CURRENT MANAGEMENT OF ACUTE ISCHEMIC STROKE: AN EVIDENCE BASED REVIEW

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ABSTRACT

Cerebrovascular disease is the second most common cause of death and leading cause of acquired disability. The approach to management has in general been nihilistic. Most patients are offered supportive care and despite evidence for the efficacy of excellent therapies that can significantly improve outcomes, very few individuals actually benefit from such advances. This review highlights some of the recent advances in the management of acute ischemic stroke. We also present evidence for optical supportive care that should be offered to all patients who suffer from this devastating disease.


INTRODUCTION

To day, worldwide stroke is the second most common cause of death after coronary heart disease (CHD)¹ and accounts for 4.38 million deaths annually with almost three million of those in developing countries. Most strokes are not fatal² and consequently mortality data underestimate the true global burden of stroke which is chronic disability³. Estimates of the incidence of stroke come from a number of population based epidemiologic studies. One of the largest studies to examine the incidence of vascular disease including stroke is the Oxford Vascular Study (OXVASC) in which >91,000 individuals were followed over a 3-year period in Oxfordshire, United Kingdom (UK). The rate per 1000 population per year of first-ever incident cerebrovascular events was 2.27 (95% CI 2.09–2.45) which was higher than event rates in the coronary and peripheral vascular beds⁴,⁵ (Table I). Event rates rose steeply with age with 80% of strokes occurring in the 14% of the study population aged 65 and older.

The last two decades have witnessed promising therapies for treating acute stroke that will be reviewed here. There remains though an underutilization of acute therapies with well established evidence of efficacy e.g. intravenous treatments such as intravenous (IV) recombinant tissue plasminogen activator (tPA) for acute ischemic stroke (AIS) patients. Only a small number of eligible stroke patients are treated with fibrinolytics. For example in Canada, it is estimated that the proportion of ischemic stroke patients eligible for IV tPA (i.e. presenting within 3 hours from stroke onset) is as high as 35%⁶ while only 1.4% of patients receive IV tPA therapy.⁷ Cost, fear of the risk of complications and a general nihilist attitude accounts for the most common reason for the lack of uptake for utilization of this important stroke therapy.

Nomenclature, definitions

We can divide Stroke broadly into either ischemic or hemorrhagic types with ischemic strokes accounting for the majority of stroke (>.80%).⁷ The treatment of these stroke subtypes is dramatically different and as a result, one of the first steps in managing stroke patients is to evaluate patients for the presence of haemorrhage. Clinical features of hemorrhagic and ischemic stroke overlap and thus hyperacute CT imaging is essential to make the correct diagnosis.

We also further sub-divide ischemic strokes on clinical findings and the results of investigations in subtypes. The value of identifying stroke subtype is that identifying the most likely mechanism of vessel occlusion helps guide early treatment and subsequent investigations. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria is one of the most widely employed classification systems for ischemic stroke.⁸ Ischemic stroke, based on the presumed pathophysiological mechanism of occlusion are subdivided into small vessel occlusion (lacune), large artery atherosclerosis (embolus or thrombosis) and cardioembolic. The TOAST criteria also recognizes that a proportion of ischemic stroke will remain cryptogenic in etiology or will result from some combination of mechanisms or other causes such as dissection or a vasculitis.
There are several aspects to the management of acute ischemic stroke that can be broadly reviewed in the context of prehospital care, emergency management and long term care. This review will focus on issues related to the acute care only.

**PREHOSPITAL CARE**

Neurological damage begins early after an arterial occlusion. Thus the treatment of acute stroke is exquisitely time sensitive and the speed and accuracy of evaluating and managing patients is important of optimizing patient outcomes. The phrase "time is brain" was adapted from the acute coronary care literature ("time is muscle")\(^9\) to emphasize that stroke is a treatable neurological emergency and that brain tissue is rapidly and irretrievably lost as stroke progresses. It has been estimated based on data extrapolated from experimental studies of ischemic stroke that with each minute that passes there is a loss of 1.9 million neurons.\(^10\) Accordingly, timely reperfusion of ischemic brain is the goal of most acute stroke therapies.

With the development of reperfusion therapies for acute stroke, there has been an increased focus on developing prehospital pathways to identify stroke patients in the field, initiate appropriate prehospital therapies,

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### Table I

| Incidence of First and Recurrent Stroke Compared to Ischemic Heart Disease and Peripheral Vascular Disease in Oxford Vascular Study Population,\(^9\) Reproduced from Donnan and Colleagues\(^10\) with Permission |
|---|---|---|
| **Cerebrovascular Events** | | |
| Ischemic stroke | 550 | 2.01 (1.85–2.19) |
| Intracerebral haemorrhage | 41 | 0.15 (0.11–0.20) |
| Subarachnoid haemorrhage | 27 | 0.10 (0.07–0.14) |
| Transient ischemic attack | 300 | 1.10 (0.98–1.23) |
| All Events | 918 | 3.36 (3.14–3.58) |
| **Coronary vascular Events** | | |
| Sudden cardiac death | 163 | 0.60 (0.51–0.7) |
| STEMI | 159 | 0.58 (0.49–0.68) |
| N-STEMI | 316 | 1.16 (1.03–1.29) |
| Unstable angina | 218 | 0.80 (0.70–0.91) |
| All coronary events | 856 | 3.13 (2.93–3.35) |
| **Peripheral vascular Events** | | |
| All events | 188 | 0.69 (0.59–0.79) |

STEMI = ST-segment elevation acute myocardial infarction. N-STEMI = non-ST-segment elevation acute myocardial infarction. *Number of events during 3 years. †Number of events per 1000 population per year.
and ensure transport hospital capable of treating stroke. The narrow time window for the delivery of IV tPA requires well-developed prehospital algorithms to ensure that eligible patients are transported to hospital capable of providing acute stroke care. Presently, only about half of patients with signs and symptoms of acute stroke will use emergency medical services (EMS) to first access medical care.

EMERGENCY MANAGEMENT

As patients with an acute stroke have severe disability, the initial management often occurs in the emergency department (ED) of hospitals. A number of conditions can mimic stroke including seizures, tumours, infection, hypoglycaemia and other metabolic abnormalities. Stroke mimics are common and 13-31% of patients initially diagnosed with acute stroke in the emergency room were on discharge diagnosed with other conditions. In addition to clinical assessment that includes a neurological examination, a limited number of diagnostic studies are recommended including: blood glucose, electrolytes, complete blood count with platelet count, prothrombin time, activated partial thromboplastin time, international normalized ratio, renal function studies and a 12-lead ECG. All patients require early brain imaging to help make decisions about the emergency management. A non-contrast-enhanced computer tomography (NCCT) scan is recommended to exclude nonvascular causes of neurological symptoms and identify brain haemorrhage. NCCT will often show early signs of brain ischemia and identify arterial occlusion; however the sensitivity decreases at earlier time points. The sensitivity of magnetic resonance imaging (MRI) with diffusion weighted susceptibility images (DWI) is greater than NCCT for the detection of acute stroke (83% vs 26%). DWI MRI sequences measures the degree of free diffusion of water molecules. With cerebral ischemia and subsequent cytotoxic edema, water diffusion becomes restricted and will result in abnormal DWI signal that can be seen within minutes of stroke onset. Early infarction signs such as extent of brain parenchymal hypotension and hyperattenuated within the intracranial artery within the affected hemisphere increase the risk of poor functional outcome but do predict response to fibrinolytic therapy. Other than the identification of intracerebral haemorrhage, no finding on NCCT should preclude treatment of AIS patients with tPA within 3 hours of symptom onset.

General Supportive Care

There is general agreement that ventilatory assistance should be provided to patients with decreased level of consciousness or bulbar dysfunction compromising the airway. Supplemental oxygen should be provided to prevent hypoxia but in general most stroke patients do not need or benefit from routine oxygen supplementation. Hyperthermia is very common in the setting of an acute stroke. Fever in the setting of acute stroke has been consistently associated with stroke severity, infarct size and poor neurological outcomes and should be treated with antipyretics such as acetaminophen. A few small trials of have examined whether prophylactic antipyretic use improves clinical outcomes. These studies have shown a small mean decrease in body tem-
Cerebral autoregulation is disrupted by acute ischemia and subsequent tissue acidosis which in turn leads to maximal vasodilatation. As a result with vascular occlusion, overly aggressive treatment of blood pressure could reduce CBF through stenotic and collateral vessels and cause tissue in the ischemic penumbra to progress to infarction. This theoretical presumption is supported by a small randomized trial that measured CBF with single photon emission computed tomography in acute stroke patients randomized to antihypertensive therapy or placebo. In four stroke patients that had decreases in blood pressure of greater than 16% there was an associated reduction in CBF seen. Based on concerns about reducing blood flow to the ischemic penumbra in acute stroke, patients not receiving tPA therapy should be treated with antihypertensive medications only when blood pressure exceeds 220/120 mm Hg. This blood pressure upper limit corresponds to around a MAP of 150 mm Hg, which is the normal upper limit of cerebral autoregulation.

In acute stroke, the need to permit elevated blood pressures in order to maintain CBF ("permissive hypertension") needs to be balanced with the potentially harmful effects of severe hypertension. Acute blood pressure elevation in stroke is thought to increase the risk of ICH and may worsen cerebral edema. The benefits of early BP reduction though have yet to be confirmed in large clinical trials. Only five trials and a total of 218 patients were identified in a recent systematic review of blood pressure alterations in acute stroke and the conclusion was that data was too limited to assess the effect of BP modulation on clinical outcomes.

Treatment with intravenous Thrombolysis

Treatment with tissue plasminogen activator (tPA) is the most significant advance in the management of acute stroke during the last 15 years. Early vessel recanalization and cerebral reperfusion is goal of most acute stroke therapies and as it is the most effective means to salvage penumbral tissue and improve clinical outcomes. A meta-analysis of pooled data from 53 studies of acute stroke therapies that reported recanalization rates, found that good functional outcomes at 3 months were more frequent in recanalized vs non-recanalized patients (odd ratio 0.24, 95% CI 0.16-0.35) with no difference in symptomatic haemorrhage.

Currently the only approved and recommended reperfusion therapy for acute ischemic stroke (AIS) is thrombolysis with intravenous tPA administered within 3 hours of symptom onset. Intravenous tPA was approved for use in AIS by the US Food and Drug Administration in 1996 based partly on the National Institute of Neurologic Disease and Stroke (NINDS) tPA Stroke Study. In the study, 624 patients with ischemic stroke were treated with placebo or tPA (0.9 mg/kg IV, maximum 90 mg; 10% given as a bolus with the remainder given over 1 hour) within 3 hours of symptom, onset and almost half of patients were treated within 90 minutes. The NINDS study...
Intra-Arterial Thrombolysis

Endovascular methods of achieving vessel recanalization in AIS include mechanical and pharmacologic approaches. Intra-arterial (IA) delivery of fibrinolytic agents offers the potential advantage of more rapid removal of thrombus compared to intravenous approaches as agents are infused at high concentration in close proximity to site of occlusions with a microcatheter system. IA therapies, at least in theory, may expand the time window for reperfusion therapy by reducing or eliminating systemic exposure to fibrinolytic agents.

The only randomized trial to assess the efficacy and safety of IA fibrinolytic therapy was the Prolyse in Acute Cerebral Thromboembolism Trial (PROACT-II). In PROACT-II, 180 patients with acute stroke of less than 6 hours and angiographically confirmed occlusion of the MCA were randomized to receive IA recombinant prourokinase (r-proUK) plus heparin or heparin alone. The primary outcome was the proportion of patients with mild or no neurologic disability at 90 days. Based on an intention to treat analysis, 40% of r-proUK treated patients had good outcomes, which was significantly better than the 25% of control patients. Rates of partial or full recanalization were also markedly higher in the r-proUK group than controls (66% versus 18%). Mortality rates were around 25% for both groups. Symptomatic haemorrhage rates were however higher in the r-proUK patients compared to controls (10% vs 2% respectively).

The results of the PROACT II trial were considered insufficient to obtain US Food and Drug Administration approval and a confirmatory phase III trial was never completed. The results of the PROACT II trial have been extrapolated to support the intra-arterial use of tPA and to urokinase (UK) which is similar in structure to the r-proUK prodrug. The only other randomized trial data of IA fibrinolysis comes from the recently published MELT trial. In this study, conducted in Japan prior to the availability of IV tPA, ischemic stroke patients presenting within 6 hours were randomized to IA UK or placebo. The trial was halted prematurely largely over ethical concerns about the randomization once IV tPA was approved for use in Japan.

In addition to pharmacologic approaches to recanalization there has been a number of endovascular approaches to treat intracranial or extracranial occlusions that do not involve the delivery of fibrinolytics (see Molina and Saver for review). Mechanical approaches include emergency angioplasty and stenting, mechanical disruption and extraction of the clot. At present, the only FDA approved devices approved for the revascularization of patients with AIS secondary to large vessel occlusive disease are the Merci Retriever device (Concentric Medical) and the Penumbra System (Penumbra Inc) aspiration catheter. While these devices have been shown to achieve high rates of recanalization when used in AIS, randomized controlled trials showing that these devices improve clinical outcomes have not yet been completed. As a result, at present the use of these mechanical devices while promising are primarily limited to the setting of clinical trials.

The treatment of acute stroke with endovascular therapies suffers a number of important limitations that prevent their widespread adoption. Endovascular procedures requires substantially more infrastructure support, skilled neurointerventionalists are not widely available, treatment is limited to more proximal vessel occlusions, and time to initiate therapy is longer than IV fibrinolysis. From 1999-2001 in the US the number of acute stroke patients receiving IV fibrinolysis was approximately 10 times that of patients treated with IA therapies (0.6% and 0.07%, respectively). Current guidelines recognize the value of IA fibrinolysis as a treatment option for patients with major anterior circulation stroke within 6 hours of symptom onset and up to 24 hours for vertebrobasilar occlusion. IA treatments should not take precedence over the administration of IV tPA to eligible patients.
Anticoagulants

Anticoagulation therapy is used very frequently after an acute ischemic stroke. There is however, no evidence that anticoagulation with either unfractionated or low molecular weight heparin (LMWH) reduces the rate of recurrent stroke, improves neurological outcomes, or can be either along with or in place of IV tPA. The largest study of anticoagulation in AIS was the International Stroke Trial (IST). This trial was a randomized, open-label trial, which compared the safety and efficacy of ASA and subcutaneous heparin (5000 or 12,500 IU) in 19,435 patients. Neither heparin regimen offered any clinical advantage over ASA. The higher dose of heparin was associated with an excess of morbidity and mortality. Post hoc analysis of the IST data examined stroke patients with atrial fibrillation and presumed cardiac embolism. Even in this subgroup of patients, the absolute risk of recurrent stroke in the first 14 days was relatively low (3.9%) and that there was no net benefit to use of heparin. Other trials have similarly found no benefit emergent anticoagulation for AIS outside of prevention of deep vein thrombosis and pulmonary embolism.

Antiplatelet Agents

ASA has been evaluated for the treatment of AIS in two large randomized controlled trials (CAST and IST) and one smaller trial (MAST). In the CAST trial performed in China, 21,106 patients with acute ischemic stroke were randomized within 48 hours to ASA or placebo. There was a small but significant reduction in mortality amongst ASA allocated patients (RRR=14%, ARR=0.6%) and patients treated with ASA had significantly fewer recurrent strokes than patients in the placebo arm (1.6% vs 2.1%, respectively). ASA was associated with slightly more (0.2%) recurrent hemorrhagic strokes but this did not affect overall mortality as ASA patients were less likely to be dead or dependant at discharge (11.4 fewer per 1000). These data when pooled with the IST and MAST trials show that for every 1000 acute stroke patients treated, ASA causes about two hemorrhagic strokes but prevents about 11 other strokes or deaths in hospital. Based on these results, ASA is recommended within 24 hours to 48 hours of stroke onset provided there are no strong contraindications, and hemorrhagic stroke has been excluded. In patients treated with fibrinolytic therapy, ASA should not be given in the first 24 hours. ASA should also not be considered a substitute other acute interventions for stroke as the benefit of IV tPA given within 3 hours of symptom onset is an order of magnitude greater than of ASA. The numbers needed to treat (NNT) to achieve a one better outcome is approximately 3.1 with IV tPA compared to >100 for ASA.

Neuroprotection

The development of neuroprotective therapies that attenuate the cascade of pathophysiological events that occur with ischemia in acute stroke has been disappointing. A large number of neuroprotective agents have been developed based on animal models of focal ischemia all have failed in the translation to clinical practice. Most recently, the results of a large trial using NXY-059 were reported. NXY-059 is a free radical trapping agent that was extensively tested in animal models of focal ischemic stroke. The initial clinical trial suggested the drug was safe and effective in improving stroke outcomes but a subsequent phase III trials found no evidence of efficacy. Currently there is no effective neuroprotective therapy but several clinical trials are testing new agents.

Preventing Early Complications

Stroke Care Units

The intervention that perhaps has the greatest potential to improve outcomes of stroke patients is the establishment of specialized stroke care units (SCU). A recent Cochrane analysis pooled data from 31 trials and a total of 6936 patients examining the benefits of routine management of stroke patients in SCUs. Stroke patients that received organized care in a SCU had significantly lower odds of being dead or dependant at followup (OR = 0.79, 95% CI 0.71 to 0.88) than patients receiving care on general medical wards. Subgroup analysis showed that stroke patients benefit regardless of sex, age, or stroke severity. Stroke units, while not as potent an intervention as tPA therapy, can have a much larger impact on a population level as almost all stroke patients can benefit. Based data extrapolated from a community based epidemiological study, it is estimated that the establishment of SCUs has the potential to prevent death and disability for 50 patients per 1000 strokes compared to six per 1000 for tPA treatment and four per 1000 with ASA therapy.

The precise components of an SCU that account for the benefit in functional outcomes are not well delineated. It is established that SCUs that occupy a separate physical space are associated with better outcomes than care provided by mobile stroke teams in general wards. Likely interventions that are important for improved outcomes include early mobilization, better blood pressure control, and prevention of complications such as deep venous thrombosis through closer adherence to current evidence based guidelines. All stroke patients should be admitted to SCUs. Stroke units ideally should be geographically distinct, with well-defined protocols that address common problems such as early mobilization, screening for dysphagia, treatment of infections with antibiotics, and subcutaneous administration of anticoagulants for DVT prophylaxis.

Venous Thromboembolism

Venous thromboembolism is an important cause of morbidity in stroke patients. The risk of venous thromboembolism increases with age, and in patients with ischemic stroke. The risk is particularly high in the first few days after stroke onset, when the incidence of deep vein thrombosis (DVT) is estimated to be as high as 10 to 20%.

It is recommended that all stroke patients receive antithrombotic therapy as soon as possible after stroke onset. The choice of antithrombotic therapy depends on the specific clinical situation and the needs of the individual patient. For patients with a high risk of thromboembolism, such as those with atrial fibrillation or a history of venous thromboembolism, anticoagulation with warfarin or a direct oral anticoagulant (DOAC) may be indicated. For patients with a low risk of thromboembolism, aspirin or a low-dose DOAC may be sufficient.

In addition to antithrombotic therapy, stroke patients should be monitored for signs of deep vein thrombosis, such as swelling or pain in the legs, and should be encouraged to ambulate as soon as possible after stroke onset. Venous thromboembolism should be suspected in any patient with new onset leg pain, swelling, or erythema, especially if there is a history of stroke or other risk factors.
boembolism in patients with AIS approaches that of surgical patients and without thromboprophylaxis, about 20% of patients will develop pulmonary embolus (PE) and 1-2% stroke patients will have a fatal PE. Unfractionated heparin is associated with an 81% reduction in deep vein thrombosis and 58% reduction in PE with a small increased risk of hemorrhagic transformation of the infarct. The recently completed PREVAIL trial showed that thromboprophylaxis with low molecular weight heparin may further reduce the risk of venous thromboembolism by 43% compared to unfractionated heparin; however, most (95%) of the DVT detected in the trial were asymptomatic. Current guidelines recommend thromboprophylaxis for all ischemic stroke patients with anticoagulants although there is still controversy over whether low molecular weight heparin or unfractionated heparin is superior.

**Acute Neurologic Complications**

Many patients with ischemic stroke will worsen during the first 24-48 hours after stroke onset. The main neurologic causes of early worsening are the development of intracerebral haemorrhage, development of space occupying cerebral oedema, and less commonly seizures. The risk of hemorrhagic transformation of ischemic stroke is increased with fibrinolytic drugs, anticoagulation or antiplatelet agents. Haemorrhage after ischemic stroke can be petechial which is often asymptomatic or result in hematoma formation that increases intracranial pressure and results in neurological decline. There are currently no proven therapies for the treatment of hemorrhagic transformation. Seizures occur in about 3% of stroke patients within the first 24 hours. Prophylactic anticonvulsant therapy is not recommended.

One to ten percent of patients with supratentorial infarction will develop life-threatening, space occupying brain oedema (“malignant infarction”) usually in the second to fifth day after stroke. The prognosis of patients with malignant middle cerebral artery (MCA) territory infarctions is poor with mortality rates of around 80% and no effective medical therapy. There is an accumulating evidence from three European randomized trials (DECIMAL, DESTINY and HAMLET) that suggests that decompressive surgery improves functional outcomes in patients with malignant MCA infarction. Pooled data from these 3 trials showed that patients in the decompressive surgery group (treated within 48 hours, mean age 45) were more likely than controls to have favourable outcomes (75% vs 24%; pooled absolute risk reduction 51% [95% CI 34–69]) and survived their stroke (78% vs 29%; 50% [CI 33–67]). Favourable outcome in these trials was defined as moderate to moderately severe disability. Surgery in these trials was performed within 48 hours of stroke onset and the NNT for survival with a moderate deficit was four. These results highlight that decompressive hemicraniectomy increases survival but at a cost of more survivors with at least moderate deficits. The timing of surgery and the clinical characteristics of patients’ most likely to benefit are still not well established. Decompressive hemicraniectomy is usually reserved for younger patients and after discussion about the potential outcomes, including survival with moderate to severe disability.

The only other clear indication for surgery in acute stroke is for space occupying cerebellar infarction. In about 11-25% of cerebellar stroke the oedema becomes space occupying within the posterior fossa and brain stem compression and acute obstructive hydrocephalus results. The indications for surgical intervention in cerebellar strokes are a decreased level of consciousness and/or clinical signs of brainstem compression. The management involves the insertion of an external ventricular drain (EVD) and/or suboccipital decompressive craniectomy; however the optimal procedure is controversial. While the efficacy is not supported by clinical trials, case series have established decompressive surgical evacuation of space-occupying cerebellar infarction as a potentially life-saving procedure.

**REFERENCES**

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CONFLICT OF INTEREST
Authors declare no conflict of interest