

# Targeted treatment of severe head injury

**Head injury is poorly classified for treatment and so its categorisation is not as useful as it could be to guide therapy.**

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It has been increasingly appreciated in recent times that head injury is not a homogeneous concept and is poorly classified for the purposes of treatment.<sup>1</sup> The separation of patients into 3 categories of severity (mild, moderate and severe) remains a blunt measure used to guide therapy in individual patients. Patients with severe traumatic brain injury (TBI), i.e. a Glasgow Coma Score (GCS)  $\leq 8$ , may have different pathologies, including an extradural haematoma, subdural haematoma, cerebral ischaemia, cerebral hyperaemia, vasospasm, diffuse axonal injury, and/or focal haemorrhagic contusions. Moreover, autoregulation of the links between cerebral blood flow (CBF) and blood pressure, carbon dioxide tension, and cerebral metabolic requirements may be variably impaired in individuals – all of which have major implications for treatment. Yet traditional management tends to treat all individuals similarly. For example, intracranial pressure (ICP) is usually treated in a standardised stepwise approach. Yet in individual patients, elevated ICP may be associated with cerebral hyperaemia or cerebral ischaemia, subclinical seizures, or impaired autoregulation (where it is the elevated blood pressure that is the underlying problem). To target these appropriately would require accurate diagnosis and a different approach to management.

## **Yet traditional management tends to treat all individuals similarly.**

Alongside this recognition of the heterogeneity of head injury is the growing appreciation of the role of secondary injury in determining outcome. Secondary injury accounts for everything that occurs after the primary injury that contributes to worsening brain damage. It may take the form of pathophysiological events initiated by the primary injury (such as brain swelling due to biochemical cascades), or secondary insults at a time when the brain is vulnerable, such as hypotension and hypoxia. Secondary injury represents an opportunity to intervene and improve outcome, but our tools for recognising it before damage has been done have been poor. Recent advances in the intensive care unit (ICU) environment, however, have improved our ability to detect potential secondary injury early and avoid its consequences.

The combination of these 2 principles is gradually changing thinking about treatment of severe TBI, increasing emphasis on new methods for detecting secondary injury, and using aggressive individualised therapies targeted to the underlying pathophysiological disturbance. Aggressive treatment is often criticised conceptually because of the concern that reducing mortality results in a larger proportion of severely disabled survivors. However, the secondary injuries that

lead to death are the same ones that cause disability in survivors. Therefore, the concept is that avoidance of secondary injury not only should reduce mortality but also should improve the quality of survival. This recognition, and the increasing complexity of managing these patients, is giving rise to the need for dedicated neuro-critical care specialists. The following are selected examples of changes in monitoring and management of severe TBI.

## **Alongside this recognition of the heterogeneity of head injury is the growing appreciation of the role of secondary injury in determining outcome.**

### *Monitoring*

#### **Intracranial pressure monitoring**

Although not a new development, the adherence to the current adult and paediatric guidelines is improving. Still, there is large variability in the degree to which different centres adhere to these guidelines. Although various reports have been published suggesting that ICP monitoring does not improve outcome, these are usually retrospective reports in which the indication for monitoring was not controlled, leading to more severely injured patients in the monitored group. Also, it is becoming increasingly apparent that there are major differences in the quality of care delivered to patients in different centres, even where most patients receive monitoring. These reports are counterbalanced by a much larger body of literature reporting better outcomes with ICP monitoring.<sup>2</sup> The adage that it is not the monitor that makes the difference, but rather the clinician's response to the monitor, remains true. Several methods may reduce ICP, but may be misapplied and therefore cause harm, as was evident from the indiscriminate use of hyperventilation several years ago. The use of ICP-reducing therapies better targeted to the underlying problem is key.

#### **Autoregulation monitoring**

It has long been known that cerebral arterioles maintain a relatively constant CBF by constricting and dilating in response to increased and decreased blood pressure respectively within a range of mean arterial pressure of approximately 40 - 150 mmHg. It is also known that this ability to autoregulate may be variably impaired when the brain is injured. In the normal circumstance, increased blood

pressure results in reduced cerebral blood volume (and slightly reduced ICP) but does not affect CBF significantly. When autoregulation is impaired, increased blood pressure may lead to *increased* cerebral blood volume (and ICP) and vasogenic oedema, while decreased blood pressure may lead to cerebral ischaemia at unpredictable levels of cerebral perfusion pressure (CPP). Impaired autoregulation is associated with poor outcome, which may reflect its association with more severe injury, but also may represent secondary injury caused by clinicians' poor management of blood pressure in this circumstance. Examination, and even continuous monitoring, of autoregulation is possible, and may provide more information to the clinician about how best to manage blood pressure in an individual patient.<sup>3</sup>

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### Cerebral haemodynamics monitoring

Cerebral haemodynamics vary markedly between individuals. In part, this relates to the relative strength of the various regulatory mechanisms that affect CBF, including pressure autoregulation, carbon dioxide reactivity and the relation between brain metabolism and blood flow. Patients may develop cerebral ischaemia, vasospasm, or cerebral hyperaemia, each of which has unique implications for brain metabolism and the management of ICP. However, we have been poor at diagnosing various pathological states in the ICU. Fortunately this is improving with technological advances, including several imaging and bedside techniques. Imaging of the brain has rapidly expanded with the introduction of new modalities such as mobile Xe perfusion scanning, SPECT, perfusion CT/MRI, and PET. Although these modalities may produce very useful information, they are limited by the fact that they provide information only about one point in time and the patient usually has to be transported out of the controlled ICU environment. Bedside techniques are more continuous and can give up-to-date information about

a dynamic condition and its response to treatment, but are limited by their focal or regional nature. Bedside techniques include brain tissue oxygen monitoring, jugular venous saturation, focal CBF monitoring, and transcranial Doppler.

### Brain tissue oxygen monitoring

Brain tissue oxygen tension (PbtO<sub>2</sub>) can be measured using a thin catheter placed into white matter at the same time that the ICP monitor is inserted. Using a Clarke-type polarographic probe, the monitor measures local tissue oxygen tension reliably, but in a very focal area. To some extent, these readings can be extrapolated when being measured in relatively uninjured brain, but if there is significant focal injury the decision has to be made whether one should measure PbtO<sub>2</sub> in the injured or uninjured tissue. Regardless, the monitor provides important new information not previously available. Low PbtO<sub>2</sub> is associated with poor outcome in adults and children.<sup>4,5</sup> In children this appears to be an even stronger predictor of outcome than ICP. Knowledge of PbtO<sub>2</sub> may also help to better treat high ICP and allow targeted treatment. For example, high ICP associated with hyperaemia is typically associated with high PbtO<sub>2</sub> and high transcranial Doppler flow velocities. PbtO<sub>2</sub> is also helpful to track the response to specific therapies, such as increased CPP. PbtO<sub>2</sub>-directed treatment appears to benefit patients;<sup>4</sup> however, a randomised controlled trial is still pending. Other techniques to measure different aspects of brain oxygenation, such as jugular venous saturation and near-infrared spectroscopy, have different limitations and are currently not as widely used in neurotrauma.

### EEG monitoring

Continuous electroencephalography (EEG) monitoring is being increasingly used in neurocritical care units.<sup>6</sup> Modern devices use sophisticated algorithms to assist non-specialist clinicians in rapidly identifying important patterns on the EEG recording. The primary focus of EEG monitoring is to detect subclinical seizures. These increase ICP and metabolic demand, but because they are subclinical, often go unrecognised. Identification of these seizures allows targeted therapy. The additional benefit of EEG monitoring is that it enables assessment of the level of sedation and metabolic suppression achieved with barbiturate therapy, and may even provide some insight into the occurrence of cerebral ischaemia.

### Microdialysis

Microdialysis is a method by which a metabolic profile of the brain can be

obtained *in vivo* by using a microcatheter placed in brain tissue.<sup>7</sup> Of all the substances that can be so analysed, most research has focused on cerebral lactate, pyruvate and glucose as markers of cellular energy function. The data obtained are semi-continuous and can be performed at the bedside. Elevation of the lactate/pyruvate ratio is typically seen in cerebral ischaemia and mitochondrial dysfunction, and has been used to tailor therapy. For several reasons though, including the cost and infrastructure required to use microdialysis effectively, the technique tends to be used mostly at research centres.

### Glucose monitoring and management

Aggressive monitoring and control of serum glucose has gained popularity in general critical care but remains controversial.<sup>8</sup> In neurotrauma also, it is well known that hyperglycaemia is associated with poor outcome, especially if there is underlying cerebral ischaemia or hypoxia. It is not definitively known yet whether this association is merely an epiphenomenon or represents treatable secondary injury. On the other hand, hypoglycaemia may be equally devastating to neuronal function, and tight glucose control increases episodes of low cerebral glucose and brain metabolic disturbances. To date, very little evidence is available to guide optimal glucose management in neurocritical care patients.<sup>9</sup> In general, because of the concerns about hypoglycaemia, there is a tendency to be less strict about the range of glucose control in neurotrauma patients.

**Cerebral haemodynamics vary markedly between individuals.**

### TBI therapies

#### Active cerebral perfusion pressure management

In the last decade focus on maintaining an adequate cerebral perfusion pressure (CPP) has increased. The logic is clear – CPP is the driving force behind CBF, and below a critical CPP threshold CBF progressively decreases and anaerobic glycolysis increases. This led to an approach in which clinicians aimed for higher CPP (>70 mmHg) to avoid ischaemia, using mostly fluids or vasopressor therapy. However, this approach is not without risk. Aggressive elevation of CPP increases the risk of vasogenic cerebral oedema, especially if

autoregulation is impaired, and increases systemic complications, most notably acute respiratory distress syndrome.<sup>10</sup> Therefore, any benefits from avoiding cerebral ischaemia may be offset by the complications. More recently, a moderated form of CPP management has been suggested, in which a lower threshold value of CPP = 60 mmHg is tolerated in adults.<sup>11</sup> In children, such recommendations are complicated by the different physiological ICP and blood pressure thresholds across the age range. Currently, a CPP of 40 - 65 mmHg is recommended only at the level of an option.<sup>12</sup> To some extent this will depend on the age of the child, and also whether autoregulation is intact or not. A newer concept of targeting CPP to a surrogate measure of the adequacy of global CBF, such as monitors for brain tissue oxygen, local CBF, autoregulation-determined 'optimal' CPP, or lactate/pyruvate ratio (in microdialysis) is also gaining favour because one may avoid the needless exposure to the adverse effects of higher CPP if the patient does not need it.

## Continuous electroencephalography (EEG) monitoring is being increasingly used in neurocritical care units.

### Hypertonic saline

The principle behind osmotherapy in TBI management is to increase the osmotic gradient across the blood/brain barrier and encourage fluid egress from the brain. Traditionally, mannitol was the agent used primarily for this purpose. However, there are several potential side-effects of mannitol, and it is not always effective. Hypertonic saline (HTS) is used in varying concentrations as a bolus or semi-continuous infusion to treat high ICP or more generally to raise the serum sodium concentration. HTS may be more physiological than mannitol, is at least equally efficacious in reducing ICP, and has the added benefit of small-volume fluid resuscitation.<sup>13</sup> In our practice we use HTS to avoid hyponatraemia, and prefer to manage the patient with a serum sodium concentration in the region of 145 - 150 mmol/l if increased ICP is a problem. Needless to say, because hypernatraemia is a risk, management of serum sodium in this way requires a protocol of strict surveillance of serum sodium concentrations and the rate and amount of HTS given.

## Decompressive craniectomy is now far more aggressively employed than a decade ago.

### Decompressive craniectomy

Decompressive craniectomy is now far more aggressively employed than a decade ago. The history of the operation, however, goes back to the beginning of the 20th century, since which it has fluctuated in popularity. Its modern resurgence has much to do with the recognition of the poor method with which it was applied in earlier times, modifications to the procedure, and better selection of patients. In the operation a large bone flap is removed from the cranium and the dura is widely expanded with a graft to increase the amount of volume available for brain swelling and in so doing reduce the ICP. Traditionally the procedure was done often only when patients had been subjected to prolonged exposure to increased ICP or restricted to being a salvage procedure in the most severely injured patients. The modern approach is to identify patients who are not responding adequately to medical measures for reducing ICP early and to perform an adequate controlled decompressive craniectomy while avoiding hypertension in the postoperative phase. Done in this way, decompressive craniectomy markedly reduces ICP and improves brain oxygenation.<sup>14</sup> Importantly, the procedure does not appear to result in increased numbers of saved but disabled individuals. Two randomised controlled trials in adults are currently being performed.

### Hypothermia

Hypothermia has long been studied in TBI. Although promising in the laboratory, it still has largely not translated very successfully into clinical practice for TBI. Neither adult nor paediatric trials so far have demonstrated convincing benefit. However, there have been methodological concerns for some of these trials, including the most recent paediatric study in which patients in the treatment arm had lower blood pressure.<sup>15</sup> This, in addition to issues about what temperature is ideal, how soon patients are cooled, what method is employed, and how fast patients are rewarmed, raises the question of whether protocols could be adjusted to better manage patients at lower temperatures. Currently there is an ongoing multi-centred trial of hypothermia in children aimed at cooling patients by 6 hours post-injury ([www.coolkidstrial.org](http://www.coolkidstrial.org)).

## Conclusion

In summary, there is growing recognition of the heterogeneity in head trauma and the role of secondary injury in determining outcome. Technological advances have helped us to identify disturbances better and to target therapy more appropriately. As a result, however, the complexity of managing these patients has increased. Effective use of these tools requires the training of clinicians with skills in neurocritical care, and is expected to benefit patients.

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### *In a nutshell*

- Head injury is not a homogeneous concept and is poorly classified for the purposes of treatment.
- Patients with severe traumatic brain injury (TBI), i.e. a Glasgow Coma Score (GCS)  $\leq 8$ , may have different pathologies, including an extradural haematoma, subdural haematoma, cerebral ischaemia, cerebral hyperaemia, vasospasm, diffuse axonal injury, and/or focal haemorrhagic contusions.
- Alongside this recognition of the heterogeneity of head injury is the growing appreciation of the role of secondary injury in determining outcome.
- Secondary injury accounts for everything that occurs after the primary injury that contributes to worsening brain damage.
- The combination of these 2 principles is gradually changing thinking about treatment of severe TBI, increasing emphasis on new methods for detecting secondary injury, and using aggressive individualised therapies targeted to the underlying pathophysiological disturbance.
- There is now a large body of literature reporting better outcomes with ICP monitoring.
- Impaired autoregulation is associated with poor outcome, which may reflect its association with more severe injury, but it may also represent secondary injury caused by clinicians' poor management of blood pressure in this circumstance.
- Cerebral haemodynamics vary markedly between individuals.
- Low brain tissue oxygen tension ( $P_{btO_2}$ ) is associated with poor outcome in adults and children. In children this appears to be an even stronger predictor of outcome than ICP.
- Continuous electroencephalography (EEG) monitoring is being increasingly used in neurocritical care units.
- Microdialysis is a method by which a metabolic profile of the brain can be obtained *in vivo* by using a microcatheter placed in brain tissue.
- To date, very little evidence is available to guide optimal glucose management in neurocritical care patients. In general, because of the concerns about hypoglycaemia, there is a trend to be less strict about the range of glucose control in neurotrauma patients.
- In the last decade focus on maintaining an adequate cerebral perfusion pressure (CPP) has increased.
- Decompressive craniectomy is now far more aggressively employed than a decade ago.
- The modern approach is to identify patients who are not responding adequately to medical measures for reducing ICP early and to perform an adequate controlled decompressive craniectomy while avoiding hypertension in the postoperative phase.
- Hypothermia has long been studied in TBI. Although promising in the laboratory, it still has largely not translated very successfully into clinical practice for TBI.