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BMJ Uncertainties

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

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We have read and understood BMJ policy on declaration of interests and declare the following interests: GP is chief investigator and MJN is a local principal investigator for the HTA funded SOS trial (NIHR 17/120/01).

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Introduction:

More than 50 million people suffer a traumatic brain injury (TBI) each year. Forceful impact to the head can impair mental status and lead to neurobehavioral deficits. Most traumatic brain injuries are mild.[1]

Severe TBI (defined by a Glasgow Coma Score ≤8 at presentation) accounts for approximately 20% of all TBI cases and has a reported incidence of 70 per 100,000 worldwide.[2] [3] Severe TBI encompasses multiple pathologies, which often combine to cause more harm than the initial primary head injury. Injuries may be focal or diffuse and over time can coalesce through local response to injury, or systemic exacerbation. These physiological changes can increase the volume of the intracranial contents, leading to rising intracranial pressure (ICP) and further secondary injury to brain tissue. The normal range for ICP is 7 to 15mmHg in the horizontal position, with fluctuation depending on age, posture and clinical condition.[4] In the context of TBI, a continued and sustained rise in ICP well above this threshold can result in progressive cerebral ischaemia, herniation syndromes or death. In a retrospective single centre cohort of 459 patients with severe TBI, an elevated ICP >22mmHg for >37 minutes was associated with worsening functional outcomes.[5] The clinical consequences of such neurological injury are devastating for patients; in a recent well conducted international cohort study including 2113 patients with severe TBI, 21.3% of had died and 43.1% had survived with an unfavourable neurological outcome at six months.[3] The latter metric describes a Glasgow Outcome Score Extended (GOSE) of <5, implying a permanent need for help with activities of daily living or absence of awareness of self/environment.[6]

Early resuscitation and emergency care of severe TBI involves a number of routine critical care interventions alongside regular consideration of emergency neurosurgery, to reduce cerebral oxygen demand, optimise perfusion to the brain and limit further secondary injury. These interventions are often bundled together as 'tier zero' measures in expert consensus guidelines (figure 1).[7] [8] If ICP increases despite the optimisation of physiology and provision of such therapies, then several additional medical treatment options are commonly used to reduce ICP (tier one and two interventions in figure 1). It is uncertain which of these treatments are safe, when they should be deployed and whether they can improve survival or prevent disability.

Additional rescue therapies (tier 3 interventions in figure 1) for those with refractory intracranial hypertension are used in <10% patients with severe TBI.[9] There are major limitations in the evidence for these treatments and as such they are not covered in this article.

What is the evidence of uncertainty?

Potential therapeutic interventions to reduce ICP in severe TBI include the use of osmotherapy, individualisation of cerebral perfusion pressure (CPP) targets, hyperventilation and surgical drainage of cerebrospinal fluid (CSF). These interventions are currently used with widespread variation. A recent study of 758 patients with severe TBI from 52 European centres concluded substantial between centre variation in use of higher therapeutic intensity level treatments.[10] There have been no large randomised controlled trials (RCT) to guide pragmatic use and relevant observational datasets have clear limitations.

Osmotherapy

Intermittent bolus dosing of hyperosmolar therapy is currently recommended within international guidance for severe TBI patients with ICP monitoring and sustained ICP elevation.[8] Limited guidance is provided on agent, dose, concentration or route. Both 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. A large observational study of 758 patients with severe TBI indicated that osmotherapy is used in approximately one in five cases within the first 48h of care.[10] However, there was wide variation in drug choice, timing and dosing regimens. A Cochrane review conducted in 2020 comparing HTS to other intracranial pressure lowering agents identified no placebo-controlled trials and only six small comparative studies (comparing HTS to mannitol), including 287 patients. The authors identified serious risks of bias in the current evidence and recommended further research at scale.[11]

Given the lack of evidence, clinicians may opt for HTS based on perceived benefits during acute resuscitation, or lower risks of harm. Osmotic diuresis following mannitol can exacerbate hypotension and potentially worsen secondary brain injury. In addition, a post-hoc analysis of an international multicentre RCT evaluating the use of erythropoietin as a neuroprotective agent in 606 patients with moderate to severe TBI, concluded that mannitol may be associated with a higher incidence of acute kidney injury (OR 1.27 95%CI:1.1-1.5) when compared to HTS.[12]

Individualisation of cerebral perfusion pressure targets

ICP monitoring enables the continuous calculation of cerebral perfusion pressure (CPP), defined as the pressure gradient across the cerebral vascular bed. International guidelines advise targeting a CPP of 60-70mmHg.[7 8] 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 vasopressor use to increase the MAP when the ICP is elevated (and therefore increase the CPP) are common interventions.[10] In addition, guidelines derived from a Delphi process of international expert opinion have proposed a 'bedside MAP challenge' may help determine individualized response to higher CPP targets in the context of elevated ICP.[8] A vasopressor is initiated or titrated to increase the MAP by 10% for up to 20 minutes while clinical effect is determined by a bedside clinician, through ICP monitoring and general critical care assessment.

While such interventions may optimise the ICP, they may also cause harm. A prospective comparative effectiveness study conducted in two observational cohorts and including 1008 patients with severe TBI reported a mean positive daily fluid balance to increase the odds of ICU mortality (odds ratio 1.10, 95% CI 1.07 to 1.12) and worse functional outcome (odds ratio 1.04, 95% CI 1.02 to 1.05) per 0.1L increase.[13] A recent systematic review in 2020 evaluating the role of vasopressor use to augment CPP and improve neurological outcome in patients with severe TBI identified only 2 non randomised studies, including 133 patients.[14] The authors conclude that evidence for vasopressor administration to target specific CPP goals in this population is limited. Potential harms of vasopressor use in critically ill patients are well documented, including organ ischaemia, hyperglycaemia and tachycardia.[15]

It is also uncertain if blood pressure management should be tailored to injury subtype (local versus diffuse) and/or cerebral autoregulation status.[16] In severe TBI, failure of autoregulation can lead to further compromise in perfusion to the injured brain and exacerbation of anatomical brain injury. Indices to assess the level of cerebral autoregulation present may allow estimation of an individualised 'optimal' CPP. A four centre feasibility randomised controlled trial recently compared a standard CPP target (60-70mmHg), to a CPP target guided by prospective assessment of cerebral autoregulation in 60 patients, 68% of whom had severe TBI.[17] The intervention was reported as feasible and safe, with no differences in predefined safety end points between groups and a non-significant 17% absolute risk reduction for mortality (p=0.160).

Hyperventilation

Lowering the partial pressure of carbon dioxide in arterial blood ($PaCO_2$) below the normal range of 4.7 to 6.0 kPa can be achieved in sedated patients with severe TBI, through mechanical hyperventilation. This intervention can potentially reduce cerebral blood flow and cerebral blood volume, therefore reducing elevations in ICP. However, sustained hyperventilation has adverse effects such as a potential increase in ischaemic brain volume.[18] Recent international expert consensus guidelines recommend normocapnia (4.7 to 5.1kPa) as a baseline tier 1 strategy for all patients with severe TBI who have ICP monitoring, and induced mild hypocapnia (4.3 to 4.6kPa) as a tier 2 strategy in the event of sustained ICP elevation.[8]

There is limited evidence to support these recommendations. A Cochrane review on the use of hyperventilation for severe TBI conducted in 1997 identified only one randomised controlled trial, including 113 participants.[19] This study reported non-significant results, suggesting a potential reduction in mortality with hyperventilation targeting profound hypocapnia (3.2 to 3.7kPa) at 1 year post injury (relative risk 0.73, 95% CI 0.36 to 1.49), but a potential increase in the risk of death or severe disability (relative risk 1.14, 95% CI 0.82 to 1.58). A recent narrative review identified no further randomised trials on the topic.[20] Despite this lack of evidence, a recent international cohort study of 758 patients with severe TBI concluded that 10% still receive moderate hypocapnia ($PaCO_2$ 4.0-4.5 kPa) and < 2% intensive hypocapnia ($PaCO_2$ < 4.0 kPa).[10] This study reported no observed association between risk of mortality or unfavourable outcome and the use of hyperventilation.

Cerebrospinal fluid (CSF) drainage

Removal of cerebrospinal fluid through placement of an external ventricular drain (EVD) can reduce ICP, thereby improving CPP and potentially reducing the need for further harmful interventions. However, neurosurgical intervention in a theatre environment comes with baseline risks of bleeding, infection and theatre transfer. Evidence to guide decision making in this area is limited, leading to uncertainty on necessity and optimal timing. A systematic review in 2020 evaluating the optimal timing for EVD placement following severe TBI identified 21 relevant studies including 4542 patients.[21] None of these studies directly compared EVD insertion at different timepoints. Pooling of data from single arm studies was deemed inappropriate due to the high levels of identified bias and heterogeneity amongst included studies. The authors conclude a pressing need for further

research. An international questionnaire study of 68 European neurotrauma centres in 2017 with a 97% response rate highlighted wide variation in practice.[22] The indication for EVD insertion in severe TBI was described as routine practice by 14% responding centres, guided by hydrocephalus on brain imaging by 23% or specifically for CSF drainage by 60%. The intervention was considered as a tier one intervention by 27% sites and tier two by 33% sites; international guidelines currently suggest consideration as a tier 1 intervention.[8]

Neuromuscular blockade

Neuromuscular blocking (NMB) agents are used in patients with severe TBI to facilitate mechanical ventilation to specific targets and ensure avoidance of stimulation related ICP surges (such as coughing/straining). However, many of these issues can be resolved with adequate sedation/analgaesia. Prolonged use of NMB agents can also potentially mask the presence of seizure activity, or increase the risks of critical illness polyneuropathy. Only 25% of European centres report use as a tier 1 intervention.[22] International expert consensus guidelines recommend consideration as a tier 2 intervention, with continuation only in the event of proven efficacy (reduction in ICP), as interpreted by the bedside clinician.[8] There is limited data to guide best practice. A systematic review in 2015 evaluating the role of NMB in patients with TBI identified 32 studies, including 22 prospective cohorts.[23] All studies were of small sample size, and used surrogate physiological endpoints, including ICP response to stimulation, energy expenditure or the effect of NMB bolus on generic physiological parameters. The authors conclude ongoing uncertainty and call for large well-designed studies.

Is ongoing research likely to provide relevant evidence?

We searched the trial registries clinicaltrials.gov and ISCRTN for on-going trials.

A UK based open label randomised trial of osmotherapy in severe TBI with equimolar doses of mannitol or HTS, has completed its pilot phase and is currently progressing to full trial recruitment.[24] This study is designed as a superiority trial with a primary endpoint of neurological outcome at 6 months, assessed using the Glasgow Outcome Score Extended. This trial should definitively address the uncertainty regarding osmotherapy agents, although the UK setting may limit generalisability.

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) compared to conventional strategies.[25 26] The recent completion of a 4-centre feasibility study evaluating the role of pressure reactivity index guided management strategies in treatment of severe TBI compared to usual care also suggests future research in this area may be developing.[17] Such trials will be challenging to conduct at scale, given the complexities of the intervention, limited availability of the relevant software and heterogeneity of disease.

We identified a single ongoing trial on use of NMB agents in severe TBI.[27] This trial aims to recruit only 34 patients and is principally evaluating physiological outcomes, therefore it is unlikely to impact significantly on current uncertainties in clinical practice. We did not identify any ongoing or planned trials on vasopressor use, fluid therapy, hyperventilation strategies or CSF drainage in severe TBI.

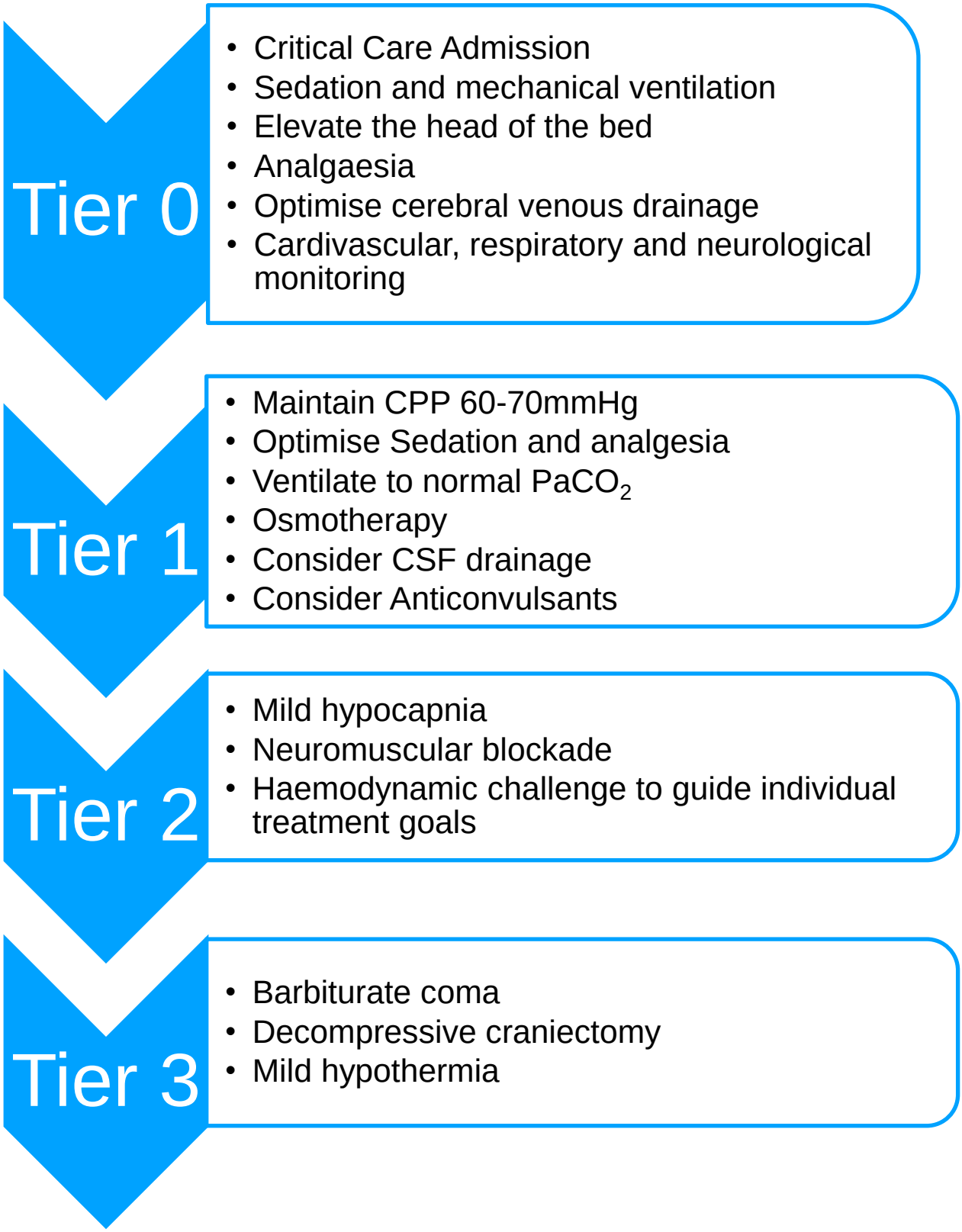
What should we do in light of the uncertainty?

Given the uncertainty about the individual and relative effectiveness of most interventions, a personalised approach to treatment is advised, taking into consideration the cause of raised ICP, magnitude, time course, response to treatments and quality of the evidence.

Different treatment algorithms consider indicators such as intracranial pressure, cerebral perfusion pressure, and brain tissue oxygenation to guide timing and choice of interventions. There is uncertainty 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, led by a multidisciplinary team and tailored to individual injury pattern and clinical progress (Figure 1).

Figure 1: Key treatments used to manage raised intracranial pressure based around the Seattle International Severe Traumatic Brain Injury Consensus Conference. [8] Higher tiers involve higher risks. CPP – Cerebral Perfusion Pressure; CSF – cerebrospinal fluid;



Sources and search selection

We searched PubMed, EMBASE and 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 13th April 2022. We prioritised recent systematic reviews and key trials for inclusion. We used the Brain Trauma Foundation and Seattle International Brain Injury consensus conference guidelines 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 world wide web using the google search engine.

Box 1: What you need to know

- A tiered approach using multiple interventions to target 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, due to a paucity of data from adequately powered, randomised controlled trials. Such interventions are challenging to study further due to frequent use in clinical practice and published expert consensus recommendations advocating use.

- Use your clinical judgement to balance the possible benefits and potential risks of treatments and explore with your patients and their loved ones, what an acceptable outcome is to guide decision making.

Box 2: 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 Headway – the UK national acute brain injury charity – who have advised the investigators on outcome measures that matter most to patients with TBI.

Box 3: 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 die as a consequence. Amongst those who do survive around one in three are 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 which aligns with the patient's known values and preferences of their loved ones.

Box 4: 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?

Box 5: Ongoing trials evaluating interventions in neurocritical care

1. 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/

2. 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

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 compared to in adults with TBI improves long term neurological and functional outcomes. The trial aims to recruit 860 participants. ACTRN12619001328167 https://www.bonanza.org.au

4. 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 if 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

Box 6: 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 to standard UK neurocritical care practice?

P- Adult patients intubated and ventilated with severe traumatic brain injury (GCS≤8)

I- Individual and combined tier 1 / 2 interventions

C- standard neurocritical care practice targeting a CPP 60-70mmHg and ICP ≤20mmHg

O- 6-month survival without severe disability (Glasgow Outcome Scale>5)

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