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CRITICAL CARE MANAGEMENT OF ADULT TRAUMATIC BRAIN INJURY

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Abstract

Severe traumatic brain injury is associated with significant morbidity and mortality. The critical care management of traumatic brain injury requires a coordinated and comprehensive approach to treatment, including strategies to prevent secondary brain injury by avoidance of systemic physiological disturbances, such as hypotension, hypoxaemia, hypo- and hyperglycaemia and hyperthermia, and maintenance of adequate cerebral perfusion and oxygenation. Management protocols have evolved with international consensus, providing guidelines that assist clinicians in delivering optimal care. Those from the Brain Trauma Foundation are continuously updated to incorporate new trial data (https://braintrauma.org/coma/guidelines).

Keywords: Cerebral perfusion pressure; head injury; intracranial pressure; neurointensive care

Royal College of Anaesthetists CPD matrix: 2F01, 3C00, 3F00

Learning objectives

After reading this article, you should be able to:

- understand the pathophysiology associated with severe traumatic brain injury
- understand how optimisation of systemic physiology can minimise further brain injury
- understand intracranial and cerebral perfusion pressure-guided management
- identify strategies that can be used to control raised intracranial pressure.

Severe traumatic brain injury (TBI), defined as post-resuscitation Glasgow coma score ≦8, has high rates of mortality and disability and is a major socioeconomic burden. In the UK more than 1 million people live with some level of physical disability following head injury, as well as cognitive impairment or behavioural problems that adversely impact their quality of life or ability to work. TBI was historically considered to affect predominantly young males, but falls in elderly patients now form a significant cohort and add further complexity to its clinical management.

PATHOPHYSIOLOGY

TBI includes a continuum of primary and secondary injury processes. Primary injury describes the irreversible structural damage, such as contusion or shearing, sustained at the time of impact, whereas secondary injury is the subsequent cascade of injurious processes, including metabolic, excitotoxic and inflammatory responses [1]. Secondary injury may be exacerbated by systemic physiological insults and is potentially amenable to treatment.

Intracranial effects

Intracranial bleeding and cerebral oedema cause direct structural damage and may lead to increased intracranial pressure (ICP) which may in turn impair cerebral perfusion and precipitate cerebral ischaemia. This may be exacerbated by disturbances in cerebral autoregulation and systemic factors such as hypoxia, hypotension and anaemia.

Damaged neurones release excitatory neurotransmitters which result in depolarisation of postsynaptic membranes and uncontrolled intracellular influx of electrolytes. Water then enters cells along the resultant osmotic gradient, leading to cell swelling and rupture of cell membranes. Additionally, high concentrations of intracellular calcium activate enzymatic processes which also lead to cell death. Cytotoxic brain oedema occurs because of cell membrane dysfunction and increased intracellular fluid accumulation. Vasogenic oedema on the other hand is related to disruption of the endothelium and uncontrolled transit of electrolytes and water into the extracellular space. These two processes produce a positive feedback loop of worsening cerebral oedema and ischaemia (see figure 1).

Increases in cerebral extracellular lactate concentration may occur as a consequence of ischaemia, but it is now recognized that lactate is more than a mere by-product of anaerobic metabolism. In an energy-deprived brain glutamate stimulates astrocytic production of lactate which is released into the extracellular space and 'shuttled' into neurons where it can be used (together with glucose) as an additional substrate to sustain increased energy requirements. A process of non-ischaemic cerebral metabolic crisis can also occur, either as a consequence of mitochondrial dysfunction or because of large increases in metabolic requirements.

Systemic effects

Catecholamines released following TBI can cause neurogenic pulmonary oedema and myocardial ischaemia. In addition, catecholamine-induced myocyte dysfunction and inflammatory responses can lead to the neurogenic stunned myocardium syndrome. This is a reversible neurologically mediated cardiac injury characterised by ECG changes, elevated cardiac troponin and a spectrum of ventricular dysfunction in the absence of coronary ischaemia. Cardiogenic pulmonary oedema and non-haemorrhagic systemic hypotension occur infrequently after TBI, but are associated with high mortality. In response to injury, neurones and glial cells produce pro-inflammatory cytokines generating local and systemic inflammatory responses. Disruption of autonomic and neuroendocrine pathways can also cause immunosuppression which is associated with a high rate of infective complications.

Endocrine and electrolyte abnormalities, particularly disturbances of sodium and glucose homeostasis, hypothalamic-pituitary-adrenal axis dysfunction and secondary adrenal insufficiency, are common after TBI. Risk factors include older age, diffuse axonal injury, severe cerebral oedema, traumatic vasospasm and skull base fractures.

CRITICAL CARE MANAGEMENT

The critical care management of TBI comprises meticulous general intensive care support in addition to interventions targeted to the injured brain (table 1).

Cardiovascular and respiratory support

Even transient episodes of hypotension are associated with worse neurological outcomes after TBI and should be avoided or immediately treated. The most recent Brain Trauma Foundation guidelines include age-specific blood pressure targets (Table 1) [2]. Euvolaemia should be maintained with isotonic crystalloids [3]. Hypotonic solutions can worsen cerebral oedema and should be avoided. Vasopressors may be required to maintain cerebral perfusion in the presence of adequate filling, and norepinephrine is widely used. Non-invasive cardiac output monitoring can be useful to optimise fluid status.

Pulmonary complications such as pneumonia and acute lung injury (ALI) are common after TBI and should be treated aggressively. High tidal volume ventilation is a major risk factor for the development of ALI after brain injury, and lung-protective ventilation strategies are essential. Moderate levels of PEEP ($\leq$15 cmH_2O) do not significantly increase ICP, and may be safely used as part of a ventilation strategy to maintain PaO_2 < 11 kPa. Hypercapnia causes cerebral vasodilation and an increase in ICP whereas hypocapnia causes cerebral vasoconstriction and worsens cerebral ischaemia. For this reason maintenance of normocapnea is recommended, and routine hyperventilation is no longer used to control ICP.

Analgesia and sedation

Adequate sedation is a key component of the management of severe TBI to control ICP and reduce cerebral metabolic demand and tolerance of the injured brain to ischaemia [4]. Propofol is widely used because it effectively reduces ICP and allows rapidly titratable sedation levels. The infusion rate should not exceed $4mg.kg^{-1}.hr^{-1}$ and midazolam is often added to minimise total propofol dose. Sedation holds are not appropriate in patients with decreased intracranial compliance. Analgesia is usually provided with paracetamol and infusion of opioids such as fentanyl. Neuromuscular blocking agents should not be used routinely but reserved for patients with refractory intracranial hypertension.

Electrolyte and endocrine disturbance

Fluid and electrolyte abnormalities, particularly sodium disturbance, should be managed using a systematic approach to diagnosis and treatment (table 2). Hyper- and hypoglycaemia are associated with worse outcome and should be avoided. Both intensive and loose glycaemic control are harmful after TBI, and intermediate glucose concentrations (7.0-10.0 $mmol.L^{-1}$) should be targeted [5].

Screening for pituitary insufficiency should be considered in high-risk patients and those with unexplained hyponatraemia or hypoglycaemia, or a persisting requirement for high-dose vasopressors. Hydrocortisone may be required for refractory hypotension and supplemented with a mineralocorticoid if hyponatraemia persists.

General supportive measure

Anaemia

Restrictive transfusion strategies used in general critical care may not be suitable in TBI patients because of the susceptibility of the injured brain to ischaemia, but the optimal haemoglobin level to trigger red cell transfusion after TBI has not been defined [6]. The only randomised controlled trial (RCT) specifically evaluating transfusion thresholds (70 vs 100 $g.l^{-1}$) in TBI found no statistically significant difference in outcome, but a higher risk of thromboembolism in the higher transfusion threshold group.

Coagulopathy

Coagulation disturbance develops in up to one third of TBI patients; both hypo- and hypercoagulation states can occur. The causes are poorly defined but likely related to release of large amounts of tissue factor, altered protein C homeostasis, and platelet dysfunction. Functional assays and thromboelastometry may be more useful than routine laboratory tests in determining the degree of coagulation disturbance and most appropriate treatment.

Sympathetic hyperactivity

Disruption of inhibitory centres in the brainstem may cause paroxysmal sympathetic hyperactivity which is characterised by cyclical agitation, dystonia, pyrexia, tachycardia, hypertension and diaphoresis. Treatment includes opiates (particularly morphine), β adrenoreceptor antagonists and centrally acting α_2 adrenoreceptor agonists such as clonidine or dexmedetomidine. Haloperidol should be avoided.

Seizures

Early post-traumatic seizures (within 7 days) occur in more than 20% of patients after TBI. While seizures should be treated aggressively, there is no high quality evidence that prophylactic anticonvulsants are effective in the prevention of early onset seizures or that they reduce the incidence of late post-traumatic seizures. Phenytoin has been widely used for seizure prophylaxis but levetiracetam is becoming a popular first-line agent because of the adverse side effect and drug interaction profile of phenytoin. If prophylaxis is used, anticonvulsants should be continued for no more than seven days in patients who remain seizure free.

Other supportive measures

TBI patients are at high risk of stress ulceration and often have impaired gastrointestinal motility. Early enteral feeding is recommended and laxatives are important to avoid constipation which can cause an increase in ICP. Positioning the head of bed at 30° - 45° reduces ICP and the risk of ventilator-associated pneumonia. The risk of DVT is high after TBI. In addition to physical methods of prophylaxis from admission to the ICU, pharmacological thromboprophylaxis after 24 hours of clinical and radiological stability is usually recommended.

Intracranial and cerebral perfusion pressure-guided management

Haematoma, cerebral oedema and hydrocephalus can all cause intracranial hypertension. Management has conventionally focussed on maintenance of ICP below a pre-defined and arbitrary threshold (< 20 - 25 mmHg), but there has been a shift of emphasis from primary control of ICP to a multi-faceted approach of maintenance of cerebral perfusion and brain protection [7]. Cerebral perfusion pressure (CPP) is the difference between mean arterial pressure and ICP. For the accurate calculation of CPP, the arterial pressure transducer must be referenced at the same level as ICP (tragus of the ear). Measuring blood pressure at the level of the heart results in a calculated CPP that is erroneously high when the head of the bed is elevated.

A CPP target between 60 and 70 mmHg is recommended [2]. Routine attempts to achieve CPP > 70mmHg should be avoided because of the risk of complications, particularly ALI related to fluid and vasopressor administration to increase systemic blood pressure. Cerebrovascular reactivity may be impaired after TBI, varies with perfusion pressure, and optimises within a narrow range of CPP

specific to an individual. ‘Optimal’ CPP can be identified by monitoring techniques such as the pressure reactivity index (PRx) [7]. Individualized CPP management within this ‘optimal’ range minimises the risks of excessive CPP on the one hand and of cerebral hypoperfusion and secondary brain injury on the other, and is associated with improved patient outcomes.

A fundamentally different approach to TBI management was developed in Lund in the 1990s when lower CPP was targeted to reduce capillary hydrostatic pressure and limit intracranial blood volume. An initial case series suggested improved outcomes compared to controls but this has not been established in controlled trials.

Management of intracranial hypertension

ICP > 20 mmHg is associated with worse outcomes after TBI but there is no clear evidence to support the use of ICP monitoring to guide treatment. The only RCT investigating this issue (BEST-TRIP) found no difference in outcomes when treatment was guided by ICP monitoring compared to treatment guided by imaging and clinical examination in the absence of ICP monitoring in TBI patients. This study did not test the value of ICP monitoring *per se* but rather the efficacy of the management of intracranial hypertension identified by two different methods. Since both treatment approaches provided satisfactory outcomes despite the absence of ICP monitoring in one, the study challenges the established practice of maintaining ICP below a universal and arbitrary threshold. Individualized interpretation of ICP values in association with other monitored variables, such as autoregulatory reserve, cerebral perfusion pressure (CPP) and cerebral oxygenation, allows identification of circumstances in which modestly elevated ICP (25-30 mmHg) might be cautiously accepted.

The 2016 Brain Trauma Foundation guidelines recommend that ICP should be monitored in all salvageable patients with severe TBI and an abnormal CT scan, or a normal CT and two of the following: age >40, motor posturing, or hypotension (systolic blood pressure <90mmHg) [2].

ICP-lowering strategies are usually administered in a stepwise manner, starting with safer, first-line interventions while higher risk options, such as surgical decompression, are reserved for patients with

multimodal brain monitoring evidence of brain hypoxia of cerebral metabolic distress, or those at imminent risk of cerebral herniation (Table 3) [8].

Hyperosmolar therapy

Hyperosmolar therapy has been a cornerstone of the management of intracranial hypertension for decades [9]. Mannitol (0.25-1.0g.kg-1) is recommended for the acute treatment of elevated ICP, but has never been subject to a randomised comparison against placebo. The side effects of mannitol include hypotension and the risk of excessively high serum osmolality after repeated administration. Mannitol is most effective when used to treat monitored increases in ICP, and its use in the absence of ICP monitoring should be limited to patients with signs of transtentorial herniation or progressive neurological deterioration [3]. Hypertonic saline increases serum osmolality directly rather than by inducing osmotic diuresis, and also has potential haemodynamic, vasoregulatory and immunological advantages compared to mannitol. However, the optimal osmolar load and mode of administration (bolus or continuous infusion) of hypertonic saline has not been clearly defined. Several studies have compared mannitol and hypertonic saline but the results are heterogeneous and it is unclear which is more effective.

Surgical Intervention

An expanding intracranial haematoma may be evacuated to reduce mass effect and ICP, and limit further secondary injury. Not replacing the bone flap is an option to minimise the impact of further brain swelling, and this approach is currently being evaluated by the RESCUE ASDH trial (http://www.rescueasdh.org). Cerebrospinal fluid drainage via a ventricular catheter should be considered in patients with an initial GCS <6 during the first 12 h after injury [2]. Secondary decompressive craniectomy involves removal of a large area of the skull vault and opening of the dura to treat refractory ICP. The recently published RESCUEicp trial demonstrated that decompressive craniectomy for refractory intracranial hypertension (>25mmHg for >1hr) was associated with lower mortality but higher rates of vegetative state and severe disability in survivors compared to maximal medical therapy.

Therapeutic hypothermia and normothermia

Therapeutic hypothermia is the most effective neuroprotectant in pre-clinical studies of TBI, but has not translated into improved outcomes in clinical studies [10]. A multicentre RCT, which addressed many of the criticisms of earlier studies including timing and duration of hypothermia, found no difference in outcomes between therapeutic hypothermia (32–34°C) or fever control (35.5–37°C). The recent Eurotherm3235 study investigated therapeutic hypothermia as part of tiered approach to ICP management but was suspended early because of worse functional outcomes and higher mortality in the hypothermia group. While this study provides evidence against the early (second tier) use of hypothermia to control ICP, it does not address its role in the management of refractory intracranial hypertension for which it is most commonly used in clinical practice.

Pyrexia is common after TBI and has consistently been associated with poor clinical outcomes. There is evidence that fever reduction improves brain metabolism, suggesting potential neuroprotective effects from maintenance of normothermia after TBI.

Neuroprotective therapies

There are a number of other therapies which have shown promise in pre-clinical and early clinical studies, but which have ultimately not translated into benefit in larger prospective clinical trials. In preclinical models progesterone reduces inflammation, promotes cell proliferation and is antiapoptotic, but large phase 3 clinical trials have not demonstrated improved survival or neurological outcome in moderate and severe TBI. Erythropoetin (EPO) has non-haemopoietic mechanisms which may be beneficial for endothelial cells, neurons, and glia. Again, pre-clinical studies have confirmed a neuroprotective effect of EPO which was not confirmed in two large RCTs. A recent meta-analysis reported that EPO was associated with a significant reduction in mortality after TBI, but the effect on neurological outcome did not reach statistical significance.

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Figure 1

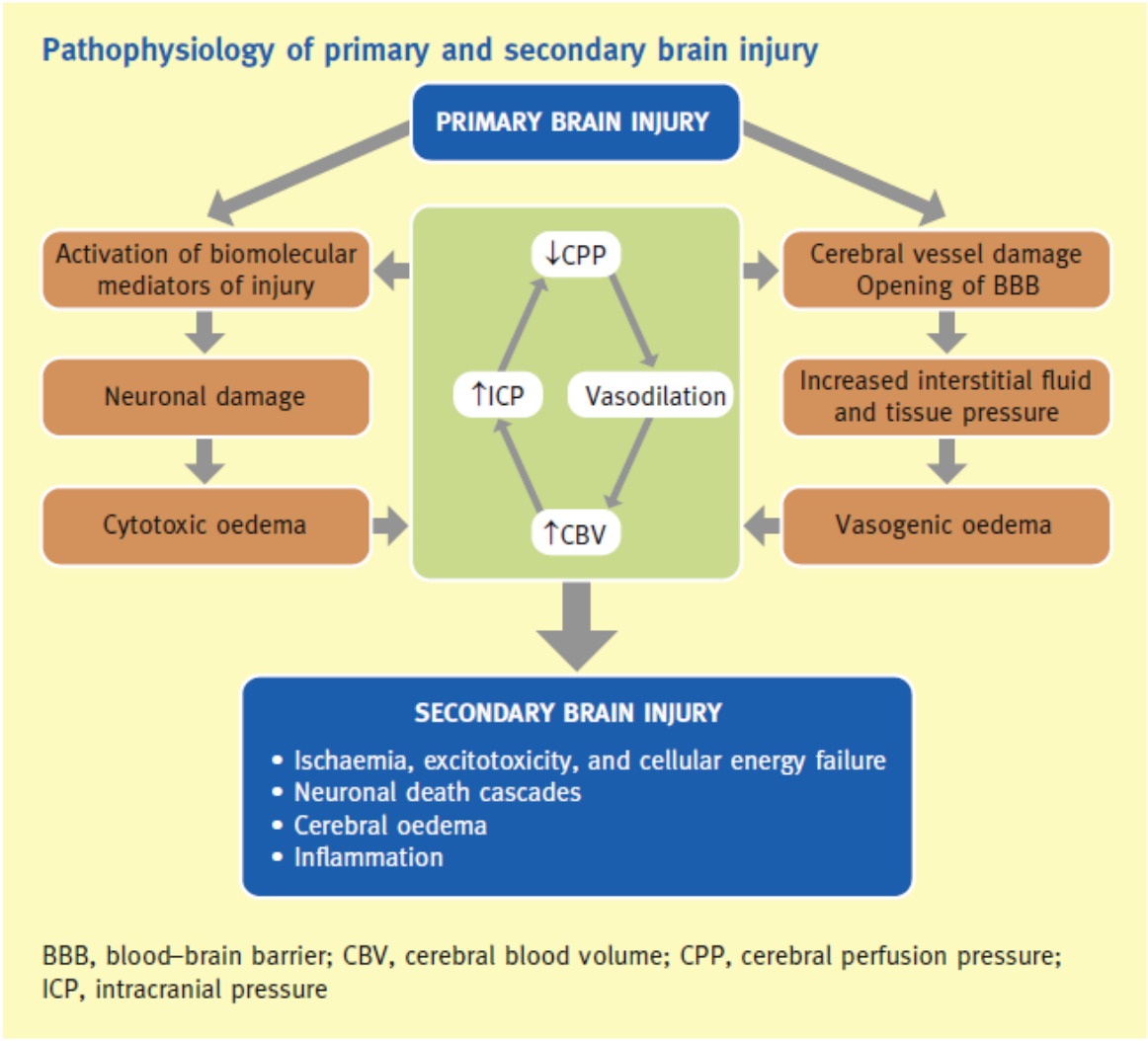
Pathophysiology of primary and secondary brain injury
PRIMARY BRAIN INJURY
Activation of biomolecular mediators of injury
Neuronal damage
Cytotoxic oedema
↓CPP
↑ICP
Vasodilation
↑CBV
Cerebral vessel damage Opening of BBB
Increased interstitial fluid and tissue pressure
Vasogenic oedema
SECONDARY BRAIN INJURY
• Ischaemia, excitotoxicity, and cellular energy failure
• Neuronal death cascades
• Cerebral oedema
• Inflammation
BBB, blood–brain barrier; CBV, cerebral blood volume; CPP, cerebral perfusion pressure; ICP, intracranial pressure

TABLE 1

The critical care management of severe head injury

Ventilation	• PaO_2 > 11 kPa • $PaCO_2$ 4.5 – 5.0 kPa • PEEP ($\leq$15 cm H_2O) to maintain oxygenation • ventilator 'care bundle' to minimize risk of pneumonia
Cardiovascular	• systolic blood pressure: - >100 mmHg for patients aged 50 to 69 years - >110 mm Hg or above for patients aged 15 to 49 or >70 years • normovolaemia • vaspressors/inotropes if insufficient response to fluid
ICP and CPP targets	• CPP 60 – 70 mmHg • ICP < 22 mmHg
ICP / CPP management	• sedation/analgesia • euvolaemia plus norepinephrine to maintain CPP • tiered approach to management of intracranial hypertension (table 3)
General	• normoglycaemia (7.0-10.0 $mmol.L^{-1}$) • normothermia • enteral nutrition • Hb 70 - 90$g.l^{-1}$ (optimal target undefined) • thromboembolic prophylaxis • seizure control

TABLE 2

Distinguishing characteristics and treatment of sodium disturbances after head injury

Finding	SIADH	CSWS	CDI
Plasma volume	Raised	Lowered	Lowered
Sodium balance	Positive/equal	Negative	Equal
Water balance	Positive	Negative	Negative
Serum sodium	Low	Low	High
Serum osmolality	Lowered	High/normal	High
Urine sodium	High	High	Normal
Urine osmolality	High	Normal/high	Low
Management options	• electrolyte-free water restriction - initially to 1000-1500ml/day • demeclocycline – inhibits renal response to ADH • ADH-receptor antagonists – inhibit binding of ADH to renal receptors	• volume and sodium resuscitation • fludrocortisone may limit the sodium loss	• replace fluids to maintain normovolaemia • DDAVP if high urine output (>250 ml/h) continues

SIADH, syndrome of inappropriate ADH secretion; CSW, cerebral salt wasting syndrome; CDI, central diabetes insipidus; ADH, antidiuretic hormone; DDAVP, 1-deamnio-8-D-arginine vasopressin

Normal values: plasma osmolality 278-305 mmol/kg; plasma sodium 135-145 mmol/l; urine osmolality 350-1000 mmol/kg; urine sodium 20-60 mmol/l or 100-250 mmol/24hr.

TABLE 3

Tiered treatment of intracranial hypertension

Tier	Therapy/Intervention	Risks/considerations
1	Elevate head of bed to 30°	May be contraindicated in spinal injuries Hypotension
	Maintain $PaCO_2$ 4.5 – 5.0kPa	
	Propofol (2 - 4mg.kg^{-1}.hr^{-1})	Hypotension Propofol infusion syndrome
	Antiepileptic drugs for seizures	Specific drug side effects
2	Increase sedation	Hypotension
	Neuromuscular blockade	Myopathy, neuropathy
	Hyperosmolar agents Mannitol Hypertonic saline	 Hypotension, hyperosmolarity Optimal osmolar load unknown
	Normothermia	
	Cerebrospinal fluid drainage via an external ventricular catheter	Risks of external drain insertion including bleeding and infection
	Short-term, temporising moderate hyperventilation ($PaCO_2$ 4.0 – 4.5kPa)	Cerebral ischaemia
3	Therapeutic hypothermia	Arrhythmia, infection, fluid & electrolyte abnormalities
	Barbiturates	Hypotension, increased duration of ventilation, infection
	Decompressive craniectomy	Bleeding, infection, risk of survival with poor outcome