Medical Management of Ischaemic Stroke

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ABSTRACT

Stroke is a medical emergency as it is the third commonest cause of death and the most important cause of acquired severe disability in adults. Stroke services, funding and research have lagged behind cardiac medicine but evidence is now available to support a much more interventional approach to the assessment and management of patients with ischaemic stroke. Randomised controlled trials and meta-analyses of the most important interventions are the main sources of evidence for this review. This evidence supports the immediate assessment of patients with suspected stroke, including access to brain imaging, and consideration of urgent revascularisation strategies such as intravenous recombinant tissue plasminogen activator. Patients not eligible for thrombolysis should receive aspirin and specialised care in a stroke unit. Many other treatments have been evaluated for acute ischaemic stroke of which some have been shown to be ineffective such as haemodilution or anticoagulation, whilst other interventions have not been adequately investigated such as neuroprotection and blood pressure lowering strategies. There is now good evidence to support a much more active assessment and treatment of patients with stroke but it is recognised that stroke services still need substantial development to maximise the benefits from the current proven interventions. (**Critical Care and Resuscitation 2005; 7: 189-194**)

Key words: Ischaemic stroke, medical management, review

The rationale for the medical treatment for stroke is to revascularise the brain, protect the brain from the deleterious effects of ischaemia and protect the patients from the deleterious effect of having a stroke. In this paper I will discuss the evidence supporting different medical treatments in these three areas. But first it is useful to summarise the epidemiology of stroke to put these treatments into context.

Stroke is the third leading cause of death in developed countries after ischaemic disease and all cancers combined. Recent evidence from England has demonstrated that the population reduction in blood pressure, cholesterol and smoking has helped reduce the age specific incidence of stroke by 40% but the overall incidence of stroke remains at a similar level to that seen two decades ago, due to the ageing of the population.[1] This striking finding is also likely to be true in other developed countries, and this will lead to stroke being increasingly seen in frailer aged patients. This has profound consequences for the assessment of stroke treatments. For example, the average age of patients with first ever stroke is now between 70 and 75 years old, with perhaps a third of all patients with stroke over 80 years old, yet most randomised controlled trials (RCT's) of thrombolysis have excluded patients aged 80 years of over. Another problem of stroke medicine is the lack of adequately powered acute intervention trials, with most new acute trials only able to reliably detect large treatment effects (e.g. a 10% absolute benefit in the primary outcome) when, in reality, most medical treatments have much smaller absolute treatment effects (e.g. 1 - 3%). The cause of this may be the result of the fairly late development of stroke units (compared to coronary care units, for example), the lack of stroke specialists and funding, or the lack of a concerted effort to promote large streamlined stroke trials. This has resulted in a disappointing evidence base for acute ischaemic stroke medical interventions compared to other conditions e.g. acute coronary syndromes.

Terminology is causing increasing confusion in stroke medicine. Stroke is a clinical diagnosis that can be made at the bedside (i.e. a clinical syndrome

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characterised by rapidly developing clinical symptoms and/or signs of focal, and at times global - applied to patients in deep coma and those with subarachnoid haemorrhage -, loss of cerebral function, with symptoms lasting more than 24 hours, or leading to death, with no apparent cause other than that of vascular origin).[2] You do not see a stroke on a computed tomographic (CT) scan but you might see a lesion that has caused a stroke! A transient ischaemic attack (TIA) is a syndrome with symptoms lasting less than 24 hours and which after adequate investigation is presumed to be due to inadequate cerebral or ocular blood supply as a result of low blood flow, arterial thrombosis or embolism associated with diseases of the arteries, heart or blood. In these days of hyperacute stroke assessment a useful concept is to describe the initial presentation of stroke or TIA as "Brain Attack", and classify the syndrome at 24 hours as either non-vascular, TIA or stroke (figure 1.). This may help create a paradigm shift in the assessment of patients with stroke which is certainly required if revascularisation with thrombolytic therapy is to have any success. Stroke is a medical emergency and prompt and comprehensive assessment is required.[3] All hospitals routinely admitting patients with suspected stroke should have access to medical and nursing staff with stroke expertise and access to 24 hour brain imaging. Recent work has suggested that the early reliable identification of the underlying pathology of

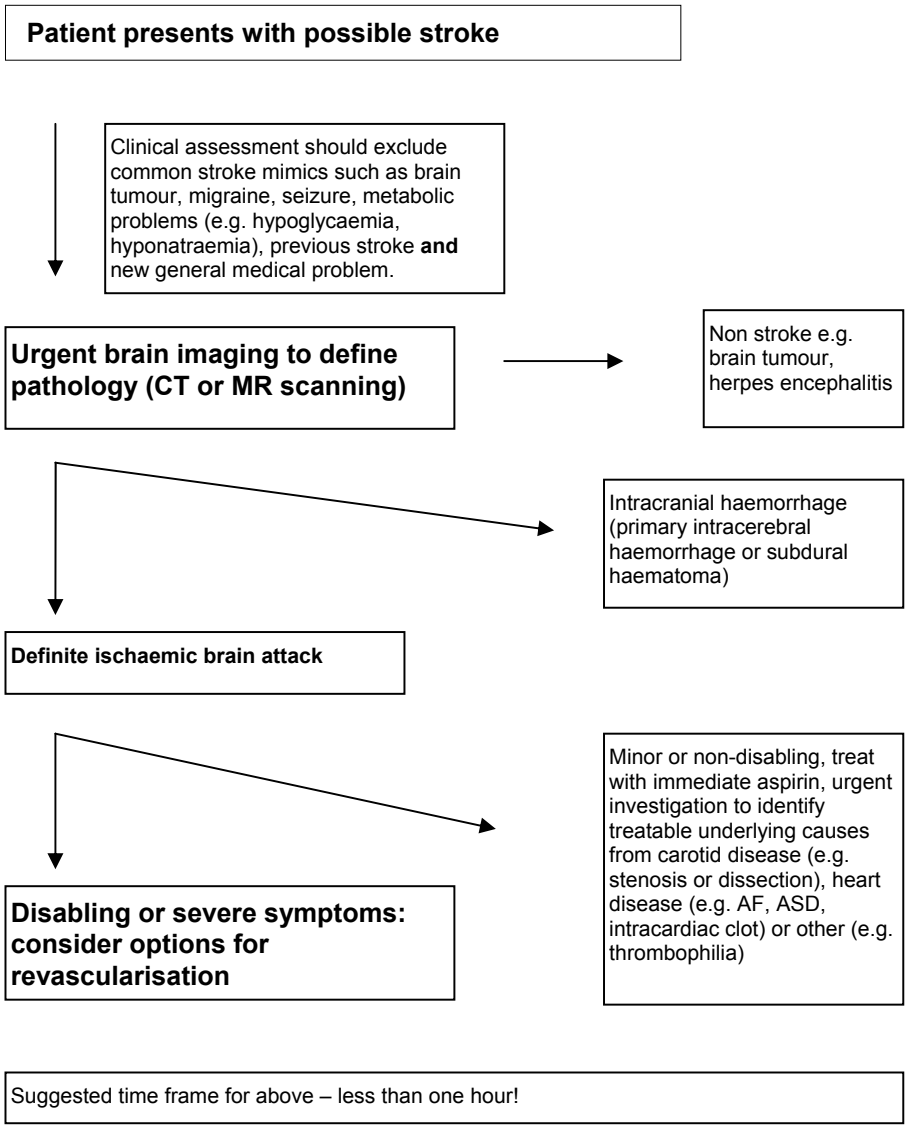

Figure 1. Flow diagram for patients presenting with possible stroke.

stroke (e.g. the exclusion of intracranial haemorrhage by CT scanning) is cost effective as diagnostic certainty helps target subsequent investigation and reduces hospital length of stay.[4]

Once clinical assessment and brain imaging has determined with reasonable certainty that the patient has an ischaemic brain attack, appropriate medical management depends on the severity of the symptoms and the general condition of the patient. The best care of a severely demented patient with a moderate stroke may well be a swift return to the nursing home once a safe swallow has been determined. A mild to moderate stroke in an otherwise well person needs urgent consideration of the best medical (or surgical) treatment for that individual and appropriate ongoing care. In this regard, stroke medicine is well catered for as the stroke group of the Cochrane Collaboration was one of the early groups established and appropriate reviews have been completed for numerous potential interventions and these summaries are free to all Australians on the internet (http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME). In brief, none of the suggested interventions for neuroprotection have been shown to be effective (although most have not been powered adequately to exclude moderate benefits), no subgroup has been shown to benefit from anticoagulation, aspirin is effective but at a disappointingly modest level and thrombolysis shows the greatest promise albeit with many questions still remaining. Following immediate treatment, stroke unit care has the greatest potential to improve long-term outcome.

Medical treatment for ischaemic stroke

The results of the RCT's to date have comprehensively demonstrated that the greatest impact arises from attempts to revascularise the brain, rather than protect it. This certainly has attractive face validity. If the stroke is due to vascular occlusion, revascularisation should be the first treatment considered. The RCT's have also demonstrated that the main factor limiting revascularisation treatment is the potential for causing deleterious haemorrhagic transformation of the infarct (HTI). Unfortunately all the medical treatments that could improve circulation have the potential to increase the chances of HTI. HTI is a natural phenomenon and occurs frequently at the microscopic level (maybe even universally) and even in the absence of any antithrombotic treatment, HTI severe enough to be symptomatic or cause haematoma formation occurs in approximately 1.5% (confidence interval 1.8 to 2.2%) of those with ischaemic stroke and the greatest risk in patients with large infarcts, mass effect or early hypodensity noted on brain imaging.[5] Aspirin, heparin and thrombolysis are the commonest medical treatments used for acute ischaemic stroke and the risks of HTI increase as you move from antiplatelet agents, to anticoagulants and is greatest with thrombolysis. All three classes of agents have been extensively evaluated and the trial results have been systematically reviewed in the Cochrane Library.

Aspirin has such a modest benefit that over 40,000 patients had to be randomised in RCT's before the benefit could be confirmed.[6] For approximately every 100 patients treated with aspirin, to be started within the first 48 hours of ischaemic stroke onset, there is one extra independent survivor. Thus in Australia this routine treatment will benefit approximately 400 patients a year (1% of 40,000) if given to nearly all patients with ischaemic stroke. It doesn't seem to matter whether the aspirin is started very early (i.e. within hours) or somewhat later (e.g. between 24 and 48 hours) thus suggesting the major benefit is reducing the risk of early recurrent ischaemic stroke in the first few weeks. The absolute benefit of early aspirin in the first 2 weeks of stroke is about the same as the absolute benefit in the following 50 weeks. Current best practice is to give aspirin as soon as brain imaging has excluded an intracranial bleed and a decision has been made not to proceed with urgent thrombolysis.

Heparin anticoagulation has been used for over 50 years to treat stroke yet no trial has demonstrated a definite benefit. In fact the systematic review shows remarkable consistency across trials of very different design.[7] The more anticoagulant therapy is given the greater the chance of HTI, and sadly the benefits of reducing early ischaemic stroke are exactly countered by the risks of neurological worsening from the rare but definite risk of early HTI.[7] Some physicians believe that patients with atrial fibrillation should be given early anticoagulation but the largest trial that was able to explore this with sufficient numbers of patients demonstrated that in the AF patient subgroup the reduction in early ischaemic stroke was still matched by an equivalent rate of HTI, and thus no net benefit.[8] One possible reason for this was discussed early. AF patients usually have large vessel cardioembolic strokes (e.g. large infarcts) and these infarcts also have the greatest risk of HTI. Presumably patients with very small lesions (e.g. those with TIA), have the smallest risk of HTI with early anticoagulation but this has never been formally tested in a RCT. The current expert level of evidence tends to favour early anticoagulation only for patients with a clear cardioembolic cause of stroke (e.g. AF) provided the patient has only had a mild ischaemic stroke or TIA. Patients with disabling ischaemic stroke and AF are best treated with aspirin for 2 weeks and only anticoagulated at that stage if long-term anticoagulation is still considered worthwhile. Neither

clopidogrel or dipyridimole have been tested in acute ischaemic stroke and combination antiplatelet agents are also untested for this period, although trials of combination therapy are now in progress.

Despite thrombolysis carrying the highest risk of HTI (and other intracranial bleeds), the benefits can be so substantial to outweigh the definite risks of intracranial haemorrhage.[9] The absolute benefits seen in the most positive trial, the NINDS trial, were about 10 - 15% more independent survivors – an unusually powerful treatment effect. However, there are many caveats of treatment. Treatment is generally only approved for one agent, recombinant tissue plasminogen activator (alteplase or rt-PA) to be given intravenously within a very tight time window (3 hours) and supervised by an experienced multi-disciplinary stroke team (Table 1).

Patients with all types of ischaemic stroke can be considered for rt-PA treatment, but in view of the risks of haemorrhage, many clinicians reserve treatment for patients with moderate to severe stroke. Audit has demonstrated that the results of treatment in routine practice can be very variable and treatment outside published guidelines can result in more harm than good.[10,11] Thrombolysis with rt-PA has now been approved in many countries and this approval is usually based on the results of one positive small trial (the NINDS study of only 624 patients) supported by a meta-analysis of the other less promising trials.[9,12] This level of evidence has divided the stroke world, with some advocating that there is enough data and thrombolysis should be standard therapy, whilst others argue that although alteplase is very promising further trials are required.[13] The compromise solution is to re-organise stroke services to be able to offer thrombolytic treatment with rt-PA to those who meet current licensed approval (e.g. the Therapeutic Goods Administration in Australia). This generally means highly selective treatment for the few who can present, be assessed and scanned and started on treatment within 3 hours of stroke onset. In Australia few such patients are treated and thus rt-PA currently has a negligible public health impact.[14]

International research efforts are now underway to explore alternative means of patient selection such as magnetic resonance imaging (the EPITHET trial[15]), extending the time window to 6 hours with an intravenous rt-PA regime (IST-3; www.ist3.com) or evaluating newer thrombolytic agents (e.g. the DIAS trials of desmoteplase). Further guidance on the use of rt-PA for stroke is available from published guidelines.[3] In the few centres that have immediate access to interventional neuroradiology, an intra-arterial approach can be considered.

Table 1. Eligibility for intravenous recombinant tissue plasminogen activator

Inclusion criteria
- Ischemic stroke with clearly defined time of onset that allows treatment to be started within 3 hours of onset
- A stroke deficit measurable on the National Intitute for Health Stroke Scale
- Baseline CT scan showing no evidence of intracranial haemorrhage

Exclusion criteria
- Stroke or head injury in past 3 months
- Surgery in previous 14 days
- History of intracranial haemorrhage
- Blood pressure above 185mmHg systolic or above 110 mmHg diastolic
- Rapidly improving stroke symptoms and signs
- History suggestive of subarachnoid haemorrhage
- Urinary or gastrointestinal tract haemorrhage in previous 21 days
- Arterial puncture at non-compressible site in past week
- Seizure at stroke onset
- Currently on anticoagulants and prothrombin time greater than 15 seconds, or elevated partial-thromboplastin time
- Platelet count below 100,000/mm^3
- Glucose below 2.7 mmol/L or above 22.2 mol/L
- Aggressive blood pressure treatment required to lower blood pressure to above limits

The two main trials of intra-arterial therapy used a different thrombolytic drug, pro-urokinase, but this agent is not widely available and has not been approved in Australia (and many other regions) for use in stroke. Fewer than 200 patients have been included in RCT's but in the largest study, the PROACT 2 study,[16] a regime of 9mg of recombinant pro-urokinase plus heparin was associated with much greater recanalisation than heparin alone (66% versus 18% at 2 hours, $p< 0.001$) at a cost of 10% of symptomatic HTI versus 2%. The patients all had signs of middle cerebral artery infarction and were treated within 6 hours but an indication of the generalisability of this type of treatment is illustrated by the somewhat depressing fact that they had to screen over 12,000 patients to randomise just 180 (< 2% recruited). Given the severe prognosis of some patients with basilar artery thrombosis, there is a case to consider intra-arterial thrombolysis for these patients, albeit acknowledging that the evidence is poor at present.[17]

Other treatments

The fibrinogen depleting agents such as ancrod has largely been abandoned following disappointing trial results.[18] There is currently no evidence that steroids, piracetam, mannitol, blood pressure lowering, calcium channel blockers, magnesium, amphetamines, excitatory amino acid antagonists, gangliosides, glycerol, haemodilution or methylxanthine derivatives have any benefit (see Cochrane Library). However, many of these interventions have been inadequately evaluated. The potential advantage of neuroprotective agents is that they could be given by paramedics to facilitate very early treatment (as no brain scan is required) and this is being tested in a very early treatment trial of intravenous magnesium. Blood pressure lowering is another potential therapeutic intervention which could have the advantage of wide generalisability if proven to be effective.

There is no doubt that the current treatment of ischaemic stroke is inadequate. Current trials should help clarify the role of thrombolysis and newer agents, or combination strategies need to be evaluated in many more trials.

Physiological intervention and stroke unit care

After establishing the diagnosis of ischaemic stroke and considered whether revascularisation is feasible, subsequent general care can have a significant effect on outcome. This evidence arises from two main sources. Most importantly, there is now very strong evidence that care in a comprehensive stroke unit has a major benefit (5 more independent survivors per 100 treated). It is important to note that the units evaluated in the stroke unit overview were those providing specialist acute care and multidisciplinary rehabilitation for up to several weeks, or units providing multidisciplinary specialist stroke rehabilitation within 1-2 weeks of admission providing care for up to several months if required.[19] A specialist stroke unit has many attributes, e.g. interested and specialised staff, participation in regular continued professional development, good interdisciplinary professional care and early involvement of family and carers. The benefits are almost certainly due to a myriad of different interventions such as early mobilisation, careful care of swallow abilities and provision of alternative nutrition, skilled nursing care and position etc. Other groups have gone further to study whether tight physiological control has important benefits and the early evidence from preliminary studies suggests that this may be an equally important intervention.[20] However, we await the larger studies confirming such benefits. Trials are now underway investigating tight glucose control, treatment of pyrexia, oxygen supplementation and multi-dimensional interventions.

Treating the cause of the stroke

Stroke is a syndrome and ischaemic stroke can be due to a very heterogenous range of causes. An important aspect of the medical care of patients with stroke is the appropriate investigation and identification of the cause of stroke for each patient. This will lead to appropriate adjuvant treatment and long-term secondary prevention.

Conclusion

If I had an ischaemic stroke I would ensure that my family would call an emergency ambulance to take me to the nearest stroke centre, I would consider the options of getting rt-PA (if presenting early enough), or at least give consent to one of the many trials of early revascularisation. I would then want immediate admission to a stroke unit to receive multi-disciplinary care until I was well enough to get back home. The tragedy for those with stroke is that this is not widely available in Australia or many other developed countries and we all need to strive to develop such facilities for as large a proportion of the population as possible.

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