

## CHAPTER

# 15

# *Acute Ischemic Cerebrovascular Event*

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## **Introduction**

Stroke is the third commonest cause of death worldwide, after coronary heart disease (CHD) and cancer. Asians have a lower rate of CHD and a higher prevalence of stroke.<sup>1</sup> Also among the Asians, the number who die from stroke are more than three times than that for CHD.<sup>2,3</sup> In one report, the age-standardized, gender-specific stroke mortality rate was 44 to 102.6/100,000 for Asian males, compared with only 19.3 for Australian white males.<sup>4</sup> In addition to this, stroke is identified as a leading cause of disability in different parts of the world and is associated with a tremendous cost burden to society.

As far as India is concerned stroke related statistical data is limited. A recent review has found that in India, during the last decade, the age-adjusted prevalence rate of stroke was between 250-350/100,000 and the age-adjusted annual incidence rate was 105/100,000 in the urban community of Kolkata and 262/100,000 in a rural community of Bengal. The ratio of cerebral infarct to hemorrhage was 2.21 with Hypertension being the most important risk factor. This review found that strokes represented 1.2% of total deaths.<sup>5</sup>

Most strokes (88 per cent) are ischemic. The rates of intracerebral hemorrhage and subarachnoid hemorrhage are much lower (9 and 3 per cent,

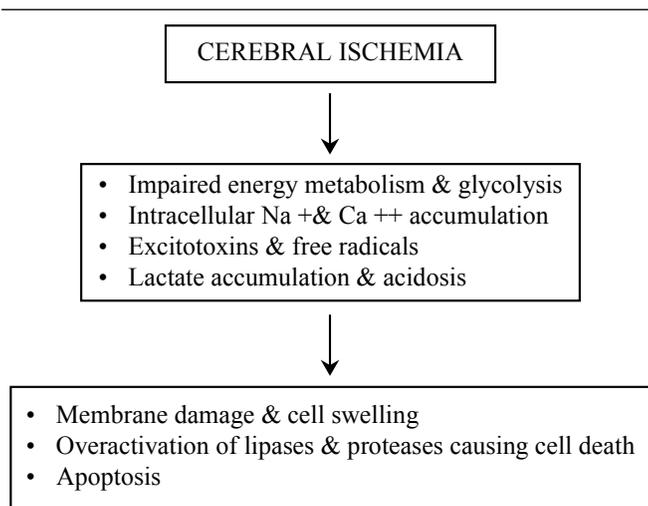
respectively).<sup>6</sup> Recent trials use a mixture of clinical and radiographic evidence to define ischemic stroke versus transient ischemic attack (TIA). An ischemic stroke is defined as acute onset of neurologic symptoms lasting longer than 24 hours or radiographic evidence of an ischemic event in patients with loss of symptoms within 24 hours.<sup>7</sup> A TIA is an event that lasts less than 24 hours and that is without evidence of pathology on radiographic studies.<sup>7</sup> Although these terms are strict, the pathology and clinical significance overlap.

## **Etiopathogenesis of Acute Ischemic Stroke**

Ischemic strokes are caused by occlusion of cerebral vessels due to thrombosis or embolism. Many modifiable and non modifiable risk factors for acute ischemic stroke have been identified over the years. Some of the important ones are shown in Table 1.

After cerebral ischemia many changes take place at the cellular level. Following flow chart briefly highlights the pathophysiological changes occurring at cellular level after cerebral ischemia

Normal cerebral blood flow is 50-55 ml/100 gm per minute. Complete interruption of cerebral blood flow causes suppression of electrical activity in 12-15 seconds, inhibition of synaptic excitability in 2-4



minutes and inhibition of electrical excitability in 4-6 minutes. When cerebral blood flow drops to 18 ml/100 gm per minute threshold for electrical failure is reached but tissue is still salvageable. When it reaches to 8 ml/100 gm per minute cell death can result. The area between these two thresholds is the area around the core of the infarcted brain and is called as the ischemic penumbra. Acute stroke therapy aims at salvaging this area in particular.

## Clinical Features

Clinical features of acute ischemic stroke depend on whether carotid or vertebrobasilar circulation is involved though a significant degree of overlap is often seen between the two systems. Table 2 briefly depicts salient gross clinical features of two systems.

## Evaluation and Management of Acute Ischemic CVA

In the last decade management of acute ischemic stroke has been revolutionized by the introduction of “clot bursting” therapy with tissue plasminogen activator, or “t-PA “. Currently intravenous tissue plasminogen activator (t-PA) is the only drug approved by the US Food and Drug Administration (FDA), for the treatment of acute ischemic stroke within 3 hours of symptom onset.<sup>8</sup> Many stroke patients do not receive intravenous t-PA as they present beyond the 3-hour therapeutic window.

**Table 1 : Risk factors for ischemic stroke**

Non modifiable risk factors	Modifiable risk factors
• Age	• Arterial hypertension
• gender	• Transient ischemic attack
• Race	• Prior stroke
• Family history	• Asymptomatic carotid bruit
• Genetics	• Cardiac disease
	• Aortic arch atheromatosis
	• Diabetes mellitus
	• Dyslipidaemia
	• Cigarette smoking
	• Alcohol consumption
	• Elevated homocysteine
	• Low serum folate
	• Elevated anti cardiolipin antibodies
	• Oral contraceptives
	• Obesity
	• increased fibrinogen

**Table 2 : General clinical features of ischemic stroke**

Carotid circulation	Vertebrobasilar circulation
• Hemiplegia / hemiparesis	• Ataxia
• Aphasia	• Dysarthria
• Homonymous Hemianopia	• Vertigo/ Nausea / vomiting
• Conjugate eye deviation towards the infarct	• Conjugate or dysconjugate gaze palsies
• Hemianesthesia with hemiplegia on same side	• Crossed sensory motor paresis
• Apraxia / Neglect/ Extinction	• Horner's syndrome
	• Loss of consciousness

More recently developed therapeutic strategies offer the hope of safe and effective treatment beyond the 3-hour time window in selected patients. Plus in country like India where in many situations there are financial and technical constraints; thrombolysis is always not possible. Therefore other options like role of antiplatelet agents and anticoagulant and other issues like blood pressure management,

management of intracranial hypertension, and temperature management are equally important.

### **Initial management**

The initial management of acute ischemic stroke involves medical stabilization, including airway protection and ventilatory and hemodynamic support, followed by neurologic assessment, brain imaging, and evaluation of the appropriateness of thrombolytic therapy.

#### *Airway and ventilatory support*

Patients with acute stroke are at risk for respiratory failure from aspiration pneumonia owing to facial or bulbar weakness or an altered level of consciousness. Hypoxemia worsens cerebral ischemia and patients must be monitored closely with a goal to keep oxygen saturation greater than 95%.<sup>9</sup> If a patient requires endotracheal intubation, short-acting sedatives should be used. For lack of trials, ideal mode of ventilation in intubated stroke patients is not known. A commonly used mode is pressure support ventilation. Synchronized intermittent mandatory ventilation or assist control ventilation is recommended for patients who have intracranial hypertension or are comatose.<sup>10</sup> Excessive positive end-expiratory pressures (i.e., > 10 cm H<sub>2</sub>O) may be deleterious in patients with elevated intracranial pressure (ICP).<sup>11, 12</sup>

#### *Blood pressure and fluid management*

Patients with acute ischemic stroke often have elevated blood pressures in the first few days after symptom onset. This may be accounted by a variety of reasons, including physiologic compensation for cerebral ischemia, increased ICP, pain, or long-standing underlying hypertension.<sup>9</sup> Theoretical advantages of treating hypertension in acute ischemic stroke include concerns for hemorrhagic transformation of the ischemic infarct and worsening cerebral edema. Lowering blood pressure may compromise cerebral blood flow in the area surrounding the infarct resulting in stroke extension.

In normotensive individuals, cerebral blood flow is auto regulated over a mean arterial pressure (50–150 mm Hg).<sup>13</sup> Chronically hypertensives require a higher range of mean arterial pressures to maintain normal cerebral blood flow.<sup>14</sup> As many stroke patients have long-standing hypertension, blood pressure lowering may result in cerebral hypo perfusion and worsening ischemia. It is generally accepted that elevated blood pressures should not be lowered, unless the patient has received thrombolytic treatment, has a hypertensive emergency (aortic dissection, hypertensive encephalopathy, acute renal failure, acute pulmonary edema, or acute myocardial infarction), or has another contraindication to elevated blood pressure such as recent surgery. In the absence of controlled clinical trials, the American Stroke Association guidelines recommend that antihypertensive agents should be withheld unless the systolic blood pressure is greater than 220 mm Hg or the diastolic blood pressure is greater than 120 mm Hg.<sup>14,15,16</sup> If patients have received thrombolytic therapy, the guidelines advocate maintaining systolic blood pressure less than or equal to 180 mm Hg and diastolic blood pressure less than or equal to 105 mm Hg.<sup>8,15,16</sup> If blood pressure lowering is indicated, it should be instituted cautiously to avoid hypotension. A variety of intravenous agents may be used to lower blood pressures.  $\beta$ -adrenergic blockers (labetalol), calcium channel blockers (nicardipine), and angiotensin-converting enzyme inhibitors (enalapril) are preferred in patients with acute stroke because these agents are less likely to cause cerebral vasodilatation and ICP elevation, effects that might be anticipated with sodium nitroprusside or hydralazine.<sup>9,10,17,18,19</sup>

Arguments exist for inducing BP elevation in acute ischemic stroke to increase blood flow to the ischemic penumbra across patients with a broad BP range and in patients with intra and extra cranial stenosis. Typically, mean arterial pressure is increased 20% to 25% from baseline using intravenous isotonic fluids, phenylephrine, dopamine, or norepinephrine, while the patient's

neurologic status and hemodynamic stability are monitored closely. The impact of this therapy on stroke outcome is being evaluated in ongoing clinical trials. Some patients with acute cerebral ischemia resulting from severe extra cranial or intracranial vessel stenosis may benefit from induced hypertension.<sup>20</sup>

In addition to maintain cerebral perfusion it is important to assess the patient's volume status and correct any dehydration. Because stroke patients may be dehydrated on admission, and many of them cannot tolerate intake of oral fluids, normal saline infusions typically are started immediately. Hypotonic fluids should be avoided because these may contribute to worsening cerebral edema and increased ICP.<sup>21</sup>

#### *Neurologic examination*

Once patients vitals are taken care of, a quick neurologic assessment should be done in an efficient and reproducible manner by using the National Institutes of Health Stroke Scale (NIHSS).<sup>16,22,23</sup> This is a series of neurologic tests designed to assess the patient's level of alertness; comprehension; and motor, sensory, visual, and language function (Table 3).<sup>8</sup>

#### *Role of brain imaging*

CT and MRI assess rapidly the type of stroke (hemorrhagic versus ischemic) and the condition of the cerebral vasculature. Advances in CT and MRI techniques of cerebral perfusion help in identifying patients with salvageable brain tissue, who could benefit from recanalization therapies.

**CT Scan :** It is the most widely used and available brain imaging modality. A noncontrast head CT scan quickly excludes an intracranial hemorrhage and sometimes reveals an occluded artery that appears hyperdense owing to fresh clot in the vessel lumen (Fig. 1).

The admission CT scan also may show early signs of infarction like sulcal effacement, hypoattenuation (hypodensity) of the brain parenchyma, or loss of gray-white matter differentiation.<sup>24</sup>

**Figure 1 : CT scan of the head showing a thrombus occluding the stem of the left MCA (Arrow showing hyperdense MCA sign)**



Because a noncontrast head CT scan may fail to detect subarachnoid hemorrhage in approximately 10% of cases, a lumbar puncture to assess for the presence of subarachnoid blood is mandatory in patients who present with a clinical history of a sudden severe headache and a normal brain CT scan.

CT angiography of the head and neck may be used to assess the intracranial and cervical circulation for stenoses and occlusions. This may be particularly useful in patients who present just outside of the treatment window for intravenous thrombolysis, and who may be candidates for intra-arterial clot lysis because it can provide valuable information as to the location and extent of the clot. CT angiography also may be useful to assess the head and neck vessels in patients who cannot undergo MRI because of any reason. Perfusion CT assesses cerebral perfusion of the brain by tracking the first pass of an intravenously administered bolus of contrast material. It is found that perfusion CT may be capable of differentiating between regions of brain infarction and ischemic penumbra.<sup>25</sup> A complete CT examination including noncontrast CT, CT angiography, and perfusion CT can be performed in short time and therefore is of great help in acute setting when thrombolysis is considered.

**Table 3 : National Institutes of Health Stroke Scale**

Tested item	Title	Responses and scores
1a	Level of consciousness	0 = Alert 1 = Drowsy 2 = Obtunded 3 = Coma/unresponsive
1b	Orientation questions (two)	0 = Answers both correctly 1 = Answers one correctly 2 = Answers neither correctly
1c	Response to commands (two)	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task
2	Gaze	0 = Normal horizontal movements 1 = Partial gaze palsy 2 = Complete gaze palsy
3	Visual fields	0 = No visual field defect 1 = Partial hemianopsia 2 = Complete hemianopsia 3 = Bilateral hemianopsia
4	Facial movement	0 = Normal 1 = Minor facial weakness 2 = Partial facial weakness 3 = Complete unilateral paralysis
5	Motor function arm a. left b. right	0 = No drift 1 = Drift before 10 seconds 2 = Falls before 10 seconds 3 = No effort against gravity 4 = No movement
6	Motor function leg a. left b. right	0 = No drift 1 = Drift before 5 seconds 2 = Falls before 5 seconds 3 = No effort against gravity 4 = No movement
7	Ataxia	0 = Absent 1 = Ataxia in one limb 2 = Ataxia in two limbs
8	Sensory	0 = Normal 1 = Mild sensory loss 2 = Severe sensory loss
9	Language	0 = Normal 1 = Mild aphasia 2 = Severe aphasia 3 = Mute or global aphasia
10	Articulation	0 = Normal 1 = Mild dysarthria 2 = Severe dysarthria
11	Extinction or inattention	0 = Normal 1 = Mild (loss 1 sensory modality) 2 = Severe (loss 2 modalities)

*MRI Scan* has better resolution of the brain parenchyma and, in particular, evaluates the brainstem and cerebellum with higher resolution than CT. Advantage of diffusion weighted imaging (DWI) MRI sequence is that it shows an abnormal signal within minutes of ischemia onset, whereas noncontrast brain CT may take several hours for an infarction to become apparent.<sup>26,27</sup> Magnetic resonance angiography (MRA) evaluates the blood vessels of the brain and neck. One of the drawbacks of MRA is that it may overestimate the degree of arterial stenosis or give the impression of an arterial occlusion when a complete occlusion may not exist. Contrast-enhanced MRA is thought to decrease the likelihood of overestimation of the severity of luminal stenosis. MRI perfusion-weighted imaging (PWI) was developed to measure relative blood flow in the brain. Perfusion maps take 5 to 40 minutes of post processing time. The use of PWI and DWI together may identify patients who would benefit from arterial recanalization therapy outside the established 3-hour time window for intravenous t-PA by delineating the region of ischemic penumbra better.

However, in our setting with limited resources, CT scan is still the most widely used and probably most useful imaging modality when it comes to acute stroke management.

#### *Emergent laboratory evaluation and other tests*

In addition to brain imaging, several laboratory tests must be performed quickly to evaluate whether the patient is a candidate for t-PA. These include complete blood count including absolute platelet count, coagulation parameters, and serum glucose.<sup>8,9,15,28</sup> An electrocardiogram is indicated in all patients with acute stroke to detect myocardial ischemia and cardiac arrhythmias, such as atrial fibrillation. In selected patients, one should consider obtaining arterial blood gas measurements (Patients with respiratory distress or loss of consciousness), chest X-ray (for patients with respiratory distress or hypoxia), blood cultures (for patients with fever raising a concern for septic emboli), 2D ECHO in

patients suspected to have cardioembolic stroke, liver and renal function tests, toxicology screen, EEG especially in patients with unexplained altered sensorium.

#### *Characteristics of patients with ischemic stroke who could be treated with recombinant tissue plasminogen activator.<sup>15</sup>*

- Diagnosis of ischemic stroke causing measurable neurologic deficit
- Neurologic signs should not be clearing spontaneously
- Neurologic signs should not be minor and isolated
- Caution should be exercised in treating a patient with major deficits
- Symptoms of stroke should not suggest subarachnoid hemorrhage
- Onset of symptoms less than 3 hours before beginning treatment
- No head trauma or prior stroke in previous 3 months
- No myocardial infarction in the previous 3 months
- No gastrointestinal or urinary tract hemorrhage in previous 21 days
- No major surgery in the previous 14 days
- No arterial puncture at a noncompressible site in the previous 7 days
- No history of previous intracranial hemorrhage
- Blood pressure not elevated (systolic < 185 mm Hg and diastolic < 110 mm Hg)
- No evidence of active bleeding or acute trauma (fracture) on examination
- Not taking an oral anticoagulant, or if anticoagulant being taken, international normalized ratio is 1.7 or less
- If receiving heparin in previous 48 hours, activated partial thromboplastin time must be

in normal range

- Platelet count equal to or greater than 100,000 mm<sup>3</sup>
- Blood glucose concentration equal to or greater than 50 mg/dL ( $\geq 2.7$  mmol/L)
- No seizure with postictal residual neurologic impairments
- CT does not show a multilobar infarction (hypodensity  $> 1/3$  cerebral hemisphere)
- Patient or family members understand the potential risks and benefits from treatment

#### Treatment of acute ischemic stroke

##### a. *Intravenous thrombolytic therapy within the 3-hour time window*

t-PA is a fibrin-specific thrombolytic agent that activates plasminogen to form plasmin, a protease that cleaves fibrin and breaks the clot. The National Institute of Neurological Disorders and Stroke (NINDS) acute stroke study group enrolled 624 patients presenting within 3 hours of symptom onset in a randomized, double-blind, placebo-controlled, two-part study evaluating the effect of intravenous tPA (at 75% of the recommended dose for myocardial infarction) for all types of ischemic stroke.<sup>8</sup> The study showed improved neurologic outcomes in the t-PA group, at the end of 24 hours as well as at 3 months using different neurologic rating scales. All outcome measures showed benefit in the t-PA group with 11% to 13% absolute difference in neurologic scores in the tPA-treated patients. The symptomatic intracranial hemorrhage rate was higher in the t-PA group (6.4%) than in the placebo group (0.6%) ( $p < .001$ ). Mortality rates at 3 months were similar in both groups, 17% for the t-PA group and 21% for the placebo group ( $P = 30$ ). Based on these results, the FDA approved the use of intravenous t-PA within 3 hours from stroke onset at a dose of 0.9 mg/kg, with a maximum dose of 90-mg.<sup>8,28</sup> Since the approval of intravenous t-PA, two prospective, monitored, phase 4 studies have shown similar

beneficial results.<sup>29,30</sup>

Table 4 shows the proposed protocol during intravenous thrombolysis.<sup>8</sup>

##### b. *Intravenous thrombolytic therapy beyond the 3-hour time window*

This issue is being studied through many trials but the recent evidence is against the use of thrombolytics beyond the 3 hr-time window. The Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) trial was a randomized, placebo-controlled trial evaluating the use of 0.9 mg/kg of intravenous tPA in the 3- to 5-hour treatment window.<sup>31</sup> The study was stopped early when interim analysis revealed a low likelihood of benefit in the treatment group. Other trials with t-PA beyond 3-hr window also did not show significant benefit.<sup>32,33</sup> Several clinical trials evaluated intravenous streptokinase for acute stroke in Europe and Australia. European trial used a 6-hour time window for intravenous treatment with 1.5 million U of streptokinase (100% of myocardial infarction dosage).<sup>34,35</sup> The Australia Streptokinase Trial (ASK) used the same dose, but shortened the time window to 4 hours.<sup>36</sup> All these trials were stopped early because of an unacceptable high number of deaths and symptomatic intracranial hemorrhages in the treatment groups.

##### c. *Newer thrombolytic agents*

Many recent studies are evaluating alternative thrombolytic agents, such as ancrod (Viprinex), a viper-derived enzyme that cleaves fibrinogen and promotes endogenous release of plasminogen activator from the vessel wall.<sup>9,37,38</sup> Desmoteplase, a protease found in vampire bat saliva, (DEDAS and DIAS trials).<sup>39</sup> Glycoprotein IIb/IIIa antagonists also are being evaluated alone (AbESST) and in combination with low-dose intravenous t-PA (the Clear Stroke Trial).<sup>40</sup> The ReoPro Retavase Reperfusion of Stroke Safety Study–Imaging Evaluation (ROSIE)

**Table 4 : Treatment of ischemic stroke with intravenous t-PA**

- Determine the patients eligibility for treatment
- Infuse t-PA at a dose of 0.9 mg/kg (maximum 90 mg) over a 60 minute period with the first 10% of the dose as bolus over a 1 minute period
- Perform neurologic examination every 15 mts during infusion, every 30 mts for the next 6 hrs and every 60 mts for the next 16 hrs (preferably in an ICU). If severe headache, nausea and vomiting, acute hypertension occur, discontinue the infusion and get urgent CT done.
- Measure blood pressure every 15 mts for 2 hrs, every 30 mts for 6 hrs, and every 60 mts for 16 hrs. Repeat measurements more frequently if systolic pressure is > 180 mmHg or diastolic pressure is > 105 mm of Hg, and administer antihypertensive drugs as needed to maintain blood pressure at or below these levels.

trial is studying the use of abciximab alone and in conjunction with escalating doses of reteplase.<sup>41</sup>

Although several novel agents hold promise for stroke patients, current care of patients with acute ischemic stroke still emphasizes NINDS/FDA-defined use of intravenous tPA dosed at 0.9 mg/kg with a maximum dose of 90 mg. The risk of symptomatic intracranial hemorrhage is approximately 6% when the NINDS/FDA-approved guidelines are strictly followed.

d. *Intra-arterial thrombolysis*

Here idea is to directly administer thrombolytic agent intraarterially into the clot with the help of a catheter. The catheter is passed through the clot which is mechanically disrupted. This allows for a lower t-PA dose and a decreased risk of systemic hemorrhagic complications. But the biggest disadvantage of this therapy is the time and expertise required for catheterization, restricting this therapeutic modality to medical centers that have interventional neuroradiologists. Other agents which have been used intraarterially and have shown varying benefits include prourokinase and urokinase.<sup>42,43</sup>

Intra-arterial thrombolytic therapy for acute stroke may be considered in patients with middle cerebral artery occlusions who can be treated within 3 to 6 hours (more time window than I.V. Thrombolysis) after symptom onset and who have no (or minimal) signs of infarction on their baseline CT scans.<sup>9,28</sup> Intra arterial thrombolysis has also been tried in patients with basilar artery and internal carotid artery bifurcation (carotid T) blocks.<sup>9,28</sup>

e. *Combined intravenous and intra-arterial thrombolysis*

This approach has been tried in one study.<sup>44</sup> The results of this study suggest that a combined intravenous plus intra-arterial approach to recanalization is feasible and safe. But further trials are needed to establish this as a primary modality.

f. *Mechanical thrombolysis*

This includes removal of clots from the cerebral circulation by endovascular devices. These devices have been tested in patients with acute stroke who are ineligible for or who failed intravenous t-PA treatment. Moderate benefit in recanalisation and neurodeficit was found.<sup>45,46,47</sup> However this also requires a trained hand, good infrastructure and a bigger financial burden on the patient.

g. *Primary angioplasty and stenting* have been shown to be superior to thrombolytic therapy in patients with acute myocardial infarction. This method is most effective in atherosclerotic arteries that have in situ thrombus rather than in blood vessels that are occluded by embolic material.<sup>48</sup> Artery-to-artery embolism or cardioembolism causes many strokes, and these types of clots tend to recur into an occlusive position despite angioplasty. With further technologic refinements, this field may play a more important role in the management of acute ischemic stroke in the future.

#### h. *Neuroprotective strategies*

Neuroprotective agents which looked promising in laboratory models of focal ischemia have not shown benefit in clinical studies. Mild-to-moderate hypothermia (2–5° C below normal brain temperature) is said to reduce ischemic damage and improve behavioral outcomes in animal models.<sup>49</sup> The beneficial effects seem to be greatest when hypothermia is initiated early. The Stroke-Acute Ischemic NXY-059 Treatment (SAINT) trials are randomized, double-blind, placebo-controlled, phase 3 trials evaluated therapeutic benefit of intravenous NXY-059, a nitroxyl radical trapping agent, administered within 6 hours of stroke onset and showed statistically significant improvement.<sup>50,51</sup> Other agents which are being evaluated as neuroprotectives include intravenous magnesium within 2 hours and high dose albumin within 5 hours of symptom onset.<sup>52,53</sup>

Citicoline (or CDP-choline), a compound normally present in all cells in the body, is both a neuroprotective drug, when administered exogenously, and an intermediate in membrane phosphatide biosynthesis. A review of trials involving use of citicoline in acute ischemic stroke concluded that treatment with oral citicoline within the first 24 hours after symptom onset in patients with moderate to severe stroke increases the probability of complete recovery at 3 months.<sup>54</sup>

#### i. *Antiplatelet therapy in acute ischemic stroke*

For patients who are not eligible for t-PA, aspirin is the only antiplatelet drug that has been evaluated in the acute treatment of stroke. A study enrolled 21,106 patients to receive aspirin 160 mg/d or placebo within 48 hours of stroke onset with continued therapy for 4 weeks.<sup>55</sup> The aspirin-treated group had a small but significant decrease in mortality (3.3% versus 3.9%;  $P = .04$ ) and recurrent ischemic stroke (1.6% versus 2.1%;  $P = .01$ ). The International Stroke Trial (IST) enrolled 19,435 patients for

randomized treatment with aspirin alone (300 mg/d), subcutaneous heparin alone, aspirin and heparin combined, or neither agent within 48 hours of stroke onset.<sup>56</sup> In the aspirin-only group, there were significantly fewer recurrent strokes within the first 2 weeks (2.8% versus 3.9%) and a trend toward a reduction of death or dependence at 6 months (61.2% versus 63.5%). These trials indicate that patients should be treated within 48 hours of ischemic stroke with aspirin. In patients who receive tPA, antiplatelet therapy should start 24 hours after thrombolytic therapy.<sup>8,9</sup>

#### j. *Anticoagulation in acute ischemic stroke*

The rationale behind the use of anticoagulants for acute ischemic stroke is that the majority of ischemic strokes are caused by a thrombus obstructing an artery supplying a region of the brain. Therefore, one could postulate that prevention of further clot formation or propagation could affect survival and recurrence. A systematic review of 22 trials studying different types of anticoagulation in acute ischemic stroke concluded that immediate anticoagulation for acute ischemic stroke is not associated with net short-term or long-term benefit. There is no support for routine use of any type of anticoagulant in this setting.<sup>57</sup>

However a subgroup analysis of patients who presented with atrial fibrillation and acute ischemic stroke showed a significant reduced risk of recurrent ischemic strokes (4.9% versus 2.8%), but the increased risk of intracranial hemorrhage in this study negated any potential benefits (2.1% versus 0.4%) at 14 days.<sup>56</sup> In another subgroup analysis, few studies found better outcome among patients with large artery atheroembolic strokes.<sup>58,59</sup>

Thus there is still no clear answer over the issue of anticoagulation in acute stroke though they still continue to be used in situations like cardioembolic and atheroembolic strokes, strokes after dissection of vessels supplying the

brain and strokes in known hypercoagulable states of hereditary & acquired nature. In these settings their use seems to be justified.

#### *Complications of acute ischemic stroke and its treatment*

##### *a. Hemorrhagic transformation*

A dreaded complication of thrombolytic therapy in stroke patients is intracranial hemorrhage. Symptomatic intracerebral hemorrhage occurs in approximately 6% of patients who receive intravenous t-PA & it has been associated with high morbidity and mortality.<sup>8,60</sup> Risk factors for symptomatic intracerebral hemorrhage after thrombolytic therapy include very severe stroke, early infarct signs on admission brain CT (> 1/3rd hemispheric involvement), older age, elevated systolic blood pressure, low platelet count, elevated serum glucose (> 400 mg%), history of diabetes, history of congestive heart failure, longer time to treatment, and low levels of plasminogen activator inhibitor (PA-i).<sup>61,62,63,64,65,66</sup> If one or more of these risk factors are present then that should not be considered a contraindication to tPA treatment in a patient who otherwise qualifies for thrombolysis based on the NINDS criteria.

Most t-PA related intracranial hemorrhages occur in the first few hours after treatment as the biologic half-life of tPA at the clot site is approximately 45 minutes. If a patient has a significant neurologic change during intravenous t-PA administration, the infusion should be stopped, and an emergent head CT scan should be obtained. Laboratory tests should be performed immediately, including coagulation parameters, fibrinogen, and complete blood count with platelets. If a symptomatic intracerebral hemorrhage is diagnosed, emergent infusion of fresh frozen plasma (5–10 mL/kg) and cryoprecipitate (0.1 bag/kg) is recommended.<sup>67</sup>

##### *b. Cerebral edema*

Patients with large hemispheric infarctions involving the middle cerebral artery territory and patients with large cerebellar infarctions are in a particular danger of mass effect and brain herniation, brainstem compression, coma, and death. Mass effect caused by ischemic infarcts typically peaks 3 to 5 days after symptom onset. The best way to detect this complication is careful and frequent clinical examination for signs of herniation and alteration of sensorium. Continuous intracranial pressure (ICP) monitoring may not be that useful because the clinical deterioration caused by regional tissue injury and compression precedes a global increase in ICP in most patients.<sup>10,68</sup>

In patients with suspected elevated ICP, initial management should consider adequacy of airway, breathing, and circulatory function. The head should be elevated 30° to decrease ICP and optimize cerebral venous return. Hyperosmolar therapy should be instituted using mannitol, hypertonic saline, or both. Mannitol extracts intracellular and interstitial water from the brain. It is administered as a 0.5 to 1 g/kg loading dose and can be followed by boluses of 0.25 g/kg every 6 hours. The main complications associated with mannitol use are hypovolemia, hypotension, and electrolyte disturbances resulting from osmotic diuresis. Hypertonic saline has been proposed as an alternative to mannitol and may be of particular advantage in hypovolemic patients. These treatments should not be stopped abruptly as rebound edema may occur. Between the two few studies show potential benefits of hypertonic saline over mannitol in the treatment of stroke-related brain edema and increased ICP.<sup>69,70</sup> Hyperventilation should be used only in emergency situations and as a temporary measure until more definitive therapies can be initiated as it may compromise cerebral blood supply. Corticosteroid therapy does not improve cerebral edema associated

with ischemic or hemorrhagic stroke and better be avoided.<sup>71</sup>

Clinical studies of craniectomy suggest a decrease in mortality and, in some reports, improved neurologic outcome in-patients with hemispheric infarctions with severe raised ICP.<sup>72,73</sup> Decompressive surgery also may benefit patients with large cerebellar infarctions, in particular patients with brainstem compression, and neurologic deterioration.

c. *Deep venous thrombosis*

Deep venous thrombosis and pulmonary embolism are a cause of early death in 5% of stroke patients.<sup>74</sup> Low-dose heparin or low-molecular-weight heparin may be used for prevention of deep venous thrombosis. Patients who have received thrombolytic therapy should not receive anticoagulation therapy for deep venous thrombosis prophylaxis in the first 24 hours.<sup>8,9</sup> Sequential compression devices should be used if the patient is unable to receive heparin or low molecular weight heparin.

d. *Hyperglycemia*

Worsened outcomes have been reported in patients with elevated admission glucose levels. Hyperglycemia has been associated with increased cerebral edema volumes and higher hemorrhagic transformation rates with or without intravenous t-PA administration.<sup>64,75,76</sup> Dextrose-containing intravenous infusions should be avoided in the acute setting of stroke as stroke patients already tend to have stress related hyperglycemia. All patients should have serial blood glucose checks and adequate correction using short-acting insulin.

e. *Fever*

Hyperthermia adversely affects stroke outcome in animal models and in observational clinical studies.<sup>49,77,78</sup> Pneumonia and urinary tract infections are common in stroke patients and must be worked up aggressively in a febrile patient. Deep venous thrombosis also may

cause fever and should be considered in-patients with unexplained fevers. Fever is treated with antipyretics and other routine cooling therapies.

## Summary

Ischemic stroke is one of the prominent causes of mortality and morbidity all over the world. Though this subject has always received great amount of attention from medical researchers, there are still many grey areas in its etiopathogenesis and few advances have been made in the treatment of acute ischemic stroke.

Different types of thrombolytic therapies have shown promise in this area. Intravenous t-PA in particular seems to be a reasonable option and can be administered to all patients with acute ischemic stroke who present within 3 hours of stroke onset and meet the NINDS inclusion and exclusion criteria. The risk of symptomatic intracranial hemorrhage with intravenous tPA is approximately 6%. Intra-arterial tPA and mechanical thrombectomy are alternative treatment strategies for acute stroke patients who are ineligible for or fail intravenous tPA treatment. However the benefits of these early trials need to be substantiated with larger randomized trials. In country like ours where affordability is always an issue the other conventional aspects of acute ischemic stroke management like maintenance of euglycemia, euolemia, and normothermia, management of blood pressure, cerebral edema and other complications and judicious use of antiplatelet agents and anticoagulants in appropriate situations still remain principal modalities of management.

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