41 *Recent Advances in Ischemic Stroke*

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Abstract: Stroke as defined by WHO is responsible for 5 million deaths and of the other 15 million who survive the stroke, 5 million are disabled by their stroke. In the Indian context in the year 1990, 61900 people died because of stroke and the disability life years lost amounted to 28.5 million which is nearly 6 times higher than that due to malaria. The prevalence of stroke in the Indian context occurs at a much younger age and therefore is a source of great socio-economic burden.

There has been tremendous progress in the diagnosis of stroke with the advent of newer imaging techniques like CT scan, MRI and Pet scan. Though we can prevent stroke by following certain lifestyle measures but once the stroke occurs, the importance lies in early evaluation and prevention of the development of brain ischemia leading to infarction so that there is no residual or minimal deformity. It is established that the various risk factors like hypertension, diabetes etc. should be effectively controlled as also the lipid management while smoking should be stopped altogether. The point of importance is that we should try and provide treatment to stroke afflicted patients in the first hour that is the golden hour. The use of thrombolytic therapy and various interventional therapies along with anti-platelet agents in appropriate dosages can be very helpful if used judiciously and in effective dosages. The key in the stroke management lies in the prevention and early intervention.

INTRODUCTION

World Health Organization defines the clinical syndrome of "stroke" as 'rapidly developing clinical signs of focal (or global) disturbance of cerebral function with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than vascular origin'. Worldwide, about 20 million people suffer from stroke each year; 5 million will die as a consequence and 15 million will survive; of those, who survive, 5 million will be disabled by their stroke. *The Global Burden of Disease (GBD) Study,*[1] *in 1990, reported 9.4 million deaths in India of which 61,900 were from "Stroke" and the disability adjusted life years (DALYs) lost almost amounted to 28.5 million – nearly six times higher than that due to malaria.*

India will face an enormous socioeconomic burden to meet the costs of rehabilitation of "stroke victims" because the population is now surviving through the peak years (age 55-65) of occurrence of stroke (CVD). 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 persons.[2] Another recent survey on 20,842 rural residents in East India reports a crude prevalence rate for stroke in elderly (age 41-60 yr) at 540/100,000. Furthermore, in two prospective stroke studies, during the period 1963-1968 and 1978-1982 in Bombay, using identical methodologies, it was observed that there was a significant drop in case fatality rate (32 to 12%), thereby resulting in a higher survival (68 to 88%) but with residual disability. *Thus, these changing*

trends have posed a major social challenge in occupational rehabilitation and in solving the needs for stroke survivors.[2,3]

Furthermore, published reports suggest that CVD occurs at all ages in both sexes and with increasing frequency with advancing age. Prospective studies on acute stroke have shown that hypertension, diabetes mellitus, low normal hemoglobin and tobacco use (smoking / chewing) are important risk factors (RFs).[4,5] Likewise, case-control analysis by logistic, regression model in the recent ICASS study (Indian Cooperative Acute Stroke Study - 2002-2004) has revealed that the odds for developing stroke were significantly higher in patients with a history of hypertension [OR 3.2, 95% CI: 1.6-6.5] and ischemic heart disease [OR 2.9, 95% CI: 1.5-6.3].[3]

ISCHEMIC HYPOXIC CEREBRAL INJURY—BASIC CONSIDERATIONS

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 ischemia ("penumbra"), and neuronal death occurs in this central area unless perfusion is quickly restored. On the other hand, nerve cells in the zone of penumbra remain viable for at least three hours ("therapeutic window") and can be salvaged by reperfusion, 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 ischemic-hypoxia is one of the key events that fails to maintain normal concentrations of cellular adenosine triphosphate (ATP) leading to delay in re-synthesis 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 leukocyte-endothelial interaction, receptor activation, post-ischemic hypo/ 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 "ischemic-modifying factors" ("Ischemic Cascade Hypothesis").*[6]

Imaging and Newer Diagnostic Modalities

Spectacular advance in imaging techniques such as CT (Computerized Axial Tomography), MRI (Magnetic Resonance Imaging) and ultrasonography has nearly replaced conventional contrast angiography. These tests also give physiological information on the progress of underlying histological and functional changes. However, the precise role of *leukoariosis* and / or "silent infarcts" *on decline of cognitive functions* is yet not clear. *Technology to image genes and their impact on cellular functions* has been perfected in laboratory animals. *Genetic profiling* of individuals in terms of risk of vascular disease and assessing prognosis is not far away.[7]

Therapy in Acute Ischemic Stroke

Medical Management

The goal of therapy is to avoid development of brain ischemia/infarction and, if already present, to prevent its progression or recurrence. The treatment is divided into three phases: Phase I-saving life and speeding recovery; Phase II-rehabilitation to achieve adaptation (physical, occupational and social, etc.) for a gainful employment; and Phase III - measures to prevent recurrence of stroke.

General Measures in Prevention of Medical Complications

The maintenance of vital signs (temperature, pulse, respiration, blood pressure), patency of airway, fluid and electrolyte balance, and prevention of complications like pulmonary aspiration, seizures, thrombophlebitis, bedsores, etc. are mandatory. The beneficial role of oxygen therapy (Hyperbaric or Normobaric) has been redefined.[8]

To achieve early hospital discharge and home-based rehabilitation as cost-effective management, the role of "Intensive Stroke-Care Units" for specialized care of "stroke-victims" is advocated.[9] *It is reemphasized that general medical and meticulous nursing care are of paramount importance.*[6]

Blood Pressure (BP) and Stroke

High Blood Pressure (HBP) is most common risk factor for stroke. In acute stroke "cerebral autoregulation" is impaired and local blood flow to infarcted brain tissue is solely dependent on level of mean arterial BP. Therefore, rapid lowering of BP by sublingual drugs (e.g. Nifedipine) are best avoided. In presence of severe HBP (BP 220/120 mm Hg and above) smooth lowering of BP by titratable agents (e.g. IV labetolol or enalapril) is advisable.[6]

Evidence of the positive, association of blood pressure with the risk of stroke across a broad range of baseline blood pressure levels has been described. As a result, it would be anticipated that the most effective blood pressure lowering based stroke prevention strategy is one that targets individuals at high risk of stroke and that achieves the maximum possible reduction in blood pressure.[10]

Do 'Beta Blockers' Raise Stroke Risk?

In meta-analysis of randomized controlled trials, where, 105,951 subjects with uncomplicated hypertension participated, the authors compared the group receiving beta blockers against other antihypertensive drugs, placebo or no treatment and reported significantly high risk of stroke, 26% for atenolol.[11] *Furthermore, ASCOT-BPLA* (the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm) *Study reported that antihypertensive regimen based on atenolol and bendroflumethiazide was less effective than one based on amlodipine and perindopril in the prevention of strokes and cardiovascular events.*[12,13]

The reviewers concluded that "use of beta blockers to treat primary hypertension is associated with higher risk of stroke than treatment with other antihypertensive agents. Beta blockers should therefore not be first-line treatment for primary hypertension.[11]"

Antithrombotic Agents in Cerebral Ischemia[14]

Platelet Antiaggregants

Aspirin (Acetylsalicylic acid) prevents platelet adhesion/aggregation, by blocking production of platelet derived thromboxane A2, but suppresses the release of prostacyclin from vascular endothelium. It is widely used in secondary prevention of strokes. In treatment of TIA/RIND and in secondary prevention of strokes, the optimal dose is still debated but results based on recent studies indicate that low dose therapy (100 mg/day or less) may be as effective as high dose (325 mg/day or more).[15,16] In a combined analysis,[17] of 40,000 randomized patients with acute stroke showed a significant reduction of 7 per 1000 in recurrent ischemic events (1.6% for aspirin against 2.3% for controls, 2P < 0.000001); and hemorrhagic transformation of original infarct occurred in 1% of treated versus 0.8% in placebo group (2P = 0.07). The reviewers concluded: "early aspirin is of benefit for a wide range of patients, and its prompt use should be routinely considered for all patients with suspected acute ischemic stroke, mainly to reduce the risk of early recurrence".[17] They also noted that among 9000 patients (22%) who were randomized without prior CT scan, aspirin appeared to show net benefit "with no unusual excess of hemorrhagic stroke; moreover, even among the 800 (2%) who had inadvertently been

randomized after a hemorrhagic stroke, there was no evidence of net hazard (further stroke or death: 63 in aspirin group versus 67 in control group)".[17]

Other antiplatelet drugs like sulfinpyrazone or dipyridamole used alone do not offer any specific advantage. In the ESPS-II (European Stroke Prevention Study-II) study it was suggested that combination of aspirin (50 mg) with extended release dipyridamole (200 mg bd) had additive benefit due to putative synergistic activity in reduction of recurrent strokes and vascular events.[18]

Thienopyridine Derivatives (Ticlopidine, Clopidogrel, etc.) 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. However, the drug is expensive and relatively toxic (i.e. reversible neutropenia and diarrhea are some of the side-effects); hence, routine hematological check up is necessary.[19] In four randomized trials of 22,656 patients having TIA/ischemic stroke, thienopyridines reduced the odds ratio (OR) for vascular event by 9% (OR 0.91; CI 0.84-0.98; 2P = 0.01) preventing 11 events per 1,000 patients treated for two years.[20]

In a recent **MATCH study** (Management of Atheroembolic stroke with Clopidogrel in High-risk patients) 7599 patients having ischemic strokes or TIA received Clopidogrel (75 mg) alone or Clopidogrel (75 mg) plus Aspirin (75mg). Here, no significant difference was reported in primary end point outcomes (i.e. ischemic stroke, myocardial infarction, vascular death, or rehospitalization for acute ischemia) thereby showing no real benefit in the use of such a combination.[21] However, results of other studies are awaited.[22]

Glycoprotein IIb/IIIa receptor antagonists: Abciximab (0.125 microgram/kg/min infusion over 12 hours) is a potent antagonist of platelet glycoprotein IIb/IIIa receptors. However, in the, primary safety endpoint outcome, symptomatic intracranial hemorrhage was reported more with abciximab than with placebo (3.6 vs 1%); at three months, there was a trend towards higher rate of minimal residual disability (53.9 vs 36.4% by Rankin scale) in Abciximab group.[23] Data on use of *Eptifibatid, Tirofiban* are not available for ICVD.

Anticoagulation Therapy in Cerebral Ischemia

Anticoagulation is controlled therapeutic inhibition of blood coagulation factors by specific drugs (e.g. heparin, heparin analogues and warfarin group of drugs). They are administered on theoretical grounds that it halts formation or extension of a thrombus, maintains collateral flow, and thereby possibly prevents recurrent stroke. Parenteral heparin and long-term oral anticoagulants have been extensively tried in acute ischemic strokes. Though such treatment can prevent extension of thrombus, its value in completed stroke is doubtful and its use is often fraught with dangers. On the other hand, in recurrent TIAs, thrombosis in-evolution, cardioembolic strokes in acute coronary syndrome and in those with valvular or nonvalvular atrial fibrillation,[24,25] in subjects not responding to platelet antiaggregant, and in pulmonary embolism, the judicious use of anticoagulants is considered beneficial. However, possible hemorrhagic complications, despite monitoring of International Normalized Ratio (INR), continue to pose a problem about its safety. To minimize the risk of hemorrhagic complications, ischemic infarction should be confirmed by CT or MRI Scan and possibly by CSF test and not based on clinical acumen alone.[6]

The International Stroke Trial (IST),[26] examined the value of heparin versus aspirin in ICVD. Here, 19,435 patients within 48 hours of acute ischemic 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 30 mg of aspirin per day. In the final analysis of death or nonfatal recurrent stroke, there was no added advantage in the group who received heparin treatment.[26] It should be noted that IST was not a blinded study and nearly in one-third patients CT scanning to exclude hemorrhage was not done. To minimize the risk of hemorrhagic

complications, it is mandatory that the ischemic infarction is confirmed by investigations like CT scan. The value of Diffusion Weighted Imaging (DWI) and Magnetic Resonance Angiography (MRA) in acute ischemic stroke substantially improves the accuracy of diagnosis of stroke subtypes.

Likewise, Gubitz G, et al[27] in a **COCHRANE review (2004)** based on six trials (21,966 patients) in acute ischemic stroke, noted that "there was no evidence that anticoagulants reduced the odds of being dead or dependent at the end of follow-up (OR = 0.99; 95% CI 0.93 to 1.04). Although anticoagulant therapy was associated with about 9 fewer recurrent ischemic strokes per 1000 patients treated (OR = 0.76; 95% CI 0.65 to 0.88), it was also associated with a similar sized 9 per 1000 increase in symptomatic intracranial hemorrhages (OR = 2.52; 95% CI 1.92 to 3.30). Similarly, anticoagulants avoided about 4 pulmonary emboli per 1000 (OR = 0.60, 95% CI 0.44 to 0.81), but this benefit was offset by an extra 9 major extracranial hemorrhages per 1000 (OR = 2.99; 95% CI 2.24 to 3.99). Sensitivity analyses did not identify a particular type of anticoagulant regimen or patient characteristic associated with net benefit."[27]

In **SPORTIF Trial,** (Stroke Prevention with the Oral direct Thrombin Inhibitor in atrial Fibrillation) Ximelagatran, an oral direct thrombin inhibitor was compared with warfarin (INR 2-3) in a cohort of atrial fibrillation with high risk factors for stroke similar to SPAF III. There was no significant difference in ischemic stroke outcomes, RRR for Ximelagatran was 14% and P 0.0065. US-FDA approval has been with held on account of hepatic dysfunction.

These trials do not demonstrate benefit from early anticoagulation in improving outcome, reducing mortality, and preventing early recurrent stroke. These results suggest that most patients with acute stroke should not be treated with unfractionated heparin or other rapidly acting anticoagulants after stroke. Prevention of deep vein thrombosis and pulmonary embolism among bedridden patients is the only established indication for early anticoagulation after acute ischemic stroke. Bleeding complication in ischemic infarct remains a serious concern.

Cardioembolic Strokes— Anticoagulation in Prevention

Cardioembolic strokes are common in subjects having non-valvular atrial fibrillation, post acute coronary syndrome (e.g. mural thrombi, ruptured chordae tendinae, ventricular aneurysm, etc.), valvular rheumatic heart disease, cardiomyopathy, septal defects and patent foramen ovale (PFO). In atrial fibrillation, the stroke recurrence risk is as high as 12 percent per year. Though aspirin, anticoagulation or both are essential drugs the question remains as to which drug is superior in stroke prevention. Clinical trials are summarized in Table 41.1.

SPAF III[28] and EAFT[29] show that warfarin significantly reduces stroke occurrence recurrence (first occurrence of recurrence) risk in patients with atrial fibrillation at INR 2 to 3.9 but at INR greater than 3.0 the chances of bleeding in high-risk group were high. "Choice of antithrombotic therapy depends upon the etiology of stroke. Oral anticoagulation treatment is the preferred choice for inferred cardioembolism in setting of atrial fibrillation, while the varying rates of hemorrhage with oral anticoagulants continue to favor antiplatelet therapy in other setting of inferred etiology. Combinations of antithrombotic therapy vary in their lowering of stroke rate and some raise the risk of hemorrhage. Insufficient data exist to determine whether antithrombotic therapy combined with antihypertensives, statins or other agents will further reduce the risk of stroke in synergistic or supplemental fashion or give no additional benefit.[30]"

Non-cardioembolic Stroke— Anticoagulation Therapy

WARSS (Warfarin Aspirin Recurrent Stroke Study) – a large randomized double blind study, using warfarin (INR 1.4-2.8) versus aspirin (325 mg), was planned to compare prevention of recurrence in non-cardioembolic strokes between the two groups. They enrolled 2206 patients with 59% were males over 60 years of age. Over a two year period, the combined death and/or recurrent stroke rate was 16.9%. In this study, in the two treatment arms there was no statistically

significant difference in the rate of recurrent stroke but the warfarin group had significantly more minor hemorrhages. It was suggested that warfarin can be used as a "Fall Back therapy" in the event of aspirin failure.[28,30]

In the **WASID (Warfarin Aspirin Symptomatic Intracranial Disease Study)** patients with angiographically proven intracranial large artery disease were analyzed retrospectively. In this subgroup analysis, recurrent stroke rate for patients on aspirin for stroke prevention was 10.4/100 patient-years whereas patients on warfarin had stroke rate of 3.6/100 patient-years suggesting the superiority of warfarin arm.[30,31]

In a subsequent prospective randomized trial similar to WARSS with higher INR (2-3) for warfarin as well as higher dose (1300 mg) for the aspirin group, the final analysis showed no difference in stroke or vascular death rate between the two groups.[30] "In the aspirin arm, there was a decreased death rate (RR 0.46, CI 0.24-1.79) and a non significant increase in stroke (RR 1.23, CI 0.84-1.79)." On account of higher rate of hemorrhage into warfarin group as compared to aspirin arm the study was possibly terminated.[30]

In a **COCHRANE** review (2004)[32] in 4000 patients having TIA or minor stroke in retrospective analysis found no difference in the outcome of vascular death and stroke, even at different INR intensities, between anticoagulation versus antiplatelet therapy. On the other hand, at high INR (3-4.5) the anticoagulation group had increased risk of bleeding (RR 9.02 CI 3.9-20).

Concluding Remarks: Antithrombotic Agents in Cerebral Ischemia[14]

The current evidence suggests that aspirin is treatment of choice when compared to anti-coagulants for patients with non-cardioembolic stroke. The usefulness of combination therapy (Aspirin vs with or without warfarin) is still debated. Likewise, the combination of aspirin with clopidogrel has no added advantage (MATCH Trial). However, anticoagulant therapy significantly benefits high-risk patients with atrial fibrillation in the elderly subjects whereas aspirin may still be the drug of choice in stroke prevention in low risk group in the younger age. There is dire need for well-planned randomized double blind controlled studies to define the role of Antithrombotic agents in "cryptogenic stroke (PFO/ASD related) antiphospholipid antibody syndrome, arterial dissections and intraluminal clot syndromes. Evaluation and treatment of associated risk factors in all categories needs greater emphasis.

Thrombolytic Therapy

Spontaneous recanalization 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 three hours of ictus in MRI positive and CT negative ischemic infarct (i.e. when "window of therapeutic opportunity" is open).[6]

Intravenous Thrombolytic Therapy

The European Cooperative Acute Stroke Study (ECASS), a multicentric randomized double blind placebo-controlled trial, where rt-PA (recombinant tissue activator of plasminogen) was given in the dose of 1.1 mg/kg t-PA intravenously within 3-6 hours of acute hemispheric ischemic 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 endpoints 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 favorable effect on primary endpoint indicating benefit of early treatment but this efficacy was limited only to a defined subgroup with highly specific criteria of early infarct by CT.[33]

National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group (1995)[34] 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 ischemia (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) favored rt-PA group. The NINDS and ECASS trials showed that thrombolysis with rt-PA within 3 hours can be an effective treatment in acute ischemic stroke, and nearly 30% patients are likely to have none or minimal disability at 3 months assessment as compared to placebo group.[33,34]

Subsequently, ECASS-II trial was planned similar to NINCDS study within 6 hours of acute ischemic 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 favorable outcome. These results do not confirm statistical benefits for alteplase. Symptomatic intracranial hemorrhage occurred in 8.8% (36 patients) receiving alteplase as against 3.4% (13 patients) in the placebo group.[35] Thus, controversy on efficacy of alteplase between 3 to 6 hours of acute ischemic stroke continues.[33,36]

On the other hand, the risk of intracerebral hemorrhage 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.[33]

The DIAS Study (Desmoteplase in Acute Stroke)[37] recruited a placebo-controlled, double blind, randomized trial 104 patients with a perfusion or diffusion mismatch—the MRI correlate of the ischemic penumbra—and tested safety and efficacy. Early reperfusion was associated with favorable outcome and therefore seems to be a suitable surrogate in reperfusion trials. DIAS suggested that selection patients rather than a defined time-window might be the key to effective thrombolytic therapy. However, final results are awaited.

Intra-arterial Thrombolytic Therapy

Recent advances in super selective 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 recanalization. Successful thrombolysis in vertebro-basilar occlusion has been reported with survival in 14 out of 19 patients, and favorable outcome in 10. All 24 patients where the occlusion persisted died ($p = 0.000007$).[38] Similar encouraging results have been reported by other centers.[39,40]

The favorable results of PROACT-I study[41] have been reconfirmed by randomized-controlled PROACT-II trial with favorable outcome in 40% of r-proUK patients as against 25% of controls.[42] Recanalization was achieved in 66% of treated group and 18% of control group ($p = 0.001$) but intracranial hemorrhages were noted in 10% of treated group versus 2% of the controls ($p = 0.06$).[42] Results of other placebo-controlled randomized trials are awaited. At present, intra-arterial thrombolytic therapy appears possible only in a select subgroup of patients within 3 hours of onset of ischemic stroke, satisfying strict neuroradiological exclusion criteria to prevent misdiagnosis; and at centers where specialized teams of neurologist and neuroradiologist are available to monitor recanalization and reperfusion by transcranial Doppler evaluation and by diffusion and perfusion MRI studies.[43,44]

Concluding Remarks

Recent reanalysis of NINDS trial show that despite concerns to the contrary, baseline differences between the groups of patients randomized to either placebo or alteplase did not invalidate the trial's raw results, which favored alteplase. However, NINDS trial is still the only randomized control trial of alteplase showing benefit as per its prespecified outcome measures and yet it does not show its effects on mortality. Although thrombolysis has potentials to benefit individual patient, it has also the potential to harm others as well, and whether the benefit outweighs the risk is still unclear.[45,46]

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

Neuroprotective Agents

Cerebral ischemia induces release of excitatory amino acid neurotransmitters 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-isoazole propionic acid [AMPA] channels). Cell destruction most likely occurs from production of nitric oxide and subsequent formation of other free radicals. NMDA channel has at least 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.

Voltage dependent calcium channel antagonists (dihydropyridine compound "nimodipine") are drugs which have cytoprotective action in ischemic stroke. The American Nimodipine Study Group found that nimodipine had no overall beneficial effect when treatment was started within 48 hours; but there was definite benefit if therapy began within 18 hours of ictus in CT negative cases. As dihydropyridine compounds produce hypotension, blood pressure should be constantly monitored and the concurrent use of serotonin depletors (e.g. reserpine) and alpha blockers which may cause postural hypotension should be avoided.[47]

Raised Homocysteine (tHcy) Level— *"An Independent Risk Factor"* for Vascular Disease

Elevated levels of tHcy have been reported as significant and an "independent risk factor" for myocardial infarction and stroke, though precise mechanisms linking raised tHcy to vascular disease have not been established. It has been suggested that raised tHcy harms endothelial cell functions, increases oxidative stress and thereby risk to thrombosis.[48] Treatment with vitamins (B6, B12, Folic acid) reverses the raised levels of tHcy and thereby possibly prevents progression of vascular disease. Some studies have shown clinical benefit with higher dose of vitamin B12 therapy in coronary angioplasty and peripheral vascular disease.[49] On the other hand, results of randomized controlled trials (VISP- Vitamin Intervention in Stroke Prevention; VITATOPS - Vitamins to Prevent Stroke) have not supported above hypotheses. Thus, vitamin therapy (B6, B12, Folic acid) in prevention of recurrent stroke continues to be debated.[50]

Statins and Stroke—Current Views

Recent data from **SPARCL Study** (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) suggest that statins reduce a risk of recurrence of stroke and that stroke prevention may be independent of their effects on lowering low-density lipoprotein.[51]

Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins, have also been considered beneficial in prophylaxis against myocardial infarction, stroke and other vascular events. The integrity and function of endothelium depends on synthesis of nitric oxide

and inhibition of smooth muscle proliferation, endothelial leukocyte adhesion and platelet aggregation. Inhibition of generation of NO by nitric oxide synthase has atherogenic effect. Among other factors, Homocysteine, amino acid derived from methionine, requires folic acid, B12/B6 for methylation. High concentration of plasma Homocysteine is associated with increased risk of cardiovascular disease and dietary supplementation with high dose of folic acid (5 mg daily) has now shown enhanced endothelial function by their action on cellular nitric oxide. It has been postulated that neuroprotective effect of statins may have multiple mechanisms, like upregulation of eNOs and increase blood flow, reduce inflammation or it may be an independent "class effect".[52]

Stenting and Angioplasty in Symptomatic Carotid Stenosis

The **SAPHIRE Study** (Stenting and Angioplasty with Protection at High-risk for Endarterectomy)[53] assessed results of stenting against Carotid Endarterectomy (CAE) in 334 subjects with greater than 50% symptomatic or 80% asymptomatic stenosis. It was suggested that "stenting arm" had lower cumulative incidence of stroke, myocardial infarction or death at 1 year compared to those who had CAE. Recurrent intervention was less common in the patients in the stenting group. Although the trial was stopped early because of recruitment problems, the results indicate that carotid stenting with embolus protection is at least as good as CAE. Secondary outcome measures suggest that carotid stenting with embolus protection is safer and even better than CAE in patients with substantial comorbidity or who are at least 80 years of age. However, this trial has several shortcomings. First, there is no evidence that surgery of an asymptomatic internal carotid artery stenosis should be done before coronary bypass surgery. Second, the endpoint was unusual in its inclusion of myocardial infarction. Third, the results are almost exclusively triggered by the myocardial infarction part of the composite endpoint. Finally, these findings cannot be generalized to patients without severe coexisting ischemic heart disease and high surgical risk.

Current status in carotid stenting has been reviewed by Yadav, et al,[53] and Rajgopal and Yadav.[54] Though CAE appears well established in tight symptomatic carotid stenosis (>70%) by both **NASCET**[55] and **ECST**[56] trials, stenting with or without embolic protection devices are getting accepted as alternative mode of treatment in cases with CAE is not feasible or difficult. It has been reported that fewer complications occur with stenting as compared to CAE (e.g. neck hematoma, cranial neuropathy, etc.).

However, restenosis rate was higher with carotid intervention (14% Vs 4%) when compared with results of CAE. Recent carotid stenting trials, with improvement of technology has shown that carotid stenting is an attractive alternative to carotid endarterectomy and, over the next 10 years, it is possible that stenting will supplant endarterectomy as the preferred treatment for patients with carotid disease. Therefore, it is imperative for physicians to become familiar with the basics of this procedure, along with the management of patients after carotid artery stenting.

Stem Cell Therapy in Acute Stroke

Ethical and moral issues have prevented experimental trials on stem cell therapy in human subjects with acute ischemic stroke. Animal experiments in various models do suggest that this avenue of therapy needs to be explored. However, reliable and variable reports are yet not available.

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