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ISCHEMIC STROKE CARE - OFFICIAL GUIDELINES FROM THE PAKISTAN SOCIETY OF NEUROLOGY

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Pakistan is the sixth most populous country in the world, with an estimated population of 165 million. Non communicable disease including stroke now accounts for 41% of the total disease burden of Pakistan. In a population dense country like Pakistan, an estimated 4.8% may be suffering from stroke; this translates to 7.2 million individuals, compared to 700,000 annually in the United States.

Data on the modifiable risk factors for stroke show an alarmingly high prevalence within the population of Pakistan. Hypertension- the single most preventable cause of stroke- affects one in three adults aged greater than 45 and 19% of the population aged 15 and above. The National Health Survey of Pakistan showed that diabetes mellitus is present in 35% of people greater than 45 years of age. Coronary artery disease can cause cardio-embolic stroke and is a surrogate for atherosclerosis in the cerebrovascular system: a population based cross sectional survey showed a prevalence of 1 in 4 middle aged adults with men and women at equal risk. The overall prevalence of obesity is 28 % in women and 22 % in men. The prevalence of tobacco use is 40% in men and 12% in women.

Such a scenario calls for a systematic, need based and cost-effective guideline for diagnosis, acute management and secondary prevention of stroke which is cognizant of the resource limitations of Pakistan. These guidelines are a step in that direction.

PROPOSAL AND DESIGN

Methods:

The primary author (AK) reviewed all the data on current stroke identification, management and secondary prevention as well as international guidelines. These guidelines focus on ischemic stroke only. For the purposes developing these guidelines, special attention was given to studies in which Asians participated as subjects or those which had broad international implications for stroke care. Besides the review of current trials, weightage was given to Cochrane reviews since these meta analyses look at a wider spectrum of papers. The manuscript was reviewed by several national neurology practitioners that encounter stroke patients. Recommendations are based on local feasibility and relevance. Cost effectiveness and public health implications have also influenced the strength of these recommendations- individual patient care and sophisticated testing is still left to the discretion of the treating physician. These guidelines emphasize the basic tenets of good stroke care.

PREHOSPITAL STROKE TRIAGE

Recognition and Triage:

In the current extended family set up with intense population density, stroke is often recognized immediately. However delays in presentation to care may happen after the phase of recognition and may involve financial constraints, lack of knowledge of therapeutic options and inappropriate triage/delay by the primary physician. There are several quick historical tools that enable the effective recognition of stroke- and are included in the detailed paper. Physicians and nurses are encouraged to familiarize themselves with these and utilize them to effectively triage stroke patients. In the absence of stroke centers, these patients are best directed to hospitals with a track record of admitting and managing stroke patients.

IN HOSPITAL MANAGEMENT OF STROKE

Emergency Department:

Once on the ED bed, a rapid airway, breathing and circulation assessment should be performed, followed by initiation of high flow oxygen, if hypoxemic. Once stabilized, an assessment of neurological deficits should be performed, which would require a history and physical examination.

If no documented piece of history is available, information should be obtained from the time of onset which is defined as last seen normal, brief description of symptoms, previous similar episodes, presence of risk factors for cerebrovascular disease, as well as any history of drug abuse, migraine, seizure, infection, trauma, or pregnancy This should be followed by a physical examination. The NIHSS stroke scale score lends itself well to a directed neurologic examination and can quantify the degree of neurologic deficit- those with an NIHSS stroke scale greater than 20 have a greater chance of harboring a lesion amenable to lysis.

The emergency department management of suspected stroke should be prompt but comprehensive, and if recombinant tissue plasminogen activator (rt-PA) is available at the facility, should follow the NINDS recommendations for stroke chain of survival: 10 minutes for the emergency physician evaluation, specialist (neurologist) assessment within 10 minutes, and 25 minutes to CT scan, allowing rt-PA administration within 45 minutes to an hour.

Imaging of the brain is recommended in some form before initiating stroke specific therapy. An emergency non contrast head CT accurately identifies most cases of intracranial hemorrhage and helps discriminate non vascular causes of acute neurologic symptoms e.g. brain tumour. The CT is also adequate pretesting for rt-PA prior to infusion and shows certain important prognostic signs. Although multimodal MRI are available in certain centers they are expensive and add little to the clinical management of stroke patients in this region if no neurointerventional therapy is planned or offered.

Ancillary testing at the very least should consider a 12 lead EKG, Blood tests for diabetes, abnormal lipids and coagulations, screen for chronic renal failure. Carotid testing should be offered if intervention is accepted by the family.

Establishment of stroke units:

After the patients have received acute stroke care in the emergency department, improved clinical outcomes are realized only when subacute stroke care is provided through the use of focused and organized approaches during hospitalization, including the use of stroke units. These stroke units integrate acute and rehabilitative care by a well-trained, multidisciplinary group including physicians, nurses and rehabilitation personnel. The magnitude of the benefits of stroke unit care is comparable to that of intravenous tPA and is applicable to the full spectrum of stroke patients.

MANAGEMENT ISSUES AND RECOMMENDATIONS

Arterial Hypertension: An elevated arterial blood pressure is often detected in the first hours after stroke. According to consensus, target blood pressure in patients who are not candidates for rt-PA should have a systolic blood pressure of less than 220 mm Hg and a diastolic blood pressure of less than 120 mm Hg. A blood pressure less than these values does not warrant anti-hypertensive medicines. In addition, the administration of sublingual nitrates or nifedepine to precipitously lower blood pressure is also contraindicated for any patient if he or she presents with hypertension and focal neurological symptoms. Those that receive intravenous rt-PA require strict control of blood pressure to below 185/110.

Thrombolysis: The current FDA approved treatment for acute stroke presenting within 3 hours of symptom onset is intravenous recombinant tissue type plasminogen activator (rt-PA). This recommendation in based on the observed outcomes of the NINDS trial, performed in 1996, which assessed early and late neurological outcomes in a group of patients treated with rt-PA once a hemorrhage was ruled-out on a CT scan. In this trial there was a relative risk reduction of 33% at 3 months and a symptomatic ICH rate of 6.8%. The dose of rt-PA was 0.9 mg/kg. A lower dose of 0.6 mg/kg has been used successfully in a Japanese trial and requires testing in Asian populations.

Temperature: Increased body temperature in the setting of acute stroke is associated with poor neurologic outcomes. Although trials testing acute hypothermia as a neuroprotective therapy in stroke are underway, it seems prudent to avoid hyperthermia and treat temperature elevations aggressively after stroke. Common reasons are aspiration pneumonia, IV line phlebitis and urinary tract infection, these may worsen outcomes therefore

aggressive search for the source of infection and early institution of antibiotics is suggested. Avoid the cannulation of a paralyzed extremity to reduce the chances of iatrogenic infections.

Hyperglycemia: Hyperglycemia has detrimental outcomes after stroke. It increases the chances of hemorrhagic conversion. Persistent hyperglycemia at the rate of > 200 mg / dl independently predicts stroke expansion. A reasonable approach is to initiate treatment to reduce blood glucose when the glucose level exceeds 200 mg/dL, the desired level of glucose should be between 80- 140 mg / dl. It is encouraged to have glucometers in hospital units and train staff to manage insulin infusions in a systematized manner.

Anticoagulation: The early administration of either dose adjusted IV heparin or a low molecular weight heparin is associated with an increased risk of bleeding (intracerebral and extra-cranial) complications. These medications increase the risk of symptomatic hemorrhagic transformation in those with severe stroke. Urgent anticoagulation with the goal of preventing early recurrent stroke, halting worsening, or improving outcomes after ischemic stroke is not recommended. This is regardless of etiology of stroke e.g. cardio embolic stroke. Anticoagulation is contraindicated within 24 hours of administration of rt-PA.

Antiplatelet Agents: Antiplatelet therapy with aspirin 160 to 325 mg daily, given orally (or per rectum in patients who cannot swallow), and started within 48 hours of onset of presumed ischemic stroke reduces the risk of early recurrent ischemic stroke without a major risk of early hemorrhagic complications and improves long-term outcome. The acute administration of clopidrogel, ticlopidine or any other alternate antiplatelet agent has not been tested in acute stroke. Large trials such as International Stroke Trial (IST) and Chinese Acute Stroke Trial (CAST) have proved the benefits of long term daily aspirin in prevention of major vascular events post stroke, with the latter being exclusively an Asian study, and hence complementing our population better.

Nutrition and Hydration: Patients should receive isotonic hydration and free fluids should be avoided. Nutritional supplementation is not necessary. However an evaluation for aspiration is needed prior to initiation of diet and the diet should be modified accordingly.

Aspiration: A wet gurgling voice after stroke, a marked facial weakness, marked cognitive slowing or inattention suggest the need to screen for silent aspiration. The presence of a gag reflex doesn't equate with an organized swallowing capacity. A patient with stroke should be screened for the presence of swallowing problems with the water swallowing tests and modifications in the diet should be made accordingly. Aspiration is the major risk factor for pneumonia after stroke. Patients who fail the initial swallowing screen should get a nasogastric tube placed for medications and feeds. Those who are having difficulty handling even their basic secretions, may actually benefit from nil per oral policy in the initial 24 hours.

Prevention of bed sores: All patients unable to mobilize independently are at risk of developing pressure sores. They should ideally be provided with a pressure relieving mattress as an alternative to a standard hospital mattress. Also there should be standing instructions for re-positioning these patients every two hours to avoid pressure sores.

Deep vein thrombosis: Avoidance of deep vein thrombosis in immobilized patients via frequent movements and the use of low dose s/c heparin is suggested in the acute phase. Intermittent compression devices are recommended in those where the risk of ICH is high.

Early Rehabilitation: Patients with stroke should be mobilized rapidly. There is very frequently a delay and this would avoid significant complications.

Steroids: Contrary to the popular practice, steroids do not appear to have any beneficial role in management of patients with presumed acute stroke. According to the last Cochrane database systematic review of seven trials in 2002, treatment with corticosteroids did not appear to show any improvement in functional outcomes of stroke survivors. Furthermore, usage of steroids in these cases may elicit unwanted adverse effects such as hyperglycemia and infections.

Neuroprotection and Neurotonics: No single trial has shown convincing benefit of stroke neuroprotection and efficacy of intervention is doubtful. At the same time, the widespread practice of administration of these agents remains in vogue in Pakistan. These must be stopped because of the economic toll on patients and their families are not justified.

POST HOSPITAL STROKE MANAGEMENT

All stroke survivors are at a high risk of stroke recurrence, by mechanisms which may be dependent on the pathophysiology of the primary stroke. The following discussion focuses on measures that are globally beneficial.

Antithrombotic therapy: In general any antiplatelet agent initiated after stroke has an odds ratio of 28% in the reduction of nonfatal stroke and a 16% reduction in fatal stroke. Aspirin in a dose ranging from 75 to 300 mg is efficacious in stroke prevention. There is no evidence that increasing the dose of aspirin provides additional benefit in those patients who have a stroke while on aspirin. The higher dose ranges are associated with a greater risk of gastrointestinal hemorrhage. Clopidogrel is marginally better at increased cost and is therefore suggested in those with concomitant peripheral vascular disease and / or intolerance to aspirin. The combination of aspirin and dipyridamole may offer additional protection. However there are concerns in patients with angina (a frequent co-morbid) and this combination must be avoided in those patients. Combination therapy in stroke patients with aspirin and clopidogrel has reported higher risks of symptomatic ICH. The use of these agents in combination for TIA is not known, with early reports suggesting benefit. Dose adjusted warfarin is suggested in an INR 2-3 for those who have intermittent or continous atrial fibrillation. Cilostazol is another inhibitor of platelet aggregation that works by inhibiting the cellular phosphodiesterase. However, at present there is insufficient evidence to support its use for all stroke patients.

Blood Pressure Control: The association between both systolic and diastolic blood pressures (BPs) and the risk of ischemic stroke is continuous. As compared to compelling evidence of role of blood pressure control for primary prevention of stroke, data on secondary prevention is lacking. It is known that a mean blood pressure fall of 5 mm Hg leads to a one third reduction of stroke. This association should hold true, if not stronger, for individuals who have had a cerebrovascular event before. Effective blood pressure control as defined by The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) would be the management of choice for stroke patients. This would mean a target blood pressure control of <120 systolic and <80 diastolic, along with lifestyle changes and dietary modification. This target would be irrespective of co-morbids.

The only large trial assessing efficacy of antihypertensives for secondary prevention of stroke was the PROGRESS trial, looking at the outcomes of patients receiving an ACE-I (perindopril) with a diuretic (indapamide). This combination led to a 43% reduction in recurrence of stroke. It appears that for at least 70% of patients with hypertension >160/90 mmHg, a two drug regimen would be necessary. Recommending these two classes of antihypertensives based on evidence appears to be a safe option; randomized controlled studies for Asian population are warranted nonetheless where the population attributable risk of hypertension as a cause of stroke may be very high. It should however, be emphasized that the goal is to reduce blood pressure and any anti hypertensive which will ensure compliance in the long run will be preferable. Therefore the drug should be selected depending on the availability and the financial status of the patient.

Lipid Control: Unlike coronary heart disease, association of dyslipidemias with stroke occurrence as well as recurrence is weak. However, recent trials have shown the benefits of using statins for prevention of stroke in those with Coronary artery disease. Simvastatin and Pravastatin were the drugs used in these trials. This effect may not hold true for patients with cerebrovascular disease, where despite significant reduction in incidence of coronary events, the reduction in incidence of recurrent strokes was not significant, as concluded by the Heart Protection Study (HPS).

In contradistinction, Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) study has shown that Atorvastatin 80 mg/day significantly reduced the risk of stroke in patients who previously had a stroke or transient ischemic attack (TIA) and who had no known cardiovascular disease. The proposed underlying mechanisms by which statins reduce this incidence are poorly understood, but it is widely believed that the results are more dramatic than simple fall of cholesterol levels might suggest. Therefore, statins may have a multifactorial effect in prevention against cerebrovascular diseases. It appears that statins may reduce the risk of stroke in those with previous stroke or TIA and therefore these may be considered an independent atherosclerotic equivalent for the initiation of statins in selected patients.

Therefore, patients with ischemic stroke or TIA with elevated cholesterol, comorbid coronary artery disease, or evidence of an atherosclerotic origin should be counseled regarding lifestyle modification, dietary guidelines, and medication recommendations Statin agents are recommended, and the target goal for cholesterol lowering for those with CHD or symptomatic atherosclerotic disease is an LDL-C of <100 mg/dL and LDL-C of <70 mg/dL for very-high-risk persons with multiple risk factors.

Also patients with ischemic stroke or TIA presumed to be due to an atherosclerotic origin but with no preexisting indications for statins (normal cholesterol levels, no comorbid coronary artery disease, or no evidence of atherosclerosis) are reasonable candidates for treatment with a statin agent to reduce the risk of vascular events.

Diabetes mellitus: Diabetes being a factor associated with primary stroke is well known, but there is insufficient data to support its role in recurrence. The recommendations for glucose control, hence, should be the same for patients with and without a prior stroke.

Control of other modifiable cardiovascular risk factors in a patient with diabetes is one of the most essential and challenging issues. Aggressive blood pressure control in these patients is critical for decrease in recurrence. Furthermore, aggressive lipid control is also warranted for such patients. All classes of anti-hypertensives are approved for use in diabetes, though it is largely agreed that more than one agent should be used, and also that one of the agents should either be an ACE-I or ARB. This recommendation holds for patients with cardiovascular as well as cerebrovascular events.

Smoking: Smoking has been repeatedly identified as a significant risk factor for the occurrence of ischemic stroke. The most important Asian study assessing relationship between smoking and incidence of stroke in this population was one of the arms of Japan Public Health Centre -based prospective study on cancer and cardiovascular diseases (JPHC Study) cohort 1. This looked at almost 40,000 Japanese middle aged men and women followed up over a period of 12 years to see development of strokes, and confirmed a positive relationship between smoking and risk of total stroke and subarachnoid hemorrhage after adjustment for known cardiovascular risk factors and selected lifestyles.
In the presence of such convincing evidence against the use of tobacco, physicians should ask their patients repeatedly to quit smoking for both primary and secondary prevention.

A detailed smoke cessation guide is available at the NIH smoking cessation website. This guide is a good reference for patients to ease the difficulties they face while attempting to quit. (http://www.smokefree.gov/pubs/clearing_the_air.pd). Nicotine products and oral medications have been shown to be useful in helping patients quit smoking.

Obesity: The prevalence of obesity in Pakistan is determined to be as high as 23% among urban males and 40% among urban females, while rural areas report lower prevalence. This was based on Body Mass Index, BMI calculation using the Asia-pacific criteria. [BMI is the most widely used measurement for obesity which approximates body mass using a mathematical ratio of weight and height [(weight in kg ÷ height in meters2)]. However, it is now believed that abdominal obesity, rather than generalized obesity, has a stronger association with cardiovascular morbidity. Abdominal obesity, defined by a waist circumference more than 102 cm (40 in) in men and 88 cm (35 in) in women, was shown to be an independent risk factor for ischemic stroke in the Northern Manhattan Stroke Study. Optimum cut-offs for abdominal obesity for South Asian population have been proposed by Misra et al comparing waist circumference (WC) to standardized Asia-Pacific BMI cut-offs and equating cardiovascular risk factors. Even though no consensus exists in principle accepting or rejecting this proposal, it should be understood that South Asian population has far severe implications for each unit of weight gained compared to the western populations, hence calling for a more aggressive dietary control.

Exercise - regular physical activity: This has an indirect effect on stroke prevention through lowering of blood pressure. A meta-analysis by Whelton et al. in which the experience of 1,108 normotensive persons enrolled in 27 randomized controlled trials was included, identified a 4.04 mmHg (95 percent CI, 2.75-5.32) reduction in systolic blood pressure in those assigned to aerobic exercise compared with the control group. The magnitude of the intervention effect appears to be independent of the intensity of the exercise program. It is recommended that persons exercise for at least 30 minutes on most, if not all, days of the week.

Dietary salt restriction: This again has impact on stroke risk indirectly through its impact on lowering blood pressure. At least three meta-analysis of the efficacy of reduced sodium intake in lowering blood pressure have been published since 1993. In all three reports, sodium reduction was associated with a small but significant reduction in systolic blood pressure in normotensive persons. In the NHANES I Epidemiologic Follow-up Study, He et al. reported that a 100 mmol higher level of sodium intake in overweight persons was associated with a 32 percent increase in stroke incidence, a 89 percent increase in stroke mortality, a 44 percent increase in CHD mortality, a 61 percent increase in CVD mortality, and a 39 percent increase in mortality from all causes. These data support the premise that a lower intake of dietary sodium reduces the risk of subsequent CVD.

Depression: The prevalence of depression in Pakistan has been estimated to be as high as 34%. Stroke survivors are at a greater risk of developing depression, and this affects their recovery from stroke. Data from a local hospital revealed prevalence of post-stroke depression to be 37.9 % using DSM IV criteria among 174 patients presenting to the outpatient clinics, with most patients presenting within three months of the primary stroke. Early identification and management of depression post stroke is vital to ensure early recovery, and preventing cognitive impairment. Conventional tricyclic antidepressants are contra-indicated among stroke patients due to their adverse effects. SSRIs have a low

adverse effect profile and a good efficacy, making them invaluable in patients with multiple co-morbidities.

FUTURE DIRECTIONS AND NEED

Pragmatic Population based interventional risk reduction programs are needed to reduce the burden of stroke in vulnerable populations.

Research into the known and emerging risk factors for stroke is required to enhance the cost effectiveness and relevance of these interventions.

(Detailed version of these guidelines including references could be downloaded from Pakistan Society of Neurology web site: www.pakneurology.net)