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’. The term “transient ischaemic attacks” (TIA) implies warning symptoms of stroke usually lasting upto 30 minutes to one hour, and complete recovery within 24 hours. Second TIA often causes more damage than the first. Without proper treatment one out of ten subjects who have had TIA will develop a stroke within a year. Current data on prospective well defined population based studies confirm increased incidence of first-ever-stroke (FES) in developing countries. It suggests the arrival of “stroke epidemic” in India, and unless this is well controlled by comprehensive stroke care programme we will face the heavy burden of stroke. JAPI recommends “time to prioritize prevention strategies”.

The normal functions of the brain are dependent upon a relatively constant supply of oxygen and glucose derived from the blood perfusing it (55 to 70 ml of blood per 100g of brain per min). The principal source of energy is almost exclusively oxidation of glucose. If the blood flow is critically reduced below 15 ml per 100 g per min, the resulting ischaemia with hypoxia, when sufficiently prolonged, may cause death of neurons and glia.

Experimental studies on pathophysiological events leading to cerebral ischaemia have shown that there is a dense central core of tissue injury, surrounded by a less dense zone of ischaemia (“penumbra”) and neuronal death occurs in this central focus unless perfusion is quickly restored. On the other hand, cells in the zone of penumbra remain viable for about three hours (“therapeutic window”) and can be salvaged by reperfusion or neuroprotective agents. Energy depletion from brain hypoxia is one of the key events that fails to maintain normal concentrations of cellular adenosine triphosphate (ATP).

The symptoms of TIA are usually located in the carotid-middle cerebral axis or in the vertebro-basilar territory: Carotid territory TIA may manifest as: i) Ipsilateral mono-ocular blindness (“amaurosis fugax”) with contralateral homonymous visual field defect; ii) Contralateral weakness or clumsiness of hand, arm face or leg, iii) Confusional state or aphasia iv) Combination of above symptoms. Vertebro-basilar TIA syndrome may manifest as: i) Diplopia or “out of focus” vision; ii) Vertigo, incoordination or both; iii) Bilateral or alternating paresis of limbs; iv) Slurred speech; v) Swallowing difficulty; vi) Memory problems (transient amnestic syndromes); and combination of above.

The diagnosis of TIA is based on information given by patient or reliable observers. No investigative modality can substitute for careful history. A typical history of TIA is sudden onset of symptoms reaching maximum intensity over next few minutes. The symptoms may wax or wane but vague episodes are not TIA. Accompanying neurologic deficit should resolve within an hour and disappear completely by 24 hours. The usual duration of TIA is 5 to 30 minutes but symptoms lasting less than few seconds are usually not TIA. When
TIA persists longer than one hour, the underlying mechanism may be a micro infarct!

**Risk factors**

Apart from conventional non-modifiable risk factors like (i) age, (ii) race, (iii) gender, (iv) family history, the treatable (modifiable) risk factors such as (i) arterial hypertension, (ii) diabetes mellitus (poorly controlled), (iii) cardiac disease (ischaemic heart disease and cardiomyopathies of varied etiologies etc), (iv) tobacco use (smoking or chewing), (v) lipoprotein abnormalities (high cholesterol levels), and (vi) miscellaneous factors (e.g. oral contraceptives, alcohol consumption, high fibrinogen level, protein C and S deficiency, hyperhomocysteinemia etc) may be identified. Poorly controlled hypertension is treatable risk factor and improved management leads to decline in stroke burden. The average risk of stroke after a TIA is up to 3% in the first 2 days, 5% in the first week and up to 12% at 90 days. Recent studies have shown that patient’s 90 day risk can be lowered from 12% to about 2% with timely (<24hr) investigation and aggressive management.

**Diagnosis**

TIA is considered a medical emergency and diagnosis should be established to prevent a major stroke. The following tests are considered most informative: i) Physical examination, ii) Blood tests, iii) Electrocardiogram, iv) Echocardiogram, v) Neuroimaging - computerized axial tomography (CT) to rule out stroke mimic lesions (e.g. post epileptic Todd’s paresis, tumors). Magnetic Resonance imaging and angiography (MRI and MRA) may show embolic vascular lesion. Studies like brain SPECT may detect evidence of cerebral hypoperfusion.

**Differential Diagnosis**

The following conditions can mimic episode of TIA i) hypoglycemia, ii) akinetic seizures with transient paresis iii) vertigo or dizziness from labyrinthine disorders, iv) focal or visual or sensory symptoms in migraine patients, v) episodic confusional states in temporal lobe lesions. Here meticulous history and careful physical evaluation with appropriate or specific diagnostic test will prove helpful in majority.

**Management**

TIA is no longer considered a benign event, but a critical medical emergency which demands immediate evaluation to prevent disabling stroke. 90-day post TIA risk of stroke is estimated at 10%, and in nearly half of them stroke occurs within the first two days, particularly if TIA is related to internal carotid artery stenosis. Subjects who arrive within 180 minutes of symptoms should undergo urgent clinical evaluation and selected laboratory tests (blood count, platelet count, prothrombin time with INR, electrolytes and glucose levels) to determine if the patient is a candidate for thrombolytic therapy. Computerized Tomographic scanning of head may be done to exclude cerebral or subarachnoid haemorrhage or brain tumor. Thus confirmation of TIA, by clinical and diagnostic evaluation, is mandatory. The evaluation by tests should focus on ascertaining underlying etiology. The goal of therapy is to prevent development of cerebral infarction and, if already present, to restrict its progression.

**Blood Pressure**

In acute stroke, “cerebral autoregulation” is lost and blood flow in the infarcted areas is solely dependent on mean arterial BP. In presence of severe hypertension (e.g. BP over 220 / 120 mmHg) parenteral therapy with titratable agents such as I.V. labetalol or enalapril which reduce blood pressure smoothly are recommended. Calcium channel blockers are best avoided because they produce severe drop in blood pressure in some patients. On the other hand, raised blood pressure levels in hypertensive and non-hypertensive stroke subjects often fall unpredictably within 24 hours to few days, worsening perfusion in ischaemic penumbra leading to irreversible injury. Therefore, any significant hypotensive episode should be promptly treated to prevent extension of cerebral infarction.

**Measures to Improve Cerebral Blood Flow**

Haematocrit is one of the chief determinants of whole-blood viscosity. It is postulated that lowering the haematocrit value to 30 to 33 per cent with haemodilution therapy improves CBF and oxygenation of infarcted tissues. However, results of recent randomized trials have failed to show consistent beneficial effects of hemodilution therapy.

**Specific Therapy**

**Platelet Antiaggregants**

Acetylsalicylic acid (aspirin) prevents platelet aggregation by blocking production of platelet derived thromboxane-A2 but it also suppresses release of prostacyclin from vascular endothelium. The effects of aspirin are immediate and last for 7-10 days of life of platelet. It is widely used in primary and secondary prevention of strokes. Antiplatelet drugs reduce risk of recurrent stroke by 25% (Antiplatelet Trialists collaboration 1994). The benefit of therapy is not influenced by age, sex and presence of hypertension or diabetes. In the treatment of TIA, RIND (Reversible intermittent neurologic deficit) and in secondary
prevention of strokes, the optimal dose is still debated. Low-dose therapy (75-100 mg/day) is as effective as higher dose (325mg/day or more) (UK TIA study Group 1991, Dutch TIA trial 1991 and Swedish Aspirin low dose trial collaborative group 1991). Other antiplatelet drugs like sulphipyrazone or dipyridamole used alone do not offer any specific advantage. However, in female “non-responders” aspirin combined with dipyridamole (upto 200 mg twice a day) may prove more effective on account of its synergistic activity. Aspirin therapy does alter clotting of blood and thereby carries a marginal risk for intracerebral bleed but it does not appear to increase the frequency of carotid-plaque haemorrhage. Soluble aspirin is often associated with side effects like epigastric pain, peptic ulcer disease and GI bleed. Use of enteric coated aspirin with ranitidine may increase safety of long term use.

Dipyridamole is vasodilator and inhibitor of platelet phosphodiesterase enzyme and a potent platelet antiaggregant. Dipyridamole in combination with aspirin is often treatment of choice in a subject with an impending stroke. Sustained release preparations of Dipyridamole (200 mg twice a day) in combination with 75 mg aspirin are often prescribed.

Ticlopidine (a thienopyridine derivative) inhibits platelet aggregation by interfering with ADP – induced transformation of glycoprotein IIb / IIIa receptors on platelet membrane. It has shown more than 30% reduction in “stroke risk” when compared to aspirin therapy. It is equally beneficial to men and women. Subjects with diabetes mellitus, those on antihypertensives and those with elevated creatinine levels benefit more with ticlopidine (250 mg b.i.d.) than aspirin. However, the drug is relatively toxic (i.e. reversible neutropenia, diarrhoea). Clopidogrel (75 mg / day) is reported to be safer than ticlopidine. In a recent trial (MATCH study), combination of clopidogrel (75 mg) and aspirin (75 mg) showed no real benefit in outcome of vascular end-points. Newer antiplatelet agents like Abciximab are potent antagonists of platelet glycoprotein IIb / IIIa receptors but hazards like symptomatic intracranial bleeding are a major concern.

In treatment of non-cardioembolic TIA long term antiplatelet therapy is advocated. As per recommendations from National Stroke Association guidelines, the combination of Aspirin (50mg) and sustained release Dipyridamole (200mg) is considered reasonable option as preventive therapy for recurrence of stroke. The choice of combination of clopidogrel with aspirin is also recommended for prevention of stroke recurrence. However choice of combination of antiplatelet drugs with anticoagulation is NOT recommended. On the other hand in treatment of cardioembolic TIA anticoagulant therapy is preferred.

**Anticoagulants**

**Heparin is heterogeneous mixture of glycosaminoglycan of variable molecular weight (4000-40,000 daltons), its anticoagulation action is immediate with a half life time of 60 minutes. It prolongs activated partial thromboplastin time (aPTT), whole blood clotting time as well as activated clotting time. aPTT value of 1.5-2 times control is considered therapeutic range. Somehow heparin of bovine origin enhances platelet aggregation causing thrombocytopenia (mild in 80%). Heparin induced thrombocytopenia with recurrent thromboembolism (“white-clot syndrome”) is a rare complication.

During the stage of heparinisation partial thromboplastin time (aPTT) is kept up to 2.0 times the control, and 3000 to 5000 units of heparin are often given on 6 to 8 hourly basis. In practice, an intravenous bolus of 100units/kg body weight followed by continuous infusion (1000 units per hour for 24 hours). Newer synthetic short-chain (low molecular weight) heparins or heparinoids are safer and effective but expensive.

To minimize the risk of haemorrhagic complications, it is necessary that cerebral ischaemia or hypoperfusion is confirmed by special investigations like Magnetic resonance imaging (perfusion weighted and diffusion weighted images). If a subject worsens under anticoagulant therapy diagnostic re-evaluation should be done and even a second CT or MRI may have to be carried out to ascertain the cause of worsening (extension of ischaemic injury or intracranial bleeding).

Oral anticoagulant drugs have structural similarity to vitamin K and they inhibit hepatic synthesis of clotting factors II, VII, IX, and X. The therapeutic effect is delayed upto 72-96 hours after initiation of therapy. Of the many oral anticoagulant drugs, coumarin sodium (2 to 5 mg/day) is generally well tolerated. Prothrombin index (ideally INR) of 2.0 to 3.0 is usually maintained for months or longer, keeping a close watch on haemorrhagic complications (like GI or urinary tract bleed) in elderly subjects or in severely hypertensive patients. In the presence of actively bleeding ulcers, malignant hypertension, hepatic failure and poor patient compliance, anticoagulant treatment is contraindicated.

Newer anticoagulant drugs like Dabigatran etexilate (reversible direct thrombin inhibitor) and Rivaroxaban (direct inhibitor of Factor Xa) are being studied in various trials for their effectiveness as an alternative to Warfarin, however the cost factor is a big challenge.

In summary, a recent Cochrane review (2004) concluded that in patients with TIA or minor stroke, there was no significant difference in outcome of vascular events in those receiving anticoagulant
versus antiplatelet drug therapy. The current evidence suggests that aspirin is treatment of choice when compared to anticoagulants for patients with non-cardioembolic stroke. 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. Furthermore, evaluation and treatment of associated risk factors in all categories needs greater emphasis.

**Statins and Ischaemic Stroke**

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. It has been postulated that beneficial 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”. Recent data from SPARCL Study (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) suggest that statins reduce risk of recurrence of stroke.

**Surgical Management**

Thromboendarterectomy (TEA) within a few hours or days after an acute ischaemic injury is considered risky, because early reperfusion may convert pale lesion into a haemorrhagic one. However CEA has been established as a useful procedure in prevention of stroke in subjects having TIA from lesions in extracranial carotid circulation. Duplex ultrasound is non-invasive investigation of choice as a screening test to locate the plaque and measure the degree of obstruction and ulceration. Frequent embolization of platelet fibrin material from ulcerated plaque is considered an important cause of recurrent TIA. Here Real time, B-mode Duplex scanning of carotid artery provides good information on thickness of arterial wall, residual lumen and plaque characteristics. However B-mode scanning is less accurate for assessing mild degree of stenosis. Phonoangiography, periorbital directional Doppler ultrasonography, oculoplethysmography, and ophthalmodynamometry are other screening tests. MRA and CT angio images of the carotid artery demonstrate vessel wall, residual lumen, and pathological process within the plaque. It also helps in detecting dissection. At present, MR angio or CT angio has become an important noninvasive test for evaluation of lesions of intracranial and extracranial vasculature. If surgery (CEA) is planned, digital intravenous subtraction angiography (DISA) may be carried out as an alternative to conventional digital intraarterial arteriography. Demonstration of a stenotic lesion greater than 70% or presence of ulcerated plaque is considered important criteria for CEA in subjects with recurrent TIA in that territory. Perioperative morbidity and mortality under 5% is considered an acceptable risk.

Recent well-designed controlled studies (NASCET – North American Symptomatic Carotid Endarterectomy Trial) have confirmed beneficial results of endarterectomy in tight cervical stenosis (70-99%). It has been observed that there is 17% absolute and 35% relative risk reduction for ipsilateral stroke and stroke death, if endarterectomy is combined with best medical care. Patients who benefit the most from surgery are those with highest risk-factors. During immediate post-operative period higher doses of aspirin and control of all risk-factors are mandatory. The benefit by carotid endarterectomy in symptomatic lesions with mild stenosis (30-69%) or in asymptomatic cases is controversial.

**Stenting and Angioplasty in Symptomatic Carotid Stenosis**

Though CEA appears well established in tight symptomatic carotid stenosis (>70%), stenting with or without embolic protection devices are getting accepted as alternative mode of treatment in cases with CEA is not feasible or difficult. It has been reported that fewer complications occur with stenting as compared to CEA (e.g. neck haematoma, cranial neuropathy etc.).

The SAPHIRE Study (Stenting and Angioplasty with Protection at High Risk for Endarterectomy) assessed results of stenting against carotid endarterectomy (CEA) in subjects with greater than 50% symptomatic or 80% asymptomatic stenosis. It was reported that “stenting arm” had lower cumulative incidence of stroke, myocardial infarction or death at one year compared to those who had CAE. Recurrent intervention was less common in the patients in the stenting group. The results indicate that carotid stenting with embolus protection device is at least as good as CEA, particularly in patients with substantial comorbidity or for inaccessible lesions in elderly patients.

**Summary**

TIA is a serious condition and a medical emergency requiring immediate evaluation and treatment to prevent a stroke. Confirmation of diagnosis is vital. Medical conditions like hypoglycaemia, migraine etc which mimic TIA should be identified. TIA syndrome
An algorithm with key points for evaluation of TIA is listed below.

**Initial Work-Up for Suspected TIA**

- Confirm TIA history. (exclude: hypoglycemia, syncope, migraine aura, focal epilepsy, labyrinthine disorder)

Acute onset (did transient symptoms occur < 24 to 48 hours ago)?

- Yes
  - Send patient to hospital emergency department for evaluation.
  - Urgent outpatient evaluation to identify cause of TIA; if imaging studies are not available in a timely fashion, admit patient. Identify and treat stroke risk factors. Begin medical therapy, including antiepileptic therapy, as soon as possible.

- No
  - Is patient a candidate for thrombolytic therapy?
    - Yes
      - Medical and neurologic examination
      - Frequent vital signs, with attention to blood pressure and heart rhythm
      - Head CT
      - Cardiac monitoring: ECG
      - Initial laboratory tests: complete blood count with platelet count; electrolyte, glucose, and renal function measurements; PT; aPTT; and INR
      - Carotid artery evaluation
      - Head MRI and MRA of intracranial and neck vessels, if available and appropriate

  - No
    - Perform certain tests (*) within 25 minutes of patient’s arrival in emergency department: screen for inclusion/exclusion criteria for IV tPA therapy.

**Fig. 1 : Initial work-up for the patient with possible transient ischemic attack (TIA). (IV = intravenous; tPA = tissue-type plasminogen activator; CT = computed tomography; ECG = electrocardiography; PT = prothrombin time; aPTT = activated partial thromboplastin time; INR = International Normalized Ratio; MRI = magnetic resonance imaging; MRA = magnetic resonance angiography) (Solinski NJ. Transient Ischaemic Attacks. American Family Physician 2004;69:1665-1674)**

in carotid territory needs special evaluation by Duplex sonography to detect significant stenosis (>70%) near bifurcation. Recurrent TIA in the same territory leaves neuro deficit and this needs prevention by appropriate therapy (platelet antiaggregants, anticoagulants, surgical intervention). An algorithm listing initial workup for TIA is shown in Figure 1. Associated risk factors (e.g. high blood pressure, tobacco use, uncontrolled diabetes mellitus, high cholesterol level and obesity etc) need special emphasis. Lifestyle modification and lack of physical exercise cannot be ignored. In high risk group where TIA lasts longer than 10 minutes with significant neuro deficit in elderly subjects having diabetes or hypertension will need special attention and treatment. Diagnostic tests should include cardiovascular evaluation and ultrasound scanning of carotid arteries. Special neuroimaging tests like CT/MRI and CTA/ MRA to visualize cerebral vasculature and detect asymptomatic lesions are helpful in planning long term management and prevention of stroke.

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