A new understanding of increased pressure within the skull in brain diseases

RESEARCH TEAM:

Chief Investigator:

Prof Neil Spratt FRACP, PhD

School of Biomedical Sciences and Pharmacy, University of Newcastle, John Hunter Hospital, and Hunter Medical Research Institute, Newcastle, NSW, Australia.

Co-investigators:

Dr Damian McLeod PhD, Dr Lucy Murtha PhD, and Dr Daniel Beard PhD,

School of Biomedical Sciences and Pharmacy, University of Newcastle, and Hunter Medical Research Institute, Newcastle, NSW, Australia.

Research

The skull encases and protects the brain, but after injury, increasing pressure within the skull can worsen injury. As occurs elsewhere in the body, when the brain is injured (from e.g. trauma, stroke or bleeding) swelling occurs. It has been recognised for more than a century that because the skull is basically a 'closed box', swelling causes pressure to rise. However our group made experimental discoveries that showed that pressure within the skull rises even after small stroke without noticeable brain swelling. Critically, we also showed that increasing the pressure after stroke causes reduction in blood flow particularly to the vulnerable brain region immediately surrounding the stroke. Such pressure rise is therefore the likely culprit causing the expansion of stroke that occurs in some patients with initially mild strokes during the first days in-hospital.

We were suspicious that the intracranial pressure rise may be related to increases in the volume of fluid around the brain – the cerebrospinal fluid (CSF). We found that there is a substance within this fluid post-stroke that triggers the pressure rise. Excitingly, our experimental studies also showed that the pressure rise can be completely prevented by a short duration of body cooling.

Dangerous pressure rises are also an important feature of multiple other brain diseases, and existing treatments are limited. As in stroke, causes other than brain swelling have not generally been considered. In this project our aim was to conduct experimental studies to determine the best way to apply cooling, as a precursor to clinical trials; to explore the mechanisms causing the rise, in order to develop additional therapies; to confirm pressure rise in patients with minor/treated stroke; and to determine whether this newly identified mechanism contributes to pressure rise in other brain disorders.

Outcome

We confirmed significant elevation of intracranial pressure in patients with minor symptoms 24 h after stroke.

We found that CSF from patients with bleeding into the fluid around the brain (subarachnoid haemorrhage, or intracranial haemorrhage with intraventricular extension) caused intracranial pressure to rise, but over a completely different time course than for ischaemic stroke.

We were able to measure CSF production with very high accuracy and reproducibility. We showed that a commonly used medication, acetazolamide (used to treat some disorders of intracranial pressure elevation), very consistently halved the CSF productions rate. However surprisingly, other existing and a proposed new medication, thought to act on CSF production, had no effect. This suggests that although multiple pathways may have some effect on CSF production, some are much more important than others.

We tested a gradual cooling protocol over 2 hours to 32.5 °C, achievable in patients. Even when the target temperature was only sustained for 30 minutes, it completely abolished subsequent pressure rise within the skull. Interestingly, a similar cooling protocol, but cooling to 34 °C, only resulted in partial abolition of the intracranial pressure elevation, and did not prevent enlargement of the stroke lesion. Similarly, skin cooling alone, while maintaining body core temperature, did not prevent subsequent intracranial pressure rise. These findings give us the information needed for a rationally-designed clinical trial of short duration hypothermia.