ABSTRACT

Stroke or cerebrovascular accident is a common neurological disorder in the community most often managed by the physician as it occurs in patients who already have hypertension, diabetes. Until recently stroke was looked upon with a nihilistic attitude, as “nothing much can be done”. A definitive treatment, which is useful to reduce the mortality and morbidity has emerged in the last decade – thrombolysis. Unfortunately this treatment has not been made use of due to several reasons, which includes lack of awareness of this effective treatment among patients and the primary care physicians. The approved treatment of thrombolysis consists of intra venous of tPA (tissue plasminogen activator) which should be administered within three hours of onset of stroke. The time window period is extended to 4.5 hours recently utilizing the advances in imaging techniques like MR perfusion and diffusion weighted imaged, multi modal CT. Direct lysis and removal of the clot (in contrast to intravenous thrombolysis) beyond 4-5 hrs time window is being practiced in several centers, who have the expertise of Interventional radiologists or stroke physicians doing such procedures – intra arterial injection of tPA, mechanical removal of clot.

Where thrombolysis is not feasible, aspirin is a very useful drug in acute stroke. Meticulous attention to general management of maintaining blood pressure, glucose, temperature, hydration etc will help to reduce the brain insult. Appropriate measures like anti brain oedema agents, surgical decompression are suggested to deal with cerebral edema and raised intracranial pressure in the first week of stroke, to reduce the morbidity and mortality.

I hope this brief article enthuses more physicians to actively pursue this mode of treatment to benefit a larger number of patients.

Stroke is the 3rd leading cause of death and the leading cause of disability. Two thirds of stroke deaths world wide are seen in developing countries. The incidence as well as 30 day case fatality rates are higher in India. Community surveys from India show a crude prevalence rate for strokes presumed to be of vascular origin in the range of 200/100 thousand persons. Ischemic stroke constitute 80-85% of all the strokes and the clinical approach and the management will be highlighted.

DIAGNOSIS

The clinical picture is one of sudden onset of any of the following - hemiparesis, monoparesis, language dysfunction, dysarthria, ataxia, hemi anopia, diplopia. Once a clinical suspicion of stroke is considered a focused neurological examination will confirm, not only the diagnosis but also the neurological deficits (hemiplegia, dysarthria, dysphagia, ataxia), the degree of deficits, the vascular territory involved (carotid, vertebro basilar). Stroke should be differentiated from stroke mimics, which include hypoglycemia, hyperglycemia, seizure – postictal, hemiplegic migraine and subdural hematoma.

INVESTIGATIONS

The plain CT head Scan is the bulwark for the diagnosis of ischemic stroke, funnily in a negative way that is with a clinical diagnosis of acute onset of right hemiplegia if the CT Head scan is normal it rules out intracerebral hemorrhage and by default supports the clinical diagnosis of ischemic infarct and hence the importance of clinical neurology even in the modern diagnostic era. The early signs of MCA territory ischemic stroke consists of hyperdense middle cerebral artery (MCA) hypodensity of insular ribbon, basal ganglia and sulcular effacement, loss of grey white matter differentiation. However even these early signs are often difficult to identify in the first few hours of stroke.

Where possible MRI adds to the information which includes diffusion weighted image (DWI) which picks up the infarct within minutes of occurrence. The perfusion studies have the advantage of extending the time window for thrombolysis beyond three hours. Multimodal CT imaging CT perfusion, CT angiography is the other method of assessing ischemic penumbra. The combination of DWI / PWI is the imaging of choice for the identification of core infarct and ischemic penumbra which can assist in choosing patients for thrombolysis in the 3 -6 hours time window. MR Angiography will delineate both extra cranial and intra cranial vasculature, and occlusions / stenosis if any.

In addition to brain imaging several laboratory test must be
performed – complete haemogram, blood sugar, blood urea, creatine, electrolytes, coagulations parameters, ECG and other relevant investigation as required.

MANAGEMENT

The pathogenesis of ischemic stroke is occlusion of a cerebral vessel (internal carotid or middle cerebral artery) which results in ischemic infarct of the cerebral tissues perfused by these vessel. The infarct has a core area with destroyed neural tissue and a surrounding penumbra where the tissue is sub optimally functioning but not structurally dead. The aim of the treatment is directed to (a) opening up of the occluded vessel (Thrombolysis) (b) to keep the tissue in the penumbral region alive so that when the circulation is restored they can be fully functional (neuro protective measure) (c) to manage cerebral edema and raised intracranial pressure. (Anti – brain edema measures and surgical decompression). (d) General measures.

a. Thrombolysis

First three hours

The emergent diagnosis of an acute ischemic stroke is mandated by the only proven treatment available - thrombolysis - by tissue plasminogen activator – (tPA) which should be given within three hours of onset illness. The initial time window of three hours has been fixed because thrombolysis after this period is likely to cause hemorrhagic complication in the infarcted tissue. The number needed to treat to prevent one death or disability in this time window is eight. This therapy has 30% higher rate of favorable outcome and 21% versus 17% mortality rate in the placebo group and treatment group respectively. Thrombolysis would save 110 people from death or disability for every thousand treated. The best results are found in younger patients with mild to moderate deficits treated in the earlier part of three hours, normotensive with small to moderate clot burden. a) Inclusion criterion are Ischemic stroke causing measurable neurologic deficit. Cranial computed tomography (CT) negative for hemorrhage. Onset of symptoms <3 hours before beginning treatment. Patient or family understands the potential risks and benefits from treatment. Exclusion criterion are Minor and isolated neurologic signs neurologic deficit that is clearing spontaneously CT evidence of multilobar infarction (e.g. hypodensity >1/3 cerebral hemisphere) evidence of bleeding disorder or recent surgery or trauma.

Several randomize control trials have substantiated the utility of thrombolytic treatment. If the patient is a candidate for thrombolysis arriving within 3 hours, IV alteplase. a total dose of 0.9mg per kg is given, 10% of which is given as a bolus and the rest as a IV drip. Irrespective of occlusion are not, patients are given IV alteplase which is safe and effective in routine clinical use when used within three hours of stroke onset, even by centers with little previous experience of thrombolytic therapy for acute stroke. This study encourages wider use of thrombolytic therapy for suitable patients in stroke centers.

Even though the specific treatment is available with good results, in view of the time constraint of three hours and lack of awareness both in the medical and the lay community the benefit is made use by less than 10% of deserving patients.

Thrombolytic therapy beyond the three hours:

IVt-PA administration is expanded beyond three hours and upto four and half hours time window. A meta analysis of tPA stroke trial suggests that alteplase is beneficial not only within the standard three hour time window, but upto 4.5 hours after stroke onset. The European Cooperative Acute Stroke Study (ECASS) in their two trials evaluated the use of IVtPA within six hours of symptom onset and observed that the tPA treated group fared slightly better at three months than the placebo group. However even though the time window is expanded the earlier the patients are treated the better is the outcome emphasizing that “time is brain”.

If CT Angiogram or MR Angiogram reveals a major arterial occlusion (internal carotid, middle cerebral, basilar), intravenous therapy is followed by intra arterial therapy, to tackle the clot burden with alteplase, if there is no improvement within 30 minutes of iv tPA. Combined intravenous and intra-arterial thrombolysis may be more effective than either therapy alone in patients with large vessel occlusion. An Initial dose of 0.6mg per kg of IVtPA over 30 minutes within three hours of stroke onset, followed by intra arterial tPA within five hours, if vessel occlusion is still present within five hours on angiography. Local intra-arterial thrombolysis alone is the treatment of choice where patients are ineligible for systemic alteplase therapy, like general bleeding disorder.

Different methods of intra-arterial thrombolysis can be tried in addition to local injection of alteplase; These are mechanical clot removers – MERCI concentric retriever device. The recanalisation rate with this device was 48% with a 7.8% rate of symptomatic intracranial haemorrhage and overall half of these had good neurological outcome at 90 days. Mechanical thrombolysis with endovascular devises are tried in patients where IVtPA has failed or ineligible. Another method to deal with the clot in large vessel is by ultrasonic fibronolysis with EKOS microlys catheter. The catheter has an ultrasound transducer and its tip causing lysis of thrombus by ultrasound energy. Endovascular Laser treatment is another method to tackle the thrombosis locally.

Thrombolytic therapy after six hours

Local intra arterial thrombolysis with various devices as
Acute Cerebrovascular Stroke: Advances in Evaluation & Management

The Desmoteplase in Acute Ischemic Stroke (DIAS) trial examining the efficacy and safety of desmoteplase administered 3-9 hours after ischemic stroke in selected patients with diffusion – mismatch has better clinical outcome. This was further supported by EPITHET trial. What if thrombolysis is not feasible?

For patients who are not eligible for tPA Aspirin is the only antiplatelet drug that is useful in acute treatment of stroke. Aspirin should be started within 48 hours of ischemic stroke and in those who receive tPA it should be started 24 hours after thrombolytic therapy. The results of two large randomized, non blinded intervention studies namely International Stroke Trial (IST) and Chinese Acute Stroke Trial (CAST) indicate that Aspirin given within 24-48 hours after stroke seems to significantly reduce mortality and the rate of recurrent stroke. Heparin, standard or low molecular is not recommended in the management of acute stroke as there was overall no benefit or little benefit counter balanced by increased number of hemorrhagic complications.

b. Neuro protection – Neuro protection of tissue in penumbra region would help to wait for restoration of circulation. Not withstanding a number of drugs which have been tried and which are also currently in use, suffice it to say that none of them have proven benefit and as such are of no clinical utility.

c. Management of cerebral oedema and raised intracranial pressure.

Cerebral Edema compromises further, cerebral function and also leads to mass effect and brain herniation with secondary brain stem compression, leading to coma and death. Characteristically the edema peaks from the third to fifth day after the stroke. The management of raised intracranial pressure consists of, in addition to proper maintenance of airway and blood pressure – an elevation of head to 30 degrees for proper cerebral venous return, hyperosmolar therapy with mannitol 0.5 to 1 gram per kg loading dose followed by 0.25 gram per kg every 6 hours. Hypertonic saline as an alternative is used particularly in hypovolemic patients. Hyperventilation to reduce the intracranial pressure has only a short time effect and to be used in emergency situations like shifting the patient for surgery. Corticosteroids are of no benefit and infact may worsen the outcome.

In patients with large cerebral infarction and mass effect with mid line shift, craniectomy in selected cases is utilized to decompress the brain particularly in patients below 60 years, within 48 hrs of stroke onset. In addition to reducing the mortality improved functional outcome is also observed. Cranectomy has gratifying results in patients with cerebellar haemorrhages or large cerebellar ischemic infarcts compressing the brain stem.

d. General Measures – Little things matter much and so also in the general management of stroke. Meticulous attention to the following, helps to salvage brain function and this attention makes all the difference between better results of stroke unit compared to general wards.

i. Blood glucose – it is important to note that hypoglycemia may mimic a stroke which fortunately is attended to, by rapid estimation of blood glucose in casualty in most of the hospitals. The blood glucose level must be kept within normal range (80 – 130 mg) correcting the hypoglycemia as well treating hyperglycemia with insulin on sliding scale, if serum glucose is more than 200mg % . Hyperglycemia increases cerebral edema and also haemorrhagic transformation of infarcted tissue, so avoid dextrose infusions.

ii. Blood pressure – Management of hypertension in acute stroke is very important. Hypertension to be treated only if more than 220/120mm hg – to be reduced by 10-20%. Pre-existing anti hypertensive therapy to be continued orally or via nasogastric. We start reducing the blood pressure after 48 hrs, for the simple reason that the infarcted tissue has lost the inbuilt mechanism of maintaining the blood supply (autoregulation) and so is dependent upon the systemic blood pressure to perfuse the ischemic tissue hence reduction of blood pressure will only further aggravate ischemia in the penumbral region. Antihypertensive therapy (for BP of less than 220/120 mm hg) is indicated in the first 48 hrs of acute stroke, if other compelling reasons exist, like acute myocardial infarction, severe congestive heart failure, hypertensive encephalopathy. Hypertension of more than 180/110mm/hg needs to be treated if the patient is taken up for fibrinolysis. The drugs used for rapid reduction are (a) Labetalol 10-12 mg IV over 1-2 min may repeat or double every 10 min (maximum dose 300mg) . IV labetalol drip 1-2 mg/min can be increased upto 2-8 mg/min. Nicardipine 5 mg/hr IV infusion as initial dose; titrate to desired effect by increasing 2-5 mg/hr every 5 min to a maximum of 15 mg/hr. Aim for a 10% to 15% reduction of blood pressure. Enalapril IV 0.625- 1.25mgIV may repeat if inadequate response. Sodium nitroprusside 0.5 mg/kg/min IV titrate upto 0.5 to 10mcg/kg/min.

iii. Intravenous fluids – excessive iv fluid administration should be avoided so also the intravenous dextrose
preparations. The standard procedure is to give 50 – 100ml saline per hour, or as required.

iv. Oxygen - routine use of nasal oxygen is not indicated unless there is demonstrable hypoxia.

v. Temperature Any rise in body temperature adversely affects the cerebral metabolism and contributes to the damage to penumbra. Fever increases cerebral metabolism in an already compromised cerebral blood flow state, hence hyperthermia should be treated by periodic administration of anti pyretics.

vi. Oral intake – As long as the patient is unconscious or even in the altered state of sensorium naso gastric feeds to be recommended. However it is to be noted that the aspiration risk is still present with this method. Oral intake is to be encouraged only after assessing normal swallowing function, metoclopramide may be used for facilitating gastric emptying.

vii. Antibiotics to be used only in presence of infection and not as prophylaxis.

viii. Antiepileptic drugs to be started only when seizures occur and not as prophylaxis

ix. Patients who are bedridden must receive prophylaxis for deep vein thrombosis with low molecular weight heparin, if contra indicated, with intermittent external compressing stockings.

x. Where possible indwelling catheter should be avoided, ( intermittent catheter preferable),

It needs to be emphasized that general medical management is as important as high-tech neuro intervention, for better outcome of patients with cerebrovascular stroke

REFERENCES


