MANAGEMENT OF ACUTE STROKE

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STROKE

It is a syndrome of rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting for 24 hours or more, or leading to death, with no apparent cause other than vascular origin. The definition includes sub-arachnoid haemorrhage (SAH) but excludes TIA's, subdural haematoma, and haemorrhage or infarctions caused by infections or tumours. It also excludes silent cerebral infarctions. The following proportions of causes of first stroke can be expected: cerebral infarction 76%; intracerebral haemorrhage 10%; SAH 4%; not known 10%.

NEURONAL DEATH IN STROKE

Neurons die within minutes of oxygen deprivation. Thus, some neuronal death occurs in the areas of no blood flow within minutes of stroke onset. Around such an area of necrosis exists a region of hypoperfusion, electrically silent tissue that barely receives enough blood flow to keep neurons alive. This tissue area is called "ischaemic penumbra." The major goal of acute stroke management is resuscitation of the ischaemic penumbra. If perfusion to the penumbra occurs expeditiously, neurons recover and the patients improves; with no perfusion, a time related attrition converts ailing neurons to frank infarct.

PATHOPHYSIOLOGY

It is not just the degree, site or the duration of an ischaemic insult after a stroke that affects the outcome but the stroke itself can initiate a cascade of events resulting in further cerebral damage. Important factors in this damage are unregulated influx of calcium ions into the nerve cells, lactic acidosis and free radical production. In the region of ischaemia there is marked ATP depletion with an increase in extracellular "K" (efflux from injured depolarized cells) and cellular acidosis. Calcium influx leads to release from the nerve endings of endogenous neurotransmitter such as glutamate, which is formed from glycolytic intermediates of Krebs cycle. This neurotransmitter released from the ischaemic cells excite neurons and leads to further influx of Na and Ca, thus starting a vicious cycle. The rising calcium triggers the release of damaging proteases, phospholipases, free fatty acids, lipases and free radical, which leads to further damage. Free radicals have an unpaired electron and are highly reactive and damaging to the cellular systems. Free radicals as well as the phospholipases destroy the phospholipids of neuronal membrane. This progression of an acute stroke leads to cerebral oedema, haemorrhagic transformation of the cerebral infarct and further arterial occlusion, which
accounts for the early deterioration in some cases. Castillo et al.\(^3\) have reported early deterioration in ischaemic stroke associated with raised CSF and plasma Glutamate levels.

**GENERAL MANAGEMENT OF ACUTE BRAIN FOCAL ISCHAEMIA**

**INVESTIGATIONS**

**CT Scan:** Haemorrhage can be seen within a few minutes as an area of increased attenuation (i.e. white with a little surrounding oedema which is dark grey in colour), but after a few weeks the lesion becomes cystic and of low attenuation; therefore, it may be impossible to distinguish infarct from haemorrhage if CT is not performed within two weeks. CT may be normal or may show only subtle changes in the first few hours after an ischaemic stroke, but most become visible by 24 to 48 hours as a dark area (low attenuation). It too may have mass effect acutely due to oedema. It is at its maximum visibility at 3-5 days when oedema is at its greatest. Despite a typical history, however, CT sometimes shows no abnormality as the infarct responsible is beyond the resolution of the CT scan\(^4,5\). Urgent scanning is needed to exclude surgically treatable conditions (e.g. subarachnoid haemorrhage, cerebellar haematoma, space occupying lesion) if:

- There is clinical deterioration in the patient’s condition, such as progressive or fluctuating symptoms, the patient becomes drowsy or comatose, has brain stem symptoms or signs, has papilloedema, has severe headache or deteriorates unexpectedly.
- The diagnosis is in doubt because of other unusual features
- Hydrocephalus secondary to intracerebral haemorrhage is suspected.
- Trauma is suspected.

- The patient is on anticoagulant treatment, or has a known bleeding tendency.
- If anticoagulation, thrombolytic or antiplatelet therapy is being considered.

**MRI:** It is more reliable than a CT scan in documenting the extent and location of even small areas of infarction in all areas of the brain, including the posterior fossa, which is usually not documented by CT because of bone artifacts. It can detect the traces of old haemorrhage (haemosidrine deposits) indefinitely. New MRI sequences are sensitive to the changes of cerebral ischaemia and can provide information about underlying pathophysiology.

Not only is a CT or MRI scan required to establish the pathological diagnosis (infarction, haemorrhage or subarachnoid haemorrhage) but it helps to exclude other conditions that may mimic stroke (e.g. subdural haematoma, intracranial tumours etc.) and facilitates appropriate management, as we shall see later on. All patients should undergo scanning within 48 hours, if possible; if facilities are limited, early scanning is indicated in all those in whom active management (thrombolysis, surgery, anticoagulation, antiplatelet therapy) is contemplated.

**CAROTID ULTRASONOGRAPHY:** Using duplex imaging and colour-coded Doppler measurement of blood flow velocity should be performed in patients with TIA or stroke in the carotid territories, to identify internal carotid artery stenosis, occlusion and dissection. Ascelulation for a carotid bruit does not identify all patients with significant internal carotid artery stenosis.\(^6\)

**DIGITAL SUBTRACTION ANGIOGRAPHY:** It carries a 1-2% risk of stroke and should be performed only by experienced radiologist.\(^6\)
Management of Acute Stroke

- To confirm severe carotid stenosis if there is doubt after non-invasive imaging.
- To confirm occlusion or dissection in patients suitable for anticoagulation.
- In subarachnoid and intracranial haemorrhage to diagnose the source of bleeding.
- In younger patients with recurrent or unexplained symptoms.

**BLOOD TESTS**

- Full blood count, including platelet count, is essential to detect polycythaemia, platelet disorders and infections.
- ESR: If raised suggest infection, systemic vasculitis or carcinoma and should lead to further investigations (e.g., auto-antibody screen, chest radiography etc.)
- Fasting blood glucose: To detect diabetes mellitus.
- Fasting lipids should be measured in all but the very elderly.
- An investigation of blood clotting is needed in intracerebral and subarachnoid haemorrhage.
- Thrombophilia screen: For anticardiolipin antibody, protein C & S, antithrombin III levels and factor V Leiden polymorphism is indicated in patients with cerebral venous thrombosis and in those < 60 years with otherwise unexplained TIA or ischaemic stroke.
- Syphilis serology should be undertaken in most patients - the diagnosis may not otherwise be suspected.
- Blood cultures are indicated if bacterial endocarditis is suspected.

**CARDIAC INVESTIGATIONS**

These are indicated towards detecting the sources of cardiac embolism.

- ECG should be performed in all patients. In patients with atrial fibrillation a rhythm strip should be included.
- ECHO cardiography: Ideally all patients should undergo echocardiography; if facilities are limited, it is clearly indicated in those < 60 years, and in older patients with significant cardiac abnormality or recurrent unexplained stroke.
- Transoesophageal echocardiography (TOE): If conventional echocardiography shows no abnormality, TOE should be considered because it is more likely to identify an atrial abnormality or patent foramen ovale.

**Lumbar puncture** Is indicated after CT or MRI has excluded distortion of intracranial structures in suspected meningitis or encephalitis. It may also be used to detect blood and xanthochromia in patients with suspected SAH if the initial scan is normal, and to detect increased WBC count and oligoclonal immunoglobulins in those with suspected vasculitis.

**TREATMENT**

**Bed rest:** Patients should be maintained on bed rest for 24 hours to avoid postural hypotension. Since autoregulation is usually ineffective in the area of ischaemic brain, cerebral blood flow declines if systemic blood pressure falls because of postural changes or volume restriction.

**Elevated blood pressure:** Unless the systolic BP exceeds 220 mmHg or diastolic pressure exceeds 120 mmHg (sustained on repeated measurement), elevated BP should not be treated within the first few days of ischaemia stoke. The ischaemic penumbra loses autoregulation & perfusion is directly
related to the mean arterial pressure.\textsuperscript{2,7,8,9} Acute elevation in BP is often transient, and spontaneous declines are common. Overzealous treatment of hypertension following acute ischaemic stroke can convert the ischaemic penumbra into an infarct. Thus BP should be reduced in all limited stepwise fashion, as below:

- Initial BP >220/120, systemic organ failure: Reduce BP by 20-25%; IV nitroprusside or parental b-blocker
- Initial BP >220/120, no systemic organ failure: Reduce BP by 10-15%; oral ACE-I or CCB
- Initial BP <220/120: No anti-hypertensive therapy for 72 hours; then do not reduce below 160-170/90-100 for 1 week

The two exceptions to this general recommendation are as followed: (1) after use of tPA, BP should be maintained below 185/110 mmHg, and (2) in the presence of MI, heart failure or aortic dissection, elevated BP should be treated aggressively.

**Hypotension:** Should be corrected by raising the foot of the bed & by fluid replacement.\textsuperscript{7}

**Hyperglycaemia:** High cerebral glucose levels under anaerobic conditions leads to increased glycolysis during the ischaemic episode with the accumulation of lactic acid, which is neurotoxic to the ischaemic penumbra.\textsuperscript{2,10,40} Plasma glucose of above 200 mg/dl is associated with poor outcome. This is independent of age, stroke severity and stroke sub-type. General consensus is that blood glucose levels should be maintained between 75-150 mg/dl (the maximum upper limit acceptable is up to 200 mg/dl).\textsuperscript{7}

**Pyrexia:** Fever in acute stroke is not uncommon. Whatever the cause, fever should be suppressed in these patients. In experimental models of brain ischaemia as well as in clinical studies, even mild elevations in body temperatures consistently worsen the neurologic outcome from ischaemic insult.\textsuperscript{4,10,11} There are studies showing that lowering body temperature reduces the release of excitatory glutamate in experimental focal ischaemia, hyperthermia on the other hand is associated with worst stroke outcome, possibly because of increased glutamate release.\textsuperscript{3} As discussed in the American Heart Association International Conference on Stroke and Cerebral circulation. Two non-pharmacological approaches were discussed i.e. hypothermia and hemicraniectomy. The logistics for both the treatments were complex, but of the two, hypothermia seems to offer the most promise. Many variables remain to be determined i.e. optimal cooling temperature, time of cooling, time of rewarming, avoidance of shivering etc. but the treatment holds much promise for future. So, vigorously treat temperature if >100°F.

**Aspirin:** Aspirin induces a long lasting functional defect in platelets by permanently inactivation of prostaglandin’s G/H synthetase which catalysis the first step in the synthesis of prostaglandins (platelets last for 8 to 10 days) and subsequently blocks platelet activation by thromboxane.

The value of aspirin in acute stroke has recently been assessed in two large trials. In the “International Stroke Trial” (IST)\textsuperscript{12} 19435 patients were randomised to receive either aspirin (300 mg/day) or no aspirin, while in the Chinese Acute Stroke Trial (CAST)\textsuperscript{13} 21,106 patients were randomised to use aspirin (160 mg/day) or a placebo. Aspirin was stared, between 12 to 24 hours after stroke onset. When data of both these trials were pooled and the outcome measured at six months, those who received early aspirin had statistically significant reduction in the likely hood of death or severe disability, but the magnitude of reduction was small: death or disability was reduced by about one case per 100 treated with aspirin compared with
delayed aspirin. The public health impact for 2 weeks of aspirin therapy for acute stroke is comparable to that of one year of aspirin in the long-term secondary prevention. Because aspirin & other antiplatelet are often used on long term basis for secondary stroke prevention, it makes sense to bring aspirin therapy early (after the CT scan has excluded haemorrhage) to capture this modest benefit, in the absence of contraindications. Aspirin should not be given within 24 hours of t-PA. NB: If you are normal then up to now studies have shown that there is no benefit from taking aspirin.

**Dipyridamol:** European Stroke Prevention Study 44, measured the effects of aspirin 25 mg b.d. & dipyridamol 200mg b.d. (Persantin Retard), in six & half thousand patients with a TIA or mild stroke. The risk of further TIA was reduced by 22% with aspirin, 18% with dipyridomol & 36% with both. Aspirin & dipyridomol had an equal effect in decreasing the risk of stroke or death. The combination was additive. Aspirin with dipyridamol may be better than aspirin alone, although 50 mg was a low dose of aspirin. Aspirin & dipyridamole act in different ways to affect platelet function, dipyridomole inhibits platelet activation by raising cyclic AMP & GMP. During the 2-year follow up 12.5% suffered a stroke and 11.5% died. A 2-year stroke rate was 12.9% in Aspirin (ASA), 13.2% in Dipyridamol, and 9.9% in combined and 15.8% in placebo. Table-1

**Clopidrogl** inhibits platelet aggregation by ADP. A randomized, blinded trial compared clopidrogl with aspirin (325 mg) in patients with risk of ischaemic events (CAPRIE) 15. They selected patients with recent stroke (≥1 week, <6 weeks), myocardial infarction (<36 days) or peripheral vascular disease. Mean age was 62.5 years. Long-term administration of clopidrogl decreased the incidence of MI, ischaemic stroke or vascular deaths to 5.32% annually compared to 5.83% with aspirin, relative risk reduction of 8.7% (equivalent figures for death from any cause 3.05 vs. 3.11). Follow-up was for a mean 1.91 years (1-3 years). In 19,185 patients there were 1960 first events. 9577 on clopidrogl completed the study, while 9566 on aspirin did so. There was 21% drop out for reasons other than primary event. Table-2

In a patient population similar to the CAPRIE group Clopidrogl would prevent 24 major clinical events per year per thousand treated versus 19 with aspirin.

This is a small difference in the annual risk and further studies will be required to determine if clopidrogl should be used in preference to or along with aspirin. Aspirin appears to be better in MI, but when those with a distant previous medical history of a MI were include with those with a recent MI as a qualifying event, Clopidrogl appeared to be better than aspirin. Clopidrogl appears to be better than aspirin in preventing peripheral arterial disease.

<table>
<thead>
<tr>
<th>NUMBER OF EVENTS PREVENTED PER 1000 PATIENTS TREATED FOR 2 YEARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>ASA vs placebo</td>
</tr>
<tr>
<td>DP vs placebo</td>
</tr>
<tr>
<td>DP-ASA vs placebo</td>
</tr>
</tbody>
</table>

Patients with TIA during 2-year follow-up

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>ASA</th>
<th>DP</th>
<th>DP-ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>16.4</td>
<td>12.6</td>
<td>13.2</td>
<td>10.5</td>
</tr>
</tbody>
</table>

TABLE -1
Tissue Plasminogen Activator (tPA): The five-year, National Institute of Health (NIH) study involving 624 patients were given either t-PA (dose 0.9 mg/kg IV, not to exceed 90 mg, given as 10% bolus followed by 90% over 60 minutes; this dose is lower than that used in MI) or a placebo within three hours of onset of symptoms. Neurological and functional recovery was significantly better for t-PA-treated patients. Not only did they improve faster and leave the hospital sooner, but they also showed less disability at three months. The mortality rates at 3 months were slightly less in t-PA group (17%) compared to those in placebo group (21%). They were at least 30% more likely to have minimal or no disability at final evaluation, as measured by four outcome scales (residual neurological deficit scored on the NIH stoke scale, and three measures of disability or functional outcome). The results of this trial i.e. by the National Institute of Neurological Disorders & Stroke (NINDS, a section of National Institute of Health [NIH] t-PA trials) were published in 1995. The FDA granted labeling approval to t-PA in June 1996. The results of NINDS study showed that even with the approximately 6.4% incidence of intracerebral haemorrhage in t-PA recipient, for every 100 patients given t-PA, 12 more experience complete neurological recovery than with placebo. The risk of intracerebral haemorrhage increased significantly in patients with t-PA when early infarction changes were present in the CT scan and in patients with high NIH Stroke Scale at baseline. Neurological assessment should be made immediately after infusion of t-PA and than hourly for the first 24 hours. Central venous access and arterial punctures should be restricted during the first 24 hours. Bladder catheterization should be avoided for at least 30 minutes after t-PA infusion, and nasogastric tube placement should be avoided during the first 24 hours. Intravenous normal saline solution should be administered to ensure normovolemia. Patients who have an abrupt decline in neurological status within the first 24 hours or initiation of t-PA should be considered to have an intracranial haemorrhage until proved otherwise. If the decline occurs during t-PA administration, drug infusion should be stopped. CT of the head repeated immediately, and neurosurgical consultation should be obtained if the scan shows intracranial haemorrhage, as haematoma evacuation or external ventricular drainage, or both may be life saving. A blood sample should be obtained for measurement of haematoctrit, APTT, PT, platelet count, and serum fibrinogen level. In addition, blood should be typed and cross-matched for 4 U of packed red blood cells, 6 U cryoprecipitate or fresh frozen plasma, and 1 U of single-donor platelets so that thrombolytic effects of t-PA can be reversed if necessary. For the first 24 hours patients should not be given aspirin, heparin, low-molecular-weight heparin preparation, warfarin, ticlopidine, clopidogrel, or any other antithrombotic or platelet anti-aggregrant. For further study refer to reference no: 18, 35 & 36. Table-3


**KEY OUTCOMES OF NINDS T-PA TRIAL**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>t-PA (%)</th>
<th>Placebo (%)</th>
<th>Difference (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable outcome at three months</td>
<td>41</td>
<td>29</td>
<td>+12</td>
<td>0.008</td>
</tr>
<tr>
<td>Mortality at three months</td>
<td>17</td>
<td>21</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Symptomatic intracerebral hemorrhage at 36 hours</td>
<td>6</td>
<td>1</td>
<td>+5</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE-3**

**NINDS**= National Institute of Neurological Disorders and Stroke; **t-PA**=tissue plasminogen activator; **NS**=not significant.

**Unsuccessful t-PA trials:** Attempts to widen the therapeutic window beyond three hours for intravenous t-PA in acute ischaemic stroke have not been successful. European Cooperative Acute Stroke Study (ECASS I & II)\(^{21,22}\), along with Atlantis and A0276g all involve the use of t-PA after 3 hours. ECASS I & II and A0276g each had 6 hours time window, while Atlantis had 3-5 hours time window. The symptomatic haemorrhage transformation (HT) rates in t-PA treated patients were 7% in Atlantis and 8.8% in ECASS II\(^{22}\), just higher than the 6.4% rate seen in NINDS. However, the A0276g trial reported an 11% symptomatic HT rate, which was substantially influenced by a rate of 18.2% in patients treated 5-6 hours after symptom onset. A direct influence of the time of treatment on the incidence of HT was confounded by nine-fold increase in the number of severe strokes in patients who received t-PA between 5 and 6 hours after onset.\(^{30}\)

**The following points are worth mentioning:**

1. Therapy with t-PA for acute ischaemic stroke is effective and of overall benefit, but carries risk. About 1 in 15 recipients suffer serious brain haemorrhage, even if t-PA is used according to strict guidelines.\(^2\)

2. The t-PA dose is given intravenously over one hour; no arteriography is required.

3. The t-PA dose must be given within three hours of stroke onset.

4. When patient awakens from sleep with neurological deficit, onset of stroke must be assumed to be the time when sleep commenced.

5. It is sometimes difficult to be certain of exact time of stroke onset at initial evaluation; if time of onset is uncertain; t-PA should not be given.

6. The CT scan must document the absence of intracranial bleeding before treatment (Some authorities also recommend that t-PA not be given if the CT scan shows any evidence of early infarction)

7. Patients with severe ischaemic stroke have higher risk of t-PA associated brain haemorrhage, but they also have the most gain.\(^{18}\)

**Criteria for Thrombolysis of patients with an Acute Ischaemic Stroke using t-PA**\(^{2,26}\)

**Inclusion criteria**

- Age greater than 18 years
- Clinical diagnosis of ischaemic stroke, with onset of symptoms within three hours of initiation of treatment
- Noncontrast CT scan with no evidence of haemorrhage

**Exclusion criteria**

**History:**

- Stroke or head injury in previous three months
- History of intracranial haemorrhage that may increase the risk of recurrent haemorrhage
- Another stroke or head trauma resulting in loss of consciousness within the previous 3 months
- Major surgery or other serious trauma in previous 14 days
- Gastrointestinal or genitourinary bleeding in previous 21 days
- Pregnant or lactating patient

Clinical findings:
- Rapidly improving stroke symptoms
- Seizures at the onset of stroke
- Symptoms suggestive of subarachnoid haemorrhage, even if the CT scan is normal
- Persistent systolic pressure of >185 mmHg or diastolic of >110 mmHg, or patients requiring aggressive therapy to control the blood pressure
- Clinical presentation consistent with acute myocardial infarction or postmyocardial pericarditis requires cardiologic evaluation before treatment.

Imaging results:
- CT scan with evidence of haemorrhage
- CT scan with evidence of hypodensity (early changes of infarct) and/or effacement of cerebral sulci in more than one third of middle cerebral artery territory.

Laboratory findings:
- Glucose level of < 50 mg/dl or > 400 mg/dl
- Current use of oral anticoagulants or prothrombin time >15 sec. (INR ratio >1.7).
- Heparin use within previous 48 hours and prolonged activated partial thromboplastin time
- Platelet count of <100,000/mm³

The Streptokinase/aspirin Stroke Study:
In the Italian Multicentre Acute Stroke Trial (MAST-Italy), the benefits of streptokinase with or without aspirin were evaluated in 622 patients with acute ischaemic stroke. Patients were randomised to receive one of the four treatments: a one-hour infusion of 1.5 MU streptokinase, a 10 days course of buffered aspirin (300 mg/day), both streptokinase and aspirin, or neither. Patients were randomised if they were admitted to the hospital within six hours of suddenly developing a focal neurological deficit attributed to stroke.

Streptokinase therapy did not improve survival in these patients. Used alone or with aspirin, streptokinase increased mortality in the first 10 days of therapy (significantly if given with aspirin, non significantly if given alone). Risk of death in the streptokinase/aspirin group was more than three times the risk of death in patients who received no treatment. The other two trials conducted with streptokinase were Multicentric Acute Stroke Trial-Europe (MAST-E) and Australian Streptokinase Trial (ASK). All these trials were discontinued early due to excess of deaths in the treatment group; the streptokinase studies contributed important information regarding the patients at risk of symptomatic intracerebral haemorrhage after reperfusion therapy. All these studies identified streptokinase as an important contributor to haemorrhagic transformation (HT). Another contributor was aspirin as seen in MAST-I. However, whether the agent (streptokinase), the time of administration (4-6 hours from the onset of symptoms) or the dose of streptokinase (1.5 MU) is the most important factor contributing to the high mortality from intracranial haemorrhage in these studies remain unclear.
OTHER THROMBOLYTIC AGENTS: These were discussed in The American Heart Association International Conference on Stroke and Cerebral Circulation (February, 1999 Nashville USA).

PRO-UKINASE: In recently completed, randomised, Phase III clinical study of 180 patients, the clot dissolving drug r-Pro UK (recombinant prourokinase) showed that 40% of patients who received it within 6 hours of stroke symptoms had slight or no neurological disability 90 days after treatment, compared with 25% receiving heparin. 24% of prourokinase patients died, as did 27% in the comparison heparin group. The study is the first of its kind to show a statically significant treatment effects using a clot-dissolving agent up to 6 hours after the onset of ischaemic stroke symptoms. However, treatment with prourokinase is complex, requiring an angiogram to confirm an ischaemic stroke in the middle cerebral artery of the brain and the availability of a neuroradiologist, as it is administered intra-arterially by guiding a catheter to the site of the clot in the brain and injecting the drug. The study showed a slight risk of intracranial bleeding, but no significant difference in death rates among treated groups. Abbot laboratories, the manufacturer who financed the study, hopes to have prourokinase approved by the FDA for routine use in near future.

ANCROD: In another acute stroke treatment study, the experimental drug ANCROD was tested in 500 patients. The researchers found that 42% of stroke patients treated within 3 hours of stroke symptom onset recovered the physical and mental abilities they had prior to the stroke, compared with 34% who received placebo injections.

This snake venom derived drug, manufactured by Knoll Pharmaceuticals, was discovered when researchers realised people's blood failed to clot after being bitten by the pit viper snake. The venom was than manipulated as an anticoagulant, helping blood flow freely through the blood vessels. It is given intravenously through a catheter over a three to five days span in the hospital. ANCROD works by lowering the levels of fibrinogens.

HEPARIN IN ACUTE STROKE:

Recent clinical trials have assessed the risk & benefits of heparin, heparinoids & low molecular weight heparins in patients with acute ischaemic stroke. In the International Stroke Trial, participants were randomized to receive s/c heparin in dose of 5,000—12500 IU twice daily, or none. Fewer recurrent ischaemic strokes occurred in those given heparin, but this improvement was offset by an increase in haemorrhagic strokes as well as an excess of extracranial bleeds. There is no evidence to support the use of anticoagulants for the treatment of acute stroke, even in patients with AF. Anticoagulation is not associated with an overall reduction in death or disability as the decrease in death or disability is offset by increase in haemorrhagic stroke. There is a significant excess of extracranial bleeds. Although it prevents DVT, but the risk of fatal pulmonary emboli is lower than the risk of intracranial haemorrhage in these patients. Physical methods of preventing DVT in stroke patients should therefore be evaluated.2,8,29,30,31

Who not to anticoagulate:

- Severe stroke with poor prognosis or severe previous disability
- Large cerebral infarct, intracerebral bleed, lacunar infarct
- Bleeding diathesis
- Severe hypertension; Poor compliance; Infective endocarditis
- Ipsilateral carotid stenosis of > 70%
Who to anticoagulate within 48 hours

- TIA or ischaemic stroke with complete recovery inside 48 hours plus atrial fibrillation: do CT scan first

Who to anticoagulate within 2 weeks

- Ischaemic stroke with disability and atrial fibrillation: do CT scan first
- Acute myocardial infarction and secondary ischaemic stroke or TIA: do CT scan first
- Stroke, with no disability, with atrial fibrillation: do CT scan first
- However, the timing is uncertain. According to the National clinical Guidelines for stroke published by the Royal College of Physicians in March 2000 and IST- anticoagulation should be considered in all patients in atrial fibrillation, but not started until intracranial haemorrhage has been excluded by brain imaging and usually after 2 weeks.

Anticoagulant therapy in secondary prevention:

Patients who have had a TIA or an ischaemic stroke and are in AF should be considered for long-term treatment with warfarin (suggested target INR 2.5) as this greatly reduces the long-term risk of embolic stroke. If there is contraindication to warfarin, aspirin should be used. The optimal timing for initiation of anticoagulation after the acute event is unresolved. In order to minimise the risk of cerebral haemorrhage the initial treatment should be with aspirin until, for example, the majority of stroke deficit has resolved or, in case of more severe strokes, more than 2 weeks have elapsed. At present there is no evidence to support the use of warfarin in most patients in sinus rhythm, although there are exceptions such as patients with mechanical heart valves.

Neuroprotective Agents: The search for neuroprotective treatments is based on the understanding of the variety of cellular and metabolic processes that lead to the development of focal ischaemic injury. A plethora of cellular and molecular mechanism such as free radical production, lipid peroxidation, excitotoxicity and calcium ions over load constitute the important therapeutic targets of neuroprotective agents can help to salvage a potentially reversible ischaemic region i.e. the ischaemic penumbra. These agents increase the tolerance of neurons to ischaemia & have shown promising results. Numerous drugs with neuroprotective properties in stroke, such as Voltage dependent calcium channel antagonist (Nimodipine), N-methyl-D-aspartate (NMDA)-receptor antagonist, inhibitors of presynaptic release of glutamate (e.g., Lubeluzole), antioxidants, free-radical scavengers, GABA agonists, antibodies to intracellular adhesion molecules, gangliosides, piracetam, citicoline, AMPA-receptor antagonists, growth factors, hypothermia, Nitric oxide synthetase inhibitors (such as ARL17477) have been tried with variable results. Of these I will only discuss a few which are available in Pakistan.

Voltage gated calcium channel antagonists: Nimodipine has been the most widely tested neuroprotective and provided no benefit in 15 trials (Silver et al., 1995) involving 5320 patients. However, a meta-analysis of the nine major nimodipine trials (Mohr et al., 1994), including 3719 patients, revealed a significant improvement in functional outcome in those who received this drug within 12 h of stroke onset. This observation has led to the ongoing Very Early Nimodipine Use in Stroke (VENUS) trial conducted in The Netherlands in which a 6 h time limit for initiation of nimodipine is used. However, the Intravenous Nimodipine West European
Stroke Trial (INWEST) with i.v. nimodipine dose of 2 mg/h has revealed that under some conditions, nimodipine may be harmful, as suggested by an increased mortality that was directly correlated with the fall in blood pressure.

**Piracetam:** It has been found to be present in the phospholipid membrane models and this may account for the maintenance or improvement of membrane-bound cell functions, including ATP production, neurotransmission, and secondary messenger activity. In phase 3 trial 972 patients were randomized within 12 h to piracetam (12 g as initial intravenous bolus, 12 g daily for 4 weeks and 4.8 g daily for 8 weeks) or placebo, with no difference in functional and neurological outcome. However, a trend towards improvement of neurological score (NIH score) was observed in the subgroup of patients randomized within 7 h of onset, particularly in patients with moderate or severe degree. A new randomized, placebo-controlled, multicentric trial with a 7 h window is now being launched (PASS II)

**Citocline:** This drug is a precursor of phosphatidylcholine contained in neural cell membrane, has anti-oxidant properties, and promotes brain acetylcholine synthesis as a repairing agent. Two trials (Weiss, 1995; Clark et al., 1997), one in 259 patients, the other in 394 patients, have triggered some interest in this drug, which has shown no safety problem. This drug was given within 24 h of onset of stroke and continued for several weeks. A significant improvement in functional outcome was claimed at 3 months in the treated group, but this appeared to be the case only in subgroups of patients (mainly 500 mg subgroup; moderate to severe stroke).

**Hypothermia:** Transient mild to moderate hypothermia (30-35°C) has been shown to reduce the infarct size during temporary but not permanent focal ischaemia in rats, while prolonged hypothermia (48 h) at moderate level (29°C) had a detrimental effect in primate stroke models (Silver and Fisher, 1997). Aside from reducing metabolic demands, hypothermia appears to inhibit excitotoxicity and may have other cellular protective effects. Schwab and colleagues (1997) have shown that systemic cooling by means of cooling blankets and alcohol washing was effective in achieving sustained hypothermia (33-34°C). Several authors have demonstrated that hyperthermia (>37.5°C) is associated with worse prognosis.

**Role of carotid surgery in stroke**

Since the natural history between asymptomatic and symptomatic carotid artery stenosis varies so does its management. The risk of stroke between asymptomatic and symptomatic carotid artery stenosis is 2% and 13% per annum respectively. Symptomatic carotid stenosis is defined as, carotid stenosis ipsilateral to the vascular distribution of stroke or TIA. Two well designed randomized studies—the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) showed that in case the stenosis is >70% there is a substantial benefit achieved from surgery. Patients were randomized to either medical or medical plus surgical treatment. In medically treated patients (i.e. aspirin) there was a 26% stroke rate over 2 years, while in the patients treated medically as well as surgically there was a 9% stroke rate i.e. 17% absolute reduction or a 65% relative risk reduction.

Asymptomatic carotid stenosis is defined as the absence of clinical signs or symptoms of stroke or TIA relevant to the carotid lesion. Patients with 60% or more stenosis in whom surgery was performed were studied in the Asymptomatic Carotid Atherosclerosis Study (ACAS). It showed a reduction in stroke rate from 11 to 5% over
5 years, i.e. 53% relative risk reduction, but the absolute risk reduction was 5.9% over 5 years or 1.2% annually. While in untreated patients the risk is 2%. Secondly, after reanalysis it was found that more than half of these strokes were either lacunar or cardioembolic, which made the results unreliable. Thus presently it is not justified to do endarterectomy for asymptomatic patients.

**MANAGEMENT OF FOCAL CEREBRAL HAEMORRHAGE**

This is also supportive and one should follow the guidelines for ischaemic stroke.\(^7\),\(^{39,40}\)

Hypertension: The management of hypertension is controversial. Most of the patients with intracerebral bleed are found to be hypertensive on admission but this is usually secondary to the sympathoadrenal response and the BP tends to fall over several days. Rapid reduction of BP is not recommended because it will compromise cerebral perfusion, on the other hand, a sustained mean BP of >110 mmHg may exaggerate cerebral oedema and the risk of extension of the haematoma. Thus if the mean BP is >110 mmHg it is advisable to treat the hypertension with beta-blockers or ACE-inhibitors. Calcium channel blockers are generally not recommended as they reduce the BP without reducing the intracranial pressure, resulting in unfavorable net reduction in cerebral perfusion pressure.

Surgical intervention: In case the haematoma is >3 cm in diameter and the clinical state is deteriorating surgical evacuation of the clot can be life saving, because once the patient becomes comatose with fixed dilated pupils the chances of recovery are negligible. In comatose patients with a large haemorrhage causing midline shift or hydrocephalus, osmotic agents coupled with induced hyperventilation to a PO2 of 25 to 30 mmHg can be used to reduce the ICP. These measures provide enough time to place a ventriculotomy or ICP monitor to enable the clinician to use these medical measures with greater precision. In case of persistent or progressive elevated ICP urgent surgical evacuation of the haematoma should be done. Cerebellar haematomas of <2cm in diameter leaves most of the patients awake and infrequently leads to deterioration. Haematoma of 4cm or more in diameter, especially if located in the vermis, poses the greatest risk; some surgeons have recommended evacuation of such clot irrespective of the clinical state. Surgery is also indicated in case the haematoma causes mass effect or there is hydrocephalus or the patient is stuporous or displays arrhythmic breathing because once the patient becomes comatose and develops pupillary changes the outcome of surgery is poor. Patients with haematoma between 2 and 4 cm in diameter require careful monitoring and in case the clinical state deteriorates or there is obliteration of the perimesencephalic cisterns, particularly if coupled with hydrocephalus will require surgery.

**ANEURYSMAL SUBARACHNOID HAEMORRHAGE**

The definitive therapy for a ruptured saccular aneurysm consists of surgical clipping of the aneurysm to prevent rebleeding. Medical therapy aims to reduce the risk of rebleeding and cerebral vasospasm and to prevent other medical complications before and after surgical intervention.\(^7\)

Patient should be kept quiet on bed rest.

Fluid administration to maintain above normal circulating volume and central venous pressure.

Analgesics and sedation: Administration of appropriate analgesics for treatment of headache and gentle sedation. These measures also helps in reducing the BP

Stool softeners minimise straining with subsequently increased intracranial pressure.
Hypertension: It should be treated, but not aggressively, since some of the elevated pressure may represent a normal compensatory mechanism to maintain cerebral perfusion pressure. In the face of increased intracranial pressure or cerebral arterial narrowing, systolic pressure should be maintained below 150 mm Hg.

Nimodipine: The voltage-regulated calcium channel antagonist nimodipine should be given orally in a dose of 60mg every 4 hours for 21 days as it reduces the incidence of stroke from vasospasm. Although it does not alter the incidence of angiographically demonstrated vasospasm, it has reduced the number of strokes in each of the five randomized studies, beginning with the one conducted by Allen & Colleagues.

PREVENTING COMPLICATIONS

Dysphagia: Complications that arise from dysphagia such as aspiration pneumonia should be prevented. This applies to all stroke patients. All patients should undergo evaluation for dysphagia before a diet is prescribed. The 3-oz water swallow test is simple bedside test that can be done on admission. Patients with an equivocal or positive 3-oz water swallow test should be hydrated with intravenous fluids and undergo evaluation by a speech therapist before being fed by mouth.

A modified barium swallow study may be needed to assess risk of aspiration. Patients found to be at higher risk should be fed through postpyloric feeding tube, and the head of the bed should be at 45° angle. Because partial recovery of swallowing is common with stroke, the need for enteral feeding should be periodically reassessed. Placement of gastrostomy tube should be considered if significant dysphagia is expected for longer than 30 days. The prognosis for recovery from dysphagia is often poor with bilateral supratentorial stroke or brain-stem stroke than with other types of strokes.

Pulmonary embolism is the third most common cause of death in patients with stroke; it is fatal in 1-2% of patients who do not receive drug prophylaxis. Anticoagulants decreases its risk but are not justified because of the increase risk of both intracranial and extracranial haemorrhage. However, early initiation of physical therapy and the use of pneumatic stockings in all patients whose ability to walk is impaired is advocated.

Pressure sores and joint contractures are preventable late complications of massive strokes. Attention to skin care (i.e. side nursing), nutrition and early mobilisation can virtually eliminate the risk of pressure sores. Joint contractures can be painful and can compromise motor recovery, especially in upper extremities. Passive range-of-motion exercises should be done three times daily in patients with paretic or paralyzed limbs to prevent contractures. All patients should be advised to take occasional deep breaths to combat atelectasis. After stroke, spasticity in the arm or leg if causing symptoms, may be helped by anti-spastic drug when combined with other physical treatments, but the functional benefit is uncertain, it may also be helped by injection of botulinum toxin which can reduce tone, increase the range of joint movement and may lead to functional benefit and/or symptomatic relief.

Post infarction cerebral oedema: Neurological deterioration may occur within 2 to 5 days after an ischaemic stroke because of cerebral oedema, which can cause life-threatening herniation. Patients who deteriorate neurologically in the first week should undergo another CT evaluation of the head and should be transferred to intensive care unit if the scan confirms the presence of cerebral oedema with significant mass effect.
Evaluation with the Glasgow Coma Scale should be performed every hour, and intubation for airway protection is needed if the score falls below 8. Use of sedatives, narcotics, and paralytic agents should be avoided except at the time of endotracheal intubation so that subsequent neurological assessment remains valid. The head of the bed should be kept at 30 to 45 degree angle. Medical treatment with water restriction, intravenous mannitol may be used to raise serum osmolarity, but hypovolemic should be avoided as it may contribute to hypotension and worsening of the infarct. These medical measures in managing stroke related herniation rarely lead to sustained reduction of intracranial pressure, however, surgical decompression by means of hemicraniectomy and durotomy can be life saving.

**SUMMARY OF ACUTE**
**MEDICAL/SURGICAL INTERVENTIONS DURING STROKE**

Because of the time-dependent death of neurons in the ischaemic penumbra, emphasis should be placed on the earliest possible intervention. With the availability of new intervention, minute’s count, and the leisurely approach to acute stroke often taken in the past should be replaced by an approach that treats stroke as a true emergency. To facilitate the earliest possible treatment, the public (especially persons at high risk of stroke) must be educated to bring the patient to the hospital as soon as possible. Optimal treatment of the patients who have sustained an acute ischaemic stroke requires rapid assessment and early intervention. After diagnosis, specific interventions designed to limit or reverse the pathological process must be considered. These guidelines focus on routine treatment of acute stroke, including intracerebral haemorrhage but excluding subarachnoid haemorrhage (I have given some guidelines regarding the management of SAH). If the patient is found to have an incidental or associated diseases (e.g. heart failure) or if the patient is found to have a ‘complication’ of acute stroke (e.g. bronchopneumonia) this should be diagnosed and treated in its own right. These guidelines do not cover treatment of associated or incidental medical or surgical problems that may be present.

The main aim behind writing this paper is that since it is the third leading cause of death mistakes are sometimes made in the management of ischaemic stroke in our setting, especially regarding the abrupt reduction of the blood pressure even when it is <120/100 mmHg. This actually converts a minor infarct into a massive infarct. I am sure if we follow the strict guidelines mentioned above regarding the management of BP, we can prevent the development of this complication. The other two factors, which need to be addressed, are the control of blood glucose and the body temperature, as all these factors directly influence the outcome.

**INITIAL MANAGEMENT OF ACUTE STROKE**

Determine whether stroke is ischaemic or haemorrhagic by CT scan

Consider administration of t-PA if less than three hours from stroke; haemorrhage has been definitively excluded; and the patient is in a specialist center with appropriate experience and expertise.

**General management:**

- **Bed rest:** For at least 24 hours.
- **Aspirin:** Aspirin (300 mg) should be given as soon possible after the onset of acute stroke symptoms if the diagnosis of haemorrhage is considered unlikely or the patient is unfit for treatment with t-PA.
MANAGEMENT OF ACUTE STROKE

- **Control of blood pressure:** Do not treat BP <220/120 mmHg within the few days unless the patient has myocardial infarction, accelerated hypertension or dissection, but existing antihypertensive medication should be continued. In case of hypotension raise foot end & give IV fluids. In case of intracerebral bleed the mean BP should be kept below 110 mmHg, while in SAH the systolic BP kept below 150 mmHg.

- **Hydration:** Should be maintained within normal plasma osmolality.

- **Hyperglycaemia:** Blood glucose should be controlled within limits i.e. 75-150 mg/dl, but up to 200 mg/dl is an acceptable range.

- **Pyrexia:** Pyrexia should be controlled with paracetamol, fan or treatment of underlying cause. The temperature should normally be maintained below 100°F.

- **Anticoagulation:** This should be considered for all patients in atrial fibrillation, but not started until intracerebral haemorrhage has been excluded by brain imaging, and usually only after 14 days.

- **Centrally acting drugs:** These should be avoided if possible.

- **No other drug treatment aimed at treatment of the stroke** should be given unless as part of a randomised controlled trial (RCT).

- **Prevention of complication:** Emphasis should be placed on prevention of complications, such as, dysphagia, deep vein thrombosis, pressure sores and joint contractures.

- **Neurosurgical opinion:** This should be sought in case of neurological deterioration secondary to brain oedema, for cases of hydrocephalus, and in certain cases of intracerebral haemorrhage (leading to raised intracranial pressure).

Assess stroke mechanism (e.g. atrial fibrillation, hypertension)

**Secondary prevention**

(The strength of each recommendation is given the conventional A-C system.)

1. All patients should have their blood pressure checked, and hypertension persisting for over one month should be treated in accordance with the British Hypertension Society guidelines (A).

2. All patients not on anticoagulation should be taking aspirin (50-300mg) or a combination of low dose aspirin and dipyridamol modified release (MR). Where patients are aspirin intolerant an alternate antplatelet agent (clopidogrel 75mg daily or dipyridamol 200mg twice daily) should be used (A).

3. Anticoagulation should be considered in every patient with ischaemic stroke in AF (valvular or non-valvular) (A), mitral valve disease, prosthetic valve disease or within three months of myocardial infarction (C).

4. Anticoagulation should not be used after transient ischaemic attacks or minor strokes unless cardiac embolism is suspected (A).

5. Any patient with carotid artery area stroke and minor or absent residual disability should be considered for endarterectomy (A).

6. Carotid endarterectomy should be undertaken only by a specialist surgeon with a proven low complication rate, and only if the stenosis is measured at greater than 70% (A).

7. Therapy with a statin should be considered for all patients with a past history of myocardial infarction and a cholesterol >5.0mmol/l following stroke (A).
Rehabilitation

1. Any of the current exercise therapies practised within a neurological framework will improve patient function (A)

2. While they need therapy, patient should receive as much as can be given and tolerated (A)

3. After stroke, spasticity in the arm or the leg:
   - If causing symptoms, may be helped by anti-spastic drugs when combined with other physical treatments, but the functional benefit is uncertain (B)
   - Should only be treated specifically if symptomatic (C)
   - May be helped by injection of botulinum toxin which can reduce tone, increase the range of joint movement and may lead to functional benefit and/or symptomatic relief (A).

References


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