Established treatments for acute ischaemic stroke

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This article reviews the recommended management of patients presenting to accident and emergency departments with acute ischaemic stroke, and focuses on thrombolysis. The review includes initial management, recommended clinical, laboratory, and radiographic examinations. Appropriate general medical care, consisting of monitoring of oxygenation, fever, blood pressure, and blood glucose concentrations are examined. Criteria for thrombolysis with intravenous recombinant tissue plasminogen activator (rt-PA) are discussed. Complications of rt-PA therapy, such as haemorrhagic transformation and angio-oedema, are reviewed. An approach to management of rt-PA complications is outlined. Only a small percentage of acute ischaemic stroke patients meet criteria for rt-PA; therefore, alternative acute treatment strategies are also discussed. Acute medical and neurological complications in stroke patients are analysed, along with recommendations for treatment.

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Acute ischaemic stroke has undergone a revolution since the approval of recombinant tissue plasminogen activator (rt-PA) for treatment of patients within 3 h.[1] What was once a disease with few therapeutic options now requires the fluid collaboration of paramedics, emergency physicians, and neurologists. This paper will review the recommended treatment of patients with acute ischaemic stroke, as discussed in the most recent management guidelines.[2–4] New developments since the last scientific statements will also be discussed.

Prehospital care

The care of the acute ischaemic stroke patient begins with the ambulance system. Ambulance staff should be trained to recognise the common signs and symptoms of stroke. Appropriate education improves paramedic diagnostic accuracy to as high as 80%, as well as improving dispatch-to-hospital times.[5] Stroke is a medical emergency and should be treated with the same sense of urgency as an acute myocardial infarction or trauma.

Diagnosis

The first aim is to confirm that a patient's deficits are due to an ischaemic stroke rather than a different neurological process (seizure, migraine, encephalopathy, etc) or other medical disorder, such as an abnormal serum glucose concentration. Patients with stroke usually present with a sudden onset of symptoms, but occasionally a gradual progression of neurological deficits is elicited in the history. Most patients with ischaemic stroke are alert and this can be used to distinguish ischaemic stroke from metabolic disorders and intracerebral haemorrhage. Patients with aphasia will often be awake but have mute or broken speech, whereas patients with encephalopathy will be drowsy or stuporous. Headaches are uncommon in patients with ischaemic stroke, occurring in about 25% of cases.[3] Panel 1 lists common patterns of neurological impairment in patients with ischaemic stroke and the usual localisation.

The accuracy of a clinical examination by an emergency physician is good, with a sensitivity of about 85% and a specificity of 99%.[6,7] Common mimics of ischaemic stroke include seizure, complicated migraine, syncope, and toxic or metabolic disorders (panel 2).

All patients arriving in an accident and emergency department with a possible ischaemic stroke should have a full blood count, serum electrolytes, renal function tests, cardiac enzymes, and coagulation studies drawn and sent for immediate analysis. Time is crucial. The only required laboratory studies before giving rt-PA are serum glucose and platelet count, an international normalised ratio is also needed in patients with a history of warfarin use or suspected coagulopathy.[3,8] An electrocardiogram (ECG), should also be obtained, because cardiac abnormalities, such as arrhythmias and myocardial infarction are common in patients with stroke.[9–16] Chest radiographs

Panel 1: Common patterns of neurological impairment in acute ischaemic stroke

Left hemisphere (dominant)
Aphasia
Right-sided weakness or numbness
Right homonymous hemianopsia
Left gaze preference

Right hemisphere (non-dominant)
Neglect or extinction
Left-sided weakness or numbness
Left homonymous hemianopsia
Right gaze preference

Brainstem or cerebellum
Impaired consciousness
Ataxia or incoordination
Vertigo or dizziness
Double vision
Nystagmus
Dysphagia
Slurred speech

Search strategy and selction criteria

The authors reviewed the published guidelines from the European Stroke Initiative and the Stroke Council of the American Heart Association. We then searched for published clinical trials since the most recent guidelines were available.

rarely alter the acute management.[17,18] Selected patients should receive a urine toxicology screen, blood alcohol concentrations, pregnancy tests, chest radiography, and liver function tests.[3] Recommended laboratory and diagnostic tests are listed in panel 3.

***Panel 2:* Common mimics of stroke**

Neurological
Seizure/postictal state
Complicated/hemiplegic migraine
Subdural haematoma
Abscess
Tumour or malignancy
Hypertensive encephalopathy
Multiple sclerosis or other demyelinating process
Vertigo
Cranial and peripheral neuropathies
Spinal cord or disc disease
Transient global amnesia
Bell's palsy
Encephalitis

Metabolic
Hypoglycaemia
Hyperglycaemia
Hyponatraemia
Hepatic encephalopathy
Drug overdose

Psychiatric
Conversion disorder
Malingering

Other
Syncope

***Panel 3:* Recommended emergency diagnostic tests in acute ischaemic stroke**

All patients
Serum glucose
Full blood count
Serum electrolytes and renal function tests
Coagulations studies (prothrombin time, international normalised ratio, activated partial thromboplastin time)
Electrocardiogram
Cardiac enzymes
Non-contrast CT of head

Selected patients
Pregnancy test
Liver-function tests
Blood alcohol concentration
Urine or serum toxicology screen
Arterial blood gas
Chest radiograph
Lumbar puncture

The neurological examination is a powerful predictor of prognosis. The most widely used stroke scale in the USA is the US National Institutes of Health Stroke Scale (NIHSS),[19,20] which is described in panel 4. Ischaemic stroke patients with an NIHSS score of less than 10 have a 60–70% chance of a favourable outcome at 1 year compared with only a 4–16% chance if the score is more than 20.[21,22]

Neuroimaging

Some type of brain imaging is necessary to distinguish ischaemic from haemorrhagic stroke.[23] However, certain findings indicate an increased likelihood of intracerebral haemorrhage, such as coma, vomiting, severe headache, active warfarin therapy, and a systolic blood pressure of more than 220 mm Hg.[7,24,25] Emergency, non-contrast CT of the head is the recommended initial neuroimaging study.[3] This study identifies haemorrhage and can help distinguish non-vascular causes of neurological symptoms such as tumour.[26] CT is not ideal, however, because of the difficulty in detecting acute or small infarcts and artifact in the brainstem area.[3]

CT can identify subtle signs of early ischaemia or arterial occlusion. Loss of grey-white differentiation, especially in the insular ribbon or lentiform nucleus, and hemispheric sulcal effacement can be detected within 6 h of ischaemia. A hyperdense middle cerebral artery sign is indicative of embolus or thrombus in the vessel.[27,28] The presence of previously mentioned signs correlates with poor outcomes.[29,30] A clearly visible hypodensity on CT is rarely seen within 3 h of onset of stroke and the presence of such a finding should prompt a reappraisal of the time of onset.[31]

In some centres, multiparametric MRI is increasingly used as first-line imaging for patients with suspected ischaemic stroke. MRI is better for detection of acute ischaemia than CT.[32] Diffusion-weighted imaging sequences should be done in all acute MRI studies to allow identification of ischaemic areas within minutes of symptom onset.[33,34] The sensitivity and specificity of diffusion-weighted imaging for detecting acute ischaemia are about 100%. Diffusion-weighted imaging also provides the additional advantage of visualisation of small subcortical lesions and brainstem or cerebellar lesions, usually poorly visualised on CT.[35–42] Initial lesion volumes on diffusion-weighted imaging correlate with final infarct volumes on follow-up imaging.[37,43,44] Perfusion weighted imaging with an intravenous paramagnetic contrast agent, can measure areas of delayed perfusion. The ischaemic penumbra is the area of normal diffusion but delayed perfusion on MRI (diffusion–perfusion mismatch). However, because some areas of diffusion abnormality are actually reversible and some areas of perfusion deficit are benign oligaemia, diffusion–perfusion mismatch might actually overestimate the ischaemic penumbra.[45–48] Nevertheless, the development of MRI criteria to determine irreversible infarction and the

Panel 4: **US National Institutes of Health Stroke Scale**

1A Level of consciousness
0=alert
1=arousable with minor stimulation
2=requires repeated stimulation or is obtunded
3=coma or unresponsive

1B Orientation questions (ask two)
0=answers both questions correctly
1=answers one question correctly
2=answers neither question correctly

1C Commands (give two)
0=follows both commands
1=follows one command
2=follows neither command

2 Gaze
0=normal horizontal movements
1=partial horizontal gaze palsy
2=complete gaze palsy or forced deviation

3 Visual fields
0=no visual field deficit
1=partial hemianopsia
2=complete hemianopsia
3=bilateral hemianopsia or blind

4 Facial movement
0=normal
1=minor facial weakness
2=near total paralysis of lower face
3=complete unilateral palsy

5 Motor function (arm)*
0=no drift, hold for full 10 s
1=drift, but does not hit bed
2=falls to bed before 10 s
3=no effort against gravity
4=no movement

6 Motor function (leg)*
0=no drift, hold for 5 s
1=drift, but does not hit bed
2=drift to bed before 5 s
3=no effort against gravity
4=no movement

7 Limb ataxia
0=no ataxia
1=ataxia in one limb
2=ataxia in two or more limbs

8 Sensory
0=no sensory loss
1=mild sensory loss
2=severe or total sensory loss

9 Language
0=normal
1=mild aphasia, mild loss of fluency
2=severe aphasia, fragmented speech
3=mute or global aphasia

10 Dysarthria
0=normal
1=mild dysarthria, can be understood
2=severe dysarthria, unintelligible or mute

11 Extinction or inattention
0=absent
1=mild, extinction
2=severe neglect or inattention to one side

*a left; b right.

ischaemic penumbra is a promising and exciting area of acute-stroke imaging. Magnetic resonance arteriography is a non-invasive method of defining the cerebral vasculature and can establish the presence of large vessel occlusion in ischaemic stroke.[49] Additionally, gradient-recalled echo sequences can reliably detect acute haemorrhage.[50,51] MRI remains less available and slower than CT. Furthermore, many patients are unable to undergo an MRI scan owing to contraindications, such as a pacemaker.[52]

Newer CT methods, such as CT angiography, CT perfusion, and CT cerebral-blood volume imaging can obtain similar information to MRI. Although of emerging importance, the use of advanced imaging methods beyond routine CT should not delay treatment of a patient who is otherwise eligible for thrombolytic therapy.[2]

General medical care

Adequate oxygenation is crucial in acute cerebral ischaemia. Patients with reduced consciousness or with brainstem involvement are at increased risk of airway compromise due to impaired oropharyngeal mobility and reflexes.[53] Patients with stroke requiring endotracheal intubation have a mortality rate of 50% at 30 days. Elective intubation might be necessary in cases of brain oedema and potential airway compromise.[54,55] The target blood oxygen saturation for patients with stroke should be more than 95%. In the absence of hypoxia, the use of supplemental oxygen is of unproven benefit.[56,57]

Fever is associated with unfavourable neurological outcome and increased morbidity and mortality.[58–61] Conversely, hypothermia is associated with reduced inpatient mortality.[62] A 1°C reduction in body temperature

almost doubles the chance of a good functional outcome.[63] Patients presenting with a fever should be aggressively assessed for a source of infection and receive appropriate treatment.

Potential cardiac complications in acute ischaemic stroke are numerous. The most common arrhythmia is atrial fibrillation.[64] Other ECG changes include ST segment depression, QT prolongation, inverted T waves, and prominent U waves.[65–67] Myocardial infarction is another potential complication, thought to be related to catecholamine release.[68,69]

Appropriate management of serum glucose concentration is essential in patients with acute ischaemic stroke. Hypoglycaemia is a common stroke mimic and prompt correction will occasionally lead to complete resolution or improvement of symptoms. Hyperglycaemia is associated with unfavourable outcomes.[70–72]

Hypotension is rare in patients with acute stroke. The possible differential diagnosis includes acute myocardial infarction, aortic dissection, and gastrointestinal bleeding. An appropriate assessment should be instituted if hypotension is present. Drug-induced hypertension and haemodilution with vasopressors, colloid solutions, and intravenous fluids do not seem to be useful in improving outcomes after ischaemic stroke.[73–81]

Blood pressure (mm Hg)	Treatment
Patients ineligible for thrombolysis	
SBP≤220 or DBP≤120	Observation
SBP>220 or DBP 121–140	Captopril (orally or intramuscularly) Labetalol (intravenously) Urapidil bolus and infusion Clonidine (intravenously or subcutaneously) Nicardipine infusion
DBP>140	Nitroprusside infusion
Patients eligible for thrombolysis (pretreatment)	
SBP>185 or DBP>110	Captopril (orally or intramuscularly) Labetalol (intravenously) Urapidil bolus and infusion Clonidine (intravenously or subcutaneously) Nicardipine infusion
DBP>140	Nitroprusside infusion

SBP=Systolic blood pressure. DBP=Diastolic blood pressure.

Table: **Approach to hypertension in acute ischaemic stroke**

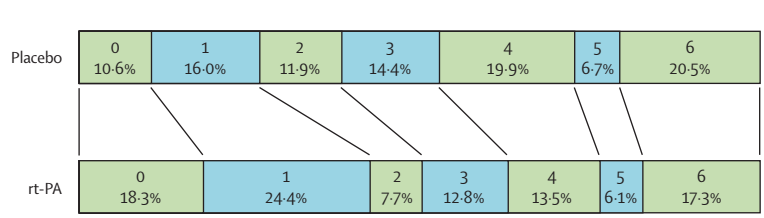

Figure 1: **Modified Rankin Scale at 3 months in NINDS rt-PA trial**
Data from reference 1. Modified Rankin Scale scores range from 0 (indicating no symptoms) to 6 (indicating death).

Hypertension in acute stroke is quite common and thought to result from stroke itself, stress, pain, pre-existing hypertension, and a physiological response to hypoxia. Blood-pressure lowering might reduce brain oedema and the risk of haemorrhagic transformation. These benefits need to be balanced against the potential reduction of perfusion to the penumbra, leading to increased ischaemia.[82] Blood pressure will fall without drug treatment in many patients.[48,83] Optimum management of hypertension in acute ischaemic stroke remains controversial. In patients not eligible for thrombolytics, antihypertensive agents are not recommended unless diastolic blood pressure is higher than 120 mm Hg or systolic blood pressure is higher than 220 mm Hg. If treatment is needed, intravenous agents that can be easily titrated, such as labetalol or nicardipine, are recommended.[3]

With thrombolytic treatment, excessive hypertension is associated with haemorrhagic transformation.[84–86] Blood pressure management is crucial.[87] Therefore, treatment is recommended if diastolic blood pressure is higher than 110 mm Hg or systolic blood pressure is higher than 185 mm Hg in the first 24 h after thrombolytic therapy.[3] The table shows an approach to blood-pressure management.

Thrombolytics

The most important therapy in acute ischaemic stroke is restoration of blood flow to the ischaemic area and penumbra. When considering thrombolytic therapy, the time of onset of symptoms is of paramount importance. Up to 25% of patients with acute ischaemic stroke arrive at an accident and emergency department within 3 h of symptom onset.[88,89] Patients who are awake and non-aphasic will often be able to provide a practical timeframe for symptom onset. A substantial problem arises in aphasic or comatose patients. In such patients, time of onset is judged to be the time the patient was last seen not showing symptoms. Therefore, if a patient wakes up with symptoms, then time of onset is the time they went to bed. If a patient has initially mild symptoms but the deficits progress, the time of initial mild symptom onset is used. However, if the patient had a clinical transient ischaemic attack with complete resolution of symptoms then a subsequent return of symptoms, the second onset of symptoms is used.

rt-PA was approved for use in acute ischaemic stroke in 1996, largely on the basis of the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA study.[1] In this pivotal study, 624 patients presenting within 3 h of symptom onset were randomly assigned treatment with 0·9 mg/kg of intravenous rt-PA or placebo. Neurological improvement did not differ between the two groups after 24 h, but outcomes were significantly better in the treated group at 3 months (figure 1). Symptomatic intracerebral haemorrhage occurred in 6·4% of patients treated with rt-PA compared with 0·6%

of those given placebo.[1] Across the entire spectrum of outcomes, the number needed to treat to cause significant improvement in one patient is estimated to be three, and number needed to treat to cause harm is 30.[90] rt-PA is effective regardless of the stroke subtype.[1] Benefits of treatment with rt-PA are sustained at 1 year and result in significant savings in post-stroke care.[22,91]

In the first European Cooperative Acute Stroke Study patients were given 1·1 mg/kg of rt-PA or placebo within 6 h of symptom onset. Placebo and control groups did not differ at 90 days.[30] A post-hoc analysis showed that patients treated within 3 h benefited from rt-PA.[92] In the second European Cooperative Acute Stroke Study, patients were given 0·9 mg/kg of rt-PA or placebo within 6 h of onset. Again, the two groups did not differ significantly.[93] Two other trials from the USA tested rt-PA beyond 3 h and showed no benefit.[94,95]

Pivotal trials for acute thrombolysis generally excluded patients older than 80 years, with the exception of the NINDS trial. Elderly people have poorer outcomes, but this seems to be due to other comorbid conditions rather than age alone.[96,97] Thrombolysis in elderly people has been examined outside the clinical trial setting and seems to be safe, without an increased risk of haemorrhagic transformation.[98,99]

The use of rt-PA in patients with mild or minor neurological deficits has traditionally been discouraged. However, the prognosis for patients with mild neurological deficits is not necessarily favourable.[100] Treatment of these patients with rt-PA can result in more favourable outcomes.[101] Additionally, rt-PA might be safe in patients with improving symptoms.[102] Similarly, patients with severe neurological deficits benefit from rt-PA, despite the increased risk of haemorrhage.[1]

Based on the evidence discussed here, rt-PA (0·9 mg/kg, max 90 mg, 10% bolus, remaining infused for more than 1 h) should be given to patients with acute ischaemic stroke who meet criteria within 3 h. Panel 5 lists published inclusion and exclusion criteria for thrombolysis with rt-PA. Even in the presence of some contraindications, certain patients can still be treated with rt-PA, but only by experienced stroke physicians. Examples might include minor gastrointestinal bleeding or a platelet count of 90 000 mm^3. The most common exclusions for rt-PA are time since onset longer than 3 h, mild symptoms, and clinical improvement.[88] rt-PA is effective in acute ischaemic stroke outside of clinical trials.[103] Treatment of acute ischaemic stroke with thrombolytics should be done only in conjunction with a physician experienced in acute stroke care and CT interpretation.

Patients receiving rt-PA should have their vital signs monitored every 15 min for 2 h, then every 30 min for 6 h, and then every h for 16 h. Arterial punctures should be avoided for 24 h. Antiplatelet agents and anticoagulants should be withheld for 24 h after the bolus is given.[1]

A combined analysis of six randomised controlled trials[104] of intravenous rt-PA showed that the sooner patients received thrombolytic therapy, the greater the benefit. The best outcomes occurred in patients treated with rt-PA within 2 h of symptom onset. The benefit of rt-PA seems to disappear at 4·5 h. The use of rt-PA in the 3–4·5 h window should only be used as part of an institutional protocol or clinical trial.[4] Some investigators have estimated that 2 million neurons are lost every minute that stroke treatment is delayed.[105] This emphasises the need for early recognition, triage, and treatment of stroke.

Although the findings of the meta-analysis suggested that treatment with rt-PA beyond 3 h is beneficial, the use of thrombolytics remains problematic. Two major trials of rt-PA beyond 3 h have shown no significant benefit.[94,95] However, MRI might be a useful device to select patients who would benefit from thrombolysis beyond 3 h.[106] Patients with a diffusion-perfusion mismatch 3–6 h after symptom onset might benefit from rt-PA treatment.[107] The use of CT-based perfusion imaging might also help select patients for thrombolysis beyond 3 h.

Intra-arterial thrombolysis at the site of occlusion through a microcatheter is experimental. A single randomised trial has shown a benefit in patients treated within 8 h.[3,108,109] Haemorrhage remains a substantial concern with intra-arterial thrombolysis. Additionally, mechanical clot disruption or removal with endovascular catheters is emerging as an alternative or adjunct therapy to systemic intravenous thrombolysis. Good neurological outcomes are more frequent at 90 days in patients recanalised with an embolus retrieval device ($p<0·0001$).[110,111] The concept of combining the quickness and availability of intravenous thrombolysis with the recanalisation of intra-arterial thrombolysis is also promising. Patients given a slightly lower dose of intravenous rt-PA (0·6 mg/kg) followed by additional

***Panel 5:* Criteria for thrombolysis with rt-PA**

Inclusion criteria

Ischaemic stroke with clearly defined time of onset
Measurable neurological deficit
Neuroimaging excluding haemorrhage

Exclusion criteria

Stroke or serious head trauma within 3 months
Major surgery within 14 days
History of intracranial haemorrhage
Systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg
Symptoms suggestive of subarachnoid haemorrhage
Gastrointestinal bleed or haematuria within 21 days
Arterial puncture at non-compressible site within 7 days
Seizure at stroke onset
Raised partial thromboplastin time
Prothrombin time >15 s
International normalised ratio >1·4
Platelet count < 100×10^9/mm^3
Serum glucose concentration <2·8 mmol/L or >22·2 mmol/L

rt-PA via a microcatheter might have better outcomes than patients treated with intravenous rt-PA alone.[112–116] Acute intra-arterial thrombolysis requires a complex and costly infrastructure. These endovascular therapies should only be attempted by experienced interventionalists in coordination with a stroke neurologist.

Anticoagulants and antiplatelet agents

Several studies have shown no benefit of anticoagulation in acute ischaemic stroke.[117–121] Long intervals from onset to treatment could be responsible for the absence of effect. However, anticoagulation, even within 3 h, is of unproven benefit.[122,123] Therefore, anticoagulants, such as heparin have no role in the routine management of acute ischaemic stroke. Despite absence of evidence, heparin and heparinoids are still frequently used.[124] According to the American Heart Association and the American Academy of Neurology, the use of anticoagulants should be restricted to special cases, such as cerebral venous sinus thrombosis and possibly arterial dissection.[125–131]

Acute aspirin has been tested in two large trials. The International Stroke Trial compared aspirin alone (300 mg per day) with two different doses of heparin within 48 h of symptom onset. Aspirin was associated with significantly fewer recurrent ischaemic strokes and no significant increase in haemorrhagic strokes at 14 days. The rate of death or dependency did not differ between the two groups at 6 months.[132] The Chinese Acute Stroke Trial[133] also compared aspirin (160 mg per day) with placebo within 48 h of symptom onset. Significantly fewer recurrent ischaemic strokes occurred in the aspirin group, but the number of haemorrhagic strokes increased. Aspirin given within 48 h of acute ischaemic stroke seems to reduce death and disability.[3] However, the use of aspirin in conjunction with thrombolytics might increase the risk of bleeding.[98,134,135] Acute aspirin is recommended for patients with acute ischaemic stroke who are ineligible for thrombolysis.

Acute clopidogrel loading (300 mg) followed by maintenance (75 mg per day) has proved safe and effective in acute coronary syndromes, but has not been adequately tested in acute ischaemic stroke.[136] Trials assessing abciximab, a glycoprotein IIb/IIIa receptor inhibitor, within 6 h of symptom onset were initially promising.[137,138] Nonetheless, a large phase-III trial was stopped early because of safety concerns.[139] Thus, neither clopidogrel loading or glycoprotein IIb/IIIa receptor inhibitors can be recommended for acute ischaemic stroke outside a clinical-trial setting.

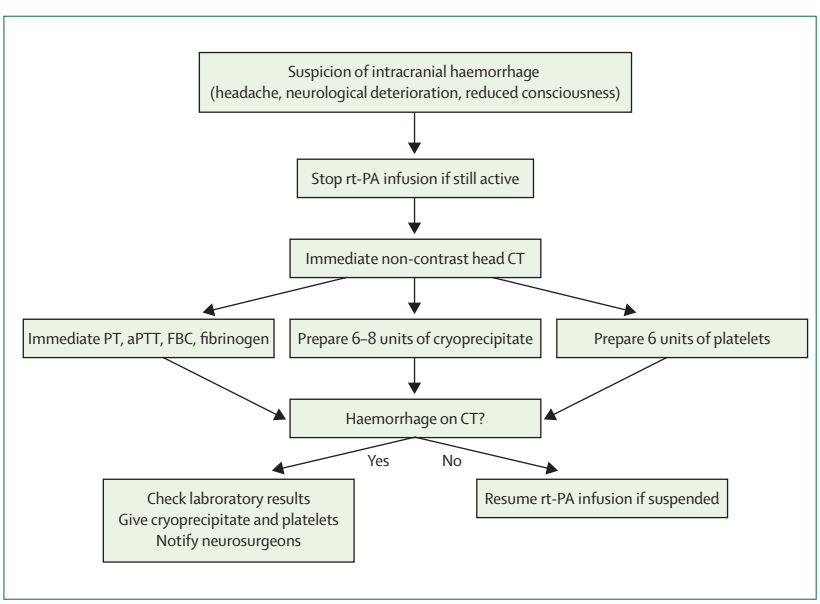

Figure 2: **Management of intracranial haemorrhage after treatment with rt-PA**
PT=prothrombin time. aPTT=activated partial thromboplastin time. FBC=full blood count.

Complications of thrombolysis

The foremost concern with respect to treatment with thrombolytic agents is haemorrhagic transformation. The NIHSS can be used to predict risk of haemorrhagic transformation after thrombolytic therapy. Patients with a score of 20 or more have a 17% risk compared with a 3% risk in those with a score less than 10.[84] Early signs of ischaemia on CT might also be predictive of haemorrhagic transformation after thrombolytic therapy. Patients with early CT changes in more than a third of the middle cerebral artery territory are more likely to have intracerebral haemorrhage if treated within 6 h of symptom onset.[30,86] However, early ischaemic changes on baseline CT scans do not exclude patients from thrombolytic therapy within 3 h.[85,140] As mentioned previously, high blood pressure is also associated with increased risk of haemorrhagic transformation.

Haemorrhagic transformation should be suspected if the patient has increased somnolence, headache, or neurological deterioration. If the rt-PA infusion is still running, it should be discontinued. A non-contrast head CT scan should be obtained to assess the presence of haemorrhage. Urgently needed blood tests include prothrombin time, activated partial thromboplasmin-ogen time, full blood count (for platelet count), and fibrinogen. If the head CT scan shows any evidence of haemorrhage, the rt-PA can be reversed with 6–8 units of cryoprecipitate and platelets. Use of fresh frozen plasma should also be considered. The rt-PA intracranial haemorrhage algorithm is shown in figure 2. This approach is empiric and has not been proven to affect clinical outcomes.

The other potentially important complication of treatment with rt-PA is orolingual angio-oedema, which affects about 5% of patients.[141] Although typically mild and transient, orolingual angio-oedema can rarely lead to life-threatening airway compromise and seems to be associated with use of angiotensin-converting-enzyme inhibitors.[142] The optimum treatment of orolingual angio-oedema has not been established, but immediate antihistamines and steroids are probably beneficial.

Acute medical complications

Patients with ischaemic stroke should be admitted to hospital for several reasons, including monitoring for complications, prevention of subacute complications, planning of secondary stroke prevention, and rehabilitation.[3] Patients admitted to an institution with a specialised stroke unit have lower rates of morbidity and mortality, both acutely and long term than those admitted to non-specialised wards.[143–151] A framework for stroke centre development and certification is in place.[152,153] Experienced physicians, nurses, and rehabilitation staff are crucial for the proper functioning of a stroke unit.

Early mobilisation in hospital helps reduce the risk of complications, such as pneumonia, deep-vein thrombosis, pulmonary embolism, and pressure sores.[154] Anticoagulants, such as subcutaneous heparin, low-molecular-weight heparins and heparinoids are useful to prevent deep-vein thrombosis and pulmonary embolism.[155–165] Systematic compression devices are also effective, whereas support stockings are of unproven benefit.[166,167]

Many stroke patients will have impaired swallowing and might require short-term or long-term tube feeding and intravenous fluids to maintain adequate nutrition and hydration.[168–170] Risk factors for dysphagia include an abnormal gag reflex, impaired cough, cranial-nerve palsies, dysphonia, and a high NIHSS score.[170–172] A bedside swallow test is a useful screening test. The test requires the patient to drink about 60 mL of water; observations for signs of aspiration, such as cough, dysphagia, and changes in voice should be made.[171–173] If swallowing is impaired, early initiation of enteral feeding via a nasogastric tube reduces mortality.[174] Early percutaneous endoscopic gastrostomy tube placement might be associated with poorer outcomes and should be avoided.[174]

Stroke patients are at an increased risk of developing infections during hospital stay. Pneumonia is an important cause of death after stroke.[175] Urinary-tract infections are common because of the need for a bladder catheter in many patients. Urosepsis can develop in about 5% of patients.[176] Despite the increased risk of infection, empiric antibiotics are not recommended.[177]

Acute neurological complications

Many patients with ischaemic stroke will worsen after admission, usually in the first 24–48 h. No reliable predictor of neurological deterioration has been identified.[178–181] Patients will sometimes develop haemorrhagic transformation, even without thrombolytic therapy. Petechial haemorrhage is often asymptomatic, whereas haematomas often cause neurological decline by increasing intracranial pressure and oedema. The risk of haemorrhagic transformation is increased with thrombolytic drugs, anticoagulants, and even early aspirin use.[1,84,86,182–184] No guidelines exist for the treatment of haemorrhagic transformation.

The incidence of seizures after ischaemic stroke varies widely in reported studies.[185–190] Seizures usually occur in the first 24 h and are partial with or without secondary generalisation. Recurrent seizures can also develop. The most serious complication related to seizures is status epilepticus, which can be life threatening.[191] Anticonvulsants are recommended if a patient has suspected or witnessed seizures. Prophylactic anticonvulsant therapy is not recommended.[192]

Brain oedema peaks at 3–5 days after hemispheric strokes. Patients with brainstem or cerebellar strokes might develop substantial oedema in the first couple of days. Few patients develop enough oedema to warrant medical intervention.[193] Patients requiring intervention usually have large multilobar infarctions.[194–197] Cerebellar infarctions with oedema can obstruct flow of cerebrospinal fluid, leading to acute hydrocephalus and increased intracranial pressure.[192]

In a patient who develops reduced consciousness secondary to cerebral oedema, multiple measures need to be undertaken. The head of the bed should be raised to about 20–30 degrees to promote venous drainage.[3] Antihypertensive agents, especially those causing cerebral vasodilation should be avoided.[198–200] However, the risk of haemorrhagic transformation with raised blood pressure also requires consideration. Hypo-osmolar fluids and hyperglycaemia can also worsen oedema.[198] Hyperventilation is a temporary, but effective measure. A reduction of pCO_2 by 5–10 mm Hg reduces intracranial pressure by 25–30%, but the effect only lasts a few h. Hyperventilation causes cerebral vasoconstriction, which might cause further infarction.[54,201,202] Intracranial pressure monitoring in ischaemic stroke can help determine prognosis, but does not influence outcome.[203] Corticosteroids have been tested in clinical trials, but no improvement in outcomes has been associated with their use.[204–206] Intravenous mannitol also reduces intracranial pressure. The dose is 0·25–0·50 g/kg every 6 h, max 2 g/kg per day; serum osmolality should rise by 10–15%.[207,208]

Hemicraniectomy controls intracranial pressure and prevents herniation.[209–217] Mannitol, furosemide, and hyperventilation are predominantly temporary measures until definitive neurosurgical decompression can be done. Hemicraniectomy might improve outcomes, especially in young patients, although benefit is unproven.[218] Suboccipital decompressive craniectomy for large cerebellar infarcts probably decrease mortality and lead to better outcomes.[219–221] Further study into quality of life of survivors is needed before such aggressive approaches can be routinely recommended.

Conclusion

Acute ischaemic stroke is a medical emergency that requires timely and appropriate therapy. Patients with suspected acute ischaemic stroke should be urgently assessed for thrombolysis. Prudent use of intravenous rt-PA according to established guidelines is effective in

improving long-term outcomes and reducing disability in patients presenting within 3 h of symptom onset. Intra-arterial thrombolysis is promising up to 6–8 h after onset, especially when patients are selected by newer imaging criteria, but has not been proven to give better outcomes and should not be substituted for intravenous rt-PA in patients who are eligible. In patients who are ineligible for rt-PA, aspirin reduces short-term recurrent stroke risk. Anticoagulants have no role in routine acute ischaemic stroke care. The importance of excellent general medical care cannot be undervalued; special attention should be paid to blood pressure and blood glucose management. Stroke patients should be admitted to hospital for the prevention of complications, appropriate assessment, risk factor modification, and rehabilitation.

Contributors

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Conflict of interest statement

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