

Update in the Management of Stroke

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Abstract

Recent advances have improved the outlook for patients with stroke, Singapore's fourth leading cause of death. Stroke unit care reduces death, dependency and institutionalisation, independent of age, gender and stroke severity. Neuroimaging is essential prior to initiation of specific therapies. While computed tomography (CT) Head remains the most widely used modality, magnetic resonance imaging (MRI), particularly diffusion weighted imaging (DWI) has enhanced the positive diagnosis of ischaemic stroke. General medical measures include close monitoring, adequate oxygenation, avoidance of excessive blood pressure lowering, reduction of hyperthermia, control of hyperglycaemia, adequate nutrition, prevention of complications and early rehabilitation. Despite the risk of fatal intracranial haemorrhage, thrombolysis may improve outcomes in appropriately selected patients with ischaemic stroke. No safe and effective neuroprotectant has been found. While suboccipital craniectomy is established for large cerebellar infarcts and haemorrhage, surgical evacuation of supratentorial haemorrhage has not been shown to be beneficial. Hemicraniectomy reduces mortality after massive hemispheric ischemic stroke. Early and sustained antiplatelet use after atherothrombotic stroke reduces stroke recurrence. Stroke recurrence is also reduced by sustained warfarin use for cardioembolic stroke, carotid endarterectomy for severe symptomatic internal carotid artery stenosis, blood pressure lowering starting after the acute phase of stroke and lipid lowering. On-going clinical trials are likely to provide better treatments in the near future.

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Introduction

Stroke is the fourth leading cause of death and a leading cause of morbidity in Singapore. The number of hospital admissions for cerebrovascular disorders has been rising dramatically over the last few years, exceeding 10,400 in 2001. With the ageing of our population, the number of stroke victims in Singapore is likely to rise.¹ Fortunately, there have been a number of important advances in the treatment of stroke that have greatly improved the outlook for this devastating disease.

Stroke Units

Stroke Unit (SU) care refers to organised in-patient care and rehabilitation of stroke patients by a multidisciplinary team of specialised staff, preferably in a defined ward, with programmes for patient and family education, and staff training. Compared to conventional care, SUs reduce long-term (median 1 year follow-up) death (OR, 0.83; 95% CI, 0.69-0.98), death or dependency (OR, 0.69; 95%CI, 0.59-

0.82), and death or institutionalisation (OR, 0.75; 95% CI, 0.65-0.87). Beneficial effects are independent of patient's age, sex, stroke severity or variations in SU organisation. Length of hospital stay is reduced by 8% (95% CI, 3-13).² Carepaths enhance care coordination, reduce readmission rates (OR, 0.11; 95% CI, 0.03-0.39) and urinary tract infection (OR, 0.38; 95% CI, 0.18-0.79).³

Neuroimaging

Computed tomography (CT) scan: Head CT is highly sensitive in detecting intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH). Early CT ischaemic changes may be detectable within 3 to 6 hours after onset of ischaemic stroke (IS).⁴ Extensive early CT ischaemic changes contraindicate thrombolysis and anticoagulant therapies. Close monitoring may be indicated for large supratentorial strokes, posterior fossa strokes and SAH. A non-contrast head CT should therefore be performed in patients with suspected stroke as soon as possible after

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presentation, and before the commencement of specific stroke treatments.

Diffusion-weighted imaging (DWI): Compared to CT, DWI is a magnetic resonance imaging (MRI) technique that is more sensitive in the early detection and localisation of brain infarcts during the first few hours of stroke.⁵ In the subacute stage of IS, DWI is also of value in detecting small subcortical and brainstem infarcts, and in the differentiation of acute from chronic infarcts.⁶ A “perfusion-diffusion mismatch”, (i.e. volume of brain tissue with perfusion deficit being significantly larger than the ischaemic lesion volume shown on DWI) may represent salvageable brain tissue (penumbra).

Using CT, MRI and ultrasound techniques, it is possible to obtain information in a patient with acute IS regarding: (a) the size and location of infarct(s), (b) the site(s) of arterial occlusion and the state of collateral circulation, and (c) the perfusion status of the ischaemic brain tissue (Table I).

General Medical Measures⁷⁻¹¹

General supportive measures serve to enhance stroke outcome, prevent complications and restore neurological function.

Close monitoring: Approximately 25% of stroke patients worsen within the first 24 hours. As there are no clear predictors for worsening, all patients should be considered at risk for the first few days post-stroke.

Adequate oxygenation: Hypoxia results in anaerobic glycolysis, lactic acidosis and reduced adenosine triphosphate (ATP) formation that can increase tissue injury. Routine oxygen administration is not needed unless there is evidence of hypoxia.

Avoidance of excessive blood pressure (BP) lowering: BP elevation is commonly detected in acute stroke e.g.

from stress. In general, elevated BP is left untreated unless it persistently exceeds 220 mm Hg systolic or 130 mm Hg mean. The threshold for reducing BP is lower if there is malignant hypertension, acute myocardial infarction, renal failure, aortic dissection or thrombolysis is planned. Parenterally administered drugs are easily titrated; sublingual calcium channel blockers are best avoided.

Reduction of hyperthermia: Animal studies have shown that temperature lowering reduces infarct size. Any source of fever should be ascertained, and fever reduced with antipyretics, and antibiotics where appropriate.

Control of hyperglycaemia: Hyperglycaemia may occur as a stress reaction to stroke. Elevated blood sugar levels have been correlated with poor post-stroke outcome, and should be lowered.

Adequate nutrition: A swallowing screen should be performed prior to oral feeding to reduce the risk of aspiration. Percutaneous gastrostomy may be offered to those who are permanently and severely dysphagic. Intravenous fluids should preferably be glucose-free to avoid iatrogenic hyperglycaemia. Intravenous hyperalimentation is seldom needed.

Prevention of complications: Large bolus feeding is best avoided to reduce the risk of aspiration. In-dwelling urinary catheters should be removed; intermittent catheterisation and urine acidification reduce urinary infection rates. Subcutaneous unfractionated heparin, low molecular weight heparin, heparinoids, pressure stockings and early mobilisation reduce the risk of deep venous thrombosis. Regular turning and skin care reduce the risk of pressure sores.

Early rehabilitation: Rehabilitation aims to restore functional independence, and should be started as soon as possible post-stroke. Early mobilisation reduces many complications. Passive ranging of movements can be started

TABLE I: COMPREHENSIVE NEURORADIOLOGICAL EVALUATION OF ACUTE ISCHAEMIC STROKE

Equipment	Localisation of ischaemic lesion(s)	Sites(s) of vessel occlusion	Status of brain perfusion	Advantages	Disadvantages
CT and US	Early CT ischaemic changes	Duplex US TCD	Not available	Bedside monitoring for microembolic signals and recanalisation possible	CT changes often subtle Duplex US and TCD are operator dependent Absence of bone windows for TCD in up to 25%
Helical CT	Early CT ischaemic changes	CTA	CT perfusion	Good depiction of vessel occlusion and brain perfusion	Not widely available High volume of iodide contrast required
MRI	DWI	MRA	PWI	Accurate identification of early infarcts and perfusion-diffusion mismatch	Not widely available Patient cooperation required

CT: computed tomography; CTA: CT angiography; DWI: diffusion-weighted imaging; MRA: magnetic resonance angiography; MRI: magnetic resonance imaging; PWI: perfusion-weighted imaging; TCD: transcranial Doppler; US: ultrasonography

in the first 24 hours, with more intensive rehabilitation when the patient's condition is stable.

Thrombolytic Therapy

Despite the increased risk of fatal intracranial haemorrhage, thrombolysis with intravenous (IV) t-PA, commenced within 3 hours of IS onset, is associated with 30% relative and 11% to 13% absolute increase in favourable outcomes.¹² The beneficial effects of IV t-PA might be extended to 270 minutes post-stroke, but not beyond.¹³

Intra-arterial (IA) thrombolysis with pro-urokinase was effective in IS associated with angiographically proven middle cerebral artery (MCA) occlusion within a 6-hour time-window.¹⁴ Combined IV/IA thrombolysis is another approach when IV thrombolysis is given within the 3-hour time-window, followed by angiography and IA thrombolysis/angioplasty if the vessel remains occluded.¹⁵ This approach carries the advantages of rapid initiation of thrombolysis with the IV approach and the higher rate of vessel recanalisation with the neurointerventional approach.

Neuroprotection

Several classes of agents were demonstrated to display significant neuroprotective effects in animal stroke models. Unfortunately, none of the agents evaluated so far has been proven to be effective in clinical trials except for nimodipine in SAH; some were associated with more adverse events compared to placebo.¹⁶

Surgical Decompression and Haematoma Evacuation

Suboccipital craniectomy, with or without ventriculostomy, is an established treatment for large cerebellar haematoma or infarct. While surgical evacuation is more commonly performed for superficially located large cortical haematoma, previous randomised trials on open surgery for large subcortical haematoma failed to show any benefit.¹⁷ Recent case series using thrombolysis and aspiration, either stereotactically guided or via ventriculostomy, show some promising results.

Hemicraniectomy has been performed in selected patients with complete MCA territory infarcts who are at significant risk of developing transtentorial herniation. Young patients with massive hemispheric strokes may be considered for this life saving procedure.¹⁸

Moderate Hypothermia

Maintenance of core body temperature at 32 to 34°C for 24 to 72 hours reduces elevated intracranial pressure (ICP) in large MCA infarction.¹⁹ Hypothermia is achieved with cooling blankets or an endovascular cooling catheter. Hypothermia is limited to 72 hours to avoid excessive adverse events including sepsis, arrhythmias, hypotension and coagulopathy. Mortality rate appears to be higher than

hemicraniectomy, mainly due to rebound increase in ICP during rewarming.

Antithrombotics

The role of antiplatelet agents in the secondary prevention of stroke is well established.²⁰ Aspirin upwards of 75 mg daily is sufficient. Other effective agents include ticlopidine, clopidogrel and aspirin-dipyridamole combination. Early aspirin therapy confers additional benefit. For every 1000 acute ischaemic stroke patients treated within 48 hours with aspirin (160 mg to 300 mg daily), there are 7 less recurrent ischaemic stroke and 9 less non-fatal strokes or deaths, but 2 more haemorrhagic strokes. The roles of new (e.g. glycoprotein IIb/IIIa receptor antagonists) and other antiplatelet combinations are being studied.

Anticoagulation

Early heparin use in stroke decreases the risk of recurrent ischaemic stroke, but may be associated with a greater risk of haemorrhagic stroke.²¹ The role of low molecular weight heparin in acute stroke is still not clear.

Anticoagulation is proven treatment in prevention of cardio-embolic strokes, aiming for an International Normalised Ratio of 2.5 for non-prosthetic valve conditions (e.g. atrial fibrillation),²² and 3.5 for prosthetic valve conditions. However, the optimal time of initiation after an acute stroke is not clear. A balance needs to be made between the risk of haemorrhagic transformation and recurrent stroke risk.

Carotid Endarterectomy

Patients with mild, non-disabling stroke or transient ischaemic attack secondary to a severe carotid stenosis ($\geq 70\%$ stenosis) have a stenosis-dependent risk for recurrent stroke, ranging from 25% to 69% in 2 years (highest risk for patients with contralateral carotid occlusion). The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) both showed a relative risk reduction in stroke of up to 65% for severe carotid stenosis 70% to 99%, in favour of endarterectomy. The surgeon had to be experienced, with a low surgical mortality of $<3\%$.²³

Carotid angioplasty with stenting is being investigated as an alternative procedure to carotid endarterectomy. It may be preferred in patients who decline surgery or are high-risk surgical candidates. Centres with high volume have reported favourable outcomes, fewer cranial nerve palsies and wound haematomas compared with endarterectomy.

Blood Pressure Lowering

In the weeks following stroke, BP lowering confers additional reduction in stroke recurrence. Antihypertensive

therapy produces a relative risk reduction (RRR) of fatal and non-fatal stroke of 0.72 (95% CI, 0.61-0.85).²⁴ It may now be appropriate to lower blood pressure using ACE-I based therapies starting 4 weeks after ischaemic or haemorrhagic stroke to further reduce unfavourable outcomes, in addition to other existing therapies, irrespective of whether the patient has a history of hypertension or not.²⁵

Lipid Lowering

It is common practice to lower LDL-cholesterol to below 2.6 mmol/L by diet and, if needed, statins. A randomised controlled trial of 20,536 adults, including 3280 with cerebrovascular disease, showed a 25% reduction in fatal and non-fatal stroke among those taking simvastatin 40 mg versus placebo. These benefits were in addition to other "cardioprotective treatments".²⁶

Other Agents

The role of other secondary prevention measures (e.g. vitamins and antibiotics) are being studied.

Conclusions

There has been significant progress in the management of stroke, bringing new hope to victims. It is likely that the best approach will be management in a stroke unit, guided by advanced neuroimaging, with a cocktail of rescue and secondary prevention treatments. More effective treatments can be expected as clinical trials in acute stroke continue.

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QUESTIONS

1. Stroke units have the following benefits except
 - a) reduced mortality
 - b) reduced death or dependency
 - c) reduced death or institutionalisation
 - d) increased length of hospital stay
 - e) benefits are independent of patient's age, sex, or stroke severity
2. The following are true about neuroimaging in acute stroke except:
 - a) brain imaging is a pre-requisite to definitive therapies
 - b) a normal CT Head reliably excludes large intracranial haemorrhage
 - c) a normal CT Head performed within a few hours of symptom onset excludes an acute ischaemic stroke
 - d) MR-DWI performed within a few hours of symptom onset may reveal an ischaemic stroke even if the CT Head is normal
 - e) cerebrovascular anatomy can be studied non-invasively using extracranial and transcranial ultrasound, MR angiography or CT angiography
3. Supportive medical measures post-stroke include
 - a) close monitoring in the early days post-stroke
 - b) swallowing assessment prior to commencement of oral feeding
 - c) education of the patient and family about stroke
 - d) early initiation of rehabilitation
 - e) all of the above
4. Randomised controlled trials have shown the efficacy of the following acute stroke treatment:
 - a) neuroprotectants
 - b) thrombolysis for ischemic stroke
 - c) evacuation of supratentorial haemorrhage
 - d) early, aggressive blood pressure lowering
 - e) prolonged hypothermia
5. Effective secondary prevention measures include:
 - a) antiplatelet agents for atherothrombotic stroke
 - b) anticoagulation for cardioembolic stroke
 - c) carotid endarterectomy for symptomatic severe carotid stenosis
 - d) blood pressure lowering starting a few weeks after stroke onset
 - e) all of the above

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