Future perspectives in stroke management

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Abstract

Clinical research relating to stroke management is at something of a watershed. On the one hand, some therapies are well proven and established, and on the other some approaches have repeatedly failed. Examples of successes include antithrombotic (aspirin, dipyridamole, clopidogrel, warfarin) and antihypertensive therapies (diuretic, angiotensin-converting enzyme inhibitors), carotid endarterectomy for secondary prevention,[1-4] and aspirin in acute ischaemic stroke.[5] In contrast, several strategies have repeatedly failed, especially the use of anticoagulation and neuroprotection in acute ischaemic stroke. This review gazes into the crystal ball to see what we might be doing when managing patients with stroke in 10 years time.

Key words: stroke, transient ischaemic attack, stroke management, primary prevention, secondary prevention, acute intervention, recovery, future.

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Definitions of cerebrovascular disease

Although the definition of stroke has largely stood the test of time, that for transient ischaemic attack (TIA) has failed, particularly with respect to the 24-hour time window by which symptoms must resolve. It is clear with modern neuroimaging that focal transient neurological symptoms that last for more than about one hour are usually associated with permanent ischaemic brain lesions (or occasionally with small primary intracerebral haemorrhage). Hence, TIA is likely to be redefined to include only symptoms which last for less than one hour.

Investigation of stroke

CT scanning is the standard diagnostic test for acute stroke and has the aims of excluding non-stroke mimics such as tumours, distinguishing between primary intracerebral haemorrhage and ischaemic stroke, and providing guidance on prognosis. However, the future lies with magnetic resonance imaging (MRI) which not only provides anatomical information but can assess: blood vessel patency (angiography), perfusion (local tissue blood supply), diffusion of water (useful for identifying dead or dying tissue), and some aspects of tissue metabolism (spectroscopy). This multimodal nature of MRI allows improved management decisions to be made and adds useful prognostic information. Hence, MRI is likely to gradually replace CT although it is vital in the mean time that all stroke patients have some form of neuroimaging, in contrast to the current situation where many patients are still not scanned,[6] or are scanned after two weeks when CT can no longer reliably distinguish primary haemorrhage from infarction.

Primary prevention

In addition to the treatment of hypertension, it is increasingly becoming clear that patients with vascular risk factors should be on aspirin[7-9] although those at low risk do not benefit.[10,11] Getting this research finding into practice will need considerable effort by clinicians, especially those in primary care. Patients at high vascular risk, in particular the elderly, may also benefit from lipid lowering, as is being assessed in the ongoing PROSPER trial.[12]

Acute intervention

Neuroprotection

Many reasons explain the failure of trials investigating the use of neuroprotectants in acute stroke. The relevance of positive studies in animal models of stroke to the clinical environment has

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been questioned[13] and guidelines have been published recently which should standardise and improve the quality of pre-clinical development.[14] A common problem is that the pharmacology of novel compounds is often ill-understood and development races through the hoops required for licensing. Nevertheless, whilst some compounds are simply ineffective,[15] others are toxic.[16,17] It is also of concern that many compounds have been studied in very few patients and then discarded because of loss of patent, e.g. prostacyclin.[18] With these points in mind, recently published recommendations should contribute to an improvement in the quality of future trials.[19] In spite of these failures, many putative neuroprotectants remain in development, including magnesium, Bay x 3702 and sipatrigine.[20-22]

Anticoagulation

Like neuroprotection, anticoagulation has been disappointing although the explanation is, at least in part, simple in that the hazard of bleeding (especially intracranial haemorrhage) simply cancels out any beneficial effects on the underlying pathophysiology.[5,23] Whilst heparins or heparinoids may have had their day in the treatment of acute stroke (although new studies are still underway),[24] newer anticoagulants such as pentasaccharides, direct acting thrombin inhibitors, or factor Xa inhibitors could be effective overall if they cause less bleeding whilst retaining their efficacy.

Thrombolysis

Although thrombolysis appears to dramatically improve outcome in patients with acute ischaemic stroke,[25] it is little used around the world, even in countries where alteplase is licensed for use in stroke. Four explanations contribute to this state of affairs; first, the four existing studies were small[26-29] – contrast their combined size of < 3,000 patients with the tens of thousands recruited into trials in acute myocardial infarction. Second, the trials gave inconsistent results in that only one was positive on its primary outcome.[27] Third, the small amount of data precludes meaningful subgroup analysis which could identify clusters of patients who might specifically benefit from treatment, or those who might be at increased risk of developing intracranial haemorrhage. Last, the single positive study only recruited patients within three hours of onset[27] and this has severely limited the pool of patients who might benefit from treatment. A large (6,000 patients) and ongoing trial of alteplase with recruitment within six hours of onset will address these problems ('International Stroke Trial 3', see http://www.dcn.ed.ac.uk/ist3/), and could finally clear up the long and tortured saga of thrombolysis in acute ischaemic stroke.

Physiology

The biggest advances in the management of the patient with acute stroke may come from better understanding, monitoring and control of physiological variables. Many patients are hypertensive, hyperglycaemic, or pyrexial, or have cerebral oedema and solid evidence informs us that these states are detrimental to outcome.[30] Large trials are now underway investigating whether blood pressure and glucose can be lowered safely and with benefit.[31,32] Meanwhile, smaller trials have assessed the feasibility and surrogate effects of active pharmacological cooling[33] and decompressive strategies.[34] Larger trials of these strategies are now underway or planned.

Acute Stroke Unit

Admission to an Acute Stroke Unit improves outcome after stroke[35] probably by integrating expert care and delivering a package of simple medical interventions, such as oxygen and fluids. Nevertheless, the requirements of controlling physiology and administering drugs, such as alteplase, mean that patients will need closer monitoring than is done currently. Hence, the future lies in setting up 'Brain Attack Units' (or 'Cerebral Care Units') along the lines of existing Coronary Care Units. Whether patients with acute coronary and cerebral syndromes should be managed together is a concept that requires testing since monitoring and treatment overlap considerably.

Promoting recovery after stroke

The value of Stroke Rehabilitation Units is now well recognised and efforts are now underway to better understand what components of therapy, nursing and medical care are vital to improving outcome. Nevertheless, it is possible that recovery can be further accelerated and enhanced using pharmacological or other means. Evidence from experimental stroke and small clinical studies suggest that agents such as amphetamine derivatives,[36] dopa and growth factors (e.g. nerve growth factor, brain-derived neurotrophic factor) may be useful and larger trials are now needed. The most radical solution for improving outcome, however, may come from the use of stem cell technology. Studies in animal models of stroke suggest that stem cells, given intravenously or locally, can dramatically enhance recovery and early clinical studies have now started. The mechanisms by which drugs and stem cells might work are currently unclear but probably include promoting plasticity, synaptogenesis, and neurogenesis.

Secondary prevention

Whilst aspirin, dipyridamole and clopidogrel are individually effective, they only each reduce stroke recurrence by around one fifth. Combining two agents roughly doubles prevention[37] so it is conceivable that combining all three might be even more effective (as it is *in vitro*),[38] providing bleeding is not a significant problem. One class of antiplatelet drugs unlikely to feature in the future is the oral glycoprotein IIb/IIIa antagonists; meta-analysis of data from four trials in patients with prior vascular disease shows these drugs increase death.[39]

Oral anticoagulation with warfarin is of undoubted efficacy in patients with non-rheumatic atrial fibrillation and prior ischaemic stroke or TIA. However, the need for regular monitoring and dose adjustment is very inconvenient, especially in a group of patients who are often less than mobile or cognitively impaired. Oral direct acting thrombin inhibitors do not need monitoring or dose adjustment and are currently being compared with war-

Key messages

- Transient ischaemic attack is likely to be redefined to include only symptoms which last for one hour
- The standard diagnostic test for acute stroke is CT scanning. This is likely to be replaced by MRI
- Primary prevention should focus on treating hypertension and putting patients with vascular risk factors on aspirin
- Admission to an Acute Stroke Unit improves outcome
- Brain Attack Units should be set up in the future

farin; they offer the possibility of much simplified treatment and less risk of over- or under-treatment.

Two other preventative approaches are currently being studied. First, statins are under investigation in several large trials involving patients post-stroke or TIA. Data from the Heart Protection Study suggest, for the first time, that statins prevent vascular events in patients with prior stroke or TIA and two further trials are underway.[12,40] It is difficult to see how statins will not feature in the routine 'cocktail' for secondary prevention in the very near future. Similarly, the positive relationship of serum homocysteine levels with stroke has fostered two large studies investigating whether triple vitamin therapy (folate, pyridoxine, vitamin B12) prevents stroke recurrence.[41,42] All of these trials will report over the next five years.

Between 5–10% of patients with ischaemic stroke or TIA have severe ipsilateral internal carotid artery stenosis. The positive trials of carotid endarterectomy reported in the 1990s have spawned two further questions. First, should patients with asymptomatic severe stenosis be operated on? One medium-sized trial suggested that this was of benefit (although the number needed to treat to prevent a stroke is high); another trial is underway. The second question is based on the comparison of angioplasty with carotid endarterectomy; ongoing trials are extending earlier research[43] by adding stent insertion to angioplasty.[44]

The future management of stroke

If the strategies outlined above are effective in improving outcome, it is possible to envisage that future stroke patients will be treated very differently from the largely nihilistic approach used today. Stroke is a medical emergency and patients need to be transferred immediately to hospital.[45] With better recognition by the public, stroke can be identified quickly and the delay to hospital admission reduced dramatically. Neuroprotective treatment could be commenced by paramedical staff in the ambulance, and neuroimaging performed within minutes of reaching hospital allowing thrombolysis to be started in those with very recent ischaemic stroke. Patients will then be managed in a high dependency Brain Attack Unit with regular monitoring and treatment of physiological disturbances such as hypoxia, dehydration, hypertension and hyperglycaemia. Sadly, little guesswork is required here since much of the above is already happening in more enlightened countries around the world!

The most radical changes may come in promoting recovery through the use of drugs or stem cells although their role, if proven, may barely make it into routine use within the next 10 years. The future for secondary prevention is more clear, and will be based on polypharmacy, comprising a combination of antithrombotic, antihypertensive and lipid-lowering drugs, and possibly vitamin therapy. A limiting factor here will be the cost of these drugs; based on this vision, a monthly bill of £60 is conceivable. As in other areas of vascular medicine, endovascular approaches could largely replace open surgery.

Editors' note

This is the final article in our stroke series. Previous articles are:

- Cerebrovascular disease (editorial) (*Br J Cardiol* 2001;**8**:482)
- The epidemiology of stroke (*Br J Cardiol* 2001;**8**:507-13)
- The pathophysiology of stroke (*Br J Cardiol* 2001;**8**:586-9)
- Acute management of stroke (*Br J Cardiol* 2001;**8**:654-7)
- Prevention of vascular disease following acute ischaemic stroke (*Br J Cardiol* 2001;**8**:704-11)
- Stroke rehabilitation (*Br J Cardiol* 2002;**9**:23-30)
- Prognosis, outcome and recurrence of stroke (*Br J Cardiol* 2002;**9**:103-5)
- PROGRESS in the secondary prevention of stroke (*Br J Cardiol* 2002;**9**:131-4)
- Stroke in the patient with coronary heart disease (*Br J Cardiol* 2002;**9**:163-7)

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