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Education

Latest developments in clinical stroke care

JS Minhas[1], TG Robinson[2]

Abstract

Stroke medicine has seen rapid developments in diagnosis and management, and consequently improved prognosis. Management of ischaemic stroke, in particular, has benefited from these advances. The approach to management has evolved from one of historical passivity to active intervention with time of the essence following stroke onset. The last decade has seen the comparative effectiveness of several pharmacological agents being tested, creating significant randomised controlled trial evidence to support the management of common clinical problems following acute stroke. While several of these interventions are widely available, some remain less accessible. This review will discuss the latest developments in clinical stroke medicine, based on a symposium presentation at the Royal College of Physicians of Edinburgh, and reference key randomised controlled trial evidence in an effort to provide a balanced perspective on our current understanding of acute ischaemic and haemorrhagic stroke.

Correspondence to:
TG Robinson
Department of Cardiovascular Sciences
University of Leicester
British Heart Foundation Cardiovascular Research Centre
Glenfield Hospital
Leicester LE3 9QP
UK

Email: tgr2@le.ac.uk

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Epidemiology

In the UK, there are 100,000 strokes each year.[1] Despite stroke incidence falling 19% from 1990 to 2010, the age standardised stroke incidence per 100,000 people is 115.[2] In England, Wales and Northern Ireland the average age for men to have a stroke is 74 and for women is 80.[1]

The risk of death following stroke is highest in the immediate aftermath and treatment strategies are aimed at lowering the risk of mortality during this period. Mortality early in the natural history of stroke is largely attributable to the stroke itself, with deaths occurring after several weeks more likely to be associated with comorbidities or direct complications of prolonged immobility and general physiological vulnerability post stroke. However, few studies have examined larger populations and included a variety of factors associated with early fatality. A large Danish registry study of 26,818 patients with first-ever ischaemic stroke examined predictors of early (3-, 7- and 30-day) and late case-fatality (90-day and 1-year).[3] As expected, overall case-fatality rates increased with increasing age.[3] The primary factors associated with early stroke death were age and stroke severity, whereas cardiovascular comorbidity was associated with late case-fatality.[3]

Inpatient stroke and its management is also an area of importance. A national retrospective cohort study compared quality of care for 21,349 in-hospital vs. 928,885 community-onset ischaemic strokes, and found in-hospital stroke episodes had increased severity and more deviation from stroke pathways, and worse outcomes.[4] Previous studies have shown a higher incidence of cardioembolic source for in-hospital strokes.[5] However, importantly, the in-patient population is more likely to have contraindications to thrombolysis than community-onset strokes.[5]

Hyperacute stroke units

In recent years, an emphasis on the organisational structure of acute stroke services has led to the delivery of multidisciplinary care in dedicated stroke wards. The Stroke Unit Trialists' Collaboration provided strong evidence for inpatient care in a stroke unit leading to an increased likelihood of stroke survivors being alive, independent and living at home 1 year after the stroke.[6] Importantly, there was no observed increase in length of stay associated with this dedicated ward environment. However, provision of specific staffing levels on stroke units remains heterogeneous with wide variations in skill-mix and size of hyper-acute stroke units. The Royal College of Physicians National Guideline for Stroke comments on the paucity of data supporting specific staffing levels.[7] However, observational evidence does suggest centres with higher volumes of acute stroke thrombolysis numbers having clinically shorter delays in administering thrombolytic therapy after stroke confirmation.[8]

[1]Dunhill Medical Trust Research Training Fellow and Honorary Specialist Registrar in Geriatrics (Stroke) and General Internal Medicine; [2]Head of Department of Cardiovascular Sciences and Professor of Stroke Medicine, University of Leicester, Leicester, UK

General management

Medical comorbidity often complicates the acute stroke period and data suggest 75% of all stroke patients admitted to a UK hospital have at least one comorbidity, and 10% have at least three.[7] Furthermore, without considering comorbidities, patients who suffer acute stroke are physiologically vulnerable and often suffer with volatility in circulating volume, immune dysfunction, respiratory compromise, dysphagia and poor glycaemic control. Unfortunately, evidence supporting identification and management of these conditions is variable. A paucity of trial evidence exists for managing poor hydration in acute stroke and furthermore, identifying hypovolaemia with standard signs and symptoms has poor diagnostic correlations.[9] In contrast, stronger evidence exists for dysphagia screening.[10]

Acute ischaemic stroke

Specific management

All patients with an acute ischaemic stroke should be given aspirin 300 mg as soon as possible but certainly less than 24 h after onset. In those patients undergoing thrombolysis therapy, anti-platelets are not advised until after 24 h and radiological exclusion of haemorrhagic complication.[11] Furthermore, acute ischaemic stroke patients should receive high dose statin therapy as soon as they are able to swallow the medication safely.[11]

Blood pressure management

Hypertension in the acute stroke setting is common, with three quarters of patients having a blood pressure (BP) > 140/90 mmHg.[12] Significant debate between continuing or stopping pre-stroke antihypertensive therapy had ensued until a recent individual patient data meta-analysis of related randomised controlled trials.[13] This determined that there was no significant benefit from continuation of pre-existing antihypertensive treatment.[13] Therefore, guidelines have recently concluded that patients should resume oral treatment once they are medically stable and as soon as they can swallow safely.[7] With respect to the de novo introduction of antihypertensive therapy following acute ischaemic stroke, the Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial (RIGHT), where transdermal glyceryl trinitrate was given within 4 h (median 55 min), showed potential benefit with BP lowering in the ultra-acute phase.[14] This was also supported by the 0 to 6 hour subgroup of the Efficacy in Nitric Oxide Study.[15] This apparent benefit in ischaemic stroke patients has led to the ongoing RIGHT-2 trial, which will assess the safety and efficacy of glyceryl trinitrate administered within 4 h of stroke onset.[16] While the Enhanced Control of Hypertension and Thrombolysis Stroke (ENCHANTED) study was designed to compare low-dose with standard-dose intravenous alteplase in patients with acute ischaemic stroke,[17] the study is also assessing the effects of early intensive BP lowering as compared with guideline-recommended management in patients with elevated BP receiving intravenous thrombolysis.[17] The results of both the RIGHT-2 and BP-arm of the ENCHANTED study will provide further insight into ultra-acute BP management.[16,17]

Head positioning

Head positioning post stroke has prompted debate with some arguing the benefits of supine positioning in improving cerebral blood flow while others argue the possible higher risk of aspiration pneumonia. The Head Position in Stroke Trial (HeadPoST) assigned acute stroke patients to receive care lying flat or sitting up with head elevated to at least 30° for the first 24 h as soon as possible following hospital admission for ischaemic or haemorrhagic stroke. The study found no difference in disability outcomes between the two patient groups with no significant between-group differences in serious adverse events including pneumonia.[18] Though relatively mild stroke patients (median National Institutes of Health Stroke Scale (NIHSS) score of 4) were recruited relatively late after stroke onset (median onset to intervention of 14 h), there was no significant heterogeneity of treatment effect in a post-hoc analysis across quintiles of baseline NIHSS score and time to intervention.[17]

Early mobilisation

The A Very Early Rehabilitation Trial (AVERT) assessed the efficacy and safety of very early mobilisation within 24 h of stroke onset in an attempt to determine whether higher doses of very early mobilisation were superior to usual care.[19] Importantly, the study determined that higher dose very early mobilisation protocol was associated with a reduction in the odds of a favourable outcome at 3 months. This has led to guidelines advising mobilisation within 24 h of onset should be for those who require little or no assistance.[7] Patients with difficulty moving should only be offered 'short daily mobilisations', typically starting between 24 and 48 h after onset.[19]

Imaging

The role of brain imaging is essential in excluding intracerebral haemorrhage (ICH) and stroke mimics, and more recently in aiding selection of patients for intravenous thrombolysis. The Penumbra and Re-canalisation Acute Computed Tomography in Ischaemic Stroke Evaluation (PRACTISE) study is examining the use of multimodal imaging in patient selection for tPA.[20] The study is randomising to either current-based imaging (non-contrast computer tomography, NCCT) or additional multimodal CT imaging (NCCT + CT angiography + CT perfusion). The results of the study may help define the need for multimodal imaging to determine individual patient thrombolysis treatment decisions.[20]

Intravenous thrombolysis

Present guidelines recommend the use of alteplase within 4.5 h of stroke onset with no upper age limit, as data support older patients benefiting as least as much as those < 80 years of age, particularly if administered in the first 3 h post stroke onset.[7] Alteplase improves the overall odds of a good stroke outcome despite the increased risk of symptomatic (including fatal) intracranial haemorrhage.[21] The latest UK guidelines recommend that for > 80 years of

age, thrombolysis treatment decisions should be carefully considered on an individual basis when administered within 3 to 4.5 h of ischaemic stroke onset; acknowledging that the benefits would have been greater if treated earlier with little change in risk of a worse outcome.[7]

As previously stated, the ENCHANTED study compared low-dose with standard-dose intravenous alteplase in patients with acute ischaemic stroke.[17] The study included a majority of patients from south-east Asia and demonstrated a significantly lower risk of symptomatic ICH and early mortality with the lower dose. Nonetheless, the trial failed to meet its primary outcome, and did not demonstrate that the lower dose was non-inferior with respect to death and disability (defined by a 90-day modified Rankin score of 2 to 6) compared to standard dose. However, non-inferiority was demonstrated with a key secondary efficacy outcome; namely, ordinal shift analysis of modified Rankin scores. Therefore, the latest UK guidelines have carefully suggested 'there may be circumstances in which the treating physician and/or the patient wish to forgo some of the potential disability benefit from standard dose alteplase in order to reduce the early risk of intracerebral haemorrhage through the use of the lower dose'.[7] More recently, there have been studies involving an alternative genetically engineered thrombolytic, tenecteplase. The perceived advantages include a higher fibrin specificity, longer half-life and increased resistance to plasminogen activator. These characteristics could result in more rapid reperfusion and a lower ICH rate. The alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST) trial of 104 patients demonstrated comparable neurological and radiological outcomes between tenecteplase and alteplase.[22] Larger randomised controlled trials of tenecteplase are ongoing.

Mechanical thrombectomy

Five trials of endovascular thrombectomy (EVT) for acute ischaemic stroke led to the most recent American Heart Association guidelines recommending the procedure as standard care for patients with proximal anterior circulation occlusions.[23] Importantly, the benefits of EVT apply irrespective of eligibility for intravenous thrombolysis, and apply across a wide range of stroke severity and age groups. Therefore, age should not be seen as a contraindication; indeed, several studies included individuals over the age of 80 with clear efficacy of the intervention.[24] However, there is need for further research to answer questions in respect of the time window for posterior circulation stroke, the identification of salvageable brain tissue over longer time periods up to 12 h, and utility of EVT in those with substantial pre-stroke functional issues (modified Rankin Score > 2).[23] The latest UK guidelines currently recommend EVT for those with a NIHSS score of 6 or more within 5 h of onset using stent retrieval of clot and/or clot aspiration techniques with prior intravenous thrombolysis unless contraindicated.[7]

In addition, there are significant service delivery challenges worldwide with this technology. Furthermore, from a UK perspective, clinical database data comparisons to trial eligibility criteria showed only around 15% of patients presenting within 6 h of stroke onset would have been eligible for EVT.[24]

Acute intracerebral haemorrhage

Patients with ICH demonstrate significant neurological vulnerability and can deteriorate rapidly. The mainstay of treatment involves imaging, reversal of anticoagulation, BP management, and in a small number of cases surgery. The likelihood of deterioration and generally poorer prognosis are the reasons why, compared to ischaemic stroke patients, patients with ICH are more likely to commence palliative care during the first 72 h regardless of age and premorbid health. Effective treatments are very limited and poor outcomes are often conveyed by clinicians to patients and families to ensure decisions on appropriate escalations of care are made early. Despite the lack of effective treatments for ICH, improved understanding of BP management in acute ICH has been gained through two key randomised controlled trials. The intensive blood pressure reduction in acute cerebral haemorrhage (INTERACT 2) trial randomised patients to intensive (target systolic BP < 140 mmHg) or guideline-based (systolic BP < 180 mmHg) BP management.[25] The primary outcome measure of death and disability showed no significant reduction with intensive lowering, though an ordinal analysis of modified Rankin scores suggested improved functional outcomes with intensive lowering. The Antihypertensive Treatment of Acute Cerebral Haemorrhage II (ATACH-2) trial used intravenous nicardipine to test the superiority of intensive reduction (target systolic BP 110–139 mmHg) vs. standard treatment (target systolic BP 140 mmHg–179 mmHg), but demonstrated no significant difference in 90-day death and major disability with an increase in serious adverse event rates, particularly renal events within the first 7 days.[26] Based on these trials, the recent UK National Clinical Guidelines for stroke concluded that patients with primary ICH presenting within 6 h of onset with a systolic BP above 150 mmHg should be treated urgently using a locally agreed BP lowering protocol to a systolic BP target of 140 mmHg.[7] Current work examining alternative pharmacological interventions includes the Tranexamic acid for IntraCerebral Haemorrhage (TICH-2) trial, which is assessing whether an antifibrinolytic drug can reduce mortality in ICH.[27]

Summary

Despite there being a significant advancement of interventions available for acute ischaemic stroke, there remain areas of acute stroke care that lack an evidence base and for which studies are still ongoing. Age and medical comorbidity are key factors in predicting outcomes, though thrombolysis and EVT are effective independent of age with no increase in adverse outcomes. Ultimately, stroke physicians continue to make evidence informed decisions based on a growing body of randomised controlled trial data across the spectrum of stroke pathologies.

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