JC: ATACH-II SECONDARY ANALYSIS ON CEREBRAL MICROBLEEDS

Cerebral Microbleeds and the Effect of Intensive Blood Pressure Reduction on Hematoma Expansion and Functional Outcomes. A Secondary Analysis of the ATACH-2 Randomized Clinical Trial.

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STUDY QUESTION:

In patients with intracerebral haemorrhage (ICH) is there an interaction between underlying small vessel disease (number of microbleeds and location) and intensive systolic blood pressure (SBP) control which may lead to a worse functional outcome or significant haematoma expansion?

HOW DOES THIS RELATE TO OUR PRACTICE ON NCCU?

Systolic blood pressure control in spontaneous ICH is frequently managed on or about 140mmHg (range 120mmHg – 160mmHg) and differs depending on the aetiology, location, and other medical comorbidities. The 120mmHg – 160mmHg range is within current research guidelines and recommendations.

WHAT DO WE CURRENTLY KNOW ABOUT THIS AREA?

Specifically, there is little known about cerebral microbleeds. It is known that these microbleeds are remnants of prior micro-haemorrhages at the level of arterioles and capillaries and that such events can be visualised on T2 weighted (blood-sensitive) GRE MRI scans. In addition, these microbleeds are markers of underlying cerebral small vessel disease usually representing hypertensive arteriopathy.

There are two competing theories as to the impact of these microbleeds in ICH:

1. The fragility of cerebral microbleeds may increase the risk of haematoma expansion (and therefore increase the burden of injury).
2. The vessels become more resilient over time and are therefore somewhat protective against further expansion.

Haematoma expansion occurs early – usually within the first few hours and as much as a 10%

increase can have a devastating effect. The jury is still out on the level of blood pressure reduction that provides the greatest benefit for reducing hematoma expansion. There is however, greater research, evidence, and understanding of the 'general principals and management of ICH':

1. ICH is graded (Lisk) into 4 categories:
    1. 0 = No Intraventricular haemorrhage (IVH).
    1. 1 = Blood in the 3rd ventricle or <1/3 of 1 lateral ventricle
    1. 2 = Blood in <1/2 of both lateral ventricles or 2/3 of 1 ventricle
    1. 3 = 1 ventricle completely filled or 2 more than 50% filled

- Poorer outcomes for ICH are frequently seen with
    - Haematoma expansion
    - ICH volume >60mls
    - IVH extension
    - ICH in certain areas (eg: cerebellum – requiring a high neurosurgical intervention; pons – 100% mortality)
    - Low GCS <5 (and less researched)

- Studies tend to remove those at highest risk – ICH has an on or about 20% mortality at 24 hours. The major RCTs exclude on or about 9 in 10 patients and as such generalisation/applicability of the results may be difficult.

- Early treatment of ICH has a positive impact – for instance, patients <70 years of age, with small ICH (<5mls), without IVH, and treated within 2.5 hours were shown to have reduced haematoma expansion and a 'favourable' OR for poor outcome of 0.28 at 90 days (FAST trial). The journal club today will look at the interplay of rapid initial treatment, prevention of haematoma expansion, and the effect of cerebral microbleeds.

- There are often difficult and competing risks – intracerebral pressure (ICP) in traumatic ICH may limit blood pressure targets and where there is suspicion of elevated ICP, CPP of 60-80mmHg is recommended and relaxing the lowering of BP targets may be needed.

- Blood pressure is frequently elevated in acute non-traumatic ICH. Most research suggests 140mmHg is a reasonable systolic target although the INTERACT2 trial provides a cautionary tail that lower blood pressure (SBP <140mmHg) may improve functional outcomes. Ordinal analysis of Rankin scores (rather than 'favourable' vs 'unfavourable' scores) and quality of life scores were improved in the more intensive therapy group. However, many patients received mannitol (ICP monitoring data was not provided) and the use of specific antihypertensives not available in all countries may reduce the external validity. Further, whilst the use of multiple

different antihypertensive agents was pragmatic in the trial, there may be some benefit from specific antihypertensives via non blood pressure pleiotropic effects that may have affected the results.

- The ATACH-2 trial showed no difference between Intensive and 'Standard' blood pressure treatment strategies for the first 24 hours on functional outcome at 3 months or haematoma expansion. The study ended early due to futility. Greater renal adverse events at 7 days were noted in the intensive therapy group.

- Commonly used medications include, but are not limited to labetalol, hydralazine, nicardipine, clevidipine, and phentolamine.

WHY WAS THIS STUDY NEEDED?

Understanding whether cerebral microbleeds require greater blood pressure control will improve our appreciation of both the pathology and management of ICH with concurrent small vessel disease. More broadly speaking it will also help smaller centres to align their practices with tertiary and quaternary referral centres.

AT JOURNAL CLUB WE SHOULD DISCUSS THE FOLLOWING:

1. Is there an interaction between underlying small vessel disease and intensive systolic blood pressure (SBP) control for functional outcome and haematoma expansion?
2. Blood pressure targets in ICH and exceptions to general rule
3. The high level of practice variation
4. Differences between the ATACH-2 and INTERACT2 trials

SHOULD WE CHANGE PRACTICE ON NCCU

No! As we will discuss at the journal club, cerebral microbleeds did not appear to have an impact on functional outcomes or mortality. Additionally, their presence was not associated with haematoma expansion or response to blood pressure management.