SECTION II

Emergencies in Medicine:
Management in the First Three Hours
Introduction

The term “Cerebrovascular Disease” (CVD) or “Stroke” refers to rapidly developing clinical syndrome of focal or global loss of brain functions lasting many hours to days, and at times leading to death, from disorders of cerebral circulation. By and large, impaired cerebral perfusion by occlusion (e.g. thromboembolism) is responsible for “Ischaemic Stroke” (ICVD) whereas “Haemorrhagic Stroke” (HCVD) results from leakage of blood from damaged cerebral vessels.

The Stroke is the third most common cause of death in the developed nations accounting for nearly 4.5 million deaths each year. Recent community surveys for “hemiplegia” presumed to be CVD identified 320 cases in 145,456 persons, indicating an overall crude prevalence rate (CPR) of 220 per 100,000 subjects. For the elderly (55-65 years), the CPR being 700 per 100,000. These data do not take into account the sudden deaths and Transient Ischaemic Attack (TIA) cases. India will face enormous socioeconomic burden on the costs of rehabilitation of “stroke-survivors” because the population is now surviving through peak years (age 55-65) of occurrence of CVD.1

In this article, current concepts in stroke pathophysiology and management are briefly reviewed.

Basic Considerations in Ischaemic-hypoxic Cerebral Injury2

The normal functions of the brain are dependent upon a relatively constant supply of oxygen and glucose, as well as other nutrients derived from the blood perfusing it (55 to 70 ml of blood per 100 g of brain per min). The principal source of energy is almost exclusive oxidation of glucose. If for any reason the blood flow is critically reduced below 15 ml per 100 g per min, the resulting hypoxia from ischemia when sufficiently prolonged may cause death of neurones and glia (cerebral infarction).

Recent studies on molecular and metabolic events leading to cerebral injury have shown that there is a dense central core, surrounded by a less dense zone of ischaemia (“penumbra”) and neuronal death occurs unless perfusion is immediately restored. On the other hand, nerve cells in the zone of ischemic penumbra remain viable for at least three hours (“therapeutic window”) and can be salvaged by reperfusion (oxygen and glucose), neuroprotective agents, etc. Major factors which enhance nerve cell injury are an increase in intracellular cytosolic calcium concentration (from failure of ionic pump...
functions or “leaks”), changes in Na/K gradients, acidosis, release of glutamate as well as “excitotoxic” substances, free radicals, and many unknown factors which in turn disrupt the blood brain barrier (BBB) and cell membrane functions. Here, energy depletion from ischaemic-hypoxia is one of the key events that fails to maintain normal concentrations of cellular adenosine triphosphate (ATP) leading to delay in resynthesis of macromolecular proteins essential for cell structure. Such energy failures also induce proteolysis and lypolysis, in addition to production of arachidonic acid, platelet activating factors, free radicals, etc. which in turn cause further neuronal damage. The role of leucocyte-endothelial interaction, receptor activation, post-ischaemic hyperperfusion damage (“reperfusion injury”); the role of nitric oxide and nerve growth factors and gene expression are under study. Thus, severity of cerebral injury is not the mere result of hypoxia from impaired perfusion but end-result of several highly complex “ischaemic-modifying factors” (“Ischaemic Cascade Hypothesis”).

Treatment of Ischaemic Cerebrovascular Disease (ICVD)

The goal of therapy is to avoid development of brain ischaemia / infarction and, if already present, to prevent its progression or recurrence. The treatment is divided into three phases: Phase I - saving life and medical management; Phase II - measures to prevent recurrence of stroke; and Phase III - Rehabilitation to achieve physical, occupations and social adaptation for a gainful employment. (Table 1)

Phase I

General Measures in Prevention of Medical Complications in Stroke. The maintenance of vital signs (temperature, pulse, respiration, blood pressure), patency of airway, uid and electrolyte balance, and prevention of complications like pulmonary aspiration, seizures, thrombophlebitis, bedsores, etc. are mandatory. Here, general medical and meticulous nursing care are of paramount importance. The role of “Intensive Stroke-Care Units” for specialised care of “stroke-victims” is now greatly emphasised.

Blood Pressure: In acute cerebral ischaemia, “cerebral autoregulation” is lost and blood ow in the infarcted tissue is solely dependent on mean arterial BP. In presence of severe hypertension (e.g. BP over 220/120 mmHg) parenteral therapy with titratable agents such as i.v. labetalol or nitroprusside, or enalapril to smoothly reduce blood pressure are recommended. Calcium channel blockers are best avoided because they often produce precipitous drop in blood pressure in many patients. On the other hand, the basal levels of blood pressure, in hypertensive and non-hypertensive stroke-subjects often fall unpredictably within 24 hours to few days and this may hamper cerebral perfusion in zone of “ischaemic penumbra” leading to further neuronal injury. Therefore, any significant hypotensive episode should be promptly treated to prevent extension of cerebral ischaemia. There is radical rethinking that “isolated systolic hypertension in elderly” is a distinct clinical entity and will require management to reduce the relative risk of cardiovascular events, and correct management of blood pressure in acute stroke is still debated.

Reduction of Increased Intracranial Pressure and Cerebral Oedema: In presence of intracranial pressure (ICP), the head should be elevated by 30 degrees. If associated with increasing drowsiness, intubation and hyperventilation to keep partial pressure of CO₂ at 25 to 30 mmHg may prove helpful. High doses of corticosteroids (i.v. dexamethosone 24-40 mg/day, or methyl prednisolone in divided doses) can reduce vasogenic cerebral oedema but their routine use in treatment of ischaemic strokes is doubtful.

Antithrombotic Therapy

Platelet Antiaggregants: ASPIRIN (Acetyl salicylic acid) prevents platelet adhesion / aggregation by...
Table 1: Stroke (CVD): Emergency Evaluation - First 3-6 Hours

Acute/unstable Focal Neurological Deficit (Hemiplegic Syndrome)
down

ALL HEMIPLEGIC SYNDROMES ARE NOT CEREBROVASCULAR ACCIDENTS (CVA)
(exclude atypical strokes having history of trauma, metabolic and electrolyte disturbances, syndrome of raised intracranial pressure, and those having fever, neck stiffness or seizures, etc. by obtaining reliable history and careful physical/neurological examination and relevant tests).
down

Patient likely to have Cerebral Vascular Accident (CVA commonly designated as “stroke”)

Check Airway Patency And Maintain All Vital Signs
(? Transfer to Intensive Care Unit for monitoring – EKG & Oxymetry)
Send blood for emergency tests (Hgb/TC/DC, BT/CT/PT/APTT, Platelet Count, Electrolytes, RBS, SGOT/SGPT/CPK, Urea/Creatinine, Smear for M.P.; Toxic screen & blood gases if possible).
Standard electrocardiogram and Chest/Skull X-rays.
down

Plan Emergency Head C.T. Scan: Confirm CVA Dx
(exclude subdural hematoma, meningo encephalitis, brain abscess, tumors etc., mimicking as “strokes” etc.)
down

BY CT OR CSF: IS HAEMORRHAGE PRESENT?

Yes

(Intracerebral Haematoma or Subarachnoid Haemorrhage)
Control Hypertension, maintain vital signs & uid electrolyte balance; use osmotic diuretics etc.
Consider Surgery: Plan Angiography, if patient alert & responsive. Avoid aggressive approach if patient in deep coma with non reactive pupils & absent caloric responses.
down

No

(Ischaemic Stroke)? Cortical? Lacunar

1. Maintain vital signs and uid balance. (ABC of resuscitation)
2. Do not precipitously lower blood pressure by powerful agents, unless B.P. is over 200 +/110 mmHg.
3. Consider thrombolytic therapy (See Table II and III) neuroprotection before treatment or else antiplatelet agents, Heparin therapy
4. Avoid: I.V. 5% glucose solution, steroids and over hydration
Plan Carotid Angiography: Consider Surgery if tight stenosis (70% +) in culprit vessel.

(For specific details on diagnosis and management, see text)
(modified from US National Stroke Association recommendations for the emergency evaluation and treatment of stroke)
Table 2: Characteristics of Patients with Stroke who may be Eligible for Intravenous Tissue Plasminogen Activator Therapy

- Age ≥ 18 yr
- Diagnosis of ischemic stroke causing clinically apparent neurologic deficit
- Onset of symptoms < 3 hr before possible beginning of treatment.
- No stroke or head trauma during the preceding 3 months.
- No major surgery during the preceding 14 days.
- No history of intracranial hemorrhage.
- Systolic blood pressure ≤ 185 mmHg.
- Diastolic blood pressure ≤ 110 mmHg.
- No rapidly resolving symptoms or only minor symptoms of stroke.
- No symptoms suggestive of subarachnoid hemorrhage.
- No gastrointestional or urinary tract hemorrhage within the preceding 21 days.
- No arterial puncture at a noncompressible site within the preceding 7 days.
- No seizure at the onset of stroke.
- Prothrombin time ≤ 15 sec or international normalized ration 1.7, without the use of an anticoagulant drug.
- Partial-thromboplastin time within the normal range, if heparin was given during the preceding 48 hr.
- Platelet count 100,000/mm³
- Blood glucose concentration > 50 mg/dl (2.7 mmol/liter)
- No need for aggressive measures to lower blood pressure to within the above-specified limits.

with suspected acute ischaemic stroke, mainly to reduce the risk of early recurrence”. They also noted that of the 9000 patients (22%) who were randomised without a prior CT scan, aspirin appeared to show net benefit “with no unusual excess of haemorrhagic stroke; moreover, even among the 800 (2%) who had inadvertently been randomised after a haemorrhagic stroke, there was no evidence of net hazard (further stroke or death: 63 in aspirin group versus 67 in control)”.

Other antiplatelet drugs like sulfinpyrazone or dipyridamole used alone do not offer any specific advantage. In the ESPS2 study it was recommended that combination of aspirin (50mg) with extended release dipyridamole (200 mg BD) has additive benefit due to synergisic activity.

Thienopyridines (ticlopidine and clopidogrel) inhibit platelet aggregation induced by adenosine diphosphate (ADP), collagen, arachidonic acid, thrombin and platelet aggregating factors (PAF). It also reduces plasma fibrinogen and increases red cell deformability. It has shown more than 30% reduction in “stroke risk” in patients when compared to aspirin therapy. It is equally beneficial to men and women. Subjects with diabetes mellitus, those on antihypertensives and those with elevated creatinine levels benefit more with ticlopidine than aspirin. In four randomised trials of 22,656 patients having TIA/ischaemic stroke, thienopyridines reduce the odds ratio of a vascular event by 9% (odds ratio 0.91; CI 0.84-0.98; 2P=0.01) preventing 11 events per 1000 patients so treated. Clopidogrel (Plavix) appears safer than ticlopidine but it is more expensive. Newer antiplatelet agents like Abciximab are potent antagonists of platelet glycoprotein IIb/IIIa and appear to be safe when administered up to 24 hours after acute ischaemic stroke (CT/MRI confirmed). At 3 months, there was a trend towards higher rate of minimal residual disability (Barthel and Modified Rankin Scale) among patients receiving Abciximab as compared to placebo group.

Anticoagulants

Parenteral heparin and long-term oral anticoagulants have been extensively tried in acute ischaemic strokes. Though such treatment can prevent extension of thrombus, its value in completed stroke is doubtful and its use is often fraught with dangers. In International Stroke Trial (IST), 19,435 patients
within 48 hours of acute ischaemic stroke received 14-day treatment with 5000 units (U) heparin twice daily, or 12500 U heparin twice daily and NO heparin, and each of these three groups received NO aspirin or 300 mg of aspirin per day. In the final analysis of death or non-fatal recurrent stroke, there was NO added advantage in the group who received heparin treatment.8

On the other hand, in recurrent TIAs, thrombosis in-evolution, cardio-embolic strokes with valvular or nonvalvular atrial fibrillation,13,14 subjects not responding to platelet antiaggregants and in deep venous thrombosis or pulmonary embolism, judicious use of anticoagulants is often advocated.

If subject worsens under anticoagulant therapy, diagnostic re-evaluation should be done by a second CT or MRI scanning with or without CSF examination (under manometric control) to ascertain the accuracy of diagnosis and cause of worsening. Active bleeding ulcers, haemorrhagic diathesis, malignant hypertension, hepatic failure, drug allergy and patient’s poor compliance, are considered major contraindications to anticoagulant therapy.

Neuroprotective Agents
Cerebral ischaemia induces release of excitatory aminoacid neuro-transmitters like glutamate and glycine which promote calcium entry into neurons through receptor mediated membrane channels (e.g. N-methyl-D-aspartate [NMDA] and alpha amino-3-hydroxy-5-methyl-4-isozole propionic acid [AMPA] channels). Cell destruction most likely occurs from production of nitric oxide and subsequent formation of other free radicals. NMDA channel has atleast six sites which may be blocked by Lubeluzole, Cerestat, Citicoline, CGS-19755, MK-801, HA-966, etc. Enzymatic inhibition of nitric oxide synthetase by N-nitro-L-arginine also appears to protect against glutamate neurotoxicity but efficacy of these agents in humans awaits further clinical trials. The results of clinical tial on voltage dependent calcium channel antagonists (dihydropyridine compound - “nimodipine”) were not encouraging.15

Thrombolytic Therapy
Spontaneous recanalisation with better survival by intrinsic thrombolysis is well documented. Increasing experience with several “clot-selective” thrombolytics agents (acylated streptokinase-plasminogen complex, single chain urokinase type plasminogen activator [SCUPA], etc.) and recombinant plasminogen activator (e.g. Prourokinase) have demonstrated significant and sustained neurological improvement when treatment is initiated within the first there hours of ictus in MRI positive and CT negative ischaemic infarct (i.e. when ‘window of therapeutic opportunity’ is open).

Intravenous Thrombolytic Therapy : The European Cooperative Acute Stroke Study (ECASS), a multicentric randomised double blind placebo controlled trial, where rt-PA (recombinent tissue activator of plasminogen) was given in the dose of 1.1 mg/kg t-PA intravenously within 3-6 hours of acute hemispheric ischaemic CVD (without major signs of early infarct on initial CT) involved 620 patients with moderate to severe deficit, 109 cases (17.4%) were excluded for violation of protocol. The remaining patients were divided in two subgroups : (i) target population (TP) and (ii) intention-
to-treat (ITT) respectively. The scales of functional invalidity (Barthel index and Modified Rankin Scale) at 90 days were chosen as primary end-points and a combination of above scales plus score of neurologic deficit (the National Institute of Health Stroke Scale - NIHSS as well as the Scandinavian Stroke Scale), duration of hospital stay and case-fatality ratio were considered as secondary end points. In this study, TP group showed a significant favourable effect on primary end-point indicating benefit of early treatment but this efficacy was limited only to a defined subgroup with highly specific criteria of early infarct by CT.16,17

National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group (1995)23 involved a multicentric trial on 624 patients where rt-PA was given in dose of 0.9 mg/kg within three hours of onset of acute cerebral ischaemia (by specific CT criteria). Significant improvement was not achieved in neurological score (NIHSS) within the first 24-hours, but post-3-months analysis of functional score (Barthel Index, Modified Rankin Scale) favoured rt-PA group. The NINDS and ECASS trials showed that thrombolysis with rt-PA within 3 hours can be an effective treatment in acute ischaemic stroke and nearly 30% patients are likely to have none or minimal disability at 3-months assessment as compared to placebo group.17,18

Subsequently, ECASS-II trial was planned similar to NINCDS study within 6-hours of acute ischaemic stroke using 0.9 mg/kg alteplase, enforcing strict neuroradiological exclusion criteria. Here, 40.3% (165 patients) in alteplase-group and 36.6% (143 patients) in the placebo-group had favourable outcome. These results do not confirm statistical benefits for alteplase. Symptomatic intracranial haemorrhage occurred in 8.8% (36 patients) receiving alteplase as against 3.4% (13 patients) in the placebo group.19 Thus, controversy on efficacy of alteplase between 3 to 6 hours of acute ischaemic stroke continues.17,20

The ATLANTIS Study found no significant rt-PA benefit on the 90 day efficacy end points in patients treated between 3 and 5 hours. This risk of symptomatic ICH increased with rt-PA treatment. These results do not support the use of intravenous rt-PA for stroke treatment beyond 3 hours.21

To minimise the risk of haemorrhagic complications it is necessary that the ischaemic infarction is confirmed by investigations like CT scan and CSF and not on the basis of clinical acumen alone. The value of diffusion weighted imaging (DWI) and magnetic resonance angiography (MRA) in acute ischaemic stroke substantially improves the accuracy of diagnosis of stroke sub-type. In one study, pre MRI diagnosis matched the final diagnosis in only 48% but this improved further to 83% by DWI studies and upto 94% with DWI/MRA studies. Thus, the diagnostic usefulness of DWI and MRA is superior to CT scan alone, and almost mandatory in trials of thrombolytic therapy in hyperacute ischaemic stroke.22

On the other hand, the risk of intracerebral haemorrhage following thrombolytic therapy rises after 3-hours, and particularly more with streptokinase. Clinical trials on streptokinase therapy, namely : Multicenter Acute Stroke Trial-Europe (MAST-E), Australian Streptokinase Trial (ASK) and Multicenter Acute Stroke Trial-Italy (MAST-I) have all been terminated for reasons of safety.17

Intraarterial Thrombolytic Therapy
Recent advances in superselective microcatheter (Tracker-18 or microsoft stream catheter) techniques permit the investigator to reach at exact site of occlusive lesion and infuse a thrombolytic agent directly on to the clot surface thereby achieving higher rate of successful recanalisation. Successful thrombolysis in vertebro-basilar occlusion has been reported with survival in 14 out of 19 patients, and favourable outcome in 10. All 24 patients where the occlusion persisted died (p=0.000007).23 Similar encouraging results have been reported by other centres.24,25

The favourable results of PROACT-I study26 have been reconfirmed by randomised controlled PROACT-II trial with favourable outcome in 40% of r-proUK patients as against 25% of controls.27
Recanalisation was achieved in 66% of treated group and 18% of control group (p=0.001) but intracranial haemorrhages were noted in 10% of treated group versus 2% of the controls (p=0.06).27 Results of other placebo controlled randomised trials are awaited. At present, intraarterial thrombolytic therapy appears possible only in a select subgroup of patients within 3 hours of onset of ischaemic stroke, satisfying strict neuroradiological exclusion criteria to prevent misdiagnosis; and at centres where specialised teams of neurologist and neuroradiologist are available to monitor recanalisation and reperfusion by transcranial doppler evaluation and by diffusion and perfusion MRI studies.28,29

It is doubtful that rt-PA by itself will constitute the magic answer to devastating consequences of ischaemic stroke and that the basic optimal medical care still remains the sheet-anchor of overall medical management of acute ischaemic stroke.17

Surgical Management
Thromboendarterectomy with or without reconstructive vascular surgery within a few hours or days after an acute ischaemic brain infarction is considered risky, because early reperfusion may convert pale infarct into a haemorrhagic one.

Recent well-designed controlled studies (NASCET, ECST)30,31 have confirmed beneficial results of endarterectomy in tight cervical stenosis (70-99%). It has been observed that there is 17% absolute and 35% relative risk reduction for ipsilateral stroke and stroke death, if endarterectomy is combined with best medical care. Patients who benefit the most from surgery are those with highest risk-factors. During immediate post-operative period higher doses of aspirin and control of all risk-factors are mandatory. The benefit by carotid endarterectomy in symptomatic lesions with mild stenosis (30-69%) or in asymptomatic cases is controversial.32,33 In a recent report, the NASCET group observed that; 'risk of stroke among patients with asymptomatic carotid-artery stenosis is relatively low. Forty-five percent of strokes in patients with asymptomatic stenosis (60-99%) are attributable to lacunes or cardioembolism'. These observations have implications for the use of endarterectomy in asymptomatic patients. On the other hand, irregularity of plaque surface at all degrees of stenosis is a major stroke risk factors.34 Thus, many centres would allow surgery if the plaque is irregular and actively embolising distally despite moderate (under 70%) stenosis. The risk of stroke is significantly greater with carotid angioplasty than with carotid endarterectomy. Nevertheless, percutaneous angioplasty with stent has been successfully tried in treatment of inaccessible distal carotid or middle cerebral and vertebro-basilar lesions. The results of other controlled trials are awaited.

PHASE II
Stroke Prevention : Modification of risk-factors has shown the decline in stroke morbidity and mortality. Among the modifiable risk factors, control of hypertension is most important. One overview of 14 randomised trials showed a 40% reduction in stroke risk in patients able to lower their diastolic blood pressure by more than 6mm of Hg. The results of HOPE study using ACE inhibitor like Ramipril are even more empathetic in overall reduction of stroke morbidity and mortality.35,36

However, a recent editorial in Brit Med Journal suggests that “what matters most is getting blood pressured controlled, and that this is overwhelmingly more important than the means.” Combinations of several drugs will be required for most patients, and such an antihypertensive treatment cocktail should include a thiazide diuretic.37

TIA precedes stroke in 10% to 14% of cases; here, prophylactic platelet antiagregant therapy (aspirin 60 to 325 mg/day) is beneficial. In TIA cases, having symptomatic carotid stenosis (70-99%), endarterectomy is currently advocated. Cardiovascular diseases with or without atrial fibrillation (especially secondary to rheumatic heart disease), coronary artery disease, recent myocardial infarction and mitral valve prolapse are other well documented risk factors, where use of oral anticoagulant
drugs has been beneficial. A variety of hematological abnormalities (e.g. increase or decrease levels of haemoglobin, protein C and S deficiencies, elevated fibrinogen and lupus anticoagulant/anticardiolipin antibodies, etc.) have been shown to correlate with higher incidence of strokes. In homosysteinemia, oral or parenteral folate / B12 drugs have been successful in prevention of strokes. Most studies find a relationship between elevated lipids and atherosclerosis in both coronary and carotid arteries and recommend trial with lipid-lowering agents. Smoking seems to be dose related: light smokers are twice at risk whereas heavy smokers are four times at risk compared to general population. Thus, tobacco use should be prohibited. The role of regular physical exercise and keeping ideal body weight needs no emphasis.

Phase III
Neuro-rehabilitation: As soon as subject shows signs of neurological recovery with some volitional movements, active physiotherapeutic measures should be started for early rehabilitation.

Concluding Recommendations
For India where the population is surviving through the peak years of stroke occurrence, preventive strategies are mandatory. Available data indicate that CVD occurs at all ages in both sexes and with increasing frequency in advancing age. From case-control data on RFs, it appears that hypertension, diabetes mellitus, low normal haemoglobin and tobacco use (smoking / chewing) are important RFs. Thus, in prevention strategies, public awareness and health education on warning symptoms of stroke (TIA) and hypertension by optimum use of mass media is vital. Mass screening surveys to identify “hypertensives” and “stroke-prone” subjects wherever feasible should be undertaken to prescribe simple, practical, non-costly remedies. Life style changes, dietary habits and intensive campaign against tobacco use will prove rewarding. Primary health care centers staff should receive training on nomenclature and clinical diagnosis because CT facilities are not available in rural and remote areas. National Councils should interact with various agencies (health, industry, finance etc.) to coordinate actions at all levels.

References
31. European Carotid Surgery Trialists (ECST) Collaborative Group. MRC European Surgical Trial: Interim results for symptomatic patients with severe (70-90%) or with mild (0-29%) carotid stenosis. Lancet 1991; 337:1235-1243.