British Journal of Anaesthesia **99 (1):** 32–42 (2007)
doi:10.1093/bja/aem139 Advance Access publication June 6, 2007

BJA

Traumatic brain injury: intensive care management

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Traumatic brain injury (TBI) is a major cause of morbidity and mortality worldwide. The modern management of severe TBI has fallen into the domain of a multidisciplinary team led by neurointensivists, neuroanaesthetists, and neurosurgeons and is based on the avoidance of secondary injury, maintenance of cerebral perfusion pressure (CPP), and optimization of cerebral oxygenation. In this review, we will discuss the intensive care management of severe TBI with emphasis on the specific measures directed at the control of intracranial pressure and CPP.

Br J Anaesth 2007; **99**: 32–42

Keywords: brain, injury; complications, head injury; head, injury; intensive care, neurosurgical; monitoring, intracranial pressure

Traumatic brain injury (TBI) has a dramatic impact on the health of the nation: it accounts for 15–20% of deaths in people aged 5–35 yr old, and is responsible for 1% of all adult deaths.[44] Approximately 1.4 million people in the UK suffer a head injury every year[38] resulting in nearly 150 000 hospital admissions per year.[40] Of these, approximately 3500 patients require admission to ICU. The overall mortality in severe TBI, defined as a post-resuscitation Glasgow Coma Score (GCS) $\leq$8, is 23%.[42] In addition to the high mortality, approximately 60% of survivors have significant ongoing deficits including cognitive competency, major activity, and leisure and recreation.[28] This has a devastating financial, emotional, and social impact on survivors left with lifelong disability and on their families.

It is well established that the major determinant of outcome from TBI is the severity of the primary injury, which is irreversible. However, secondary injury, primarily cerebral ischaemia, occurring in the post-injury phase, may be due to intracranial hypertension, systemic hypotension, hypoxia, hyperpyrexia, hypocapnia and hypoglycaemia, all of which have been shown to independently worsen survival after TBI. In 1996 and 2000 (updated in 2003), the Brain Trauma Foundation published guidelines on the management of severe TBI,[9] accepted by the American Association of Neurosurgeons and endorsed by the World Health Organization Committee in Neurotraumatology. Although many of the recommendations from these guidelines are incorporated into protocols for the management of head-injured patients in individual ICU, there is still wide variation between Units. This article outlines the basic principles of the general intensive care management of patients with severe TBI and reviews the rationale for the use of specific neurointensive care interventions.

Natural history of severe TBI

An appreciation of the severity of the injury on admission is beneficial as it predicts the likely prognosis as well as giving some indication of natural history. The most useful classification of TBI is based on the best GCS[89] after resuscitation, as it has prognostic significance.[58] After injury to the brain, an inflammatory cascade is initiated which results in worsening oedema with vasogenic, cytotoxic, and osmotic components.[93] This results in increased pressure within the confines of a fixed intracranial compartment.

It is important to realize that the type and mechanism of injury has an important bearing on the likely clinical course after TBI. High velocity injuries involving rapid acceleration and deceleration, particularly if there is a rotational element, result in shearing forces at the boundary between neocortical grey and white matter. This shearing force can lead to widespread disruption of axonal processes which can be visualized histologically as 'retraction balls'.[81] This type of injury has been termed as diffuse axonal injury (DAI),[1] and although features of this injury are not readily appreciated on CT scan, significant brain swelling is a common consequence. Clinically, DAI is recognized by a triad of a consistent mechanism of injury (rapid acceleration/deceleration/rotation, typically seen in road traffic accidents), GCS $<$8 after resuscitation

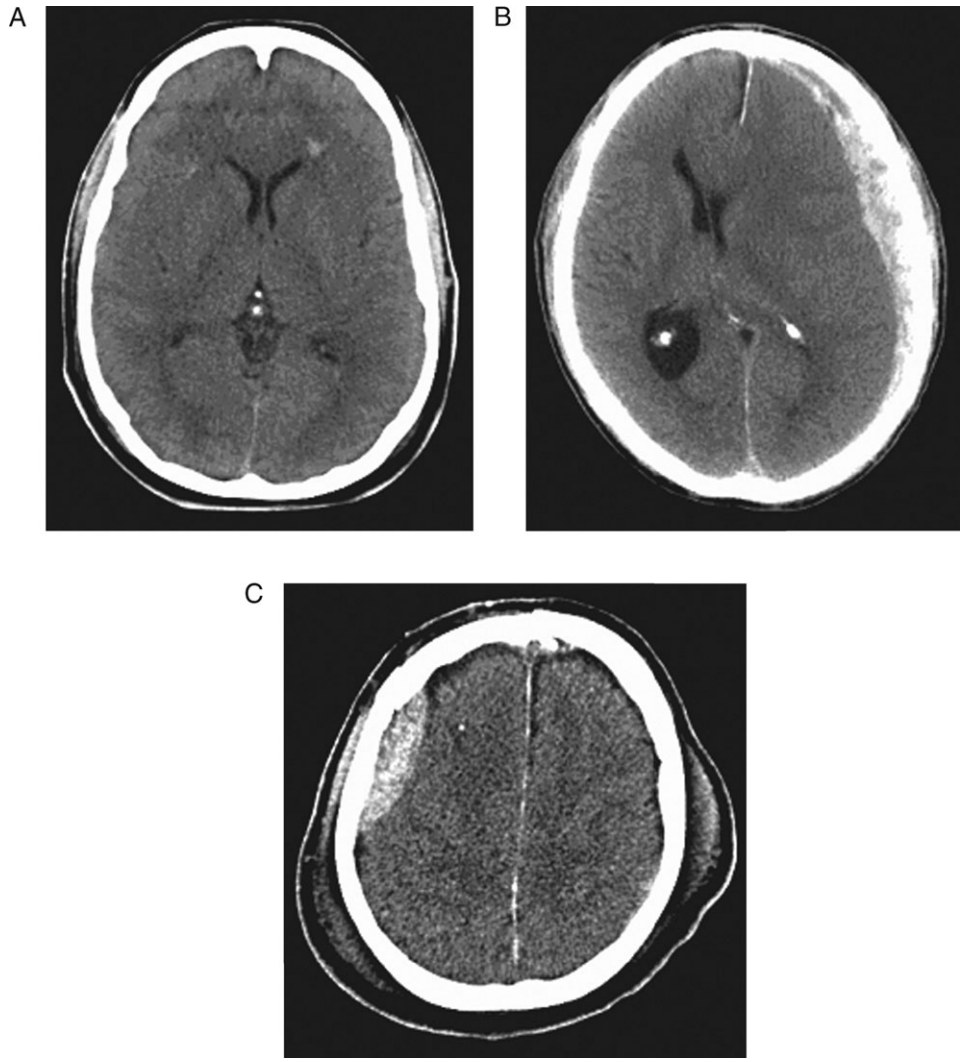

Fig 1 CT scans after TBI. (A) Diffuse brain injury: 32-yr-old male involved in a high-speed road traffic accident. In diffuse brain injury, the CT scan may look grossly normal. Note the small contusion at the tip of the left frontal ventricular horn and diffuse swelling. (B) Subdural haematoma: 39-yr-old male after fall down stairs. Note the large biconcave opacity on the left spreading over the surface of the cortex, compressing the ipsilateral ventricle and causing midline shift. (C) Extradural haematoma: 60-yr-old male after a fall. Note the biconvex opacity on the right compressing the underlying brain parenchyma. Scalp contusions are also demonstrated over the extradural and opposite to the lesion.

and a CT scan without focal mass lesion but signs of brain swelling. DAI is a histological diagnosis and the term diffuse brain injury is preferred in the ante-mortem setting. Fine petechial haemorrhages at the grey/white junction can sometimes be visualized on CT scan (Fig. 1A), but magnetic resonance imaging (MRI) is a more sensitive imaging modality, and being increasingly used as a diagnostic tool, in this patient population. The CT grading system for diffuse injury is shown in Table 1.

The temporal course over which cerebral oedema occurs after TBI has been investigated in animal models, with the peak of cytotoxic oedema occurring at 7 days post-injury.[4 50] Diffusion weighted MRI provides a dynamic measure of cerebral oedema in humans, and recent studies have highlighted the predominance of cellular oedema in human TBI.[51]

Even with focal lesions, one must always be suspicious of co-existent diffuse injury in the presence of a compatible mechanism of injury.[81] Furthermore, some types of focal lesion, such as subdural haematoma (Fig. 1B), are associated

Table 1 CT grading system for diffuse brain injury after Marshall and colleagues.[52] The cisterns referred to are the ones surrounding the midbrain as assessed on CT head scan, that is, the interpeduncular, ambient, and quadrigeminal plate cisterns

Category of diffuse injury	Definition	Mortality (%)
I	No visible intracranial injury	10
II	Cisterns present 0–5 mm midline shift and small, high, or mixed density lesions <25 cc	14
III	Cisterns compressed or absent+I or II	34
IV	Midline shift >5 mm +I, II, or III	56

with more underlying cerebral parenchymal injury than others, such as extradural haematoma (Fig. 1C).

Intensive care management of TBI

General approach

Secondary brain insults arise from both systemic and intracranial causes and may occur at any time during initial resuscitation and stabilization and during intensive care. Management of TBI in intensive care is targeted at optimizing cerebral perfusion, oxygenation and avoiding secondary insults. There is good evidence that protocolized management leads to improved outcome after TBI[32 66] and may be further improved by treatment within a specialist neuroscience critical care unit.[65] Most clinically adopted protocols for management of TBI are based around providing good basic intensive care and interventions to target cerebral perfusion pressure (CPP) and intracranial pressure (ICP). An example of such a protocol is given in Figure 2.

Ventilatory support, sedation, analgesia, and paralysis

Patients with severe head injury require mechanical ventilation[70] to maintain an arterial P_{O_2} above 11 kPa and an arterial P_{CO_2} between 4.5 and 5 kPa.[63] There is no absolute contraindication to the use of positive end expiratory pressure in hypoxaemic patients unless the increase in thoracic venous pressure causes an unacceptable increase

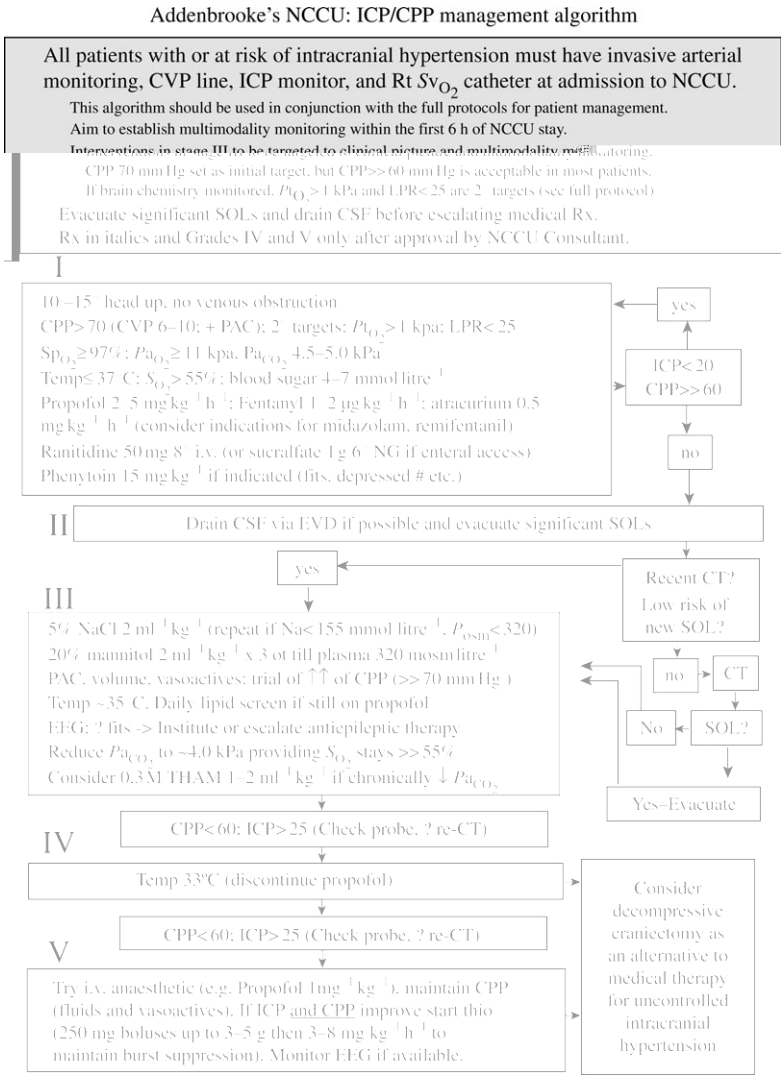

Fig 2 Addenbrooke's NCCU (neurocritical care unit) TBI Protocol. ICP, intracranial pressure; CPP, cerebral perfusion pressure; Sv_{O_2} jugular venous oxygen saturation; SOL, space-occupying lesion; Pt_{O_2} partial pressure of tissue oxygen; LPR, lactate pyruvate ratio; EVD, external ventricular drain; PAC, pulmonary artery catheter.

in ICP. Permissive hypercapnea should be avoided because of its cerebral vasodilatory effect that increases ICP.

Adequate sedation minimizes pain, anxiety, and agitation, reduces the cerebral metabolic rate of oxygen consumption, and facilitates mechanical ventilation. This is achieved with sedative drugs and opioids.[63] A short acting benzodiazepine such as midazolam is commonly used, which is very effective both as a sedative and as an anticonvulsant, although accumulation is a problem. Propofol may have benefits over midazolam because of its superior metabolic suppressive effects, and favourable short half-life. However, it is not recommended in hypothermic patients as it has a tendency to accumulate and precipitate hyperlipidaemia. Other reported problems with propofol include precipitous cardiovascular collapse[95] and the propofol infusion syndrome of metabolic acidosis, rhabdomyolysis, and bradycardia, first described in children but also identified in adults.[46] Barbiturates are used less commonly for sedation because of the high risk of cardiovascular depression and increased risk of infections,[30] but they still have a role when other methods of controlling ICP have failed.

Analgesia is provided with regular doses of acetaminophen and infusion of opioids, such as remifentanil, fentanyl, or morphine, which all have minimal effects on cerebral haemodynamics in adequately resuscitated patients.[86]

Neuromuscular block is utilized to minimize coughing and straining which may increase ICP,[41] and is provided with boluses or infusion of non-depolarizing muscle relaxants such as atracurium or rocuronium.

Haemodynamic support

TBI patients are prone to haemodynamic instability for a number of reasons. Associated injuries may lead to intravascular volume depletion and trauma to the myocardium can result in primary pump failure. Furthermore, brainstem injuries can directly affect cardiovascular stability. Maintenance of haemodynamic stability is essential to the management of severe TBI as the injured brain may lose the capacity for vascular autoregulation, either globally or locally. Hypotension must be avoided at all costs as it causes a reduction in cerebral blood flow (CBF)[16] and, below a threshold value, will result in cerebral ischaemia. Conversely, hypertension can exacerbate vasogenic oedema with a detrimental effect on ICP.[34] A balance is achieved by identifying and targeting CPP as will be discussed later.

Initially, intravascular volume should be maintained targeting a central venous pressure of 5–10 mm Hg[33] using isotonic crystalloids and colloids. If an adequate blood pressure cannot easily be achieved, introduction of a vasoactive agent is advocated. Furthermore, in patients with associated injuries with evolving shock and increasing requirements for inotropes and vasopressors, a pulmonary artery catheter or non-invasive cardiac output monitor should be considered. Adrenal insufficiency is not uncommon after severe TBI,[6] and in patients with high inotropic requirements, a short synacthen should be carried out before initiation of empirical steroid replacement.[6]

Before ICP monitoring is instituted, hypertension should not be treated unless the mean arterial pressure (MAP) is above 120 mm Hg because the high systemic blood pressure may be maintaining CBF. After ICP monitoring is instituted, the target MAP is determined by the CPP as discussed later. For the treatment of hypertension to achieve CPP targets, an infusion of short acting beta-blockers should be titrated against blood pressure. These agents do not cause cerebral vasodilation, when compared with nitrates and calcium channel blockers, and therefore do not increase cerebral blood volume and ICP.

Nutritional support

Early nutritional support is recommended, aiming to meet full nutritional requirements once haemodynamic stability is achieved.[10] A Cochrane review suggested that early feeding may be associated with a trend towards better outcomes in terms of survival and disability.[68] Furthermore, early aggressive nutritional support enhances immunologic function by increasing CD4 cells, CD4-CD8 ratios, and T-lymphocyte responsiveness.[80] The route of administration may differ according to the overall clinical condition of the patient, but there is no difference in outcome after severe TBI between enteral or parenteral nutrition.[7 17] Ideally, 140% of resting metabolic expenditure (approximately 30 total kcal kg^{-1} day^{-1}) in non-paralysed patients and 100% (approximately 25 total kcal kg^{-1} day^{-1}) in paralysed patients should be replaced. At least 15% of calories should be protein.[29]

Enteral formulas are preferable but in the case of high gastric residual volume or associated abdominal trauma, combined or total parenteral nutrition may be used. Even though there is still debate about enteral and parenteral nutrition in neurotrauma patients, it is apparent that the enteral route is more physiological, less expensive, and less risky than total parenteral nutrition.

Independent of the method of nutritional support, appropriate metabolic monitoring is required to avoid side-effects such as hyperglycaemia, ketoacidosis, gastric intolerance, diarrhoea leading to dehydration, and relative hypovolaemia compromising haemodynamic stability.

Glycaemic control

The stress response in trauma patients, including those with severe TBI, generates a hypercatabolic state leading to rapid muscle protein breakdown and hyperglycaemia.[55] At a cellular level, there are deleterious effects in macrophage and neutrophil function and there is also some evidence suggesting axonal dysfunction.[96]

It is unclear whether hyperglycaemia or lack of insulin during the metabolic stress response affects outcome, but it is clear that an adequate level of glucose in plasma is associated with lower morbidity and better outcome. Van den Berghe and colleagues[94] in 2001 randomized a large group of surgical intensive care patients and demonstrated that tight glycaemic control with intensive insulin therapy reduced the number of deaths from multiple organ failure with sepsis regardless of whether or not there was a history of diabetes or hyperglycaemia. In patients with TBI, hyperglycaemia was associated with higher ICP, a longer stay in hospital, worse neurological outcome, and reduced survival.[79] In 2004, Clayton and colleagues[18] showed a relative reduction in intensive care mortality of around 30% in patients with severe head injury after the introduction of protocol driven glycaemic control to maintain a glucose level of 4–7 mmol litre^{-1}. There is substantial evidence highlighting the adverse effects of hyperglycaemia in critically ill patients and tight glycaemic control has become a part of the routine management of general intensive care patients, although in TBI the optimal target glycaemic range is yet to be defined.

Peptic ulcer prophylaxis

Severe TBI is a well-recognized risk factor for stress ulcers (Cushing's ulcers) with an incidence of around 10%.[11] Even though the level of evidence supporting the use of antacids in this selected high-risk group of patients is sufficient, necessitating regular prescription of peptic ulcer prophylaxis, it is not yet clear which is the ideal agent, dose, or route of administration.[27 69]

Coagulopathy and deep venous thrombosis prophylaxis

Disseminated intravascular coagulation (DIC) may accompany severe TBI, secondary to massive blood replacement during resuscitation, gram-negative bacteraemia, and other traumatic injuries. Acute DIC may also be a direct consequence of severe TBI related to systemic release of high cerebral parenchymal concentrations of tissue thromboplastin and other agents which are capable of inducing a consumptive coagulopathy.[71]

The incidence of deep venous thrombosis (DVT) is related to the type and severity of injuries. It is reported as low as 3% in isolated head injury rising to around 23% in polytrauma patients.[77] There are different methods of preventing venous thrombosis, including thromboembolic deterrent stockings, sequential compression devices, low-dose unfractionated heparin (UH), low-molecular weight heparin (LMWH), vena caval filters, or a combination of these. Cerebral contusions after TBI are susceptible to evolution and this can be influenced by coagulopathy and anticoagulation.[64] These factors influence the timing and initiation of venous thrombosis prophylaxis which all carry side-effects or complications that may negatively influence the outcome after TBI. Most authors agree that after 72 h post-TBI, UH or LMWH should be commenced, but few support the use of DVT chemothromboprophylaxis as early as 24 h after blunt closed head injuries.[62 67] Although LMWH seems better than UH in preventing DVT, the incidence of adverse events is low with either option.[43]

Miscellaneous

As for all intensive care patients, chest physiotherapy, frequent turning, eye care, and full hygiene care must be provided. Laxatives are prescribed to ensure regular bowel opening to reduce the risk of intra-abdominal hypertension and its systemic repercussions. Frequent dressing of catheters and catheter sites minimizes the risk of infection. Finally, in the case of severe or refractory intracranial hypertension, lidocaine, thiopentone, fentanyl, or midazolam boluses may be used to reduce the potentially adverse ICP response to physiotherapy and endotracheal suction.

Specific management

ICP and CPP thresholds

The intracranial compartment following injury consists of brain, cerebrospinal fluid (CSF), blood and, in some cases, pathological mass lesions. The volume of these contents within the rigid skull exerts a pressure, the ICP.[60] Measurement of ICP is described elsewhere in this edition, but the importance of measuring ICP in severe TBI patients should be emphasized. First, it is a monitoring tool for the early identification of evolving mass lesions in the paralysed and sedated patient, in whom the neurological examination is limited to pupillary size and responsiveness. Secondly, the CPP can be calculated from the relationship CPP=MAP−ICP.

Although many clinical protocols are directed towards CPP targets, there is substantial evidence that ICP is an independent predictor of outcome. A number of retrospective studies have identified ICP>20–25 mm Hg as a discriminatory factor between patients with potentially good or poor outcomes.[24 36 54 76] This value is therefore empirically regarded as a pathological threshold and efforts should be made to control it below this limit.

Cerebral ischaemia is the single most important secondary factor that influences outcome after TBI[15] and to this end maintenance of CPP has become central to the management of patients with TBI. The first evidence that maintaining CPP above a predetermined target was beneficial came from a study by Rosner and colleagues[78] in 1996 which incidentally demonstrated an improvement in outcome if CPP was maintained >70 mm Hg. Although this study was non-randomized and used historical controls, it produced a paradigm shift in the management of

TBI, and 70 mm Hg was adopted as a CPP target in the first Brain Trauma Foundation guidelines published in 1996,[8] although the ideal CPP target has been a source of contention ever since. Although increasing CPP may be seen as a useful way of increasing oxygen delivery to the brain, it comes at a cost. Loss of vascular autoregulation in the injured brain is a common consequence of TBI and leads to dissociation between CBF and metabolic requirements. In this circumstance, increasing CPP can lead to passive increases in blood vessel diameter, increasing cerebral blood volume and consequently ICP. Increased hydrostatic pressure across the cerebral capillary bed can also lead to vasogenic oedema, which again increases ICP. An alternative approach, the Lund protocol, has been suggested which aims to minimize the CPP target to a level (>50 mm Hg) which avoids frank ischaemia but does not lead to further cerebral insults.[31 34] Furthermore, driving MAP with fluids and inotropes to maintain CPP is associated with cardiorespiratory complications. Robertson and colleagues[76] demonstrated that a CPP target of 70 mm Hg compared with 50 mm Hg leads to a higher fluid intake, increased use of inotropes, increased use of invasive monitoring, and a five-fold increase in the incidence of acute respiratory distress syndrome.

There is clearly a balance to be struck between improving oxygen delivery to the brain and avoiding the complications of increasing MAP. The situation is complicated by the fact that after TBI there is significant metabolic heterogeneity within the injured brain,[35 61] such that some areas may be ischaemic at a CPP value that is globally sufficient. Coles and colleagues[23] used oxygen-15 positron emission tomography to demonstrate that increasing CPP from 70 mm Hg to 90 mm Hg acutely reduced ischaemic brain volume, although the clinical significance of this observation is not clear. Ultimately, monitoring metabolic parameters in individual patients, such as brain tissue oxygen[87] and lactate/pyruvate ratio as assayed by microdialysis,[5 37] may allow further refinement of CPP targets on an individual basis. Currently, the latest consensus is to use a CPP target of >60 mm Hg[9] (note update 2003, http://www2.braintrauma.org/guidelines/index.php).

ICP and thus CPP can be controlled in a number of ways, including reduction in metabolic requirements using sedation, induced hyperventilation, hyperosmolar therapy, hypothermia, and surgical adjuncts. These will now be discussed individually.

Induced hyperventilation

A major determinant of cerebral vessel calibre is the partial pressure of carbon dioxide (Pa_{CO_2}). A reduction in Pa_{CO_2} causes cerebral vasoconstriction, reducing cerebral blood volume and consequently ICP. When utilizing hyperventilation, a balance must be struck between the beneficial effect on ICP and the potential deleterious effect on CBF.[74] Particularly in the first 24 h after TBI, CBF is reduced and aggressive hyperventilation can compound cerebral ischaemia.[57] For this reason, hyperventilation should not be applied outside a dedicated neurointensive care setting when appropriate monitoring, such as jugular bulb oxygen saturation, can be employed. A Pa_{CO_2} target of 4.5–5 kPa[63] should be used in the first instance for those patients with raised ICP, with hyperventilation to 4.0–4.5 kPa reserved for those with intractable intracranial hypertension.[22]

Hyperosmolar therapy

Hyperosmolar therapy is a key intervention for the management of cerebral oedema and raised ICP after TBI. It is particularly indicated for acute rises in ICP as it has a rapid effect. Mannitol, an osmotic diuretic, is commonly employed and the immediate efficacy is likely to result from a plasma-expanding effect and improved blood rheology due to a reduction in haematocrit. Mannitol also establishes an osmotic gradient between plasma and brain cells reducing cerebral oedema by drawing water across areas of intact blood–brain barrier (BBB) into the vascular compartment.[56 59] Repeated administration of mannitol is problematic because serum osmolarity >320 mOsm litre^{-1} is associated with neurological and renal side-effects.[12] Other potential complications associated with mannitol are severe intravascular volume depletion, hypotension, and hyperkalemia[48] and possibly a rebound increase in ICP.[53 98]

Hypertonic saline is increasingly used as an alternative to mannitol. It is available in a range of concentrations from 1.7% to 29.2% and numerous regimens have been described, making it difficult to draw conclusions about the optimal dose or concentration required to control ICP. Hypertonic saline produces a reduction in cerebral oedema by moving water out of cells, reducing tissue pressure and cell size resulting in a decrease in ICP.[83 99] This favourable effect on cerebral water content after administration of hypertonic saline has been demonstrated by a reduction in lateral displacement of the brain on serial CT scans in patients with head injury.[73] Hypertonic saline improves CBF, independently of ICP, by decreasing endothelial cell volume, increasing the diameter of the capillary lumen, and reducing erythrocyte size thereby improving blood rheology.[84] Furthermore, hypertonic saline has proven efficacy in controlling ICP in patients refractory to mannitol.[88] Other advantages over mannitol include its effectiveness as a volume expander, without hyperkalemia and impaired renal function.[73]

Salt and water balance

In the TBI patient with raised ICP, sudden changes in serum sodium concentration and osmolarity must be avoided since these factors impact on the nature and degree of cerebral oedema. The effect of hyperosmolar agents on cerebral oedema is temporary as, over time, cells within the brain retain idiogenic osmoles, probably

amino acids, to attenuate the osmotic gradient across the BBB.[25 47] If the serum osmolarity then falls, the brain is susceptible to rebound oedema. During the course of treatment of raised ICP, the serum osmolarity can be raised to 145–155 mmol litre^{-1} and the serum osmolarity to 320 mOsm litre^{-1}, but if this hyperosmolar state is reached, osmolarity must not be brought down rapidly with hypotonic fluids. The maintenance fluid of choice is normal saline with supplemental potassium.

TBI patients are susceptible to disorders of salt and water balance. Causes include central diabetes insipidus (CDI), cerebral salt wasting (CSW) syndrome, and syndrome of inappropriate anti-diuretic hormone (SIADH) secretion. Table 2 lists the differentiating features between these syndromes. The situation is further complicated by the large sodium load administered to these patients in normal saline, such that high urinary sodium no longer becomes a reliable discriminatory factor between the various syndromes. A thorough discussion of the management of these syndromes is outside the scope of this review (see other reviews[2 21]), but caution must be exercised if low sodium solutions or synthetic anti-diuretic hormone is administered even in the context of severe hypernatraemia (Na>160 mmol litre^{-1}), as a rapid decrease in serum sodium can cause fatal cerebral oedema.

Induced hypothermia

Hypothermia has been used for many years to control ICP in patients with severe TBI. In the 1990s, there was some evidence suggesting that moderate hypothermia of 33°C instituted at admission was associated with significantly improved outcome at 3 and 6 months post-injury.[49] However, effectiveness of this therapy was not reproduced in a multicentre phase 3 clinical trial. However, *post hoc* analysis by the authors demonstrated that older people may have worse outcomes with hypothermia and patients hypothermic on arrival in the Emergency Department have more severe injuries thus confounding the results.[19] A Cochrane review in 2004 analysed 14 trials with a total of 1094 patients and did not find any evidence supporting the use of hypothermia during the treatment of TBI, but did find a statistically significant increased risk of pneumonia and other potentially harmful side-effects.[3] However, delayed hypothermia in the case of uncontrollable intracranial hypertension has shown a reduction in ICP and CBF by 40% and 26%, respectively, and a significant reduction in mortality and severe disability at 6 months.[85] There is further evidence that with proactive management of the side-effects of hypothermia, an improvement in outcome can be achieved.[72] Thus, hypothermia still remains a part of many algorithms targeting patients with uncontrollable intracranial hypertension. To directly address this issue, there is currently an ongoing phase 3 clinical trial conducted in patients with severe head injury, aged 16–45 randomized to normothermia or moderate hypothermia looking into Glasgow Outcome Score at 6 months after injury.[20]

Table 2 Distinguishing characteristics and management of derangements of salt and water balance after TBI. CDI, cranial diabetes insipidus; CSW, cerebral salt wasting; SIADH, syndrome of inappropriate anti-diuretic hormone; →, no change; ↑, increased; ↓, decreased; PCWP, pulmonary capillary wedge pressure; CVP, central venous pressure

Parameter	CDI	CSW	SIADH
Serum Na	↑	↓	↓
Serum osmolarity	↑	↓	↓
Urine osmolarity	↓	↑	↑↑
Urinary sodium	→	↑↑	↑
Total body water	↓	↓	↑
Total body sodium	→	↓	→
Weight	↓	↓	↑
PCWP/CVP	→	↓	→
Haematocrit	↑	↑	↓
Management	Replace fluids to maintain normovolaemia Judicious use of small doses of desmopressin (e.g. 1 μg) if unable to maintain fluid balance	Replace urine loss with saline Fludrocortisone (300 μg od) if unable to maintain serum Na	Fluid restrict to combat dilutional hyponatraemia Demeclocycline (300 mg tds) acts on the kidney to antagonize the effects of ADH

Barbiturate coma

The use of high-dose barbiturates for the control of intracranial hypertension unresponsive to other treatments is highly contentious. Many clinical studies have demonstrated that barbiturate coma can effectively lower ICP by mechanisms including reduced cerebral metabolism, reduced CBF, and inhibition of free radicals.[26 45] The main disadvantages are two-fold. First, barbiturates cause significant episodes of hypotension, which are deleterious after TBI, and secondly, the prolonged half-life makes clinical assessment difficult after barbiturates are stopped. Continuous EEG monitoring can be used to titrate barbiturate therapy to ensure the minimum dose to achieve burst suppression and therefore minimize systemic complications. Sudden cardiovascular collapse and hyperkalaemia on withdrawal of barbiturate therapy have also been reported.[13] Despite the ability of barbiturates to control ICP, there is no good evidence demonstrating improvement in outcome[9] and there is a lingering concern that by salvaging patients with the most severe intracranial injuries, mortality may be reduced but poor outcomes such as severe disability or persistent vegetative state may be increased.

Anticonvulsant medication after TBI

There is a great deal of variation in the administration of anticonvulsant medication after TBI. It is important to

distinguish between using anticonvulsants in the acute phase after TBI (first 7 days) and their continued use in the longer term. Anticonvulsant medication in the acute phase does not reduce the incidence of post-traumatic seizures in the long term[14] and is therefore not recommended.[9] For prevention of seizures in the short term, a Cochrane review suggests a number needed to treat of 10 to benefit one with no impact on outcome or mortality.[82] These drugs are not without their side-effects, anti-epileptics should therefore not be prescribed unless there is documented clinical or EEG evidence of seizures.[9] Some neurosurgeons advocate the use of anti-epileptics in certain high-risk groups, such as those with depressed skull fractures,[90] but these must be considered on a case-by-case basis.

Phenytoin can be used as a first line agent as it has proven efficacy in partial and generalized seizures[91] (loading dose 15–20 mg kg^{-1} over 30 min followed by 100 mg i.v. three times daily titrated to plasma levels). If this fails to control documented seizures, a second anti-epileptic agent can be instituted.

Surgical interventions to reduce raised ICP

The most effective method of lowering ICP is the removal of space-occupying lesions and this must be considered at every stage of patient management. Any sudden increase in ICP must trigger a search for a new space-occupying lesion, such as haematoma or hydrocephalus, using CT scan. Other than treating specific space-occupying lesions, surgery has two other generic mechanisms for reduction in ICP. The first is external ventricular drainage (EVD) and the second is decompressive craniectomy.

EVD involves placing a catheter into the ventricular system in a sterile fashion to allow drainage of CSF. This can be performed even in the absence of hydrocephalus as a mechanism for reducing intracranial volume. As patients with raised ICP have reduced intracranial compliance, even drainage of a few millilitres of CSF can have a dramatic effect on ICP. The main advantage of this CSF drainage is that it does not come at any systemic cost to other body systems (unlike hypothermia) and it can be inserted in intensive care without the need for transfer to an operating theatre. EVDs traverse the brain parenchyma and are placed in areas of non-eloquent brain, usually through non-dominant frontal lobe. The technique is limited by the ability of the neurosurgeon to successfully strike the ventricle with the ventricular catheter and this can be technically difficult when the ventricles are collapsed. The risks relate to surgical placement, such as haematoma on insertion, and the longer-term risk of introducing infection, which increases dramatically after 5 days of placement.[39] EVDs are also prone to blockage due to plugging with choroids plexus, brain particles, and infected material.

Decompressive craniectomy is a surgical procedure in which a large area of the skull vault is removed and the dura opened to allow the brain to expand out of the confines of the rigid skull. It can be performed unilaterally during evacuation of a specific space-occupying lesion or, in diffuse injury, a bifrontal craniectomy can be used to remove the most anterior part of the skull. There is evidence to demonstrate that this procedure reduces ICP,[97] but a beneficial effect on outcome is yet to be proven. To this end, the RESCUEicp study[75] is examining decompressive craniectomy *vs* barbiturate coma for raised refractory intracranial hypertension. As the evidence base is currently limited, this method of ICP control is retained for when other techniques have failed.

Future directions

The search for effective pharmacological neuroprotection continues but, despite many high profile and costly trials, no such agent exists. The reasons for this are numerous[92] but, ultimately, with improved research methodology and a better understanding of the molecular mechanisms contributing to secondary brain injury, neuroprotective agents may yet become a reality.

As improved monitoring techniques, such as brain tissue monitors and advanced imaging methods are being further developed, our ability to recognize adverse events and identify the pathophysiological processes occurring in a given individual will improve. This may allow a more individualized approach to interventions, help refine protocols and more effective targeted management. They may also help us develop novel and effective therapies to add to protocolized management strategies in the hope that this will ultimately translate into an improvement in outcome after TBI.

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