

Clinical Practice Guidelines for the Management of Ischemic Stroke in Pakistan

S. Shafiqat

Section of Neurology, Department of Medicine, Aga Khan University Medical College, Karachi.

Background

Ischemic stroke represents a huge global burden, being the leading cause of physical disability and the third-leading cause of death worldwide. Although rigorous epidemiological data from Pakistan are lacking, stroke is certainly the commonest reason for admission to a neurology ward in our part of the world, as elsewhere. Recent years have seen a number of new developments in the clinical approach to stroke, including in the areas of diagnostic work-up, acute treatment and secondary prevention. These developments enable the formulation of clinical practice guidelines for achieving standardized management of ischemic stroke, with the overall aim of improving the care of stroke patients. This article presents a set of guidelines that may be useful to clinicians involved in the care of stroke patients in Pakistan. The term 'stroke' is used here to refer exclusively to ischemic brain infarction; this paper does not address intracerebral hemorrhage.

Diagnostic Approach

The diagnostic approach to suspected stroke is summarized in the accompanying algorithm (Figure). Any sudden-onset focal neurological deficit must be considered a stroke unless proven otherwise. The first step in the evaluation of suspected stroke is medical stabilization with attention to airway, breathing and circulation. The second step is imaging of the brain, either with CT scan, if seen within 3 hours of symptom-onset, or preferably MRI if the patient is seen later. Patients seen within 3 hours of stroke onset may be eligible for treatment with the intravenous thrombolytic agent rt-PA (recombinant tissue plasminogen activator), as noted in the accompanying algorithm; in practice, this constitutes only a very small percentage of stroke patients because most patients arrive outside the time window. Any patient being considered for thrombolytic treatment must undergo immediate non-contrast cranial CT scan. If the scan is normal, the thrombolysis checklist can be initiated.

All patients (whether they receive rt-PA or not) undergo a set of diagnostic tests to determine stroke subtype, which forms the basis for rational secondary prevention. This includes (i) cardiac evaluation (ECG and transthoracic echocardiogram with air-contrast); and (ii) cranio-cervical vascular evaluation (carotid duplex ultrasound for anterior circulation ischemia and MRA for posterior circulation

ischemia). Additional tests including Holter monitoring, transesophageal echocardiography or blood hypercoagulability profile, may be considered in cases of embolic stroke where the initial work-up is negative. The goal of this work-up is to assign patients to one of four categories: small-vessel stroke (lacunar stroke); large-vessel stroke (atherothrombosis in large-caliber artery such as internal carotid or basilar); embolic stroke (infarction in a major vascular territory such as major branches off the Circle of Willis or in the vertebro-basilar system); or unclear.

Acute thrombolysis

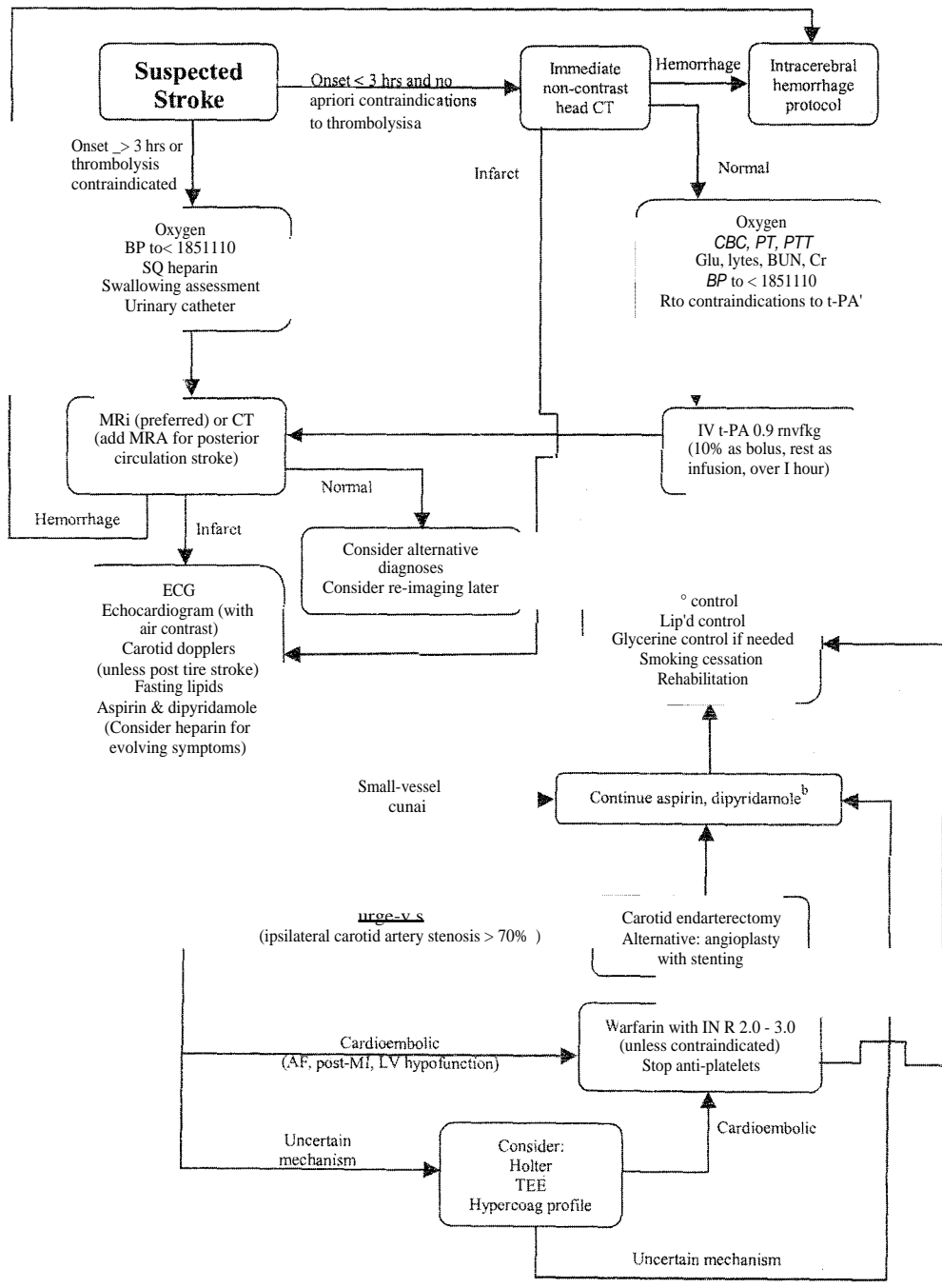
Acute treatment of the stroke patient includes intravenous rt-PA for patients seen within 3 hours of symptom-onset, as noted above. Time of onset is determined from when the patient was last seen to be well; this is especially important for patients who wake up with their deficit. The cost of the usual adult dose of rt-PA for stroke approaches Rs.100,000 in Pakistan. Although of proven efficacy is improving functional stroke outcome, the drug is associated with a 10-fold increase in the risk of symptomatic intracerebral hemorrhage. These factors underscore the need to use rt-PA in stroke after careful clinical judgment and with detailed informed consent of patient and/or next of kin. The use of rt-PA should not be considered for patients who cannot be evaluated by a neurologist. Contraindications to the use of rt-PA are summarized in Figure.

Other acute considerations

All patients (whether they receive rt-PA or not), need careful evaluation and concurrent management of co-morbid conditions as appropriate, including diabetes mellitus, coronary artery disease, renal dysfunction and/or liver disease. If needed, blood pressure should be gently brought down under systolic ≤ 185 and diastolic ≤ 110 .

Assessment should be made with regards to swallowing. For mild strokes, this can be done by asking the patient to swallow small sips of water while observing for cough or change in voice. If the patient fails to swallow properly, if stroke severity precludes swallowing assessment, a nasogastric tube must be maintained.

Most patients will also require urinary catheterization with a Foley catheter. In males without a history of prostate symptoms, a condom catheter should be tried first.



^a Contraindications to t-PA: Prior intracranial hemorrhage; history of intracranial neoplasm, aneurysm or AVM; stroke or head trauma within last 3 months; major surgery or biopsy of parenchymal organ within last 2 weeks; GI or genito-urinary bleeding within last 3 weeks; recent MI; seizure at stroke onset; disorder of hemostasis; prothrombin time > 15 seconds; use of heparin in previous 48 hours with prolonged partial thromboplastin time; use of low-molecular weight heparin during previous 48 hours; rapidly improving neurological deficit; mild, isolated neurological deficit, e.g. ataxia, dysarthria, or sensory loss alone; systolic BP \geq 185 or diastolic BP $>$ 110; platelet count $<$ 100,000/mm³; blood glucose $<$ 50 mg/dL or $>$ 400 mg/dL.

^b Dosages. aspirin 75-300 mg po daily; dipyridamole 200 mg po twice daily or 100 mg po three times a day.

P)An Iormanklementot stroke

DVT prophylaxis

All patients must receive subcutaneous heparin 5,000 BID for prevention of deep-vein thrombosis and reduction of

pulmonary embolism risk.

Secondary prevention

All patients must receive targeted secondary prevention.

Table. secondary prevention.

Therapy	Indication	Strategy
Warfarin anticoagulation	Presence of atrial fibrillation Presence of prosthetic heart valve Embolic stroke in post-MI period LV hypofunction (EF <35%)	Maintain INR 2.0 - 3.0 (2.5 - 3.5 for patient with prosthetic valve)
Anti-platelet agents*	All patients not requiring warfarin	Aspirin 300 mg qd in combination with either: (i) dipyridamole 100 mg tid or (ii) clopidogrel 75 mg qd
Carotid endarterectomy ^o y	Presence of internal carotid artery stenosis 70-99% ipsilateral to brain infarction in a patient with some demonstrable functional recovery	Referral to an experienced vascular surgeon with proven low complication rate: carotid angioplasty and stenting <, is an option but safety and long-term efficacy% unverified

* This recommendation is based on the author's best clinical judgment. Although data from randomized trials favors twice-daily Agarenox (aspirin 25 mg ,with extended-release dipyridamole 200 mg) as the most efficacious anti-platelet regimen in secondary stroke prevention. neither Aggrenox nor extended-release dipyridamole are available in Pakistan. The efficacy of combining regular dipyridamole with aspirin is unknown. The combination of aspirin and clopidogrel for secondary stroke prevention is currently under investigation.

prevention to reduce the risk of stroke recurrence. Options include anti-platelet therapy, oral anticoagulation with warfarin⁶ and carotid artery intervention.⁷ indications for their use are summarized in Table.

Risk Factor Management

All patients must undergo aggressive management of all modifiable risk factors, including blood pressure control, glycemic control in diabetics, cessation of cigarette smoking, and reduction of serum LDL cholesterol to 100 mg/dL or less with inhibitors of HMG-CoA reductase. A number of medications are available for blood pressure reduction; some evidence suggests that angiotension-converting enzyme inhibitors and diuretics may be particularly beneficial in stroke patients.⁸ The recommendation for serum LDL cholesterol reduction is based on trials of HMG-CoA reductase inhibitors ("statins") performed in patients with primary cardiac disease; results from trials in stroke patients are currently awaited.

Rehabilitation

Rehabilitation requires a holistic approach that uses multiple supportive strategies to help stroke patients achieve maximum functional recovery. All patients should be offered the benefits of rehabilitation therapy, including physical, occupational and speech therapy, begun as early as feasible. Training must be administered in multiple areas, including gait, transfers and bed mobility, as well as speech/cognition and manual dexterity (occupational therapy).

Neuroprotective agents

Neuroprotective agents are drugs that inhibit the biochemical consequences of stroke at the cellular level. Although effective in animal models, so far no agent has proven efficacious in human clinical trials; accordingly, the use of neuroprotective medication in ischemic stroke is not recommended at present.¹⁰ In Pakistan, a number of drugs are marketed with claims of neuroprotection, including agents such as Hydergine (ergooid mesylate), Nootropil (piracetam), and Encephabol (pyritinol). The use of these and similar drugs is not supported by the available evidence.

Constraints

The above guidelines are based on evidence from randomized trials or high quality observational studies, and are internationally considered to be 'standard of care'. While economic and logistical realities may make them unfeasible for many practitioners in Pakistan, at a minimum the investigational work-up of suspected stroke must include cranial CT scanning. Clinical assessment alone cannot distinguish intracerebral hemorrhage from ischemic stroke - two conditions that demand a vastly different management approach".

If the CT scan is normal or indicates infarction, anti-platelet therapy can be safely begun. If carotid artery intervention and the use of adjusted-dose warfarin with frequent prothrombin time monitoring are not feasible, further work-up is unnecessary, and the anti-platelet treatment should be used indefinitely, along with risk factor management as feasible.

References

- American Heart Association: Heart and Stroke Facts Statistics: 1997 statistical supplement. Dallas: Am Heart Assoc 1997.
- The National Institutes of Neurological Disorders and Stroke (NINDS) 14-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1551.
3. Wityk RJ, Beauchamp NJ et al. Diagnostic evaluation of stroke. *Neural Clin* 2000,19:357.
 - Clagget GP, Anderson F Jr, Levine MN, et al. Prevention of venous thromboembolism. *Chest* 1999;115:3915.
 - Diener HC. Stroke prevention: anti platelet and antithrombotic therapy. *Neural Clin* 2000,19:343.
 6. Kelley RE, Nlinagar A. Cardiovascular stroke: a; update. *South* 2003;96:343.
 - Barnett HJ, et al. Treatment of symptomatic arteriosclerotic carotid artery disease. *Prog Neurol* 2003,92-307
 8. PROGRESS Collaborative Group Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001;355:1033.
 4. Blauw GJ, Lagaay AM, Srateit AF, et al. Stroke, statins and cholesterol. A meta-analysis of randomized, placebo-controlled, double-blind trials of statin treatment in patients with acute ischaemic stroke. *Stroke* 1997 28:946.
 10. Ovbiagele B, Kidwell CS, Starkman S, et al. Potential role of neuroprotective agents in the treatment of patients with acute ischaemic stroke- *Curr Opin Neurol* 2003;5:367.