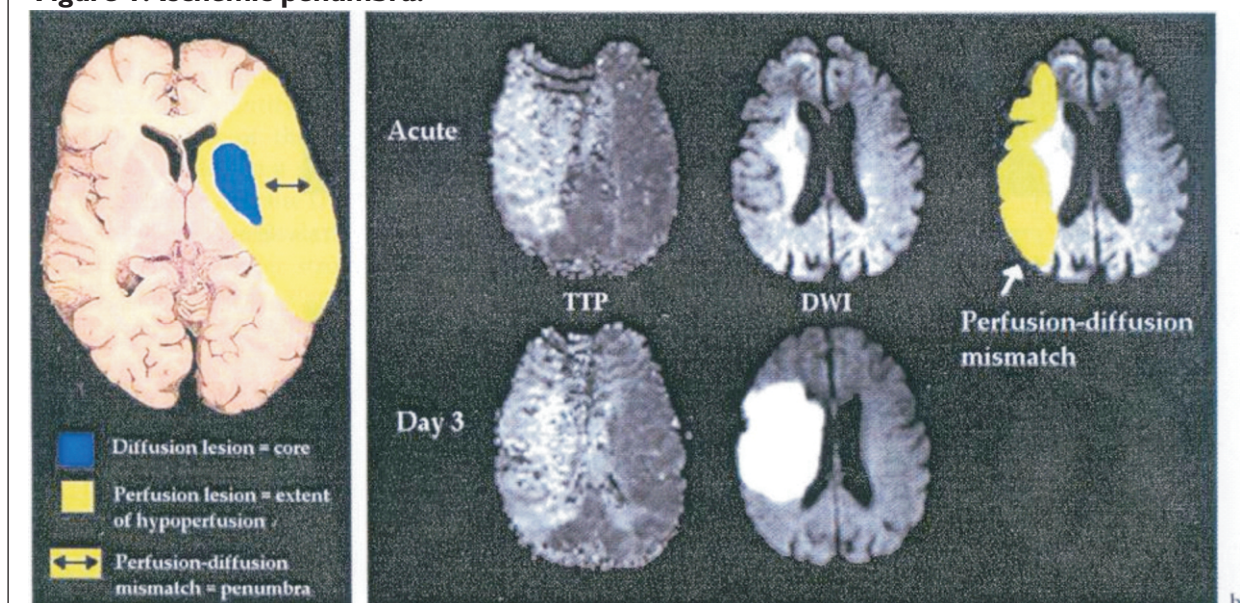
1a. Level of consciousness	5-B Best motor (repeat for each arm and each leg)
0. Alert	0. No drift
1. Drowsy	1. Drift
2. Stuporous	2. Some effort versus gravity
3. Comatose	3. No effort versus gravity
	4. No movement
1b. Level of consciousness	9. Untestable
(ask age and month)	
0. Answers both correctly	9. Limb ataxia (scored only if present)
1. Answers 1 correctly	0. Absent
2. Both incorrect	1. Present in 1 limb
	2. Present in 2 limbs
1c. Level of consciousness commands	
(close your eyes, make a fist)	10. Sensory (pinprick)
0. Obeys both correctly	0. Normal
2. Both incorrect	1. Partial loss
	2. Dense loss
2. Best gaze	
0. Normal	11. Best language
1. Partial gaze palsy	0. No aphasia
2. Forced deviation	1. Mild to moderate aphasia
	2. Severe aphasia
3. Visual fields	3. Mute
0. No visual loss	
1. Partial hemianopia	12. Dysarthria
2. Complete hemianopia	0. Normal articulation
3. Bilateral hemianopia	1. Mild to moderate dysarthria
	2. Unintelligible or worse
4. Facial paresis	X. Untestable
0. Normal movement	
1. Partial paresis	13. Neglect / Inattention
3. Complete paresis	0. No neglect
	1. Partial neglect
	2. Complete neglect
Total NIH-SSS (0 to 42)	
Numbers represent the point score assigned for each within the category.	

4. Investigations

.Noncontrast CT scanning of the brain is the most important imaging modality which differentiates an ischemic from a hemorrhagic stroke. The CT scan may provide prognostic information when early and large hypo intensities generally meaning more severe ischemic stroke. Magnetic resonance imaging (MRI) is becoming

potentially salvageable yellow are of ischemic penumbra. The second panel shows diffusion (infarcted bright area) and perfusion (yellow potentially salvageable area in upper row) mismatch on first day. When blood supply is not established even the penumbra zone becomes bright i.e. infarcted on third day scan

Figure 1: Ischemic penumbra.



more important in evaluation of the acute stroke patient. But considering its unavailability at many places, the time and the cost it requires, CT scan probably still holds an edge over it as far as acute stroke management is considered in our country.

Apart from imaging, basic diagnostic studies should be included in the initial evaluation of patients with an acute stroke. The American Heart Association recommends an ECG, chest radiograph, CBC count, platelet count, partial thromboplastin time, prothrombin time, serum electrolytes, and glucose level. Other studies should be ordered as indicated (3).

5. General Management and Pharmacotherapy

The goal of management of ischemic stroke patients in the acute phase is protection of the so-called penumbra zone. This zone comprises the brain tissue at risk of irreversible ischemic damage. This brain tissue adjacent to the ischemic core is compromised of its blood supply but if circulation is established early then this area is salvageable and the morbidity and the mortality because of the stroke can be reduced. In the following figure 1 the first panel shows blue infarcted area surrounded by

Most of the acute ischemic stroke measures focus on the protection of this particular area of ischemic penumbra. To achieve this goal, following therapeutic options can be used

- 1) Recanalisation of occluded blood vessel (thrombolytic therapy)
- 2) Reducing progression of the clot by using anticoagulants and antiplatelet drugs
- 3) Maximizing cerebral perfusion by reduction of cerebral edema and lowering of intracranial pressure etc.

Thrombolysis in ischemic stroke: Recanalisation of occluded cerebral Vessel with tPA

Currently there is lot of buzz in the stroke world about this new treatment modality in ischemic stroke. Here idea is to break the clot and reestablish the circulation in the affected are at the earliest. This is a promising newer modality which is being used world over in acute management of ischemic stroke. The drug recombinant tissue plasminogen activator (tPA) can be used by intravenous route within three hours and by intra-arterial route by experienced interventional neuroradiologist within six hours of ischemic stroke onset for clot

thrombolysis. However apart from the clinical presentation in the stipulated time window patient has to satisfy many inclusion and exclusion criteria as given in the following table before one uses this particular modality. If these criteria are not followed stringently then patient is more likely to develop intracranial bleed as a complication of therapy. Tissue plasminogen activator (tPA) in a dose of 0.9 mg/kg (maximum dose 90 mg) is given intravenously, 10% on a bolus and the remaining 90% by infusion over 60 minutes. Anticoagulants and aspirin are contraindicated for the first 24 hours after tPA therapy. Blood pressure should be monitored frequently during the first 24 hours and maintained below 185 mmHg systolic and 110 mmHg diastolic. The patient should be observed frequently for any signs of intracerebral or systemic hemorrhage. According to literature despite a significant increase in intracerebral hemorrhage (7% in tPA and 0.6% in placebo group), mortality is unchanged and neurologic outcome is significantly improved at 3 months in patients treated with tPA (4).

Table 2. Inclusion and exclusion criteria for thrombolysis in ischemic stroke (4)

- Inclusion Criteria for tPA thrombolysis
- Age more than 18 years
- Persistent neurologic deficit
- Baseline CT scan showing no evidence of intracranial haemorrhage
- Duration of symptom onset upto 3 hrs for intravenous and upto 6 hrs for intraarterial stroke

Exclusion Criteria

- Rapidly improving or minor symptoms such as isolated ataxia or sensory symptoms
- CT scan showing possible intracranial hemorrhage or large infarct (Hypo density more than one third of a cerebral hemisphere)
- History of seizure at stroke onset (Unless physician is sure that deficit is not due to Todd's paralysis)
- Stroke or serious head trauma within 3 months
- History of intracranial hemorrhage, arteriovenous malformation, or aneurysm
- Symptoms consistent with subarachnoid hemorrhage
- Major surgery or serious trauma within 2 wks
- Gastrointestinal or urinary tract hemorrhage within 3 wks
- Systolic BP > 185 mm Hg; diastolic BP > 110 mm Hg;
- Glucose <50 mg/dL or >400 mg/dL
- Arterial puncture at noncompressible site or lumbar

- puncture within 1 wk
- Platelet count < 100,000/mm³
- Heparin within 48 hr and associated with elevated APTT
- Oral anticoagulants associated with elevated PT > 15 sec or INR > 1.5
- Pregnancy

Though thrombolysis is coming up as a new hope against ischemic stroke the stringent criteria one has to follow before using it and the fear of intracranial hemorrhage as a complication, makes many a general and neurophysicians a little skeptical in offering it as a treatment modality to acute ischemic stroke patients. However one need to understand that it is a new modality, is promising and needs to be studied more before everyone accepts it freely. It took more than 50,000 thrombolysis before everyone accepted thrombolysis as a treatment modality in myocardial infarction. If this parameter is considered as a benchmark then there is still a long way to go for thrombolysis in ischemic stroke before it establishes itself as an automatic choice in treatment of patients with acute ischemic stroke. As of today it should be used in centres which have all the facilities needed for acute stroke evaluation including CT scan, and a team of neurophysician or general physician, interventional neuroradiologist, neurosurgeon and a good ICU backup and probably should not be used just like that in a widespread manner.

Where does heparin stand as of today in management of acute ischemic stroke?

Anticoagulants have been used to treat patients with acute ischemic stroke for many many years now and continue to be prescribed commonly. They basically aim at stopping the progression of the clot but not at breaking the existing clot and therefore are more concerned with prevention of stroke progression and recurrence. The usefulness of emergency anticoagulation is the subject of debate. The results of the recent trials show that early administration of either heparin or a LMW heparin is associated with an increased risk of bleeding complications which outweigh the benefit in prevention of stroke progression and recurrence (5). The risk of symptomatic hemorrhagic transformation is especially more among persons with severe events. Therefore one should avoid it especially in patients with severe strokes. Even in situations like persons with intracardiac or intra-arterial thrombi and large arterial dissection where one expects anticoagulants to show benefit, the efficacy or non efficacy of urgent anticoagulation is still not

established and there is still confusion (3). More often than not anticoagulants continue to be used in these particular situations. As per the recent guidelines of the American heart association (AHA) urgent anticoagulation with the goal of preventing early recurrent stroke, halting neurological worsening, or improving outcomes after acute ischemic stroke is not recommended for treatment of patients with acute Ischemic stroke(3).

What about antiplatelet agents?

Aspirin is the only antiplatelet agent that has been evaluated for the treatment of acute ischemic stroke. Aspirin (325 mg) should be given within 24 hours of symptom onset to patients who do not receive tPA and after 24 hours in those who do. Studies have shown that early aspirin in patients treated within 48 hours of stroke onset reduced both stroke recurrence risk and mortality. Patients with stable, complete strokes or those admitted with new-onset or crescendo TIAs are often placed on aspirin therapy prophylactically at admission. Other antiplatelet agents in common use like clopidogrel is still not studied extensively to be recommended freely in acute condition. Thus with limitation of thrombolysis therapy and doubtful efficacy of anticoagulants in ischemic stroke aspirin probably forms the cornerstone of treatment in any type of setup for patients with acute ischemic stroke.

What is status of neuroprotective drugs?

Recently many new molecules have come in market which have so called neuroprotective mechanisms. Some of them like citicoline protect the membrane of the neuron where as others like edavarone act as free radical scavengers. Piracetam is used for years now in different type of brain diseases. Out of these current evidence favors citicoline over others with studies showing some benefit with citicoline when it is used within 24 hours of stroke onset(6).

What about mannitol, steroids, pentoxifylline and anticonvulsants in acute ischemic stroke?

If one analyses stroke prescriptions, generally all these drugs are time and again found in them. But is their extensive use really justified in all the situations? The answer to these questions is a big no? The early use of mannitol is probably justified only in situations like malignant looking large middle cerebral artery stroke and large cerebellar infarcts where edema is expected early and life may be endangered. Even decompressive surgeries are to be considered in some of these cases. However In smaller infarcts, early use of osmotic

diuretics is not justified as edema in stroke is expected usually after 48 to 72 hours and does not always need treatment .So one should use mannitol early on only in large strokes and its use should be deferred till the time edema is suspected to have occurred. Steroids don't have any sort of role in acute ischemic stroke. Similarly controlled studies have not showed any efficacy of pentoxifylline, a very often used drug in acute ischemic stroke .Prophylactic use of anticonvulsants should also be discouraged and they should only be used in situations where a convulsion is known to have occurred (3).

Managing blood pressure in acute ischemic stroke.

An elevated blood pressure is often detected in the first hours after stroke. The elevation in BP may be beneficial by maintaining flow to borderline ischemic areas or the penumbra. The observation that the BP frequently rises spontaneously following cerebral ischemia is consistent with this hypothesis. Elevations in blood pressure > 160 mm Hg are detected in > 60% of patients with acute stroke(7). But at the same time for every 10-mm Hg increase >180 mm Hg, the risk of neurological deterioration increased by 40% and the risk of poor outcome increased by 23 %(8). Urgent antihypertensive therapy may be needed to treat patients with stroke who also have hypertensive encephalopathy, aortic dissection, acute renal failure, acute pulmonary edema, or acute myocardial infarction(8).Conversely, aggressive treatment of blood pressure may lead to neurological worsening by reducing perfusion pressure to ischemic areas of the brain..Because of the lack of clear data, the appropriate treatment of arterial hypertension in the setting of acute ischemic stroke remains controversial (9). However, current consensus suggest that the blood pressure level that would prompt treatment would be >180/110 mm Hg (3). A reasonable goal would be to lower blood pressure by 15% to 25% within the first day (10). Many patients are known to be taking antihypertensive before the stroke onset and one does not know what to do with that as they are likely to need the drugs in future also. The primary question is the timing of the institution of such therapy. Limited data are available to guide these decisions. It appears that medications can be administered with a reasonable degree of safety when started >1 day after stroke. Similarly one should correct hypotension quickly with intravenous fluid and if needed with vasopressors in stroke patients. Studies have noted that the rates of neurological worsening, poor neurological outcomes, or death increased when the baseline systolic blood pressure was <100 mm Hg or the diastolic blood

pressure was <70 mm Hg (11). So one should aim at blood pressure above this level.

Some other important management issues

Among this important one is the management of glucose levels in stroke patients as both hypo and hyperglycemia can worsen damage due to an infarct. Despite the lack of data to guide decisions about management, consensus exists that hyperglycemia should be controlled after stroke (12). A reasonable goal would be to treat those patients with elevated glucose concentrations (> 140 mg/dL). A commonly followed practice of using glucose containing fluids in acute stroke patients should therefore be discouraged unless and until hypoglycemic situation is encountered.

Similarly fever should also be controlled aggressively in stroke patients as it is also known to worsen the brain damage due to stroke. Monitoring of these patients should be done carefully including the cardiac monitoring, DVT prophylaxis, Bed sore care etc.

Summary

Ischemic stroke is the major type of stroke seen worldwide. Though Many newer modalities of treatment like intravenous and intra-arterial thrombolysis are showing promise there is still a long way to go before it becomes a treatment of automatic choice in ischemic stroke. The major problems in using this type of modality in country like India are the very short time window for treatment, financial aspects, a long list of exclusion criteria, and the most important being lack of awareness about stroke symptoms and new stroke symptoms among public and physicians. Antiplatelets therefore still form a cornerstone of acute ischemic stroke in country like India. Heparin and other anticoagulants are more often than not are overused and their use as of now should be limited to few select situations. Equally important is proper management of blood pressure, blood sugar, temperature, nutrition and prevention of deep venous thrombosis. As the research evolves let us hope that we find permanent answers to the rising risk of ischemic stroke.

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