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New approaches in the management of intracranial haemorrhage

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Introduction

Cranial arteries can dissect, occlude, donate emboli or constrict to produce ischaemia, they can also ooze, leak or rupture to produce intracranial haemorrhage. The responsible pathologies share many risk factors including age, hypertension and smoking. Advances in imaging, coupled with clinical observation, have recently allowed us to move on from the ambiguity of stifling terms such as "haemorrhagic stroke" to a better understanding of the causes and mechanisms of all types of primary and secondary intracranial haemorrhage. This, in turn, has led to a more tailored approach to management. The process of recruiting these patients into clinical trials that include medical and/or surgical options, is also promoting a more considered approach to intracerebral haemorrhage, compelling us to think more carefully about the exact mechanism of any haemorrhage, as well as optimum management.

Here we review three papers describing trials of acute interventions in patients with intracerebral haemorrhage. The usual limitations common to all trials in cerebrovascular disease are potentially very relevant: the exact location of a lesion is as important a determinant of resulting disability as its size, physiological frailty (e.g. sarcopaenia) and physical dependency are not always associated, and scales such as the National Institutes of Health Stroke Scale (NIHSS) add together scores from multiple ordered categorical scales of deficits as different as weakness, dysphasia and inattention to produce numbers which are then compared using simple arithmetic.

ENRICH: Trial of Early Minimally Invasive Removal of Intracerebral Hemorrhage

Decompressive craniectomy in patients with intracerebral haemorrhage is often an intervention undertaken only for deteriorating patients who are unable to tolerate the associated increase in intracranial pressure. This trial explores a less invasive method, a small craniotomy and a durotomy followed by suction, to remove intracerebral haematoma before critical clinical deterioration. 286 independent (modified Rankin Scale (mRS) 0 or 1) patients aged 18-80 years with lobar or anterior basal ganglia haemorrhages were randomised to have this surgery and standard medical management, or medical management alone. Average utility weighted mRS (UW-mRS) at

180 days post event was 0.458 in the surgery group and 0.374 in the control group, with a higher score indicating a better outcome.

It should be noted that a small number of patients in both groups went on to have decompressive craniectomy (more in the control group). It is unclear if these patients were included in final analysis.

Overall, this trial demonstrates better morbidity outcomes following surgical intervention when compared to medical management alone. However, only patients with good pre-morbid function were included, potentially narrowing the field to only a small subset of stroke patients seen in clinical practice. This may make it difficult for clinicians to confidently recommend this intervention to their frailer patients.

Pradilla G. et al. (2024) New England Journal of Medicine,, 390(14): 1277–1289

Annexa-I: Andexanet for Factor Xa Inhibitor–Associated Acute Intracerebral Hemorrhage

Andexanet alpha is a recombinant form of Factor Xa protein which binds specifically to apixaban and rivaroxaban; it is licensed for the reversal of life-threatening gastrointestinal haemorrhage but not for intracranial haemorrhage in patients taking these Direct Oral Anticoagulants (DOACs).

438 patients with intracranial (subsequently limited to intracerebral) haemorrhage taking a factor Xa inhibitor (up to 15 hours before randomisation) were assigned to receive standard medical management (mainly prothrombin complex concentrate (PCC) but at clinicians' discretion) or andexanet.

The primary endpoint was “haemostatic efficiency”, defined as a change in haematoma volume of 20% or less (excellent) or 35% or less (good) within 12 hours after baseline, an increase in the NIHSS score of less than 7 points at 12 hours, and receipt of no rescue therapies such as andexanet, PCC or decompressive surgery within 3 to 12 hours after randomization (all criteria had to be met). Hematoma volumes were estimated from cranial CT or MRI.

Haemostatic efficacy was achieved in 67% receiving andexanet and 53.1% receiving usual care, with thrombotic events in 10.3% and 5.6% and cerebral infarction in 6.5% and 1.5% respectively.

Previous trials state haematoma expansion is associated with worse outcomes. However, this trial did not directly demonstrate that reducing haematoma expansion leads to more favourable outcomes. It is therefore difficult to argue that the use of reversal agents is currently justified, particularly given the increased risk of cerebral ischaemia. Long term disability, length of stay in hospital and mortality are all important outcomes to patients and the clinicians caring for them, regardless of the mechanism.

That there were no significant differences in the mRS or death at 30 days is perhaps the take home message. Additionally, the cost difference of these interventions (according to the UK's National Institute for Clinical Excellence) is substantial, with a course of andexanet costing £15,000 compared to £255 for one vial of PCC.

Connolly S.J. et al. (2024) New England Journal of Medicine, 390(19): 1745–1755

SWITCH: Decompressive craniectomy plus best medical treatment versus best medical treatment alone for spontaneous severe deep supratentorial intracerebral haemorrhage: a randomised controlled clinical trial.

Over nearly ten years in 42 centres, 197 patients aged 19–75 years with deep intracranial haemorrhage (basal ganglia and thalamus, including those with extension into cerebral lobes, ventricles, or subarachnoid space) were randomised to either decompressive craniectomy surgery plus best medical treatment, or best medical treatment alone. Outcomes for each group were compared after 6 months.

The sobering headline is that the number of patients with an mRS of 0–3 was the same in both groups at 6 months.

44% of the surgical group and 58% of medical treatment group had an mRS of 5–6 at 180 days (and similar comparison at 365 days). Similar rates of severe adverse events occurred in both groups, although overall length of hospital stay was shorter in the surgical group. Longer term data is awaited regarding the various complications related to the surgery—this of course cannot be compared between the two groups but may be relevant.

This trial demonstrates improved morbidity and mortality rates in patients who underwent decompressive craniectomy. However, survival was associated with severe disability in both groups. Other trials (such as ENRICH) are ongoing evaluating the role for minimally invasive surgery, but this is unlikely to be of relevance to patients with the type of bleed examined in this trial. Similarly, the results of this trial cannot be applied to intracranial haemorrhages in other areas as this focussed only on severe, deep bleeds. Consequently, the inclusion criteria were very narrow compared to trials looking at other interventions e.g. blood pressure control, medical management and broader methods of haematoma evacuation. As this trial was stopped early due to lack of funding, fewer patients were recruited than initially planned. As a result, the study was underpowered for the primary endpoints planned, but remains the largest trial of this type.

Klijn C. et al. (2024) The Lancet, 403(10442): 2351–2353

Conclusion

On average in patients with ICH, around a third die in hospital, half have died 2 years post-event and less than 1 in 5 are independent at time of discharge. The above trials suggest both surgical and medical management techniques can be refined and indeed expanded to allow more options for clinicians to draw on in managing these patients. They also highlight a need for a consistent approach to objective assessment of long-term outcomes. All three trials used the mRS as an outcome measure (to varying extents). This captures the impact of disability after the haemorrhagic event but does not necessarily adequately describe patients' level of frailty or the way this may change over a longer period. For future studies, a more detailed, even descriptive approach to assessing patient outcomes may be beneficial.

Both trials examining surgical interventions showed better patient outcomes than medical management alone (average UW-mRS 0.458 vs 0.374 and mRS 5-6 in 44% vs 58%). Reduction in haematoma expansion can be achieved with factor Xa inhibitors vs usual care (67% vs 53.1%), although the rate of thrombotic events rises to 10.3% vs 5.6%. Across all patients included here, impact of disability long term remains high.

Fundamentally, it is challenging to draw comparisons between trials discussing surgical and medical interventions. This does however highlight the need for us to consider which specialist teams are best placed to manage such patients. An acute multidisciplinary team approach seems indicated to facilitate decision-making in ICH management, which could now include reducing haematoma expansion, surgery (minimally invasive or craniectomy), conservative or palliative. It does appear that there is a benefit to be gained from surgical intervention, so this may be worth exploring as something more than in an emergency option.