Clinical practice review

Acute Ischaemic Stroke: Part I. The Carotid Circulation

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ABSTRACT

Objective: *To review recent advances in the management of acute ischaemic stroke in a two part presentation.*

Data sources: *Articles and a review of studies reported from 1990 to 2000 and identified through a MEDLINE search of the English language literature on acute ischaemic stroke.*

Summary of review: *An acute ischaemic stroke is characterised clinically by the rapid development of a neurological deficit caused by a thrombus or embolus in the carotid (i.e. anterior) circulation or vertebrobasilar (i.e. posterior) circulation. Management requires urgent computed tomography to differentiate it from a haemorrhagic stroke. Ancillary investigations of echocardiography and thrombophilia screen may also be required if a cardiac embolic condition or hypercoagulable state is suspected, respectively. Cerebral magnetic resonance imaging, angiography and duplex ultrasonography with Doppler analysis of cerebral blood flow are becoming increasingly useful in determining the site and extent of the ischaemic lesion. Lumbar puncture is rarely required.*

Treatment with aspirin (150 - 300 mg) within the first 48 hr as well as management in a specialised unit focusing on resuscitation and prevention of complications (e.g. maintaining hydration and nutrition, and preventing aspiration and pressure sores, etc), has reduced morbidity and mortality associated with acute ischaemic strokes. However, while therapy to improve cerebral blood flow using thrombolytics, anticoagulants, glycoprotein IIb/IIIa inhibitors or fibrinogen depleting agents or neuroprotective agents to reduce further neuronal damage (e.g. solfotel, eliprodil, lubeluzole) have shown promise experimentally and in specific clinical circumstances, they have not produced consistent improvement in morbidity or mortality.

Conclusions: *An acute ischaemic stroke in the distribution of the carotid circulation requires aspirin 150 - 300 mg daily and management in an acute stroke unit. Thrombolytic therapy (with rt-PA within the first three hours) to improve cerebral blood flow has limited application, and current neuroprotective agents have not yet been shown to be of benefit.* (**Critical Care and Resuscitation 2000; 2: 125-139**)

Key Words: Acute ischaemic stroke, cerebral embolism, cerebral thrombosis, transient ischaemic attack, thrombolysis, neuroprotective agents, carotid endarterectomy

A stroke is characterised by the sudden development of a neurological deficit and is caused by either an ischaemic (i.e. thrombus or embolus) or haemorrhagic event. Approximately 80% of strokes are ischaemic and 20% are haemorrhagic (Table 1) with 25% of patients being less than 65 years old, 25% between the ages of 65 and 75 years and 50% over the age of 75 years.[1] Approximately 50% of patients survive with minimal to

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moderate disability although up to 30% die within three months from intracranial hypertension (caused by haemorrhage, cerebral oedema or hydrocephalus), pneumonia, pulmonary embolus, myocardial infarction and recurrent stroke.[2]

An embolic or haemorrhagic stroke usually has an abrupt onset with the maximum deficit occurring at the onset, whereas a thrombotic stroke may have an onset over a few hours (even several days) with the maximum deficit occurring after the onset. Rapid reversal of the deficit will occur with transient ischaemia and may occur with embolism but does not occur with haemorrhage.

Table 1. Incidence of cerebrovascular lesions causing a stroke

Cerebrovascular lesion	Incidence (%)
Ischaemic	
Thrombosis	35
Embolism	30
Lacunar infarcts	15
Haemorrhagic	
Hypertensive	15
Ruptured aneurysms	5
AV malformations and others	0.5

An acute ischaemic episode presents as either a transient ischaemic attack where the clinical effects are totally reversible within 24 hr, or a stroke where the clinical effects last longer than 24 hr and are associated with permanent neurological defects. The effects of a thrombotic or embolic cerebral artery occlusion relate largely to the region of brain supplied by the occluded artery. The circle of Willis (which is derived from the basilar and internal carotid arteries) supplies the anterior middle and posterior cerebral arteries (fig. 1), although strokes are often classified clinically as either an anterior circulation (i.e. carotid artery) or posterior circulation (i.e. vertebrobasilar) stroke. This section will consider the features of carotid artery (i.e. anterior circulation) ischaemic stroke.

Transient ischaemic attacks

Transient ischaemic attacks (TIAs) are defined as sudden focal neurological deficits that last for less than 24 hr and are totally reversible. However, most TIAs last for less than 1 hour (14 minutes is the median duration of TIAs of carotid distribution)[3] as a deficit that lasts for longer than one hour is usually associated with neuronal damage. TIAs are characteristically frequent and are found in patients who have cerebral arterial narrowing. They are caused by either a threshold episode of ischaemia or atheromatous plaque-induced platelet emboli.

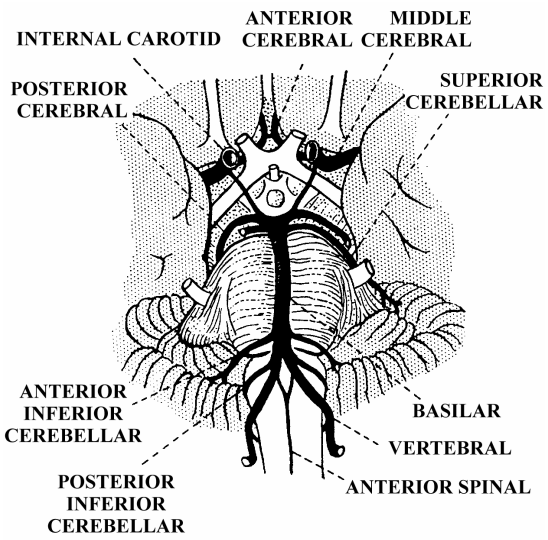

Figure 1. Arterial supply to the brain with the circle of Willis at the base of the brain formed by the basilar and internal carotid arteries. The left and right internal carotid arteries communicate with the basilar artery via the posterior communicating arteries and the left and right internal carotid arteries communicate anteriorly via the anterior communicating artery (Modified from Gardner E. Fundamentals of neurology, WB Saunders, Philadelphia 1963).

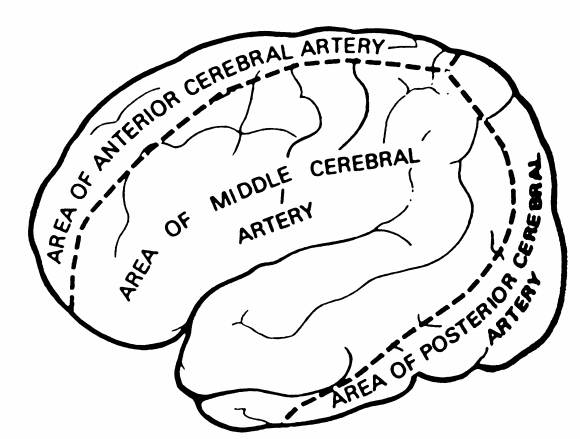

Figure 2. Approximate distribution areas of the anterior, middle and posterior cerebral arteries. (Modified from Gardner E. Fundamentals of neurology, WB Saunders, Philadelphia 1963).

The clinical features of the TIA reflect the cerebral artery involved. Unilateral signs (e.g. hemiplegia, monoplegia and 'amaurosis fugax' which classically presents as a 'blind coming down' over the eye on the same side as the carotid stenosis), sensory inattention and speech disturbances indicate a carotid or middle cerebral artery induced TIA (80% of TIAs); whereas bilateral motor and cranial nerve signs with diplopia, dizziness or dysarthria indicate a vertebrobasilar TIA

(20% of TIAs).[4] The differential diagnosis of TIAs include, syncope, seizures, migraine, Stokes-Adams attacks, hypoglycaemia and hyperventilation.[5]

In 70% of patients with TIAs a stroke will develop. In 4 - 8%, the stroke occurs within 1 month of the first TIA, in 12 - 13% during the first year and in 24 - 29% the stroke will develop within 5 years.[6] In 30% of patients the TIAs cease without causing a stroke.

Cerebral artery thrombosis

Cerebral artery thrombosis is commonly caused by atherosclerosis and occurs at an atheromatous narrowing, although it may also be caused by traumatic or postoperative carotid lesions, hypercoagulation syndromes (e.g. polycythaemia, paroxysmal nocturnal haemoglobinuria, heparin-induced thrombocytopenia), arterial or aortic dissections, an arteritis (e.g. systemic lupus erythematosis, temporal arteritis, polyarteritis, Takayasu's arteritis, heroin abuse) or vasospasm induced by severe migraine, eclampsia, amphetamine or cocaine abuse.[7]

In approximately 60% of patients, the thrombotic stroke is preceded by a TIA and is often precipitated by an episode of low cerebral blood flow (e.g. develops during sleep or shortly after rising, or during an episode of hypotension, particularly when it occurs during the intraoperative or postoperative period). In 20% of patients the stroke has an intermittent progression over hours or days.

Lacunar disease is caused by atherothrombotic occlusion of small perforating branches of the circle of Willis that penetrate the brainstem to supply the internal capsule, basal ganglia and thalamus. Thrombosis of these vessels cause small infarcts known as lacunae and may present clinically indistinct from other causes of ischaemic stroke or have characteristics such as a pure motor stroke, a pure sensory stroke, ataxic hemiparesis or a syndrome of dysarthria/clumsy hand. Lacunae may also be demonstrated at autopsy or on a CT scan without clinical manifestations. Bilateral lacunae may present with dysarthria and pseudobulbar palsy. In 25% of cases, lacunar infarcts present with TIAs. Hypertension is present in 75% of patients and up to 40% have diabetes.[8]

Cerebral embolism

In approximately 50% of patients who have cerebral embolism, the embolus originates from the heart. The cardiac disorders causing the embolus include atrial fibrillation (arising from the left atrium and accounting for 50% of cardiogenic embolic episodes)[9], endocarditic valve lesions (infective or marantic), valve prosthesis, mural thrombus overlying an area of damaged left ventricle (i.e. myocardial infarction, trauma or intraoperative damage), myxomas, cardiomyopathies or paradoxical embolus through a patent foramen ovale (usually in patients aged under 50 years).[10,11] Non-cardiac cerebral emboli arise from carotid atheroma and traumatic or postoperative carotid lesions. Other rare causes of cerebral emboli include air, fat and tumour emboli.

Any region of the brain may be affected, but the territory of the middle cerebral artery is commonly involved. The clinical symptoms develop within seconds (unlike thrombus or haemorrhage) and may be temporary as the embolus passes down the artery and breaks up to deposit in distal branches. Unlike TIAs, the neurological symptoms, if they recur, are different, as separate emboli usually travel down different cerebral branches affecting different parts of the brain.

CLINICAL FEATURES

Neurological

The clinical features of strokes that involve the carotid artery distribution include, altered conscious state, spastic hemiparesis of arm, leg and face, expressive or receptive dysphasia, astereognosis, homonymous hemianopia, sensory inattention, dressing apraxia, Gerstmann's syndrome (i.e. acalculia, agraphia, finger agnosis, inability to distinguish right from left), perseveration (i.e. repetitive feeling of clothes), and (with posterior cerebral artery infarction) cortical blindness.

In one study of 675 patients with first-ever stroke, four clinically identifiable subgroups were described:[12]

a) total anterior circulation infarcts (TACI) with a predominantly cortical and subcortical involvement due to middle cerebral artery or internal carotid obstruction. These patients presented with a triad of ipsilateral motor/sensory deficit, homonymous hemianopia and higher cortical dysfunction (dysphasia, dyscalculia, visuospatial disorder),
b) partial anterior circulation infarcts (PACI) with predominantly smaller and deeper cortical infarcts due to distal cerebral artery obstruction. These patients presented with only one or two clinical features of the above triad,
c) lacunar infarcts (LACI) due to deep perforating artery obstruction. These patients presented with a pure motor stroke, pure sensory stroke, sensori-motor stroke or ataxic hemiparesis, and,
d) posterior circulation infarcts (POCI) due to vertebrobasilar obstruction. These patients present with any of the following: ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficit; bilateral; motor and/or sensory deficit; disorder of conjugate eye movement; cerebellar dysfunction (see Part II).

While some studies have found that this classification correlated well with the radiological diagnosis,[13-15] and thus could be of value in assessing reperfusion therapy before arterial imaging is available,[16] or when an infarct is not visible on brain imaging;[17] one study using clinical criteria to diagnose acute anterior circulation stroke, found that 9% were misdiagnosed and 21% were misclassified (i.e. 70% were correctly classified but 10% were TIAs, 23% were recanalised and only 37% had persisting occlusion).[18] Patients with the wrong diagnosis, transient ischaemia, cerebral haemorrhage, small vessel disease, and patients with infarction but spontaneous recanalisaton formed 63% of the population in this study, none of whom were amenable for reperfusion therapy.[18]

Cardiovascular

Supine and erect blood pressures may reveal postural hypotension (i.e. a fall in systolic blood pressure of 30 mmHg or greater, or a fall in systolic blood pressure to 80 mmHg or greater on standing).[19] A differential blood pressure measurement in both arms may indicate proximal subclavian artery stenosis or dissecting aneurysm and an absent femoral pulse or a radial-femoral delay may indicate coarctation of the aorta.

Atrial fibrillation or the detection of cardiac bruits may suggest cardiac embolic causes of the stroke.

While cervical bruits are heard in aproximately 60% of patients with severe carotid artery stenosis and may indicate underlying carotid vascular disease,[20] they are absent in greater than one-third of patients with high grade (i.e. 70 -99%) stenosis,[21] and are also present in patients with low grade stenosis (i.e. < 30%), indicating that a cervical bruit has a low sensitivity and specificity for carotid artery stenosis. Nevertheless, a cervical bruit detected in an asymptomatic patient about to undergo a coronary artery bypass graft or in a patient who has a history of TIAs, warrants further investigation (e.g. Doppler studies) to assess carotid artery flow.

Fundoscopy may reveal hypertensive or diabetic changes, or Hollenhorst plaques (i.e. cholesterol particles that embolise to the retina) in patients with TIAs (they have also been observed following angiography and angioplasty).[22]

INVESTIGATIONS

Investigations include:

Routine tests: Chest X-ray, electrocardiogram, standard liver function tests, plasma electrolytes and blood gases are usually required. A coagulation profile and complete blood picture for haemoglobin and platelet estimation are performed in patients with intracranial haemorrhage and, in patients with thrombotic or embolic stroke, a thrombophilia screen (including antiphospholipid anmtibodies, factor V Leiden, protein C, protein S and antithrombin III levels) may also be performed.

Computed tomography (CT): Cerebral CT is becoming a routine investigation in patients with a stroke and is mandatory in patients in whom anticoagulant or thrombolytic therapy are being considered, because of its ability to detect (and exclude) intracranial bleeding (or haemorrhagic changes in an embolic stroke) or the presence of major hypodensities, which also contraindicates thrombolytic therapy and will delay anticoagulation by 7 - 10 days.[8,23] It should be performed within 3 hr of the onset of the stroke. Cerebral CT may also reveal the presence of cerebral oedema, hydrocephalus and other surgically remedial lesions.

While the CT scan may be normal during the first 24 - 48 hr after a cerebral infarct, thereafter a focal area of decreased density will usually be detected (best seen at day 7-10), if the lesion is within the 1 cm resolution of most CT scanners. Intravenous contrast may also reveal enhancement of cortical portions of the infarct after 1 - 3 weeks.

Lumbar puncture: Following the CT scan, a lumbar puncture may be performed to detect cerebrospinal fluid (CSF) haemorrhage in patients who have subarachnoid haemorrhage, intracerebral haemorrhage or a haemorrhagic infarction due to a cerebral embolus. However, examination of the CSF is required only rarely and usually in the patient in whom subarachnoid haemorrhage is suspected but not demonstrated by the CT scan.

Echocardiography: This should be performed in all patients who have high probability of a cerebral embolic disorder of cardiac origin. However, it is not routinely performed in all patients with TIAs as it has a low diagnostic yield (and therefore a high false-positive rate) in this group of patients.[24,25]

Magnetic resonance imaging (MRI): While MRI studies may not accurately determine the ischaemic region in all patients within the first few hours after the stroke onset, the MRI technique of diffusion weighted imaging (DWI) can accurately detect ischaemic lesions within 2 hr in some patients.[26,27] Moreover, DWI appears to accurately demonstrate core ischaemic lesions whereas perfusion-weighted images (PWI) display the area of dysfunctional ischaemic brain tissue with the mismatch between the acute PWI lesion and the smaller DWI lesion representing potentially salvageable brain tissue (i.e. an estimate of the ischaemic penumbra), and in patients with a PWI/DWI mismatch, early reperfusion (e.g. using thrombolytics) may be associated with substantial clinical improvement and reversal or reduction of DWI lesion growth.[28,29] The disadvantages

associated with MRI include longer imaging time and the difficulty or inability to study patients with magnetic metallic objects.

Ultrasound: Duplex ultrasonography with Doppler analysis of carotid blood flow can be used to assess the degree of carotid artery stenosis and is the investigation of choice to assess the need for angiography in patients who have TIAs. Transcranial doppler may also be used to assess blood flow in intracranial vessels in patients with cerebral ischaemic lesions.

Angiography: This is the definitive procedure for demonstrating arterial stenosis or occlusion and is always performed when surgery is being considered (e.g. vascular stenosis, AV malformation or berry aneurysms). The femoral arterial approach rather than a carotid artery stab is preferred, as the former demonstrates the integrity of the whole carotid artery as well as being less likely to produce a dissection or injury to the carotid artery or rupture of a saccular aneurysm.[30]

Radionuclide brain scanning: Radiolabelled blood (using technetium-99m) will reveal cerebral blood flow abnormalities with thrombosis and embolus and an early defect in most cases of stroke. The ischaemic penumbra can also be delineated using positron emission tomography (PET)[31] and single photon emission computed tomography (SPECT)[32] as effectively as the PWI/DWI mismatch, although availability and the delay in receiving the information limits the clinical usefulness of these techniques.

TREATMENT

The long-term management of a patient who has an ischaemic stroke involves improvement of blood supply (e.g. antiplatelet drugs, anticoagulants, endarterectomy), control of hypertension (e.g. a reduction in blood pressure by 5 - 10 mmHg in patients with TIAs reduces the incidence of subsequent strokes by up to 40%),[33] and reduction in other vascular disease risk factors (e.g. cessation of smoking, reduction in serum cholesterol). A meta-analysis of randomised controlled trials of statin drug therapy to reduce cholesterol levels, found a reduction in the incidence of fatal and non-fatal strokes and total mortality.[34]

However, the management of an acute stroke requires early therapy as the time window for at least partial reversibility of anterior circulation ischaemic injury in humans is probably within three hours of the onset of symptoms.[26] The principles of treatment of an acute ischaemic stroke include physiological system support (i.e. resuscitation) and general support (i.e. therapy to prevent complications) as well as therapy to facilitate reperfusion (e.g. aspirin, thrombolysis) and to protect the ischaemic brain tissue from further damage (e.g. neuroprotective agents).

Resuscitation and therapy to prevent complications

Specialised stroke units have been shown to reduce morbidity and mortality,[35,36] although the improved outcomes are most likely due to those features which characterise the general intensive care unit. Management includes:

Respiratory support. For example, maintaining a clear airway, and preventing aspiration, hypoxia and hypercapnoea, particularly in patients who are drowsy or unconscious, or have brainstem dysfunction with reduced glottic reflexes and who are vomiting. This may require endotracheal intubation (which is often required during anaesthesia for the cerebral CT) and mechanical ventilation. In the ventilated patient, to facilitate regular neurological assessment, propofol or small doses of midazolam and morphine are commonly used.

Cardiovascular support. The patient is often hypertensive caused in part by pain, fear and confusion. As maintenance of cerebral perfusion is paramount, a systolic or diastolic blood pressure of up to 220 mmHg and 120 mmHg, respectively, may be tolerated.[5,37] If the patient remains severely hypertensive, despite pain relief and sedation, to ensure adequate perfusion of damaged brain tissue without causing cerebral ischaemia, small doses of captopril (2 - 5 mg orally or sublingually) may be administered hourly until the mean arterial blood pressure is reduced to no less than 130 mmHg.[38,39] Patients with stroke caused by a dissecting aneurysm require intra-arterial pressure monitoring and a greater lowering of the mean arterial pressure (ideally to < 90 mmHg but usually by no more than 30% for the first 24 hours) using esmolol (e.g. 1.75 mg/70 kg/min) and sodium nitroprusside (15 - 100 μg/min).[39]

Mild or moderate hypertension is controlled over the long term only after the clinical symptoms of stroke have stabilised.[40] As a haematocrit of 42% would seem to be optimal for the delivery of oxygen to the brain and as anaemia or polycythaemia are detrimental to cerebral function, the haematocrit is kept between 35-45%.[41]

In the absence of hypoxia, routine supplemental oxygen[42] (even hyperbaric oxygen[43]) has not been shown to be beneficial in patients with acute ischaemic stroke.

Metabolic support. Hydration, electrolyte, acid-base balance and nutrition are monitored and maintained intravenously for the first 24 hr. Hyperglycaemia is associated with an increased mortality in patients with stroke[44,45] and should be treated with insulin,[45] although in one randomised controlled trial in stroke patients with hyperglycaemia, a reduction in glucose was not associated with any significant improvement at 4 weeks.[46] While prophylactic H_2 blockers (e.g. ranitidine 50 mg i.v. 8-hourly) or proton-pump inhibitors (e.g. omeprazole 40 mg i.v. daily) are of use when

administered to stroke patients requiring mechanical ventilation for more than 48 hours,[47] prophylactic antiepileptic agents are of no benefit.[39]

The ability of the patient to swallow is assessed before the patient is allowed to eat. As fluids are often not tolerated well, the patient may require soft foods initially before being given oral fluids and progressing to a full diet. If the patient is unable to swallow, a fine bore naso-enteric tube or percutaneous enteric feeding tube should be used.[48] Stool softeners lessen the likelihood of faecal impaction.

General support. If the patient is somnolent or obtunded then standard management of an unconscious or partially conscious patient apply to prevent deep vein thrombosis, pressure sores, eye trauma and contractures. While there is good evidence to suggest that low-dose unfractionated or low-molecular weight heparin prevents deep vein thrombosis, the risk of fatal pulmonary embolism is lower than the risk of intracranial haemorrhage in these patients.[49] Therefore, to decrease the incidence of deep vein thrombosis, routine leg exercises, intermittent pneumatic leg or calf compression[50] (even intermittent compression of the arms[51]), elastic (graded compression) stockings, physiotherapy and early mobilisation are used. Pressure sores are reduced by regularly altering the patient's position, supporting the area surrounding pressure points and using alternating pressure airflow mattresses.[52] Physiotherapy with active and passive range movements and splints are used to prevent contractures.[53] A penile sheath will be necessary if the patient is incontinent. A urinary catheter is used if the patient has urinary retention. Prolonged care focuses on early mobilisation and rehabilitation.

Therapy to improve cerebral blood flow

Antiplatelet agents

Aspirin. While aspirin 350 mg daily (30 - 75 mg daily is probably just as effective)[54,55] results in a 20 - 30% reduction in the incidence of stroke if administered after a TIA or minor stroke (i.e. primary prevention), from early trials it appeared less certain if aspirin would prevent stroke following cerebral infarction (i.e. secondary prevention).[56-58] However, many recent trials have firmly demonstrated the beneficial effects of aspirin on secondary prevention in acute ischaemic stroke. For example, the International Stroke Trial (IST)[59] and the Chinese Aspirin Stroke Trial (CAST)[60] together randomised about 40,000 patients within 48 hr of acute ischaemic stroke onset to aspirin or control and together demonstrated that with aspirin there was a significant reduction in recurrent stroke and pulmonary embolism within the first 14 days after stroke and a reduction by 13 in 1000 patients, of long term disability and death (the number needed to treat or NNT is 77 for one patient to receive this benefit). The addition of heparin offered no additional benefit.

Dipyridamole. In a large randomised, controlled study of patients with a history of stroke or TIA, both sustained release dipyridamole alone (400 mg/d) and aspirin alone (50 mg/d) reduced the risk of recurrent stroke or death, although the addition of both was more effective than either agent alone.[61]

Thienopyridines (e.g. ticlopidine, clopidogrel). In a large randomised, double blind, placebo-controlled trial in patients who had sustained a thromboembolic stroke, ticlopidine 250 mg twice daily significantly reduced the severity of initial (i.e. primary) stroke and incidence of subsequent (i.e., secondary) stroke, myocardial infarction and vascular death in both men and women.[62] In another trial, clopidogrel 75 mg daily also reduced the combined risk of ischaemic stroke, myocardial infarction and vascular death in patients with atherosclerotic vascular disease.[63]

In summary, aspirin (150 - 300 mg daily and continued long term) should be administered to all acute atherothrombotic strokes as soon as the diagnosis of cerebral infarction has been made (i.e. < 48 hr).[49,64,65] Aspirin has an immediate effect (i.e. within 30 - 60 minutes) whereas ticlopidine and clopidogrel take up to 3 days to produce effective inhibition of platelet function. Currently, clopidogrel (75 mg daily) is recommended for prevention of stroke in patients who are intolerant of aspirin[66] as it has a better risk profile compared with ticlopidine which has the undesirable side effect of neutropenia. Modified-release dipyridamole may be added to aspirin to further reduce the incidence of stroke in higher risk patients or used in patients who are unable to take aspirin or clopidogrel.

Glycoprotein IIb/IIIa inhibitors. Abciximab (developed from murine monoclonal antibody Fab fragments to the IIb/IIIa receptor) binds to platelets for up to 2 weeks whereas the currently available synthetic IIb/IIIa inhibitors inhibit platelet aggregation for only a few hours. In one double blind, placebo-controlled trial of patients with ischaemic stroke presenting within 24 hr of symptoms, abciximab in an increasing dose schedule did not significantly alter morbidity (although there was a trend towards a higher rate of minimal disability) or mortality compared with placebo,[67] indicating that glycoprotein IIb/IIIa inhibitors currently should not be used in the routine management of patients with acute ischaemic stroke.

Anticoagulants

There is no evidence to support the use of anticoagulants for the treatment of acute stroke as the beneficial effects of immediate heparin use (standard or

low dose, fractionated or unfractionated) in reducing early recurrent ischaemic stroke or pulmonary embolism in a patient with an acute non-progressive stroke appear to be outweighed by haemorrhagic side effects.[49,65] Physical methods (*vide supra*) should be used to prevent deep vein thrombosis in patients with stroke, although symptomatic thromboembolism should be managed with heparin. In individual cases, heparin may be administered to patients who have a documented evolving thrombosis (i.e. progressive or stepwise neurological deficit greater than 24 hr duration and evolving thrombus up to 3 days despite aspirin therapy) and only when the patient's hypertension is controlled (i.e. less than 180/100 mmHg).[8]

While anticoagulants are also administered to patients with a cerebral embolism due to an underlying cardiac disease, immediate anticoagulation with heparin is not necessary, as one large prospective randomised, double-blind multicentre study in patients with acute ischaemic stroke and atrial fibrillation found no difference in functional outcome or death at 14 days or 3 months in patients treated with dalteparin 100 IU/kg subcutaneously twice daily or aspirin 160 mg orally daily.[68] Warfarin is administered after the required delay[69] (i.e. up to 5 days[70] in patients with mild strokes, or greater than 2 weeks in patients with more severe strokes[49]) to keep the INR between 2.0 and 3.0 in patients with atrial fibrillation, or between 2.5 and 3.5 in patients with mechanical prosthetic valves.[71]

Anticoagulants rather than antiplatelet agents for TIAs may be used in patients who do not respond to antiplatelet drugs, who are not suitable for surgery, who are compliant, are relatively young and who do not have uncontrolled hypertension.[56]

Thrombolytic agents

Streptokinase. The Multicentre Acute Stroke Trial-Europe (MAST-E) study (comparing streptokinase 1500,000 u over 1 hr with placebo in patients within 6 hr after the onset of acute ischaemic stroke) was stopped when the incidence of cerebral haemorrhage and mortality was found to be significantly higher in the streptokinase group.[72,73] The MAST-I study was also discontinued due to a significant increased risk of early mortality in patients with acute ischaemic stroke treated with streptokinase and aspirin (although there was a marginal reduction in mortality and of severe disability in patients given streptokinase or aspirin alone after 6 months).[74] The Australian Streptokinase trial in patients treated within 4 hr of the onset of acute ischaemic stroke (ASK study) was also terminated early due to an increased morbidity and mortality in the treatment group.[75]

Currently, the use of streptokinase cannot be recommended in acute ischaemic stroke.[76,77]

rt-PA. The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group compared 0.9 mg/kg (to a maximum of 90 mg) of rt-PA (10% administered i.v. as a bolus and the remaining 90% administered over 1 hr within 3 hr of onset of symptoms without co-administration of heparin, in patients with acute ischaemic stroke without major infarct signs on initial CT) with placebo, and found no significant difference in mortality but an improved clinical outcome at 3 months in the rt-PA group (despite an increased incidence of symptomatic cerebral haemorrhage).[78] In this study, patients who were taking aspirin at the time of the randomisation were eligible for study participation and mortality outcomes did not seem to be affected. On reviewing the radiological findings, the beneficial effect of early thrombolytic therapy appeared to be confined to patients exhibiting small areas of parenchymal hypoattenuation on baseline CT (there was no beneficial effect in patients with normal baseline CT and an increased mortality in patients with large areas of hypoattenuation in baseline CT).[79] The European Cooperative Acute Stroke Study (ECASS) compared 1.1 mg/kg of rt-PA (to a maximum of 100 mg) administered within 6 hr of onset of symptoms in 620 patients with acute ischaemic hemispheric stroke without signs of a major infarct on the initial CT, with a placebo. The study found an increase in mortality in the treated group compared with the control group at 3 months, with no compensating improvement in functional state, although they believed that intravenous thrombolysis was effective in improving a subgroup of stroke patients who had moderate to severe neurological deficit and who had no early major CT signs of early infarction.[80] These results were also replicated in the European Cooperative Acute Stroke (ECASS II) Study using a lower dose of rt-PA (0.9 mg/kg) within 6 hr of stroke onset.[81] One study observed that patients who received 60 mg of rt-PA within 6 hr of stroke onset had significant clinical improvement in comparison with a placebo group.[82]

However, unless rt-PA is administered within the first few minutes of the thrombosis, before tissue necrosis occurs, cerebral haemorrhage may occur with rt-PA in up to 4 -10% of patients who have had a recent stroke and partial or complete recanalisation may occur in only 35% of patients.[26,56]

While a meta-analysis of 12 trials of thrombolytic therapy for ischaemic stroke found that the mortality rate was statistically higher among patients who had been assigned thrombolysis compared with those in the control group, differences in design (e.g. inclusion-exclusion criteria, agent used and dose) and ancillary

medications used, imposed significant limitations to this conclusion.[83]

Currently, thrombolytic therapy for acute ischaemic stroke requires further testing in large randomised controlled trials before it can be recommended routinely because the risks are substantial (all trials have shown an increase incidence of intracranial haemorrhage with fatal intracerebral haemorrhages increasing from an average of 1.2 - 6.3%),[2] the benefit uncertain and the time window for effective treatment unclear.[83-85]

Notwithstanding, thrombolytic therapy (with intra-venous rt-PA or intra-arterial pro-urokinase - *vide infra*) probably has a place in a rare group of patients (i.e. 4% of patients with stroke[86]) with middle cerebral artery infarction.

For example:

a) in the absence of thrombolytic contraindications (e.g. active bleeding, systolic blood pressure > 185 mmHg or diastolic > 110 mmHg, coagulopathy, recent major surgery, etc),
b) in patients who have a normal CT scan (accurate interpretation of the CT scan is critical as early signs of cerebral infarction including hypodensity and cerebral swelling, which may be missed by non neuroradiologists, are associated with an increase in mortality),[2]
c) within 3 hr of symptoms (where onset of symptoms is defined as the last time the patient was known to be at his or her baseline level of neurological function, which means at the time the patient went to sleep if the stroke was noted on awakening),
d) rt-PA (0.9 mg/kg, to a maximum of 90 mg, with 10% administered i.v. as a bolus and the remaining 90% administered over 1 hr, without coadministrat-ion of heparin), has been shown to produce a 12% absolute increase in numbers of patients with minimal or no disability at three months[87] (i.e. NNT is 9 for one to receive this benefit) with no change in mortality (although there was a 3% chance of an earlier death from rt-PA induced cerebral haemorrhage which was significantly greater in the rt-PA group compared with the placebo group). This effect is sustained for 12 months.[88]

r-proUK. In a prospective randomised controlled, multicentre, trial in patients with acute ischaemic stroke of less than 6 hr duration caused by angiographically proven occlusion of the middle cerebral artery and without haemorrhage or major early infarction signs on CT scan, patients who received 9 mg of intra-arterial recombinant-prourokinase over 2 hr plus heparin (2000 u i.v. bolus and 500 iu/hr for 4 hr) had a significantly improved outcome at 90 days compared with patients who received heparin only, although there was no difference in mortality.[89] The NNT was 7 for one patient to receive benefit.

Fibrinogen depleting agents

Ancrod. Patients with an acute ischaemic stroke who had a normal cerebral CT were enrolled up to three hours after the onset of symptoms to receive ancrod based on body weight and initial fibrinogen level (0.1 - 0.5 u/kg over 6 hr then as a continuous infusion over 2 days then two additional infusions on day 4 and 5 to keep the fibrinogen level between 0.4 g/L and 0.7 g/L).[90] While there was no difference in mortality a statistically significant favourable neurological outcome compared with patients who received a placebo was observed.[2] However, ancrod is currently not recommended in the management of acute ischaemic stroke.

Rheological agents

Oxpentifylline,[91] dextrans,[92] or haemo-dilution,[93,94] to improve the rheological properties of blood, have not been shown to be of value in patients who have had a recent stroke.[56,95]

Carotid endarterectomy

Carotid endarterectomy is indicated in patients who have TIAs or minor (nondisabling strokes) and a stenosis of greater than 70% in the region of the carotid sinus[96,97] as soon as possible after the event. In one large study the risk of immediate surgery was worth trading off against the long term risk of stroke without surgery when the stenosis was greater than 80%.[98]

While the reported risk of stroke associated with carotid endarterectomy varies from 1 to 20%,[99] if the operation is to reduce the incidence of stroke to values below that which would occur without surgery, the surgical team performing the carotid endarterectomy should have a complication rate below, 2% for asymptomatic carotid stenoses, 3% for TIAs, 5% for ischaemic stroke, and 7% for recurrent carotid disease in the same artery. In all cases, at the 30th postoperative day the mortality should not exceed 2%.[100,101] Carotid endarterectomy is also the therapy of choice in patients with symptomatic carotid stenosis between 50% to 69%, (although the benefit is approximately half that observed in patients with stenosis > 70%) if it is performed in a medical centre where the procedure has a documented perioperative morbidity and mortality of 2% or less.[102,103] If the stenosis is less than 50%, aspirin is the preferred treatment.[96,97,104]

Therapy with aspirin and advising the patient to report if signs of TIAs appear, has also been recommended for asymptomatic carotid artery stenosis, as the risk of a disabling stroke unheralded by a TIA is probably less than 2% (i.e. a rate which is below serious

morbidity from a carotid endarterectomy).[96,97,104-107] Some recommend carotid endarterectomy before coronary artery surgery in asymptomatic patients with carotid bruits who have 85% or greater carotid artery stenosis,[106] although, depending on the circumstances, either aspirin or carotid endarterectomy may be considered.[4,108,109] Endarterectomy is of no value in patients with carotid artery stenosis who have had a severe stroke.

Complications associated with carotid endarterectomy warrant monitoring in an intensive care unit for the first 24 hr as they include cerebrovascular instability (e.g. hypertension, hypotension, bradycardia), stroke, due to perioperative carotid artery thrombosis which usually occurs within 24 hr of the operation (although it can occur more than 5 days later, a transcranial doppler monitoring of cerebral blood flow during the perioperative period is useful in detecting early carotid artery thrombosis)[110], haemorrhage into the neck wound (with retropharyngeal extention and upper airway obstruction), and cerebral hyperperfusion syndrome (headaches, seizures, coma which may occur even up to 8 days after surgery due to cerebral oedema and haemorrhage of the reperfused area).[111,112] The risk of stroke, myocardial infarction and death within 30 days and 3 months of endarterectomy is reduced when aspirin (80 - 325 mg daily) is administered post-operatively (but not with 650 - 1300 mg of aspirin).[113]

If there is haemorrhagic transformation of the infarct, surgical decompression is seldom beneficial, unless the haematoma is near the surface, the patient is conscious and there are CT signs of intracerebral shift (i.e. greater than 5 mm). With acute cerebellar haematoma conservative management is usually chosen if the patient has a Glasgow coma score of 13 to 14 and the haematoma is < 4 cm. However, if the patient deteriorates (particularly within the first 1-2 days) surgical evacuation of the clot and ventricular drainage if there is acute hydrocephalus, is the treatment of choice.[114]

Carotid artery stenting. Carotid artery stenting is an alternative to carotid endarterectomy particularly in high risk patients (e.g. contralateral carotid artery occlusion, prior carotid endarterectomy, combined coronary and carotid artery procedures). Advanced age and multiple stenosis are independent predictors of stroke following the procedure.[115]

Neuroprotective agents

Inhibition of excitotoxic necrosis. Cerebral ischaemia causes the release of excessive amounts of glutamate into the extracellular space causing glutamate receptor overstimulation with consequent influx of sodium and calcium ions through the channels gated by these receptors. While there are two general classes of glutamate receptors (e.g. those that form ion channels or 'ionotropic' and those that are linked to G-proteins or 'metabotropic'), the 'ionotropic' glutamate receptors are important in ischaemic (and epileptic) neuronal diseases.[116] The 'ionotropic' receptors have been divided into three types based on their selective antagonists; N-methyl-D-aspartate (NMDA) receptors, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors and kainate receptors.[116] Under normal conditions glutamate released from presynaptic nerve terminals activates predominantly the AMPA receptors on the postsynaptic neurone. The NMDA receptor complex is a ligand-gated ion channel that increases membrane conductance of sodium and calcium when activated. It requires combined stimulation by glutamine and the coagonist glycine, and additionally, membrane depolarisation must occur to overcome a voltage-dependent block of the ion channel by magnesium.[117]

Excitation of the NMDA receptor promotes influx of calcium into the cell, which stimulates constitutive nitric oxide synthase to produce nitric oxide (NO).[118] The NO diffuses back into the presynaptic neuron, where it enhances the release of more glutamate, causing excessive influx of calcium and cell damage.[119-121] Drugs aimed at reducing or blocking mechanisms responsible for neuronal death during ischaemia by either blocking excitotoxicity directly (e.g. glutamate receptor antagonists) or indirectly (e.g. sodium or calcium channel blockers) have been investigated as possible neuroprotective agents in acute ischaemic stroke. For example:

NMDA receptor antagonists. Experimental blockade at the NMDA receptor-ion channel complex by inhibiting glutamate binding, using 2-amino-5-phosphonovalerate has been shown to prevent ischaemic neuronal damage.[26,122] However, NMDA receptor antagonists have not yet been shown to be of benefit in humans.[123] In a preliminary report of two large randomised, controlled trials in patients with stroke using the selective NMDA receptor antagonist, selfotel, no significant difference in mortality between the placebo and selfotel group had been demonstrated at the time of trial termination.[124] While the NMDA receptor antagonists eliprodil (phase III trial abandoned), aptiganel (phase III trial concluded no efficacy) and lubeluzole (phase III trial concluded no efficacy) have also shown little promise in patients with stroke,[123] encouraging results (i.e. phase III trials ongoing) have been found with magnesium sulphate (16 mmol i.v. over 15 minutes followed by 65 mmol

over 24 hr[125]) and the glycine antagonist GV150526.[123,126,127]

AMPA and kainate receptor antagonists. Several factors in the ischaemic brain may reduce the prominence of NMDA-receptor mediated neurotoxicity (including excess release of zinc which inhibits NMDA receptors[123]), increasing the influence of AMPA and kinate receptor activation to glutamate-induced excitotoxicity. The phase II trial of the AMPA antagonist YM872 is ongoing.[123]

Inhibition of ischaemic apoptosis. Ischaemic neuronal injury is a complex process with mechanisms such as an increase in intracellular calcium and zinc leading to neuronal cell necrosis and a decrease in intracellular calcium and potassium, and increased intracellular zinc being responsible for triggering neuronal apoptosis.[123] The survival of the ischaemic neuron appears to be dependent upon a critical intracellular calcium concentration with the beneficial effect of glutamate receptor inhibitors in reducing exitotoxic neuronal necrosis being counterbalanced by a deleterious enhancement of neuronal apoptosis. Dual inhibition of excitotoxic necrosis using glutamate inhibitors, with an antiapoptotic drug (e.g. cyclohexamine, z-VAD.fmk) may offer greater neuroprotection during ischaemic stroke than either alone.[128,129] Other possible therapeutic approaches include methods to reduce intracellular zinc and increase intracellular potassium concentrations.

Monoganglioside GM-1. Monoganglioside GM-1 has been used to induce neuronal regeneration after injury (200 mg i.v. within 5 hours of the stroke followed by 100 mg 12 hours later and 100 mg daily thereafter for 21 days). However, while it has not reduced mortality, it has been associated with an improved neurological status, particularly in the patients in whom it was initiated within 4 hours of symptoms.[130]

Corticosteroids. In a double-blind, randomised controlled trial, corticosteroids were found to be ineffective in the treatment of ischaemic stroke[131] and should only be used if the stroke has been caused by giant cell arteritis.[132]

Other cerebral 'protection' agents (Table 2) or cerebral oedema therapy. While cerebral 'protection' agents (e.g. nimodipine, flunarizine, vitamin C, vitamin E, superoxide dismutase, 21-aminosteroids, ebselen, trilazad, barbiturates, naloxone, nalmefene, lubeluzole, phenytoin, fosphenytoin, piracetam, clomethiazole, citicoline, Bay x 3072, BMS-204352), hypothermia and hypervolaemic haemodilution and non-specific treatment for cerebral oedema (e.g. glycerol or mannitol), have been used, they have not been shown to benefit ischaemic or haemorrhagic stroke patients.[56,133-140] Some believe that mannitol may even be contraindicated in the management of acute ischaemic stroke as it can activate apoptotic cell death and inflammatory mediators, and may cause rebound cell swelling, all of which may increase ischaemic neuronal injury.[141]

Table 2. Therapeutic agents proposed for acute ischaemic stroke and their mechanisms of action

Improve blood flow
- Antithrombins
  - Heparin (unfractionated, low-molecular weight)
- Antiplatelet
  - Aspirin, abciximab
- Fibrinogen depleting
  - Ancrod
- Thrombolytics
  - t-PA, streptokinase, urokinase, pro-urokinase
- Rheological agents
  - Pentoxifylline, dextrans

Neuroprotective
- Glutamate antagonists
  - AMPA antagonists (YM872, ZK-200775)
  - Kainate antagonist (SYM 2081)
  - NMDA antagonists
    - Competitive antagonists (Selfotel)
    - NMDA channel blockers
      - Cerestat, dextrorphan, dextromethorphan
      - Magnesium sulphate
      - Remacemide, MK-801, NPS 1506
    - Glycine site antagonists (ACEA 1021)
    - Polyamine site antagonists (Eliprodil)
- Calcium channel blockers
  - Nimodipine, flunarizine
- Free radical scavangers
  - Ebselen, tirilazad
- GABA agonists
  - Clomethiazole
- Fibroblast growth factor
- Leucocyte adhesion inhibitors
  - Anti-ICAM antibody (enlimomab)
  - Hu23F2G
- Nitric oxide inhibitor (Lubeluzole)
- Opoid antagonists (naloxone, nalmefene)
- Phosphatidylcholine precursor (citicoline)
- Serotonin agonist (Bay x 3072)
- Sodium channel blockers (fosphenytoin, lubeluzole)
- Potassium channel opener (BMS-204352)
- Mechanism unknown (Piracetam, simvastatin, oestrogens)

PROGNOSIS

Where the stroke has produced a permanent deficit, and the patient survives, motor paralysis will slowly improve up to 6 months, whereas aphasia, dysarthria, cerebellar ataxia and walking may improve up to 12 months or more. In general, 30% of patients with strokes die within 1 month and 43% are dead within 6 months. The prognosis is worse for haemorrhagic than for ischaemic strokes, as 50% of patients with haemorrhagic stroke are dead within 1 month and 68% are dead within 6 months.[142] The prognosis at one year for the four clinical stroke syndromes is listed in table 3.

Table 3. Prognosis at one year for the four clinical stroke syndromes

	TACI	PACI	LACI	POCI
Dead	60%	15%	10%	20%
Dependent	35%	30%	30%	20%
Independent	5%	55%	60%	60%

TACI = total anterior circulation infarct, PACI = partial anterior circulation infarct, LACI = lacunar infarct, POCI = posterior circulation infarct

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