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Review Article

Early management of acute ischemic stroke: review of literature and proposed guidelines

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Several promising clinical trials on interventions for the treatment of acute ischemic stroke and the approval of the use of intravenous recombinant tissue plasminogen activator (rTPA) by Food and Drug Administration in 1996, has lead to new guidelines on the management of acute stroke by the Stroke Council of the American Stroke Association (SCASA),[1] where panel has applied rules of evidence and formulation of strength of recommendations of American Heart association guidelines panels .This article is an attempt to review the recent literature on available therapies and guidelines on the subject. The treatment of acute stroke is discussed under following heading

1. Immediate emergent stroke protocol
2. Measures to restore or improve perfusion:
3. General supportive measures and
4. Treatment of acute neurological complications of stroke

ACUTE STROKE: IMMEDIATE EMERGENT STROKE PROTOCOL

Acute ischemic stroke, now called "**Brain Attack**", is an emergency. In order that these cases are managed efficiently in a coordinated manner, each institution should have a **"Stroke Team".** Several European studies [2, 3] have shown the utility of '**Comprehensive Stroke Units',** in reducing the morbidity and mortality from stroke with positive effect persisting for years (Level 1) and the benefits comparable to rTPA therapy. There is no strict definition of what constitute stroke units but conventionally should have trained staff i.e. neurologist, neurosurgeon, Radiologist, Nurses and Rehabilitation personnel, and monitoring and investigative facilities round the clock. Advantage of stroke team is that a coordinated and a specialized care can be given to all patients regardless of time interval and the type and the severity of stroke.

Five "Rs" are to be remembered as critical elements in acute stroke care[4] are (a) Recognition (Time taken by patients to recognize their symptoms and call for help), (b) Reaction (Time taken by emergency medical services to react), (c) Response (Time from emergency department to CT scan), (d) Reveal (Time taken by stroke team to respond), and (e) Perfusion (Time taken to start rTPA therapy). Guide line for rapid evaluation have been suggested [5, 6] as Door to Physician evaluation-10 minutes, Door to Stroke team notification-15 minutes, Door to CT initiation-25 minutes, Door to CT interpretation- 45minutes, Door to drug (needle)-60minutes and door to monitor bed including rTPA therapy- 180 minutes respectively.

Emergency protocol[7] on arrival in emergency department the patients should be (a) rapidly evaluated to ensure adequate airways, breathing, and circulatory status, (b) Temperature, pulse, blood pressure and oxygen saturation, should be monitored continuously especially in patients with moderate to severe symptoms, (c) Endotracheal intubation or mechanical ventilation should be instituted in those who are unable to protect the airways or have a poor ventilatory drive, (d) Stroke patients with stable respiration may receive supplemental oxygen to maintain an adequate oxygen saturation as hypoxia worsens the ischemia, (e) Intravenous (IV) access should be obtained and 0.9% normal saline is started at 50 ml/hour with saline lock in opposite arm., (e) The investigations to be done include 12 lead ECG (to exclude ischemia or arrhythmia), Blood sugar (to exclude hypo or hypoglycemia as the cause), complete hemogram, serum electrolytes, metabolic parameters and coagulation profile. A toxicological screening is needed when there is suspicion of drug abuse, (f) assessment of stroke through history for risk factors, to establish the time of stroke, physical and cardiovascular examination (may detect the cause of stroke) and neurological examination should be done to assess severity and its quantification as per by NIHS scale[8]. Lastly CT scan to exclude hemorrhage and to detect early cerebral edema.

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The risks and benefits of lowering of BP in acute stroke are still nuclear. Elevated blood pressure can results from stress of stroke, full bladder, pain, preexisting hypertension, cerebral hypoxia and raised intracranial pressure (ICP). Theoretically, reasons to lower BP include reducing formation of cerebral edema, lessening the risk of hemorrhagic transformation, prevention of further vascular damage and early recurrent stroke. In acute stroke autoregulation is impaired and their cerebral perfusion is maintained by mean intra arterial pressure. Rise in BP is a physiological response to raised ICP to maintain the cerebral perfusion pressure (CPP). Hence, its reduction may increase infarction by reducing CPP. The JNC 7 report[9] recommends control of BP at an intermediate levels (approximately at 160/110 mm of Hg). Precipitous lowering with sublingual nifedipine is to be avoided[10]. Antihypertensive therapy should be considered before and after thrombolytic therapy or when patient is having acute myocardial ischemia, aortic dissection, hypertensive encephalopathy or after significant hemorrhagic conversion of infarction[11]. The criteria are stricter under rTPA therapy protocol approved by FDA[12] (Table 2).

ACUTE STROKE: MEASURES TO IMPROVE OR RESTORE PERFUSION

Restoration or improvement in perfusion to ischemic area is most important therapeutic strategy in the management as most ischemic stroke are due to thromboembolic occlusion of an intracranial arteries. The aim is to salvage the brain tissue in ischemic penumbra on the periphery of infracted brain tissue. The measures available are (1) IV thrombolysis by rTPA and other thrombolytic agents, (2) Intra arterial thrombolysis, (3) Antithrombotic therapy,(4) Surgical treatment and (5) Volume expansion, vasodilators, induced hypertension,

1. Intravenous Thrombolysis by rTPA

The streptokinase was first used in acute stroke in 1960; the three randomized trials were terminated prematurely due to high rates of intracerebral hemorrhage and mortality in the treated group [13-15]. European Cooperative Acute Stroke Study (ECASS I) 1, trial[16] was the first large multicenter, randomized trial. It was followed by National Institute of Neurological disorders and Stroke (NIDS) trial [12] and ECASS II trial[17] NINDS trail[12] provided valid evidence for the beneficial effects of rTPA therapy when given within 3 hours. The number needed to be treated with 95% confidence interval (CI) is 6 (5-11) for regaining functional independence at 3 months and 9 (5-25) for making a full recovery at 3 months [18]. The beneficial effects were seen in all subtypes of stroke and were sustained at 1 year[18]. A fact confirmed later by meta-analysis[19] which also revealed fewer deaths or dependence (odd ratio 0.58:95% CI).46-0.74) i.e. 13 (95% CI 7-18) fewer dead or dependent patients per 100 treated with thrombolysis. It was approved, with strict guidelines, by FDA in 1996 (Table 1-3).

Recommendations SCASA[1] on rTPA therapy are i.e. (a) Clinical examination provides about the cause of neurological symptoms and screens for contraindications to rTPA therapy (Grade 1), (b) Patients generally require a limited number of investigations as apart of emergent evaluation (Grade 1) and all institution should have these diagnostic facilities round the clock. If not available, the patient should be transferred to another hospital, (c), CT scan is the most important test (Grade A) and radiologist trained to interpret should be available (Grade B), (d) DWI and PWI MRI is useful, but their use outside the research programs should not the delay rTPA therapy in eligible patients (Grade B), (e) Other tests including imaging of vessels and heart can be obtained after initial treatment except where intra arterial thrombolysis is planned., (f) IV streptokinase has not been found useful while data is incomplete on second generation thrombolytic agents

Table 1: Thrombolytic therapy

Inclusion criteria:

a. Age 18 years or more.
b. Clinical diagnosis of stroke with clear symptoms within 3 hours
c. Non contrast CT without evidence of hemorrhage

Exclusion criteria

a. Medical history of intracranial hemorrhage (ICH), intracranial neoplasm, aneurysm, arteriovenous malformation; Stroke or head trauma with in last 3 months; Gastrointestinal or urinary bleeding within preceding 21 days, Major surgery or biopsy of parenchymal organs within preceding 14 days12; recent myocardial infarction; seizures at onset; Current use of anticoagulation with prolonged prothrombin time (> 15 seconds); use of heparin within 48 hours with prong partial thromboplastin time.
b. Clinical signs revealing rapidly improving signs only, mild and isolated neurological deficit (i.e. aphasia, ataxia, dysarthria or sensory loss alone); BP > 185/110

mms of Hg or requiring aggressive therapy to control.

c. CT findings of infarct more than 1/3rd of the territory and lab findings of platelets count<100,000/cmm and Blood glucose <50 or > 400 mg/dl.

Table 2: Protocol for rTPA administration

a. After emergency protocol for acute stroke treatment and ensuring that all inclusion criteria have been made and no exclusion criteria are present, rTPA is started.

b. rTPA Dose is 0.9 mg /kg of body weight. !0% is given as a bolus dose in one minute followed by rest of the dose over one hour.

c. Systolic BP should be maintained below 185/110 as per protocol.

d. Patients should be observed in ICU ward. If patient develop decline in sensorium or neurological functions or if severe headache develops and CT immediately. If ICH occurs patients should receive cryoprecipitate, fresh frozen plasma and platelets and neurosurgical consultation should be obtained.

Table 3: Protocol for management of hypertension

When patient is eligible for rTPA therapy

a. Pre treatment: BP more than 185/110mms of Hg: Labetalol10-20 mg IV over 1-2 minutes may repeat once, or Nitropaste 1-2 inches. If BP is maintained at desired levels (<185/110) administer rTPA.

b. Blood pressure to be monitored every 15 minutes for 2 hours; every 30 minutes for next 6 hours and then every 60 minutes until 24 hours after treatment.

c. If BP is 185-230/105-120 mms of Hg: Give IV Labetalol 10 mg over 1- 2 minutes: repeat or double every 15 minutes till maximum dose of 300 mg is given under constant monitoring. Or give initial bolus dose followed by IV infusion at a @ 2-8 mg/ min.

d. If BP is more than 230/121-140 mms of Hg: Give Labetalol as above, if response is unsatisfactory infuse Nitroprusside at a @ of 0.5-1 microgm/ Kg / min under constant monitoring, preferably intra arterial

e. If diastolic BP is more than 140mms of Hg: Give Nitroprusside as above.

When patients not eligible for rTPA therapy

a. BP less than 220/120 mms of Hg: Observe (level V): treat when end organ involvement is noted e.g. aortic dissection, acute MI and pulmonary edema.

b. BP more than 220/120-140 mms of Hg: Labtalol 10-20 mg IV over one minute: repeat or double the dose every 10 minutes (maximum 300mg) or Nicardipine 5 mg/hr Iv infusion and titration to desired levels by Increasing 2.5 mg every 5 minutes (maximum 15 mg/hr). Aim for10 to 15% reduction of BP.

c. Diastolic BP more than 140 mms of HG: IV Nitroprusside 0.5 mcg/kg/min infusion under constant monitoring: Aim only 10% to 15% reduction.

2. Intra arterial thrombolysis

Intra arterial (IA) therapy was given to an increasing number of patients (Level V) using rTPA, Urokinase and Prourokinase (an inactive single chain precursor of urokinase with significant fibrin specificity) (1). Analysis of these reports revealed [20] that 64% patients had effective decimalisation, MCA occlusions responding better and ICA occlusion responded the worst. 69% of the basilar artery rcanalization was noted. Overall, 42% patients had good outcome but 18.5% had hemorrhagic complications. Advantage of IA thrombolysis is offset by inherent risk of catheter angiography and the delays in performing the procedure. Two prospective randomized of IA thrombolysis by recombinant prourokinase (r-proUK) in combination with heparin, PROACT I & II trials [21,22] reported higher rate of recanalization but there was increased risk of ICH (level1).There was no different in mortality.

Emergency Management of Stroke (EMS) investigators performed a small pilot study of combined IV and IA thrombolytic therapy compared

with IA therapy alone[23]. Thirty five patients presenting within 3 hours were randomized to receive either 0.6 mg/kg of IV rTPA or placebo and were taken immediately for angiography and if thrombus was visualized, the patients were randomized to receive IA rTPA. The dose was determined by the amount of rTPA required to establish patency, with maximum dose being 20 mg/kg. If acute thrombus was not visualized no further therapy was under taken. Of 35 patients enrolled, only 25 had thrombus seen on angiography. The combination IA & IV rTPA therapy group had 67% partial canalization at 2 hours as compared to 60% in IA group. Three patients in combined group had life threatening ICH. This trial was terminated on approval of NIND rTPA trial but it suggested feasibility of combined protocol. Physician with expertise are using IA rTPA to treat occlusion of middle cerebral artery and basilar artery even as there is no data on rTPA use.

Recommendations of SCASA[1] are : (a) IA thrombolysis is an option in selected patients with large stroke (Grade b) and requires an experienced endovascular interventional radiologist and immediate access to angiography, (b) The tested drug r-proUK is not available for clinical use, (c) The extrapolation of the result to and use of IA rTPA is based on consensus as supported by case series data which suggest beneficial effects of IA rTPA in basilar artery occlusion of longer duration, (d) The availability of IA rTPA therapy should not preclude IV rTPA therapy and (e). It is not approved by FDA.

3(a) Antithrombotic therapy: Anticoagulants: Heparin

Various authors have argued for or against the use of heparin in partial stroke, progressing stroke, recent or crescendo TIAs, cardioembolic strokes and Vertebrobasilar strokes but its usefulness for acute stroke management has remained controversial. Only one of these trials was double blind placebo controlled, where no significant difference was found between treated and placebo group [24]. In the only progressive trial, 50% of 36 patients continued to progress despite adequate anticoagulation with IV heparin [25]. IST Trial [26] though having many defects (i.e. absence of biological monitoring of level of anticoagulation and adjusting the dose to biological response, patient knew about the drugs and no prior CT Scan was done), showed a low early recurrence among patients with auricular fibrillation but the effect was negated by increased rate of bleeding (level-1)[1]. In view of recent studies reporting a low recurrence rate of 0.3% to 0.5% per day in cerebral embolism[26-28] and the occurrence of early hemorrhagic transformation in cardioembolic stroke[29], routine use of heparin in presumed cardioembolic stroke can not be recommended, and should be reserved for those having definite source of embolism. Recent Mega trials have shown that risk of early recurrent stroke in general population is low (1.07 stroke per 100 patients per week) obviating the need of early anticoagulation with heparin in acute stroke[30]. Overall these trials do not support the use of heparin for acute stroke[1].

3(b) Antithrombotic Therapy: Low Molecular Weight Heparin (LMWH)

LMWH, produced by chemical or enzymatic cleavage of UF heparin, have less affinity for plasma proteins, endothelial cells and platelets, owing to their shorter chain length, and thus have a long half life allowing daily or twice daily administration with no requirement of laboratory monitoring and fewer bleeding complications. A small trial of nadroparin[31] given subcutaneously twice daily for 10 days in 306 patients within 48 hours showed lower mortality in those receiving a larger dose at 6 months (Level I & II)[1] only. It was not confirmed by other trials [32-34] on the other hand risk of bleeding complications increased with nadroparin especially with larger dose (Level 1)[1].

3 (c) AntithromboticTherapy: Heparinoids

Heparinoids are natural or semisynthetic glycosaminoglycans that are structurally related to heparin and possess similar properties. ORG 10172(Danaproid) was tried in 1281 patients with acute ischemic stroke who presented within 24 hours and randomized to receive either drug or placebo for 7 days[28] . No favourable or likely favourable outcome was noted (Level 1). There was increase hemorrhagic transformation (Level 1)[1]. Only patient due to large artery atherosclerosis improved (Level II)[1]

3(d) Antithrombotic Therapy: Heparin as an Adjunct Therapy

Adjunct therapy use of heparin and antiplatelet agents are contraindicated during first 24 hours following rTPA therapy. In two r-proUK trials[21, 22] which included heparin as a part of adjunct therapy with placebo receiving only heparin. In the first trial[21], hemorrhagic transformation was higher with higher dose of heparin (Level II)[1] Two small studies [35, 36] tried heparin immediately following rTPA (Level V)[1] as a part of acute treatment regimen with favourable results and major bleeding complications not higher than after rTPA alone[37,38]. Additional; trial of heparin are under way [39].

Recommendations of SCASA[1] are (a) As parent rally administered anticoagulants increase the risk of

serious bleeding complication (Level 1) and do not reduce the risk of early recurrent stroke, including the patients with cardioembolic stroke (Level I) , anticoagulation in acute stroke with an aim to improve outcome and for prevention of early stroke is not indicated.(Grade A), (b) Urgent anticoagulation is not indicated in moderate to serious stroke because of high risk of intracranial bleeding complications (Grade A), (c) Anticoagulant therapy within 24 hours of treatment with IV rTPA is not recommended (Grade A), (c) Parentral anticoagulation should not be given unless possibility of ICH is excluded by neuroimaging and those receiving it should have strict dose control to keep the level of anticoagulation within the desired range, (d) As one trial showed that anticoagulants might improve out come in one subgroup i.e. stroke due to large artery thrombosis (Level II). More studies are required if any subgroup or patients at high risk of recurrent embolism may benefit from urgent anticoagulation, and (e). Additional studies are needed to define the role of adjunctive anticoagulation in addition to mechanical or pharmacological role in acute stroke (Level II-V).

3(d) Antithrombotic Therapy: Antiplatelet Agents

In the International Stroke Trial [26] 19,439 patients of ischemic stroke were randomized, (within 24 of ictus), in unblended fashion to receive 300 mg aspirin alone or with one or two doses of heparin for 14 days showed a significantly reduction of in rate of stroke by aspirin (2.8% versus 3.9% in placebo) but with no effect on mortality (Level I). A modest but significant increase in serious systemic haemorrhage was noted with a small but significant increase in the risk of ICH (Level I) but a significantly lower incidence of death at 6 month. (Level I). The CAST Trial [27] tested aspirin, 160 mg/day, in 21,106 patients (within 48 hours of ictus) in a randomized placebo controlled trial. A significant reduction in mortality and recurrent stroke was noted at 4 week (Level I) with a modest but not significant in the risk for ICH and significant increase in systemic haemorrhage was reported. At discharge mortality was significantly reduced but there was no difference in long term complete recovery or death (Level I). A preplanned combined analysis of these two studies showed decrease in stroke recurrence, mortality or dependency (Level I) but with a small but significant increase in hemorrhagic transformation of infarct (Level 1).

Of other antiplatelet agents, glycoprotein IIB & IIIA are is used as adjunct to cardiovascular procedures. Safety of one of these agents abciximab has been demonstrated in a small trial (Level II)[40].

Recommendations of SCASA[1] (a) Aspirin should be given within 24 to 48 hour of stroke onset. In most patients (Grade A), (b) Use of aspirin as an adjunct therapy to rTPA therapy is not indicated (Grade A), (c) Aspirin should be used as substitute for other interventions e.g. rTPA therapy (Grade A), (d) at present no recommendations can be made about other antiplatelet agents (Grade C)

3 (e) Antithrombotic therapy: Defibrinogenating Agent: Ancrod

Ancrod, a defibrinogenatic agent extracted from the venom of Malayan pit viper, was used in STAT (Stroke treatment with Acrod trial). Five hundred stroke cases, within 3 hours, were randomized to receive a 3 day infusion followed by bolus dose of ancrod on day 4 & 5 or placebo. The doses were adjusted with fibrinogen levels (target fibrinogen level 40-70 mg/dl.). A statistically different good out come (Level I) was noted at 3 months (41% versus placebo). The rate of symptomatic ICH was 5% in ancrod group and 2% in placebo respectively. It increased when fibrinogen level was below the target level. No difference in mortality was noted[41, 42]. At present clinical data does not support the use of ancrod (Grade A).

4. Surgical Intervention

Though, some surgeons have reported encouraging results from endarterectomy (Level V)[43-45] with a low complications[46,47] (Level V) and intracranial-extracranial (IC-EC) bypass surgery (Level V)[48.49] in patients with acute stroke and with anticoagulation followed by delayed operation[50]. These procedures are associated with high morbidity[50, 51] and a high risk of intracranial hemorrhagic complications and have failed to improve outcome (Level V) [52]. Endovascular treatment i.e. balloon angioplasty of thrombus, mechanical removal of clot from MCA, stenting of underlying atherosclerotic stenotic lesion, suctions thrombectomy, laser assisted thrombolysis of embolus and power assisted Doppler thrombolysis have been reported (Level V)[53-56]. Intravenous use of glycoprotein IIb/IIIa inhibitor has been used to enhance the clot lysis[40, 57, 58]. Because of lack of evidence for safety and efficacy of these procedures, they are not recommended (Level C)[1].

Treatment of Acute stroke: General measures

As an approximately 25-30% stroke deteriorate during first 24 hours[59], it is mandatory that they should be treated in ICU, preferably in "Stroke units" and closely monitored during this period. The aim is

to prevent complications, to institute remedial measures if complications do occur, to plan secondary preventive measures to prevent recurrence of stroke and for patient's rehabilitation. General measures include[60, 61].

1. **Air way management**[1, 62] requiring intubation and mechanical ventilation to prevent tissue hypoxia and further worsening of stroke, may be needed in 7-10% of stroke cases especially in those having altered sensorium or bulbar dysfunctions. The patients should be monitored to maintain an oxygen saturation of more than 95% (level V). Routine use of supplemental oxygen in all cases is not supported by trials (Level V). The independent predictors of poor prognosis in such patients are advanced age, poor Glasgow coma scale score and acute respiratory failure. Elective intubation may help in the management of cases with raised intracranial pressure (ICP) (Level V). Data is lacking on the role of hyperbaric oxygen in stroke Levels II and IV). General awake intubation is best as ICP is raised by rapid induction anaesthesia for intubation and by the use of paralytic agents. Thiopental can be used in haemodynamically stable patients whereas etomidate is used for unstable patients. Ronucronium is safe for neuromuscular blockade. Propofol and Midazolam are getting favour for sedation in agitated patients, especially former which also lower the ICP. Further discussion is out of scope for this review

2. **Early mobilization**, on stabilization of neurological status, is advocated to prevent pneumonia, deep vein thrombosis (DVT) and pulmonary embolism, bed sores, contractures and pressure palsies[63, 64]. Due to frequent occurrence of dysautonomia a close observation of autonomic nervous system (ANS) function is needed to avoid sudden deterioration on ambulation due to postural hypotension.

3. **Alimentation**[1]: Early alimentation is required in stroke patients due to increased nutritional requirements and presence of malnutrition and improve their outcome[65]. Swallowing impairment[66] is quite common in acute stage of stroke due to mental impairment or because of a large hemispheric stroke or brain stem stroke. Such patients are prone for aspiration pneumonia. Poor cough effort, a wet voice after swallowing , incomplete orolabial closure, high NIHSS score , dysphonia or lower cranial nerves palsy are the indicators of high risk of aspiration. Hence, swallowing reflex should be assessed by bed side water swallow test or when needed by modified barium meal examination .before allowing oral alimentation[67, 68]. Nasogastric or nasoduodenal tube may be inserted to provide feeding . Percutaneous endoscopic tube is considered a better option (Level II)[69]. Majority of available tube feeds provide 1 calorie per ml. Concentrated feeds (2 calories/ml) are used in those having cerebral edema. Hyperglycemia is associated with, hyperthermia, increased cerebral edema and hemorrhagic transformation of infarct with or without rTPA therapy and increased mortality and mortality. Similarly hypoglycemia is harmful and may cause focal signs mimicking stroke and can lead to brain injury. Hence blood sugar levels should be strictly controlled especially. The role of insulin and glucose in improving the substrate delivery to ischemic tissue is under study[70].

4. **Treatment of fever and infection**:
Fever, in post stroke period, is associated with increased morbidity and mortality during first 24 hours after stroke (Level I)[1]. Mechanisms postulated is the release of excitotoxic aminoacids, enhancement of detrimental inflammatory responses, release of free radicals or an increase in CMRO2 thereby increasing blood flow and ICP. Fever has been shown to exacerbate hypoxic ischemic injury in animals[71]. The cause of fever may be stroke itself or may be due to aspiration pneumonia and urinary tract infections in later stages. While pulmonary complications can be prevented by proper airway management, urinary infection may be prevented by acidification of urine, avoiding catheterization or when not avoidable, by intermittent catheterization. Development of fever (more than $101^{O}F$) should alert the physician for instituting aggressive treatment with antipyretic agents or external cooling (when no response to antipyretics), and aggressive treatment of systemic infections. Indomethacin can be used and has an effect

on ICP[72]. Hypothermia has been shown to be neuroprotective (Level II to IV)[1] but its efficacy is to be established (Level III & IV)[1]

5. **Prevention of DVT and Pulmonary embolism**

   Paralysis of lower limb, advance age, immobility and atrial fibrillation, use of oral contraceptives and presence of a hypercoagulable state are associated with DVT. It may be complicated by pulmonary embolism which account for 10% of death after stroke and can be detected in 1% of cases[73]. Anticoagulation (subcutaneous heparin, LMWH and heparinoid[74, 75] or aspirin[76, 77] provide level I protection while compressive stocking provide only level II protection[1].

   Recommendations of SCASA[1] are (a) The use of "Stroke units" for comprehensive care incorporating rehabilitation are recommended (Grade A), (b) Early immobilization and measures to prevent early complications are strongly recommended (Grade B & C), (c) Subcutaneous administration of anticoagulants (Grade A), aspirin (Grade A) or intermittent compression stocking (Grade B) is strongly recommended to prevent DVT in immobilized patient and (d). Treatment of infection by appropriate antibiotics and of associated medical condition (Grade A) is strongly recommended.

Treatment of Acute Neurological Complications: Raised intracranial Pressure (ICP) & Cerebra Edema[78]

Raised ICP occurs in acute stroke due to development of both cytotoxic and vasogenic brain edema reaching maximum 2-5 days after ictus. Less than 10 to 20% develop clinically significant edema needing treatment. Aim is to reduce ICP (less than 20 mms of Hg), maintaining CPP (more than 70 mms of Hg) and preventing brain injury due to herniation. Treatment modalities include (a) mild fluid restriction (Level III to V)[1], (b) avoidance of hypo-osmolar fluids (i.e. 5% dextrose), (c) treating exacerbating factors (e.g. hypoxia, hypercarbia, and hyperthermia), (d) elevation of head by 15-30 ^{0} to improve venous drainage is safe as long as CPP is more than 70 mms of Hg , (e) judicial management of BP, as discussed earlier, for maintaining an adequate CPP (Level II toV)[1] and (f) treatment of raised ICP (No controlled trial to asses the efficacy of hyperventilation, osmotic diuretics, CSF drainage and surgery (Level 11 to V)[1]. Although monitoring of ICP may help in deciding the treatment but its value has not been established. The neurological examination is more sensitive in predicting out come.

Hyperventilation which reduces ICP immediately, e.g. lowering of pCO_2 by 5 -10 mm, reduces ICP by 25-30% (Level III to V)[1], is a temporary measures only and should be followed by other definitive treatment. Steroids are not effective (level I)[1]. Furosemide (40 mg IV) or 20% mannitol (0.25-0.5 g/kg administered over 20 minutes and followed 6 hourly: maximum dose 2 g/kg/: osmolarity 5.5 mosm/g) are often used but there is no trial for proving their value (Level III to V)[1]. Glycerol has been tried in clinical trial and can lower mortality in large strokes but is not popular due to bad taste and haemolysis when given IV. A high dose of barbiturates is also used but it is associated with systemic complications (i.e. hypotension, cardiac depression, and infections). Hypothermia lowers the ICP and is being tried in trials. Hypertonic 3% saline is getting popular as it is equally or more effective than mannitol in stroke and has fewer rebound effects.

Hydrocephalus, if present, is treated by intraventricular drainage. Other measures include hemicraniectomy & temporal lobectomy (Level II to V)[1]. Ventriculostomy with suboccipital craniectomy including excision of infracted cerebellum and aggressive medical therapy is effective in cerebellar infarction (Level III to V)[1]. It may be needed for thalamic infarct or haemorrhage it causes 3rd ventricular compression and hydrocephalus. Over aggressive drainage in hemispheric infarct may be counter productive due to reverse herniation. .

Treatment of Acute Neurological Complications: Seizures

Incidence of seizure on first day of stroke, is reported in 4% to 43% cases (Level II to V) [1, 79, 80] while recurrent seizures develops in 20% to 80% patients. Intermittent seizures do not alter the prognosis but status epilepticus is life threatening[81] In view of few data, their management is based on established management of secondary seizures in other systemic conditions.

Treatment of Acute Neurological Complications: Hemorrhagic transformation

Using CT, hemorrhagic transformation was noted in 5% cases[82] and are more common with the use of antithrombotic agents especially with anticoagulants and thrombolytic agents[12, 41, 42, 83, 84]. Early use of

aspirin is also associated with a small increase of risk [26,27]. The management depends upon the amount of haematoma.

Recommendations of SCASA[1] on management of ICP are (a) Corticosteroids are not recommended for treatment of cerebral edema in stroke (Grade A), (b) Osmotherapy and hyperventilation is indicated in patients who are deteriorating due to raised ICP, including those with herniation (Grade B), (c) Surgical interventions including CSF drainage may be used to treat raised ICP secondary to hydrocephalus (grade B), (d). Surgical decompression for large cerebellar infarction causing brainstem compression and hydrocephalus, is indicated (Grade C), (e) Recurrent seizures should be treated as with any other neurological condition (Grade C) and prophylactic use of anticonvulsants in stroke is not recommended (Grade C)

Other Measures

Trial of drug induced hypertension, and isovolumic or hypervolumic hemodilution or other strategies to improve collateral flow by improving rheology of blood were unsuccessful level I[85, 86] and II to V respectively [1]. Cross linked haemoglobin carrier, diaspirin was associated with an increased mortality and morbidity (Level V)[1]. Presently, these measures are not recommended, out side the clinical trials[1]. Similarly, trials with neuroprotective agents have been inconclusive and no agents with such an effect is recommended (Grade A)[1].

STROKE TREATMENT IN FUTURE[87]

Studies to recognize the basic molecular events in acute stroke and attempts to find an effective intervention are the hope for the future treatments of acute stroke which are summarized in subsequent paragraphs.

1. Combined intra-arterial and intravenous thrombolysis with rTPA or second and third generation thrombolytic agents.
2. Use of innovative techniques to lyse the clot (microcatheters, suction devices, transcranial ultrasound) or other methods to enhance clot penetration or its dispersion mechanically.
3. Use of new fibrinolytic and antiplatelet drugs. These are in advanced stages of study with possible application in future.
4. Prevention of reperfusion injury. Mechanisms of reperfusion injuries are now better understood leading to therapeutic possibilities. Blocking of ICAM-1 dependant leukocyte binding in ischemic region with or without of other upregulated endothelial leukocyte adhesions molecules1 (E-selectin, ELAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are under investigation.
5. Use of COX II inhibitors for treatment of stroke based on the findings of its glial and neuronal induction in infarcted tissue and in penumbra.
6. Apoptosis, a programmed cell death occur late in ischemic insults. Inhibition of proteins synthesis participating in apoptosis (i.e. caspase inhibition, activation of metabotropic glutamate receptors, growth factors and protein synthesis inhibitors etc) may find a role in future.
7. Prophylactic neuroprotection by vascular and endovascular therapy, role of free radical scavengers (oral abselen, polyethylene glycolated demustase), calcium channel blockers, anti-excitotoxic therapy and hypothermia are under study again.
8. Use of combination (Steps 1-8) based on complex mechanisms involved in ischemic cascade. Combination therapy of anti-excitotoxic therapy and thrombolytic therapy with other measures have been found effective in experimental animals. This multifaceted treatment is likely to be state of art for future therapy.

References

1. Guidelines for early management of patients with ischemic stroke: A scientific statement from the Stroke Council of the American Stroke Association. Stroke 2003; 34: 1056-1083.
2. Stroke Units Trialists Collaboration: a systemic review of the randomized trials of organized inpatient (stroke unit) care after stroke. BMJ1997; 314: 1151-1159.
3. Indredavik B, Blake F, Slordahl SA, et al. Stroke unit treatment improves quality of life: 10 years follow up. Stroke 1990; 30: 1524-27.
4. Hill MD, Barber PA, Demchuck AM et al.: Building a “Brain attack” team to administer rTPA therapy for acute ischemic stroke. CMAJ 2000; 162: 1589-1583.
5. Brock BF. Response system for presenting with acute ischemic stroke. In Marler JR, Winters John P, .Emr M (eds): Proceedings of a National Symposium on Rapid Identification and Treatment of Stroke. Bethesda, MD, The National Institute of

Neurological disorders and Stroke. 1997, p-55-57.

6. Broderick JP. Logistic in acute stoke management. Drugs 1997; 54 (suppl 3): 109-116.
7. Kwiatkowsky TG, Libman RB. Emergency strategies. In Welch KMA, Kaplan LR, Reis DJ, Seisjo BK, Weir B (eds) Primer on Cerebrovascular Disease. San Diego Academic Press, 1977, pp 671- 675.
8. Brott T, Adams HP, Olinger CP., et al. Measurement of acute cerebral infarction: A clinical scale. Stroke 1989; 20; 864-870.
9. Chobanian AB, Bakris GL, Black JR, et al. The seventh report of the Joint National Committee on prevention, Detection, Evaluation and Treatment of High Blood pressure. The JNC 7 Report, JAMA 2003; 289: 2560-2572
10. Grossman E, Messerli F, Grodzicki T, et al. should a moratorium be placed on sublingual nifedipine capsule given for hypertensive emergencies and pseudo-emergencies? JAMA 1996; 276: 1328-1331.
11. Kasner SE, Grotta JC. Ischemic stroke. Neurol Clin 1998; 16: 355-372.
12. Data from The National Institute of Neurological Disorders and Stroke (NINDS): rTPA Stroke Study group: Tissue plasminogen activator for acute ischemic stroke. NEJM 1995:333 1581-1587.
13. Donnan GA, Davis SM, Chambers BR, et al. Streptokinase for acute ischemic stroke with relationship to time of administration. JAMA 1996; 276: 961-966.
14. The Multicenter Acute Stroke Trial Europe Study Group. Thrombolytic therapy with streptokinase in acute ischemic stroke. NEJM 1996: 335: 145-150.
15. Multicenter Acute Stroke Trial-Italy (MAST I) Group. Randomized controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischemic stroke. Lancet 1995, 346; 1509-1514.
16. The European Cooperative Acute Stroke (ECASS) Study: Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. JAMA 1995; 274: 1017-1025.
17. Hacke W, Kaste M, Fieschi C, et al. Randomized, double blind, placebo controlled trial of thrombolytic therapy with intravenous alteplase in acute ischemic stroke (ECASS II). Second European Australian Cooperative Stroke Investigators. Lancet 1998; 352: 2073-2075.
18. Gladstone DJ, Black SE. Update on intravenous tissue plasminogen activator for acute stroke: from clinical trials to clinical practice. CMAJ 2001, 165: 311-317.
19. Wardlaw JM, del Zoppo G, Yamaguchi T: Thrombolysis for acute ischemic stroke (Cochrane review), In the Cochrane Library Issue 2. Oxford: update Software: 2003.
20. Llinas R, Caplan LR. Evidence based treatment of patients with Ischemic Cerebrovascular disease. In National Stroke Symposium 2002held in Hyderabad 03 Feb 2002, pp23-24.
21. Del Zoppo G, Higashida R, Furlan AJ, et al. PROACT: A phase II trial of recombinant prourokinase by direct intraarterial delivery in acute middle cerebral artery stroke. Stroke 1998: 29: 4-11.
22. Furlan AJ, Higashida F, Wechler L, et al. PROACT II: Recombinant prourokinase(r-proUK) in acute cerebral thromboembolism. Stroke 1999; 30: 234 (abstract).
23 Emergency Management of Stroke (EMS) Investigators: Combined intra-arterial and intravenous rTPA for stroke. Stroke 1997; 28: 273 (abstract).
24. Duke RJ, Bloch RF, Turpie AG, at al. Intravenous heparin for the prevention of stroke progression in acute partial stroke: A randomized controlled trial. Ann Int Med 1986 105: 825-828
25. Haley EC, Jr Kassell NF, Torner JC. Failure of heparin to prevent progression in progressive ischemic infarction. Stroke1988; 19: 10-14.
26. International Stroke Trial Collaborative Group: International Stroke Trial (IST): A randomized trial of aspirin, subcutaneous heparin, both, or neither in 19,435 patients with acute ischemic stroke .Lancet 1997: 349: 1569-1581.
27. CAST (Chinese Acute Stroke Trial) Collaborative Group: CAST: Randomized, placebo controlled trial of early aspirin use in 2000 patients with acute ischemic stroke. Lancet 1997; 349: 1641-1649.
28. The Publication Committee for the Trial ORG 10172 in Acute Stroke Treatment (TOAST) investigators. Low molecular weight heparinoid, ORG 10172 (danparoid) and out come after acute stroke: a randomized controlled trial. JAMA 1998; 279: 1265-1272.

29. Hart RG. Hemorrhagic infarcts. Stroke 1986; 17: 586-589.
30. Swanson RA, Intravenous heparin for acute stroke. What can we learn from mega trials? Neurology 1991; 52: 1746-1750.
31. Kay R, Wong KS, Yu Y, et al. Low molecular weight heparin for treatment of acute stroke. NEJM 1995; 333: 1588-1593.
32. Chamorro A. Heparin in acute ischemic stroke; a case for new clinical trial. Cerebrovasc Dis. 1999 (suppl 3): 16-23.
33. Berge E, Abdelnoor M, Nakstad PH, Sandset PM on behalf of HAEST Study Group. Low molecular weight heparin versus aspirin in patients with acute ischemic stroke and atrial fibrillation; a double blind randomized study. Lancet 200; 335:1205-1210.
34. Diener HC, Ringelstein EB, von Kummer R, et al. Treatment of acute ischemic stroke with low molecular weight heparin certoparin: results of the TOPAS trial: Therapy of Patients with Acute Stroke (TOPAS) Investigators. Stroke 2001; 32: 35. Clark WM, Albers GW, Madden KP, Hamilton S for the Thrombolytic Therapy in Acute Stroke Study Investigators. The rTPA (altepase) 0-6 hour's stroke trial: Part A (A0276G) result of double blind, placebo controlled, multicenter study. Stroke 2000; 31: 811-816.
36. Lewandowsky CA, Frankel M, Tomsik TA, et al. Combined intravenous and intra-arterial rTPA versus intra-arterial therapy of acute ischemic stroke. Emergency Management of Stroke (EMS) Bridging Trial. Stroke 1999; 29: 4-11.
37. Gond M, Rudolf J, Neveling M, Heiss WD. Risk of immediate heparin after rTPA therapy in acute ischemic stroke. Cerebrovasc Dis. 1997; 7: 318-323.
38. Grond M, Stenzel C, Schmulling S, et al. Early intravenous rTPA in acute ischemic stroke in a community based approach. Stroke 1998; 29: 1544-1559.
39. Chamorro A. Immediate anticoagulation in acute focal brain ischemia revisited: gathering the evidence. Stroke 2001; 32: 577-578
40. The Aabciximab in Ischemic Stroke Investigators. Abciximab in acute ischemic stroke: a double blind, placebo controlled, dose escalation therapy.. Stroke 2000: 31: 601-609.
41. Ancrod Stroke Study Investigators: Acrod for the treatment of acute ischemic brain infarction. Stroke 1994; 25: 1755-1759.
42. Sherman DG for the STAT Writers Group: Defibrinogenation with Viprinex (ancrod) for the treatment of acute ischemic stroke. Stroke 1999; 30: 234 (abstract).
43. Meyer FB, Sundt TM Jr, Piepgras DG, et al. Emergency carotid endarterectomy for patients with acute carotid occlusion and profound neurological deficits. Ann Surg 1986; 203: 82-89.
44 Eckstein HH, Schumacher H, Klemm K, et al. Emergency carotid endarterectomy. Cerebrovasc Dis 1999; 9: 270-281.
45. Kasper GC, Wladis AR, Lohr JM, et al. Carotid thromboendarterectomy for recent total occlusion of the internal carotid artery. J Vasc Surg 2001: 33: 242-250.
46 . Heros RC. Carotid endarterctomy in patients with intraluminal thrombus. Stroke 1988; 19: 667-68.
47 Biller J, Adam HP Jr, Boarini D., et al. Intraluminal clot of the carotid artery: a clinical- angiographic correlation in nine patients and literature review. Surg Neurol 1986; 25: 467-477.
48. Yoshimoto Y. Kwak S. Superficial temporal-middle cerebral artery anastomosis for acute cerebral ischemia: the effect of small augmentation of blood flow. Acta Neurochir 1995; 137: 128-137.
49 Kakinuma K, Ezuka I, Takai N et al. The simple indicator for revascularization of acute middle cerebral artery occlusion using angiogram and early ultra embolectomy. Surg Neurol 1999; 51: 332-341.
50. Buchan A, Gates P, Pelz D, Barnet HJ. Inraluminal thrombus in the cerebral circulation: implications for surgical management. Stroke 1998, 19: 681-687.
51. Sundt TM, Sandok BA, Whisnant JP. Carotid endarterectomy: complications and prospective assessment of risk. Mayo's Clin Proc 1975; 50: 301-306.
52. Crowell RM. STA-MCA bypass for acute focal ischemia. In Schmiedek P (Ed). Microsurgery for Stroke. New York Springer Verlag: 1977, 244-250.
53. Mori T, Kazita K, Chokyu K. Short term arteriographic and clinical outcome after cerebral angioplasty and stenting for intracranial vertebrobasilar and carotid atherosclerotic occlusive disease. AJNR 2000; 21: 249-254.

54. Ueda T, Sakaki S, Nochide I, et al. Angioplasty after intra-arterial thrombolysis for acute occlusion of intracranial arteries. Stroke, 1998; 29:2568-2574.
55. Chopko BW, Kerber C, Wong W, Georgy B. Transcatheter snare removal of acute middle cerebral artery embolism: technical report. Neurosurgery 2000; 40:1529-1531.
56. Balousek P, Knowles H, Higashida R, et al. New interventions in cerebrovascular diseases: role of thrombolytic therapy and balloon angioplasty. Curr Opin Cardiol 1996; 11: 550-557.
57 Qureshi AI, Suri FK, Khan J, et al. Abciximb as an adjunct to high risk carotid or vertebrobasilar angioplasty. Preliminary experience. Neurosurgery 2000; 46: 1316-1325.
58. Lempert TE, Malek AM, Halbach VV, et al. Rescue treatment of acute parent vessel thrombosis with glycoprotein IIb/IIIa inhibitor during GDC coil embolization. Stroke 1999; 30: 693-in patients with intraluminal thrombus. Stroke 1988; 19: 667-68.
59. Davalos A, Castillo J. Potential mechanism of worsening. Cerebrovasc Dis 1997; & Suppl 5: 19-24.
60. Krieger D, Hacke W, The intensive care of stroke patients. In Barnett H JM et al. (Eds) Stroke: Pathophysiology, Diagnosis, management. 3rd Edition New York. Churchill Livingstone, 1998.
61. Langhorne P, Stott DJ, Robertson L, et al. Medical complications after stroke: a multicenter study. Stroke 2000; 31: 1223-1229.
62. Becker K. Intensive care unit management of stroke. In National Stroke Symposium organized by Nizam Institute of Medical Sciences. Endorsed by International Stroke Society. Feb 2002. National Stroke symposium endorsed by International Stroke Society, held on 3,4 Feb 20002 in Hyderabad, pp 121-135.
63. Langhorne P. Measures to improve recovery in acute phase of stroke. Cardiovasc Dis 1999: 9(Suppl 5): 2-5.
64. Tutuarima JA, van der Meulen JH, Dehaan RJ, et al. Risks factor for falls of hospitalized stroke patients. Stroke 1997, 28: 297-301.
65. Gariballa SE, Parker SG, Taub N, Castleden CM. Influence of nutritional status on clinical outcome after stroke. Am J Clin Nutr 1998; 68: 275-281.
66. Robins J. evaluation of swallowing neuroanatomy and physiology in human: a practical perspective. Ann Neurol 1999; 46: 279-280.
67. Addington WR, Stephens RE, Gillilland K, Rodriguez M. Assessing the laryngeal cough reflex and the risk of developing pneumonia after stroke. Arch Phys Med Rehabil 1999; 80: 150-154.
68. DePippo KL, Holas MA, Reding MJ. Validation of 3 oz water swallow test for aspiration following stroke. Arch Neurol 1992; 49: 1259-1561.
69. Norton B, Homer ward M, Donnelly MT, et al. A randomized prospective comparison of percutaneous endoscopic gastrostomy and nasogastric tube feeding after dysphagic stroke. BMJ 1996; 312: 13-16.
70 Scot JF, Robinson GM, French JM, et al. Glucose potassium insulin infusions in the treatment of acute stroke patients with mild to moderate hyperglycemia. Stroke 1999; 30: 793-796.
71. Busija DW, Leffler CW, Pourcyrous M. Hyperthermia increases cerebral metabolic rate and cerebral blood flow in neonatal pigs. Am J physiol 1988; 255: H343-H346.
72. Jensen K, Ohrstrom J, Cold GE, et al. The effects of indomethacin on intracranial pressure, cerebral blood flow and cerebral metabolism in patients with acute head injury and intracranial hypertension. Acta Neurochir 1991: 108-116.
73. Wijdiks EF, Scott JP. Pulmonary embolism associated with acute stroke. Mayo's Clin Proc1997: 72, 297-300.
74. McCarthy SJ, Turner J. Low dose of subcutaneous heparin in prevention of deep vein thrombosis and pulmonary emboli following stroke. Age Ageing 1996: 15: 84-88.
75. Turpie AG, Gent M, Cote R , et al. A low molecular weight heparinoid compared with unfractionated heparin in the prevention of deep vein thrombosis in patients with acute ischemic stroke. A randomized double blind study. Ann Int Med 1992; 117: 353-357.
76. Antiplatelet Trialists' collaboration. Collaborative overview of randomized trials of antiplatelet therapy. III: reduction in deep venous thrombosis and pulmonary embolism by antiplatelet prophylaxis amongst medical and surgical patients. BMJ 1998:308: 235-246.
77. Pulmonary Embolism Prevention (PEP) Trial collaborative Group. Prevention of

pulmonary embolism and deep vein thrombosis with low dose aspirin: pulmonary embolism prevention trial. Lancet 2000: 355: 1295-1302.

78. Denis LJ, Mayer SA. Diagnosis and management of increased raised intracranial tension. Neurology (India) 2001; 49(Suppl 1): S37-S 50.
79. Berlin CF, Alexandrow AV, Bellavance A, et al. Seizure Stroke Study Group: seizures after stroke: a prospective multicentre study. Arch Neurol 2000: 57; 1617-1622.
80. Pohlmann-Eden B, Cochius JI, Hooch DB, et al. Stroke and epilepsy: a critical review of literature. Cerebrovasc Dis 1997; 7: 2-9.
81. Rumbach L, Sablot D, Berger E, et al. Status epilepticus in stroke a report on a hospital based cohort. Neurology 2000; 54: 350-354.
82. Horing CR, Dorndrof W, Angoli AL. hemorrhagic cerebral infarction: a prospective study. Stroke 1986; 17: 179-185.
83. The NINDS rTPA Study Group< Intracerebral hemorrhage after intravenous rTPA therapy for ischemic stroke. Stroke 1997, 28: 2109-2118.
84. Motto C, Cicconi A, Aritzu E.et al. Hemorrhage after an acute ischemic stroke: MAST I Collaborative Group. Stroke 1999; 30: 761-761. (Grade A). 85. Italian Acute Stroke Study Group. Hemodilution in acute stroke: results of Italian hemodilution trial. Lancet 1988; I: 318-321.
85. Scandinavian Stroke Study group. Multicenter trial of hemodilution in acute ischemic stroke: results of subgroup analyses. Stroke1988; 19: 464-471.
86. Lindsberg PJ, Roine RO, Tatlisumak r et al. The future of stroke therapy In National Stroke Symposium organized by Nizam Institute of Medical Science Endorsed by International Stroke Society, held in Feb 222.