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UNCERTAINTIES

Which treatments are safe and effective to reduce intracranial pressure following severe traumatic brain injury?

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What you need to know

- A tiered approach using multiple interventions to reduce raised intracranial pressure and maintain adequate cerebral perfusion pressure is reasonable in severe traumatic brain injury
- The effectiveness and safety of several common interventions is not known, because of a paucity of data from adequately powered, randomised controlled trials
- Use your clinical judgment to balance the possible benefits and potential risks of treatments, and explore with patients and their loved ones what an acceptable outcome is, to guide decision making

Forceful impact to the head can impair mental status and lead to neurobehavioural deficits. Most traumatic brain injuries (TBIs) are mild,[1] but about 20% of patients have severe injury defined by a Glasgow coma scale (GCS) score ≤8 at presentation. Severe TBI has an incidence of 70 per 100 000 persons worldwide.[2 3]

Multiple pathologies often combine to cause more harm than the initial head injury. Injuries may be focal or diffuse and over time can coalesce through inflammation. These physiological changes can increase the volume of intracranial contents, leading to rising intracranial pressure (ICP) and secondary injury to brain tissue. Sustained rise in ICP above normal range (7 to 15 mm Hg) can result in progressive cerebral ischaemia, herniation syndromes, or death.[4] In a retrospective single centre cohort study (459 patients with severe TBI), an elevated ICP >22 mm Hg for >37 minutes was associated with worsening functional outcomes.[5] In an international cohort study (2113 patients), 21.3% of patients with severe TBI had died and 43.1% had a permanent need for help with activities of daily living or absence of awareness of self or environment[6] at six months.[3]

Early resuscitation and emergency care of severe TBI aim to reduce cerebral oxygen demand, optimise perfusion to the brain, and limit secondary injury. Several routine critical care interventions are employed, and these are bundled together as "tier 0" measures (fig 1).[7 8] If ICP continues to rise, additional treatments are commonly used (tier 1 and 2 interventions in fig 1). It is uncertain which of these treatments are safe, when they should be deployed, and whether they can improve survival or prevent disability.

This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the *Cochrane Library*. This paper is based on a research priority identified and commissioned by the National Institute for Health and Care Research's Health Technology Assessment programme on an important clinical uncertainty. You can read more about how to prepare and submit an Education article on our Instructions for Authors pages https://www.bmj.com/about-bmj/resources-authors/article-types

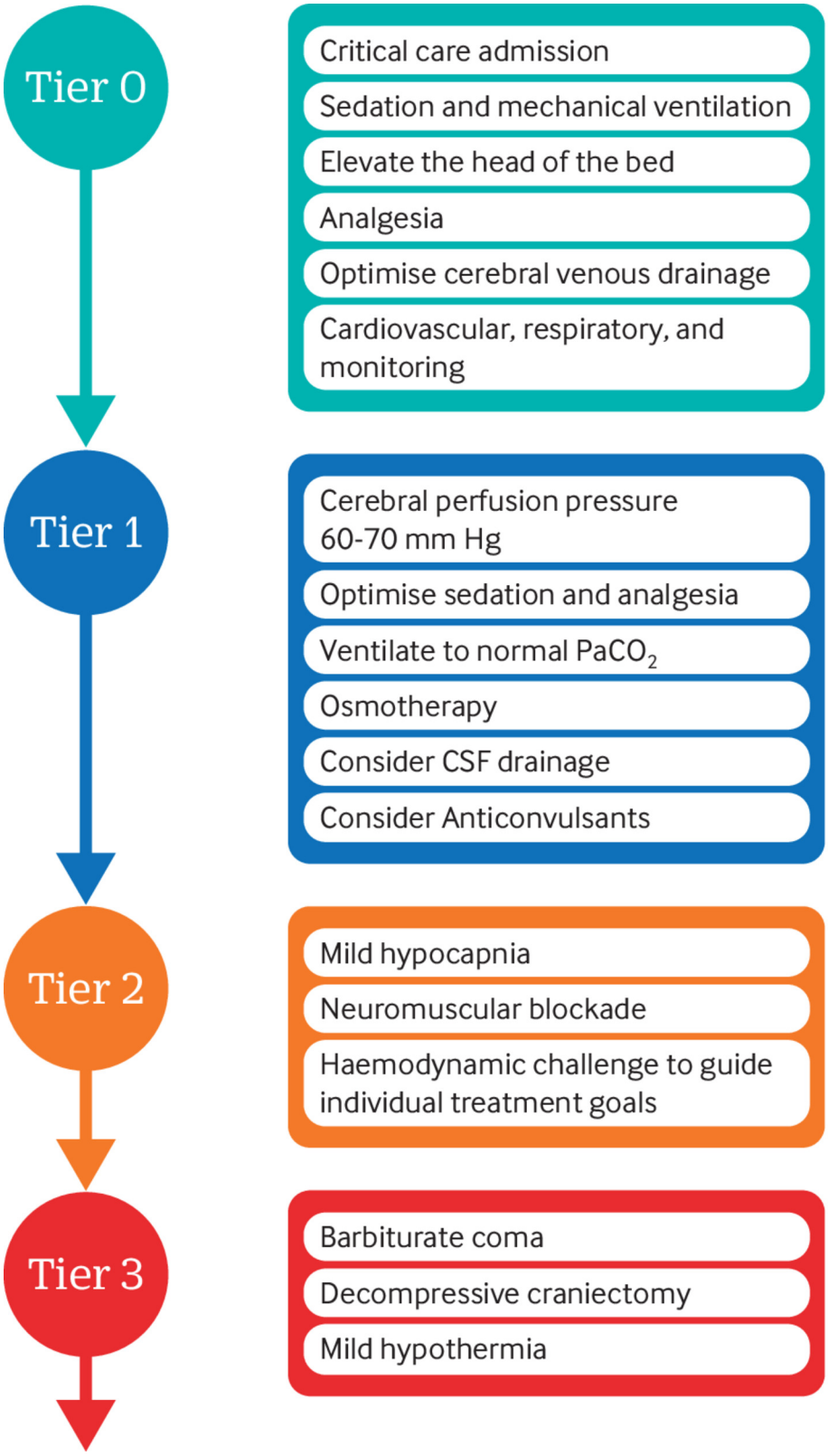

Fig 1 | Key treatments used to manage raised intracranial pressure based on the Seattle International Severe Traumatic Brain Injury consensus conference.[7] Higher tiers involve higher risks. CSF=cerebrospinal fluid

Additional rescue therapies (tier 3 interventions) for refractory intracranial hypertension are used in <10% of patients with severe TBI[9] and are not covered in this article.

What is the evidence of uncertainty?

Little evidence of high certainty exists on interventions to reduce intracranial pressure in severe TBI. International guidelines and treatment protocols are based on combined expert opinion.[7 10] A guide to GRADE evidence ratings is shown in box 1.

Box 1: GRADE Working Group grades of evidence

- High certainty—we are very confident that the true effect lies close to that of the estimate of the effect
- Moderate certainty—we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- Low certainty—our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
- Very low certainty—we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Osmotherapy

Mannitol and hypertonic sodium chloride infusions (HTS) increase the osmotic pressure of plasma and draw water from extracellular spaces in the brain tissue across the blood-brain barrier, thereby potentially decreasing ICP. Guidelines recommend intermittent bolus dosing in severe TBI but limited guidance is available on agent, dose, concentration, or route.[7] In a large observational study (758 patients) osmotherapy was used in approximately one in five patients with severe TBI within the first 48 hours,[11] with wide variation in drug choice, timing, and dosing regimens.

A Cochrane review published in 2020 (six trials, 287 patients) reported insufficient evidence comparing osmotherapy treatments in severe traumatic brain injury, and that hypertonic saline infusion was no better than mannitol. The evidence is of low to very low certainty. Adverse effects were not routinely measured.[12] Osmotic diuresis following mannitol can exacerbate hypotension and potentially worsen secondary brain injury. A retrospective analysis of an international multicentre randomised controlled trial (568 patients) found a statistically significant incidence of acute kidney injury with mannitol (hazard ratio, HR 2.3, 95% confidence interval, CI:1.2 to 4.3, P=0.01), but not with HTS (HR 1.6, 95% CI: 0.9 to 2.8, P=0.08) in moderate to severe TBI.[13]

Individualised targets for cerebral perfusion pressure

Cerebral perfusion pressure (CPP) is the pressure gradient across the cerebral vascular bed. Expert consensus guidelines advise targeting a CPP of 60-70 mm Hg.[7 8] Intracranial pressure monitoring enables the continuous calculation of CPP. CPP is calculated as the mean arterial pressure (MAP) minus the ICP. MAP is usually measured continuously in patients with severe TBI through invasive arterial monitoring.

Fluid loading and a vasopressor are commonly used to increase MAP when ICP is elevated (and therefore increase CPP).[11] Expert consensus guidelines have proposed a "bedside MAP challenge" whereby a vasopressor is initiated or titrated to increase the MAP by 10% for up to 20 minutes. Clinical effect is determined through ICP monitoring and clinical assessment.[7] Such interventions may optimise the ICP but they can cause harm. A prospective study in two observational cohorts (1008 patients with severe TBI) reported that a mean positive daily fluid balance was associated with higher ICU mortality (Odds ratio, OR 1.10, 95% CI: 1.07 to 1.12) and worse functional outcome (OR 1.04, 95% CI: 1.02 to 1.05) per 0.1 L increase.[14] A systematic review in 2020 concluded that the evidence was limited (two non-randomised studies, 133 patients) for vasopressor use in targeting CPP to improve neurological outcome or reduce mortality in patients with severe TBI.[15] Vasopressor use can lead to organ ischaemia, hyperglycaemia, and tachycardia in critically ill patients.[16]

Hyperventilation

Mechanical hyperventilation can lower the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) below normal range (4.7 to 6.0 kPa) in sedated patients. Induced hypocapnia can reduce cerebral blood flow and volume, and so reduce elevated ICP. Sustained hyperventilation can have adverse effects such as a potential increase in ischaemic brain volume.[17]

International expert consensus guidelines recommend normocapnia (4.7 to 5.1 kPa) for all patients with severe TBI on ICP monitoring, and induced mild hypocapnia (4.3 to 4.6 kPa) in sustained ICP elevation.[7] Limited evidence supports these recommendations. A Cochrane review in 1997 on the use of hyperventilation for severe TBI identified one randomised controlled trial (113 participants).[18] This study suggested possible reduction in mortality with hyperventilation targeting profound hypocapnia (3.2 to 3.7 kPa) at one year post injury (relative risk, RR 0.73, 95% CI: 0.36 to 1.49), but a potential increase in the risk of death or severe disability (RR 1.14, 95% CI: 0.82 to 1.58). A recent narrative review identified no further randomised trials.[19]

Despite this lack of evidence, a cohort study across Europe in 2021 (758 patients) reported that 10% of patients with severe TBI receive moderate hypocapnia ($PaCO_2$ 4.0-4.5 kPa) and < 2% intensive hypocapnia ($PaCO_2$ < 4.0 kPa).[11] This study reported no observed association between risk of mortality or unfavourable outcome and the use of hyperventilation.

Cerebrospinal fluid drainage

Removal of cerebrospinal fluid (CSF) through placement of an external ventricular drain (EVD) can reduce ICP but neurosurgical intervention has risks of bleeding and infection. The need for and optimal timing of EVD placement are uncertain. In a systematic review in 2020 (21 studies, 4542 patients) no studies directly compared EVD insertion at different time points following severe TBI.[20] The risk of bias and heterogeneity among studies was high. A questionnaire study of 68 European neurotrauma centres in 2017 highlighted wide variation in practice.[21] The indication for EVD insertion in severe TBI was described as routine practice by 14% of centres, guided by hydrocephalus on brain imaging (23%) or specifically for CSF drainage (60%).

Neuromuscular blockade

Neuromuscular blocking (NMB) agents facilitate mechanical ventilation and avoid ICP surges caused by coughing or straining. This can also be addressed with adequate sedation or analgesia. Prolonged use of NMB agents can mask the presence of seizure activity and increase the risk of critical illness polyneuropathy.

A quarter of 66 European neurotrauma centres reported using neuromuscular blockade as a tier 1 intervention.[21] International expert consensus guidelines recommend it as a tier 2 intervention, with continuation only if clinical assessment shows reduction in ICP.[7] Limited data are available to guide practice. A systematic review in 2015 (32 studies) noted that studies were small and used surrogate physiological endpoints such as ICP response to stimulation, energy expenditure, or effect on physiological parameters.[22]

Is ongoing research likely to provide relevant evidence?

We searched clinicaltrials.gov and ISCRTN for ongoing trials. We are conducting an open-label randomised trial in the UK on osmotherapy in severe TBI with equimolar doses of mannitol or HTS.[23] This study is designed as a superiority trial with a primary endpoint of neurological outcome at six months, assessed using the Glasgow outcome score extended. This trial (expected to report in 2024) will address uncertainty regarding osmotherapy agents, although the UK setting may limit generalisability. We identified a single ongoing trial on use of neuromuscular blocking agents in severe TBI.[24] This trial aims to recruit 34 patients and is principally evaluating physiological outcomes. It is unlikely to address uncertainties in practice. We did not identify any ongoing or planned trials on vasopressor use, fluid therapy, hyperventilation strategies, or CSF drainage in severe TBI.

We identified several trials on novel management strategies for severe TBI, including the use of brain tissue oxygen monitoring (BOOST3) and combined brain tissue oxygen and ICP monitoring (BONANZA).[25 26] A four-centre feasibility study recently evaluated the role of cerebral autoregulation and pressure reactivity index guided management strategies in severe TBI.[27] Such trials are challenging to conduct at scale, given the complex interventions, limited availability of relevant software, and heterogeneity of disease.

What should we do in the light of the uncertainty?

A personalised approach to treatment is advised, taking into consideration the cause of raised ICP, severity, time course, response to treatments, and quality of the evidence. Management is usually led by a multidisciplinary team and tailored to individual injury pattern and clinical progress.

Different treatment algorithms consider indicators such as intracranial pressure, cerebral perfusion pressure, and brain tissue oxygenation to guide timing and choice of interventions. It is uncertain if any algorithm is superior.

Using the lowest possible therapeutic intensity level to control CPP/ICP towards the optimal appears pragmatic and effective. This approach is often visualised as the described tiered strategy with escalation and de-escalation through tiers as required (fig 1).

Sources and search selection

We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases using the following text words or MeSH terms: “traumatic brain injury” and “intracranial pressure”. We searched for relevant systematic reviews, meta-analyses, and randomised controlled trials from inception to 13 April 2022. We prioritised recent systematic reviews and key trials for inclusion. We used guidelines from the Brain Trauma Foundation and Seattle International Brain Injury consensus conference as a framework for identifying therapeutic interventions. Searches were supplemented by hand searching the reference lists of all relevant studies (including existing systematic reviews), forward citation searching of included studies, and undertaking targeted searches of the internet using the google search engine.

What patients and their loved ones need to know

Severe traumatic injuries to the head can cause brain swelling, leading to pressure rising within the skull. This squashes the brain and reduces its blood supply which causes further damage. About one in three people with severe brain swelling dies as a consequence. Among those who do survive, around one in three is left with mild to severe disabilities.

Many treatments have been studied to reduce the catastrophic consequences of brain swelling. There are no single treatments with strong evidence of benefit for all patients. Doctors and nurses may sometimes have to provide treatments supported by limited evidence. More research is needed to better understand which treatments can improve survival to an outcome that aligns with the patient’s known values and the preferences of their loved ones.

Ongoing trials evaluating interventions in neurocritical care

- The Salt or Sugar (SOS) trial is comparing bolus hyperosmolar therapy with mannitol versus hypertonic saline in adults with TBI and raised ICP. The trial aims to recruit 638 patients from UK critical care units. ISRCTN16075091 https://warwick.ac.uk/fac/sci/med/research/ctu/trials/sos/
- Brain Oxygen Optimization in Severe TBI, Phase 3 (BOOST3) is a randomised trial comparing ICP guided management strategy with an ICP and brain tissue oxygen guided strategy. The US based trial aims to recruit 1094 children (aged >14) and adults with TBI. NCT03754114 https://siren.network/clinical-trials/boost-3
- The Brain Oxygen Neuromonitoring in Australia and New Zealand Assessment Trial (BONANZA) is testing whether a management strategy guided by early brain tissue oxygen monitoring in adults with TBI improves long term neurological and functional outcomes. The trial aims to recruit 860 participants. ACTRN12619001328167 https://www.bonanza.org.au
- The treatment of Intracranial Hypertension of Severe Traumatic Brain Injured Patients. Physiopathologic effects of Neuromuscular Blocking Agents (THIC Cu) is a randomised open label interventional trial, comparing the area under the curve of the temporal evolution in intracranial pressure in patients with severe TBI receiving cisatracurium or placebo. The trial commenced in 2015 and aims to recruit 34 participants. NCT02404779 https://clinicaltrials.gov/ct2/show/NCT02404779

Recommendations for future research

In adult patients with severe traumatic brain injury, which tier 1 and 2 interventions improve 6 month survival without severe disability, compared with standard UK neurocritical care practice?

- Adult patients intubated and ventilated with severe traumatic brain injury (GCS ≤8)
- Individual and combined tier 1/2 interventions
- Standard neurocritical care practice
- Six month survival without severe disability (Glasgow Outcome Scale Extended >5)

How patients were involved in the creation of this article

No patients were formally involved in the writing of this article. All authors are investigators for the SOS trial, which has used patient and public involvement throughout design and conduct. The study is also supported by the UK national acute brain injury charity Headway, which advised the investigators on outcome measures that matter most to patients with TBI.

Education into practice

- What factors do you consider when deciding how to manage raised ICP in a patient?
- How would you individualise treatments in the situation of limited evidence?
- How would you involve patients and their loved ones in exploring what an acceptable outcome would be, when considering different treatment options?

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