UPDATE IN THE MANAGEMENT OF SEVERE TRAUMATIC BRAIN INJURY

Eva Tejerina¹, Fernando Frutos-Vivar¹, Irene Cortés¹, Andrés Esteban¹,², José A. Lorente¹,²,³

ABSTRACT

Traumatic brain injury is the main cause of death and disability in the young population, which presumes a large number of years of potential life lost and a great economic impact. Vital and functional outcomes after suffering a traumatic brain injury depend both on the severity of the initial biomechanical impact (primary injury) and on the presence and the severity of systemic or intracranial insults that magnify and/or produce new brain injuries, the so-called secondary injuries. Currently, no treatment is effective in improving functional recovery, except for usual medical care. Therefore, the main purpose of the care provided to a patient with severe cranial trauma is based on preventing and treating secondary brain injuries by maintaining an adequate cerebral perfusion and oxygenation.

Increased intracranial pressure is associated with mortality and with unfavorable functional outcomes in patients with severe traumatic brain injury. The main clinical practice guidelines recommend using a number of staggered therapeutic measures. However, although these measures seem to be efficient in reducing intracranial pressure, this effect is not often translated into clinical improvement.

This review describes the essential principles of the management of patients with severe traumatic brain injury in intensive care units.

Keywords: Cranial trauma; acute medical management; intracranial hypertension; secondary brain injury; intracranial pressure monitoring; cerebral perfusion pressure

Traumatic brain injury (TBI) is the main cause of death and disability in the population below 45 years of age¹. In the United States, the overall incidence of severe TBI is estimated at nearly 558 per 100,000 inhabitants/year, approximately 43% of which present with some degree of residual disability one year after the injury¹,³, and 53,000 of which die. Although the mortality rate associated with TBI has decreased, reaching nearly 8% in the last decade¹,⁴; cranial trauma is still a major public health problem due to its severe disabling sequelae, such as cognitive deficits and motor dysfunctions, which may remain for TBI survivors. The most frequent cause of TBI are traffic accidents, followed by falls.

The vital and functional outcomes after suffering a traumatic brain injury depend both on the severity of the initial biomechanical impact (primary injury) and on the presence and severity of systemic insults (hypoxia, hypotension, hypoventilation, hypovolemia, hyperthermia, hyperglycemia) or brain insults (lesion with mass effect, intracranial hypertension, seizures) that magnify and/or produce new brain injuries, the so-called secondary injuries.

The clinical efficacy of neuroprotective treatments aimed at limiting
secondary injuries or improving functional recovery in TBI is uncertain. Therefore, the main purpose of the care provided to a patient with severe TBI is based on preventing and treating secondary injuries. This review describes the essential principles of the management of patients with severe TBI in intensive care units (ICUs).

Although there was an attempt to avoid bias, the present update is susceptible to the limitations characteristic of this type of review, such as the subjective nature of the findings and of the method used for study inclusion, the possibility of obtaining erroneous findings, and the difficulty in identifying complex interactions when analyzing a great number of studies. Three search themes were combined. The first one used the term “OR” with the following medical subject headings and text words: “treatment”, “management”, “monitoring”. The second one used the term “OR” with the following medical subject headings and text words: “traumatic”, “injury”. The third one used the term “OR” with the following medical subject headings and text words: “brain”, “cranial”, “cerebral”. These three themes were combined with the Boolean operator “AND”. No age limit was established for study subjects. Only articles in English or Spanish were analyzed. Search for the most relevant publications was conducted on the following databases: Biblioteca Cochrane Plus (Cochrane Library), DARE, Medline, EMBASE, and GPC (table 1).

Table 1: Most relevant studies on the management of severe traumatic brain injury.

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<td></td>
<td>Dexmedetomidine similar efficacy to propofol</td>
<td>James ML. (70)</td>
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### Severe traumatic brain injury

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<tr>
<th>Therapeutic measure</th>
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<tr>
<td><strong>Antiseizure prophylaxis</strong></td>
<td>Phenytoin is the antiepileptic agent of choice for the prevention of early posttraumatic seizures&lt;br&gt;Higher mortality in patients treated with valproate&lt;br&gt;Levetiracetam: similar efficacy to phenytoin</td>
<td>Temkin NR. (72)&lt;br&gt;Temkin NR. (74)&lt;br&gt;Jones KE. (75), Inaba K. (76)</td>
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<td><strong>Antibiotic prophylaxis</strong></td>
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<td><strong>Stress ulcer prophylaxis</strong></td>
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**TREATMENT OF INTRACRANIAL HYPERTENSION**

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<td>Mannitol 20%</td>
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<td>Wakai A. (104)</td>
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<td>Kamel H. (109), Mortazavi MM. (110)</td>
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<td>Insufficient evidence&lt;br&gt;Prophylactic hyperventilation is not recommended</td>
<td>Schierhout G. (112)&lt;br&gt;Muizelaar JP. (113)</td>
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<td>Effective in controlling ICP, but doubtful effects on clinical outcomes</td>
<td>Sydenham E. (115)</td>
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<td>Effective in controlling ICP, but worse functional outcomes&lt;br&gt;Effective recovery measure in the case of refractory ICH</td>
<td>Cooper J. DECRA (117)&lt;br&gt;Sahuquillo J. (116)</td>
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<td>Lumbar drainage</td>
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<td>Münch EC. (120), Abadal-Centellas JM. (121)</td>
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<td>Barbiturates</td>
<td>Effective in controlling ICP but doubtful effects on clinical outcomes&lt;br&gt;Higher effectiveness of thiopental in controlling ICP&lt;br&gt;Considering SjvO\textsubscript{2} monitoring</td>
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**Severe TBI (GCS ≤ 8)**

Orotracheal intubation and ventilation: \( \text{paCO}_2 \) 35-40 mm Hg

Oxygenation: \( \text{paO}_2 > 90 \) mm Hg or SatO\(_2 \) > 95%

Hemodynamics: Systolic BP > 90 mm Hg. Noradrenaline if required

Fluid therapy: Normovolemia. Osmolality > 280 mOsm/L

**Cranial CAT (GCS ≤ 14)**

Removable lesion

Urgent surgery

**Control cranial CAT**

Within the first 24 hours: GCS < 8

During the acute posttraumatic period (7 days):
- Changes in clinical situation
- Changes in ICP levels

**ICP monitoring**

- GCS < 8 and abnormal cranial CAT
- Normal cranial CAT and one of the following conditions:
  - Age > 40 years
  - Decerebrate rigidity
  - Systolic BP < 90 mmHg

**SjO\(_2 \) monitoring**

- In situations of reduced CBF (hyperventilation and barbiturate coma)

Goal: SjO\(_2 \) > 55%

**Other alternative monitoring systems:**

- **Pt\(_i\)O\(_2 \) monitoring:**
  - In situations of reduced CBF (hyperventilation and barbiturate coma)
  - Goal: Pt\(_i\)O\(_2 \) > 20 mmHg

- **Infrared spectroscopy.** Its routine use is not recommended

- **Microdialysis.** Its routine use is not recommended

- **Transcranial Doppler.** Its routine use is not recommended

- **Bispectral electroencephalographic analysis:**
  - Monitoring of barbiturate coma (BIS 6-15)

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**Figure 1:** Algorithm for the management of patients with severe traumatic brain injury.

TBI = traumatic brain injury, GCS = Glasgow Coma Score, PaCO\(_2 \) = arterial carbon dioxide pressure, SatO\(_2 \) = arterial oxygen saturation, BP = blood pressure, CAT = computed axial tomography, ICP = intracranial pressure, CPP = cerebral perfusion pressure, SjO\(_2 \) = jugular bulb oxygen saturation, CBF = cerebral blood flow, Pt\(_i\)O\(_2 \) = tissue oxygen pressure, BIS = bispectral index.
EVALUATION AND INITIAL MANAGEMENT

Figure 1 Algorithm for the management of patients with severe TBI. Brain ischemia is the injury that has the most negative impact on prognosis. For this reason, initial management should be focused on optimizing oxygenation, ventilation, and hemodynamics.

Oxygenation

Orotracheal intubation and positive pressure ventilation are recommended in patients with a Glasgow Coma Scale (GCS) score equal to or below 8 and/or persisting hypoxia. The purpose of these procedures is maintaining a partial pressure of arterial oxygen (paO2) higher than 90 mm Hg or an arterial oxygen saturation (SatO2) higher than 95%, in order to prevent paO2 values to be lower than 60 mmHg. Positive end-expiratory pressure (PEEP) may be used to correct hypoxemia. In normovolemic patients, the use of PEEP does not increase intracranial pressure (ICP) or reduce cerebral perfusion pressure (CPP).

Ventilation

Arterial carbon dioxide pressure (paCO2) should be maintained between 35 and 40 mm Hg. The development of acute lung injury and/or acute respiratory distress syndrome occurs in 20 to 25% of patients with severe TBI, especially in those receiving mechanical ventilation with high tidal volumes, and is an independent factor of poor neurological prognosis. In such cases, it is necessary to individually evaluate the need for assisted ventilation until achieving paCO2 values that allow for the control of ICP, as well as the use of a protective ventilatory strategy, which may induce the development of hypercapnia.

Hemodynamics

Systolic blood pressure should not be reduced below 90 mmHg; in addition, it is important to maintain adequate volemia (central venous pressure between 8 and 10 mmHg) and plasma osmolality within a range from 295 to 305 mOsm/L. To this end, as a general rule, it is recommend to avoid hypotonic fluids and to use only isotonic fluids. Hypertonic fluids theoretically reestablish cerebral perfusion with minimum brain edema and modulate inflammatory response, thus reducing neuronal injury and providing a potential benefit in the resuscitation of TBI patients. However, in a study conducted in patients with severe TBI, initial resuscitation with hypertonic saline did not improve functional outcomes at 6 months [Extended Glasgow Outcome Scale (GOSE) ≤ 4; hypertonic saline vs. normal saline: 54.3% vs. 51.5%; p=0.67] or survival at 28 days (74.3% with hypertonic saline vs. 75.7% with normal saline; p=0.88).

Conversely, fluid resuscitation with albumin in TIB patients is associated with higher mortality rates than with those of patients resuscitated with saline (42% vs. 22%).

The use of vasoactive drugs to maintain systolic blood pressure higher than 90 mmHg does not significantly increase ICP. No significant differences were found between noradrenalin and dopamine with regard to their effect on CPP in head-injured patients. However, noradrenalin seems more predictable and efficient, while dopamine could increase brain edema and has potentially detrimental effects resulting from the suppression of circulating concentrations of anterior pituitary-dependent hormones, which led some authors to discourage its use.

NEUROIMAGING TESTS

Computed axial tomography (CAT) is the imaging test of choice in the acute phase of TBI. Clinical practice guidelines recommend performing a cranial CAT scan in all TBI patients with a GCS score equal to or below 14. The findings on the first cranial CAT scan are correlated with prognosis according to the scale described by Marshall et al. This scale classifies TBI patients into six groups based on the type and severity of abnormalities on CAT imaging (e.g., removable lesions with or without mass effect), and establishes other four categories for diffuse lesions, taking into account the presence of signs of increased ICP (compressed or absent basal cisterns and midline deviation).

More recently, other predictive radiological parameters have been evaluated, such as the status of the basal cisterns, midline shift, the presence of traumatic intraventricular or subarachnoid hemorrhage, and the existence of different types of mass lesions, whose combination could improve the accuracy of the prognostic assessment of TBI patients.

Scheduling a repeat follow-up cranial CAT scan within the first 24 hours after injury, regardless of patient’s neurological conditions and of the initial findings on imaging tests, is common practice in most trauma centers. Evolutionary changes on CAT scans are considered frequent and may lead to modifications in the therapeutic approach. The
ease of access and wide availability of CAT, as well as advances in the speed of image acquisition, have considerably intensified its use. However, there are no clear indications for the systematic performance of a sequential cranial CAT in the acute posttraumatic period, and this practice has not been shown to be associated with an improvement in clinical outcomes. Two recent systematic reviews found that performing a repeat cranial CAT scan in patients with mild head injury (GCS score equal to or above 13) when there is no clinical indicators did not alter the therapeutic management or the need for neurosurgical intervention. Nonetheless, due to the lack of accurate indicators of neurological decline and to the existing disagreements between radiological findings and ICP changes (which may occur in up to 30.3% of cases), some authors recommend serial CAT scanning after severe TBI (GCS score equal to or below 8) or evidence of intracranial pathology on the initial CAT and additional controls based on clinical or ICP changes. A systematic review published in 2006 observed a higher incidence of progression of injury (average of 43%) in patients with severe TBI, defined as a GCS score from 3 to 8 and, consequently, a greater need for neurosurgical intervention (8%) in this group. The presence of more severe initial intracranial injuries and coagulopathy were the risk factors more commonly associated with progression of CAT findings.

Other authors consider it unnecessary to schedule repeat CAT scans in the absence of neurological decline, regardless of initial GCS score. In a prospective study of 651 TBI patients, none of the 156 patients who received a routine cranial CAT required a change in management. The 149 cranial CAT scans performed for clinical deterioration resulted in a change in management in 28 patients (19%).

In conclusion, current evidence allow to suggest that usual clinical practice should include systematically scheduling a control CAT scan within the first 24 hours in patients with severe cranial trauma (GCS score below 8) and performing additional cranial CAT scans during the acute posttraumatic period based on clinical and IPC changes.

Although CAT is still the imaging test of choice in the acute phase of TBI, magnetic resonance imaging (MRI) is more sensitive in detecting lesions in white matter, corpus callosum, and brainstem. Therefore, cranial MRI is more capable of identifying posttraumatic intracranial injuries (within the first 4 weeks after TBI), such as diffuse axonal injury, posterior fossa lesions, and deep injuries, and provides information with prognostic value. However, technical difficulties in performing this test have hampered its widespread use.

NEUROMONITORING

The main purpose of the different monitoring systems is to maintain an adequate brain perfusion and oxygenation through the early detection of situations of hypoxia or tissue ischemia, which are associated with unfavorable clinical outcomes.

Intracranial pressure monitoring

The placement of an ICP sensor is recommended in the following cases: severe TBI (defined as a GCS score below 8) and abnormal cranial CAT scan (hematoma, contusion, edema, compressed basal cisterns), or normal cranial CAT and one of the following conditions: age above 40 years, decerebrate rigidity and/or systolic blood pressure below 90 mm Hg. Currently, different types of catheter are available for monitoring ICP: intraventricular, epidural, subdural, subarachnoid, and intraparenchymatous. Historically, intraventricular catheter has been considered the most accurate, reliable and cost-effective system, thus being the system of choice whenever possible. Additionally, it allows for cerebrospinal fluid (CSF) drainage as a therapeutic measure to control intracranial hypertension (ICH) and can be recalibrated in situ. Its main drawback is the high incidence of infection (up to 20%) and, less frequently, of hemorrhage in the insertion route (2%).

However, the most currently used system to measure ICP is intraparenchymatous catheter. It has an accuracy similar to that of ventricular catheter but is easier to place and cause less complications. Its drawbacks are the fact that it does not allow for CSF drainage and cannot be recalibrated after being inserted. The ICP sensor is usually placed at the right side, in the case of diffuse injuries, since the right cerebral hemisphere is the non-dominant hemisphere in nearly 80% of the population. However, some authors believe that the sensor should always be placed at the side with more pathological lesions or more edema. The reliability of intraparenchymatous sensors has been a subject of debate, since they cannot recalibrated after being inserted. Some studies...
found that zero-drifts are rare and are usually below 3 mmHg. Nonetheless, two studies showed a variability in readings higher than 3 and 5 mmHg in 50% and 20% of study patients, respectively\textsuperscript{30,31}. The correlation between these drifts and duration of monitoring (especially after the first day of monitoring) is controversial, because most studies did not observe any correlation between duration of monitoring and zero-drift\textsuperscript{28-30} but one study did report this correlation\textsuperscript{31}.

Epidural, subdural and subarachnoid catheters are less accurate and therefore have a more limited use.

ICP monitoring allows for the establishment of a prognosis and for the setting of guidelines for the treatment of TBI patients. Additionally, although its use is considered a standard practice in severe TBI, the efficacy of therapeutic protocols that include ICP monitoring with regard to clinical improvement in these patients has not been well established. Generally speaking, an intervention should be made if ICP raises above 20 mmHg. Some studies showed that patients with good response to ICP control measures have lower mortality rates\textsuperscript{32}; conversely, others studies did not find any clinical benefit\textsuperscript{33} or even found a worse prognosis\textsuperscript{34}. In a recent clinical trial\textsuperscript{35} comparing the outcome of patients with severe TBI treated based on ICP monitoring or on neurological examination and serial imaging studies, it was observed that therapeutic management aimed at maintaining ICP at 20 mmHg or less did not yield better results. Furthermore, CPP values should be maintained at 50-60 mmHg or less. If autoregulation is preserved, low CPP levels are associated with increased ICP through compensatory vasodilation. Conversely, it is not recommended to increase CPP above the critical threshold (more than 70 mmHg), due to acknowledged lack of clinical benefits and the possible emergence of detrimental effects at the systemic and brain levels\textsuperscript{32,36}. The closer CPP values are to those that ensure optimal autoregulation, the more likely the patient is to have a favorable clinical outcome\textsuperscript{37}.

The incidence of infection associated with ICP catheters ranges from 1% to 27%. The colonization of external ventricular drainage systems is easier to detect, thanks to CSF samples, and its incidence is nearly 8%. The routine exchange of external ventricular drainage catheters and the administration of prophylactic antibiotics did not have an effect on infection rates\textsuperscript{38,39}. It is recommend to use closed drainage systems and to minimize manipulation and lavage to prevent CSF infection.

### Jugular bulb oxygen saturation (SjvO2)

Jugular bulb oxygen saturation (SjvO2) provides information on brain oxygen extraction and thus on overall cerebral oxygenation, which is obtained from cerebral venous drainage in the internal jugular vein. Its monitoring is achieved by retrograde catheterization of the internal jugular vein, usually the right vein, because it is the dominant one. SjO2 monitoring may be continuous, using an optical fiber catheter, or intermittent, with repeated blood sampling. Under normal circumstances, SjO2 ranges from 55 to 70%. Values below 50 to 55% usually represent a situation of global cerebral hypoperfusion, which leads to increased brain oxygen extraction. Two prospective studies of patients with severe TBI observed that the number of episodes of desaturation below the ischemic threshold (SjvO2 below 50-55%) is associated with higher mortality rates and worse functional outcomes\textsuperscript{30,41}. However, some authors believe that the normal lower limit is lower than that, even reaching values below 46%\textsuperscript{42}. In some studies\textsuperscript{43}, continuous SjvO2 monitoring has been associated with a better clinical outcome in patients with severe TBI and ICH. Nonetheless, despite the theoretical superiority of continuous SjvO2 monitoring\textsuperscript{44}, the lack of accuracy in the optical fiber catheters usually available\textsuperscript{45}, due to catheter malpositioning and displacement, movement artifacts, and the formation of thrombi, led some clinical practice guidelines to recommend collecting samples intermittently every 12 hours\textsuperscript{46}. Generally speaking, it is recommended to monitor SjvO2 in situations of reduced cerebral blood flow (CBF) (hyperventilation and barbiturate coma) and maintain SjvO2 values above ischemia threshold (> 55%).

### Tissue oxygen pressure (PtiO2)

Tissue oxygen pressure (PtiO2) is an invasive method to measure cerebral oxygenation using an intraparenchymatous catheter. It measures mean oxygen pressure at the arteriolar, capillary, extracellular, intracellular, and venous levels within a 14 mm\textsuperscript{2} area, through a redox reaction of the oxygen diffused within the catheter (Licox system). Additionally, it reflects the balance between oxygen intake and consumption at the cellular level. Normal PtiO2 values range from 15 to 30 mmHg. Values below 15 mmHg indicate the existence of tissue hypoxia, which may be moderate (between 15 and 10 mmHg) or severe (below 10 mmHg). The use of PtiO2 may provide important information that
may influence patient management. In two recent prospective studies that compared the outcomes of patients treated with a PtiO2-directed protocol to maintain PtiO2 above 20 mmHg and control ICP below 20 mmHg with those of historical controls, mortality rates were found to be significantly lower in patients treated according to the PtiO2-directed protocol. This mortality was associated with lower mean daily PtiO2 and longer duration of the episodes of cerebral hypoxia (PtiO2 below 15 mmHg)\textsuperscript{47,48}. In a systematic review\textsuperscript{49} including 3 studies and 150 patients with severe TBI, cerebral hypoxia (PtiO2 below 10 mmHg for more than 15 minutes) was associated with worse prognosis (odds ratio 4.0; 95% confidence interval 1.9-8.2) and increased mortality (odds ratio 4.6; 95% confidence interval 2.2-9.6). Currently, a clinical trial is being conducted to assess whether PtiO2 monitoring reduces the duration of episodes of brain ischemia. This study is at the recruitment stage and is expected to be completed in August 2014\textsuperscript{50}.

**Infrared spectroscopy**

The technique of infrared optical spectroscopy is used to quantify cerebral oxyhemoglobin concentration. Seventy to eighty percent of the cerebral hematic content is located in the venous bed; therefore, oximetry techniques with spectroscopy provide information mainly about the venous compartment of the brain. This technique provides information on changes in regional oximetry values in the face of therapeutic maneuvers or in the context of the development of new brain injuries. However, it is less accurate than SjvO2 in determining cerebral oxygenation\textsuperscript{51}, and its usefulness for the clinical management of critical patients is still very limited. Currently, its routine use is not recommended in patients with severe TBI.

**Microdialysis**

Microdialysis is a technique based on the principle of interchanging solutes through a semipermeable membrane located at the distal end of the microdialysis catheter, which is usually inserted into the brain area that is more vulnerable to secondary injuries and is used to interchange solutes between a solution of known composition and the fluid within the extracellular space. Cerebral microdialysis is an extremely sensitive technique that can provide early metabolic information on the development of tissue injuries. Cerebral microdialysis catheters allow for the quantification of some metabolites that mediate brain oxidative metabolism (glucose, lactate, pyruvate, and lactate/pyruvate ratio) and the monitoring of the release of excitatory neurotransmitters (glutamate and aspartate) and products of tissue degradation (glycerol), which act as markers of brain ischemia and tissue injury. Typically, cerebral hypoxia or ischemia produces an increase in the lactate/pyruvate ratio, and values above 20-25 for this ratio are considered the threshold for brain ischemia and are associated with poor prognosis in TBI patients\textsuperscript{52}. However, currently there is no enough evidence to allow researchers to establish whether the information provided by microdialysis is useful to clinical management or as a prognostic tool; therefore, its routine use is not recommended in patients with severe TBI.

**Transcranial Doppler ultrasound**

Transcranial Doppler is a non-invasive method that allows for the measurement of the velocity of cerebral blood flow. It is a useful tool for the diagnosis of complications after TBI, such as vasospasm, critical increases in ICP, critical reductions in CPP, carotid dissection, and brain death. Transcranial Doppler has been proposed as a non-invasive method alternative to ICP monitoring\textsuperscript{53,54}. Some echographic variables are correlated with increased ICP, such as decreased blood flow velocity or a progressive increase in the pulsatility index (pulsatility index = [peak systolic velocity – telediastolic velocity]/mean velocity)\textsuperscript{55} and optic nerve sheath diameter, particularly in the retrobulbar segment (with values ranging from 4.8 to 5.9 mm for a ICP below 20 mmHg, according to some studies)\textsuperscript{56-58}. However, currently there is not enough evidence to allow researchers to establish whether the provided information is accurate enough for the usual clinical management of ICP and CPP in patients with severe TBI.

**Bispectral electroencephalographic analysis (bispectral index [BIS])**

The bispectral index (BIS) is an electroencephalogram-derived (EEG) variable consisting of an absolute number ranging from 0 (electrical silence) to 100 (conscious patient). It is a simple-to-use, non-invasive method that, through continuous monitoring, allows for the establishment of whether the sedation level is adequate (with a BIS ranging from 40 to 60) and may enable the early detection of changes in the neurological
status of TBI patients. Several studies evaluated the utility of the BIS as an indicator of the level of consciousness in critical TBI patients and showed that there is a significant correlation between BIS values and different sedation scales (Richmond Agitation-Sedation Scale [RASS] and Sedation-Agitation Scale [SAS]). The BIS has also been shown to be a predictor of recovery of consciousness in TBI patients after sedation have been withdrawn. Additionally, it is a useful tool to monitor barbiturate coma in patients with severe TBI and refractory ICH, due to the correspondence between BIS (with values ranging from 6 and 15) and burst-suppression pattern in the EEG. Nonetheless, in the ICU, electromyographic and electrocardiographic activities, power supplies, and electrical devices may represent artifacts in the interpretation of the BIS.

**GENERAL MANAGEMENT**

**Figure 2 - Algorithm for the general medical care of patients with severe TBI.**

**Postural measures**

TBI patients should be placed in a position that makes brain venous drainage easier. The recommended procedures are the following: a) raising patient’s headboard between 30 and 60 degrees whenever CPP remains above 60 mmHg, for which the patient should be well hydrated and the use of drugs that reduce systolic blood pressure should be avoided, b) avoiding excessive neck flexion and rotation, c) avoiding neck compression (cervical collar, straps for endotracheal tube fixation), d) minimizing stimuli that induce Valsalva maneuvers, such as tracheal suctioning. In patients with severe TBI receiving mechanical ventilation, endotracheal lidocaine instillation may prevent increased ICP after suctioning of tracheal secretions.

**Sedation and analgesia**

Optimal sedoanalgesia reduces cerebral metabolic demand for oxygen and sympathetic response, in addition to help to prevent the development of seizures. The ideal sedative agent should have rapid onset of action and short recovery time from hypnosis (which allows for the performance of periodic neurological evaluations), be easy to titrate, and have no active metabolites. Under these premises, although there is no evidence that one sedative agent is more effective than another with regard to improvement in neurological outcomes or in mortality or with regard to effects on ICP, CPP and mean arterial pressure, propofol would be the hypnotic drug of choice in patients with severe TBI. However, propofol should be avoided in hypotensive or hypovolemic patients due to its detrimental hemodynamic effects. Conversely, the so-called propofol infusion syndrome (rhabdomyolysis, metabolic acidosis, kidney failure, bradycardia) is a complication associated with high doses of propofol (above 4 mg/kg/h). Benzodiazepines, such as midazolam and lorazepam, in addition to having a sedative effect, produce amnesia and have an antiseizure effect. Nonetheless, its use is limited by the fact that prolonged perfusion or high doses may produce oversedation resulting from drug accumulation, especially in the presence of kidney or liver dysfunction or in elderly patients. Dexmedetomidine is an alpha-2 adrenergic receptor agonist that has a sedative effect and is associated with less delirium, tachycardia and hypertension compared with midazolam, in addition to not producing respiratory depression. A recent study of patients with severe TBI and receiving mechanical ventilation showed that dexmedetomidine and propofol were equally effective with regard to sedation and had similar effects on hemodynamic and cerebral physiological variables.

The administration of opioids, whether in repeated doses or in short-term continuous infusion, may have clinically significant detrimental effects on ICP and CPP. These effects are usually transient and result from increased ICP caused by decreased vascular cerebral resistance, increased CBF, and changes in cerebral autoregulation.

**Temperature control**

Hyperthermia (body temperature above 38 °C) is observed in up to 68% of patients within the first 72 hours after TBI and is an independent predictor of poor prognosis. Fever increases cerebral metabolic demand, which is translated in increased CBF and may increase ICP. Therefore, hyperthermia should be treated in TBI patients, including the administration of paracetamol and mechanical cooling.
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Figure 2: Algorithm for the general medical care of patients with severe traumatic brain injury.
TBI = traumatic brain injury, GCS = Glasgow Coma Score, DVT = deep venous thrombosis.
**Antiseizure prophylaxis**

Seizure activity in the early posttraumatic period (the first 7 days after TBI) may cause a secondary brain injury as a result of increased metabolic demand for oxygen, increased ICP, and excessive neurotransmitter release. Antiseizure prophylaxis is indicated in the following situations: GCS score below 10, cortical contusion, depressed skull fracture, subdural, epidural or intraparenchymatous hematoma, penetrating head wound, and/or seizure within the first 24 hours of injury. Phenytoin is the recommended drug for early posttraumatic seizure prophylaxis (within the first 7 days of TBI), but does not provide any benefit when given after the first 7 days of injury. A loading dose of 15 to 20 mg/kg was given over 30 minutes, followed by maintenance doses of 100 mg every 8 hours. It is recommended to monitor levels and check potential secondary effects. A clinical trial of 380 TBI patients compared the safety and effectiveness of valproate with those of phenytoin for prevention of seizures following TBI. The rate of early posttraumatic seizures was similar in both groups (1.5% in the phenytoin-treated group and 4.5% in the valproate-treated group; p = 0.14, relative risk 2.9, 95% confidence interval 0.7-13.3) and the incidence of adverse effects was also similar, but there was a trend of higher mortality in patients treated with valproate (7.2% in patients treated with phenytoin and 13.4% in those treated with valproate; p = 0.07, relative risk 1.18, 95% confidence interval 1.09-1.27; p=0.0001).

**Steroids**

The use of steroids is not recommended to reduce ICP or improve clinical outcomes in patients with moderate or severe TBI. The administration of methylprednisolone in these patients has been associated with increased mortality and is therefore contraindicated. In a multicenter study (CRASH) of 10,008 TBI patients with GCS score equal to or below 14 within 8 hours of injury who were randomized to receive a 48-hour infusion of methylprednisolone or placebo, the risk of death from any cause at 2 weeks was higher in the corticosteroid group (21.1% vs. 17.9%; relative risk 1.18, 95% confidence interval 1.09-1.27; p=0.0001).

**Deep vein thrombosis prophylaxis**

TBI patients have an increased risk of thromboembolic events, including deep vein thrombosis and pulmonary embolism. In the absence of prophylaxis, the risk of developing deep vein thrombosis and/or pulmonary embolism is estimated from 20% to 54%. Although there is no evidence on which to base recommendations on pharmacological prophylaxis, most experts suggest that, when there is no contraindications, prophylaxis should be started within 48-72 hours after injury. Deep vein thrombosis prophylaxis with pharmacological agents is more effective than mechanical measures alone in neurosurgical patients. This evidence should be extrapolated with caution to TBI patients, since they often present with intracranial hemorrhage with risk of progression. Mechanical thromboprophylaxis, including intermittent compression and graduated compression stockings, has shown to be effective, although in a suboptimal manner, in preventing deep vein thrombosis in neurosurgical patients and TBI patients with multiple trauma. The main advantages of these mechanical...
thromboprophylaxis systems are the safety of its use, since they did not increase the risk of bleeding, and the possibility of being used in combination with other prophylactic methods. Recently, a work group has proposed an algorithm (“Parkland Protocol”) in which patients are stratified according to the risk of progression of intracranial hemorrhage and a prophylactic regimen with low molecular weight heparin for each risk group. Patients who underwent craniotomy or those with an intraparenchymatous ICP sensor are considered high-risk patients; therefore, the placement of a vena cava filter is recommended for prophylaxis. The limitation of this protocol is the fact that it has not been validated and that it does not consider the use of mechanical thromboprophylaxis as an alternative to pharmacological prophylaxis.

**Nutrition**

Neurocritical patients usually present with a hypermetabolic, hypercatabolic, hyperglycemic state, thus requiring early nutritional support. The nutrition of choice is enteral feeding, using a gastric tube. Enteral nutrition should be started early and achieve total energy requirements in the first week after trauma. Energy intake varies from 20 to 30 kcal/kg/day, with a protein intake of more than 20% of total calories (hyperproteic diet). Patients with severe TBI often have intolerance to gastric feeding due to several reasons such as gastric dysfunction or slow gastric emptying secondary to increased ICP and to the administration of opiates. The prescription of prokinetic drugs like metoclopramide or erythromycin may improve tolerance. As an alternative, it is possible to choose transpyloric or mixed (enteral-parenteral) feeding in case of failure to achieve an effective nutritional amount of more than 60% of the total calculated energy intake.

**Glycemic control**

Several studies have demonstrated that hyperglycemia is associated with unfavorable neurological prognosis in TBI patients. However, the maintenance of low blood glucose levels within very tight limits is controversial, since hypoglycemic episodes may induce or aggravate brain injury. A recent meta-analysis on intensive insulin therapy in TBI patients showed that this therapy did not reduce in-hospital or late mortality (relative risk 1.04, 95% confidence interval 0.75-1.43 and relative risk 1.07, 95% confidence interval: 0.91-1.27, respectively). Additionally, intensive insulin therapy did not have a protective effect on long-term neurological outcomes (relative risk 1.10, 95% confidence interval 0.96-1.27). However, intensive insulin therapy increased the incidence of hypoglycemic episodes (relative risk 1.72, 95% confidence interval 1.20-2.46). Consequently, based on the available evidence, a strict control of glucose levels is not recommended during the acute phase in patients with severe TBI. Blood glucose levels should be maintained between 140 and 180 mg/dl.

**Stress ulcer prophylaxis**

Severe TBI is a well-established risk factor for the development of stress ulcers in the ICU. Prophylaxis include early start of enteral feeding and the administration of proton pump inhibitors.

**Hemostatic treatment**

Intracranial hemorrhage is usually associated with TBI and may progress in nearly half of the cases, which leads to higher mortality. Conversely, almost a third of TBI patients develop coagulopathy with increased fibrinolysis, which raises the possibility that an antifibrinolytic agent such as tranexamic acid may reduce the progression of intracranial traumatic hemorrhage. Two clinical trials evaluated the effect of tranexamic acid on TBI cases: the CRASH-2 Intracranial Bleeding Study, which included 270 TBI patients with multiple trauma, and a second study including 240 patients with TBI alone. A meta-analysis of these two clinical trials showed a significant reduction in hematoma growth (relative risk 0.72; 95% confidence interval 0.55-0.94) and mortality (relative risk 0.63; 95% confidence interval 0.40-0.99) associated with the treatment with tranexamic acid. However, a systematic review concluded that there is not enough evidence on the effect of hemostatic drugs in TBI patients and that new randomized controlled trials should be conducted. In this sense, the CRASH-3 clinical trial is a study designed to quantify the effects of the early administration of tranexamic acid (1 g loading dose followed by a 1 g infusion over 8 hours) on functional outcomes and mortality in TBI patients. This study is currently at the recruitment stage and aims to include 10,000 patients.
Figure 3: Algorithm for the staggered treatment of ICH in patients with severe traumatic brain injury.

Severe TBI (GCS ≤ 8)

- Staggered treatment of intracranial hypertension

  - CSF drainage
    - 1-2 ml/min (maximum 20 ml/h)

  - Neuromuscular blockade

  - Mannitol 20%: 0.25-1 g/kg
    - Maximum: Plasma osmolality > 320 mOsm/kg or Na > 155 mEq/L
    - 7.5% hypertonic saline: 1.5-2 ml/kg for 15 min.

  Treatment of choice in cases of Na < 135 mEq/L, hemodynamic instability, or lack of response to mannitol.

- Moderate hyperventilation
  - $p_{aCO_2}$ 30 - 35 mmHg (prolonged or prophylactic use is not recommended)

- Severe hyperventilation
  - $p_{aCO_2}$ < 30 mmHg (Stop treatment if $S_jO_2 < 50%$)

- Moderate hypothermia
  - 32-34°C (48 h)

- Decompressive craniectomy

- External lumbar drainage
  - If basal cisterns are unobstructed and midline shift is < 10 mm
  - Initial drainage of 5-20 ml of CSF, under control of ICP and pupils
  - Permanent opening from 5-15 cm above the foramen of Monro

- Barbiturates
  - Sodium thiopental (6 mg/kg for 3-5 min, 3-5 mg/kg/h via continuous infusion)
  - Wave suppression pattern on EEG or BIS

  $S_jO_2$ = jugular bulb oxygen saturation, ICP = intracranial pressure, EEG = electroencephalogram, BIS = bispectral index.
TREATMENT OF INTRACRANIAL HYPERTENSION

In its 2007 guidelines, the Brain Trauma Foundation recommends the use of a number of staggered therapeutic measures for the treatment of ICH25. Nonetheless, there is no level I evidence on their effectiveness and, although they seem efficient in reducing ICP, this effect is not often translated into clinical improvement. Figure 3 Algorithm for the staggered treatment of ICH in patients with severe TBI.

Drainage of intraventricular cerebrospinal fluid

In patients with external ventricular drainage, the first measure to control ICP will be the intermittent opening of the drain, allowing it to remove 1-2 ml of fluid per minute up to a maximum of 20 ml per hour. This slow extraction should be accompanied by passive gravity drainage through an external ventricular drain, for which the most elevated part of the system should be placed 10 cm above the external auditory canal. The need of removing an amount above 20 ml per hour should be considered a therapeutic failure.

Neuromuscular blockade

The use of neuromuscular blocking agents for more than 48 hours in critical patients is associated with the development of neuromuscular complications, particularly in patients with risk factors such as sepsis and the use of high-dose steroids. Therefore, these drugs should not be used routinely, except in the cases of severe uncontrollable ICH.

Osmotic agents

Use of 20% mannitol

Mannitol produces an immediate effect of plasma expansion, which reduces hematocrit and blood viscosity. This rheological effect may explain the reduction in ICP within a few minutes. Additionally, mannitol has also a delayed osmotic effect (from 15 to 30 minutes) until the establishment of the gradient between the plasma and cells. This effect persists for a variable time (from 90 minutes to 6 hours). Mannitol is completely excreted through urine, and the administration of high doses involves a high risk of developing acute renal failure. Therefore, the administration of repeated mannitol doses should be discontinued if osmolality is above 320 mOsm per kg or if blood sodium concentration is above 150 or 155 mEq per L. More recently, mannitol treatment monitoring has been proposed to be based on serum osmole gap (osmole gap: osmolality-osmolarity), a parameter that has a higher ability to predict the development of acute renal failure, with a threshold of above 55 mOsm/L, than serum osmolality (above 320 mOsm/L)103. Additionally, it is essential to always maintain euvoemia in these patients and avoid arterial hypotension. There is not enough evidence to determine the most appropriate form to administer this drug (bolus vs. continuous infusion) or the most effective dose to control ICP; however, the recommended bolus dose is usually from 0.25 to 1 g per kg. ICH treatment with mannitol may have a beneficial effect on mortality compared with treatment with pentobarbital (relative risk for death 0.85; 95% confidence interval 0.52-1.38), but may have a detrimental effect on mortality when compared with hypertonic saline (relative risk for death 1.25; 95% confidence interval 0.47-3.33)104. Conversely, a large, retrospective study showed that the effect of mannitol on ICP is dose-dependent and the administration of high doses of mannitol provide a durable reduction in ICP105.

Hypertonic saline

Hypertonic saline have osmotic, hemodynamic, vasoregulatory and immunomodulatory properties. It produces an osmotic effect on the edematous brain tissue and reduces cerebral water content. As with mannitol, a strict control of blood sodium concentration and plasma osmolality is essential to avoid iatrogenesis; nonetheless, hypertonic saline has no diuretic effect. It has been used at different concentrations, in repeated doses or in continuous infusion at 2% or 3%, and in repeated doses at 5%, 7.5% or 23.4%106,107. The dose usually recommended is 1.5 to 2 mL of 7.5% hypertonic saline per kg, administered for 15 minutes. It can be safely administered through a peripheral venous catheter. The main complications associated with the use of hypertonic saline are: central pontine myelinolysis in patients with preexisting chronic hyponatremia, acute renal failure in situations of hypovolemia, and pulmonary edema in patients with chronic heart or lung disease. The administration of hypertonic saline is a preferable alternative than mannitol in patients with sodium levels below 135 mEq per L or prone to hemodynamic instability. Several studies have demonstrated that hypertonic saline reduces the number and the duration of ICH episodes compared with mannitol, but no...
significant differences were observed in mortality or in the degree of functional disability\textsuperscript{106,108}. Several meta-analysis of these studies concluded that hypertonic saline is more efficient in controlling ICP than mannitol, but its effect on clinical outcomes has not been sufficiently evaluated\textsuperscript{109,110}.

**Hyperventilation**

Hypocapnia secondary to hyperventilation has been shown to reduce ICP due to its cerebral vasoconstrictor effect, causing a decrease in CBF: a variation of 1 mmHg in PaCO$_2$ levels is associated with a variation of 3\% in CBF. Hyperventilation has a short-term effect (1 to 24 hours), which decreases with prolonged application, and may even lead to a rebound phenomenon after withdrawal. Hyperventilation should be considered as an emergency intervention and should not be maintained for long periods of time, regardless of the cause of ICH. CBF may be dangerously reduced in the early posttraumatic period, especially within the first 24 to 36 hours. The use of hyperventilation during this period may contribute to the development of brain ischemia\textsuperscript{111}. The available data are inadequate to ensure whether hyperventilation has a beneficial or detrimental effect on functional outcomes in TBI cases\textsuperscript{112}. The only clinical trial that evaluated the effects of hyperventilation on clinical outcomes discouraged prophylactic hyperventilation (PaCO$_2$ equal to or below 25 mmHg)\textsuperscript{113}. The relationship between CBF reactivity to PaCO$_2$ levels and the use of oxygen at the brain level is not clear. However, SjvO$_2$ or PtiO$_2$ should be monitored, since they help to identify the development of brain ischemia if hyperventilation is required to achieve paCO$_2$ levels below 30 mmHg\textsuperscript{114}.

**Hypothermia**

Hypothermia reduces cerebral metabolic rates of oxygen consumption and protects against secondary ischemic lesions, in addition to having an influence on the excessive posttraumatic release of excitatory neurotransmitters and mitigating the opening of the blood-brain barrier. However, although many studies have demonstrated the efficacy of hypothermia in reducing ICP, none of these studies showed a beneficial therapeutic effect of hypothermia on functional outcomes and mortality\textsuperscript{115}. Nonetheless, clinical practical guidelines\textsuperscript{25} still recommend using moderate hypothermia as an alternative therapy in patients with ICH refractory to conventional measures. Therefore, moderate hypothermia (between 32 and 34\degree C) may be induced in an early manner (within the first 8 hours of brain trauma) for at least 48 hours in patients that are already hypothermic or when ICP control requires additional measures, with a progressive rewarming over 24 hours. Conversely, at present there is no controlled randomized clinical trials showing the clinical benefit of reducing body temperature after TBI as a neuroprotective strategy, regardless of ICP\textsuperscript{116}.

**Decompressive craniectomy**

Decompressive craniectomy has been proposed for the treatment of ICH unresponsive to conventional therapeutic measures and, although so far there are no data confirming or refuting its efficacy, most practice clinical guidelines still recommend it as a third-tier measure in the treatment of increased ICP. The DECRA study\textsuperscript{117} consisted of a clinical trial including 155 patients with severe diffuse TBI and refractory ICH, who were randomly assigned to undergo either bifrontotemproparietal decompressive craniectomy or conventional care. The study showed that decompressive craniectomy reduced ICP and ICU length of stay but was associated with worse functional outcomes. Patients who underwent craniectomy had lower GOSE scores (odds ratio for worse score in the craniectomy group 1.84; 95\% confidence interval 1.05 to 3.24; $p=0.03$) and higher risk of having an unfavorable functional outcome (odds ratio 2.21; 95\% confidence interval 1.14 to 4.26; $p=0.02$). There were no differences in 6-month mortality (19\% in the craniectomy group vs. 18\% in the conventional treatment group). However, results for the DECRA study have been questioned due to study limitations. Firstly, the threshold to define increased ICP is relatively low, and the time established to define ICP as refractory to conventional therapeutic measures is relatively short. Secondly, there is an imbalance in baseline TBI severity between the two groups. Additionally, the surgical procedure used in the study is not representative of the most widely used procedure in clinical practice (unilateral decompression). Despite the lack of other randomized clinical trials, results from non-randomized studies and studies with historical controls in adult patients seem to suggest that decompressive craniectomy may be a useful alternative measure when conventional therapeutic measures have failed to control ICP\textsuperscript{118}. Currently, the RESCUEicp study is being conducted\textsuperscript{119} to compare optimal medical management and the
efficacy of decompressive craniectomy in treating ICH after TBI refractory to conventional therapeutic measures. The study is at the recruitment stage, having recruited 334 patients out of the 400 expected.

Lumbar drainage

Traditionally, lumbar drainage was considered contraindicated in the context of ICH due to the risk de transtentorial herniation. However, two recent studies suggest that controlled lumbar CSF drainage significantly reduces ICH refractory to second-tier measures. The possibility of herniation is minimized if the following recommendations are taken into account: a) performing a cranial CAT before inserting the external lumbar drain, b) ruling out the presence of lesions with mass effect, c) investigating whether basal cisterns are unobstructed, d) ruling out midline shift above 10 mm at the level of the third ventricle; e) draining from 5 to 20 ml of CSF under strict control of ICP and pupils, f) placing the collector system from 5 to 15 cm above Monroe’s hole and allow for continuous CSF drainage under hourly control of ICP and CPP, and g) discontinuing CSF drainage when adequate ICP control is achieved with the usual measures. The most frequent complication is catheter obstruction. No hemorrhage or infectious complications have been reported.

Barbiturates

From 10 to 15% of patients with severe TBI have ICH refractory to medical and surgical treatment. These patients have an associated mortality ranging from 84 to 100%. Barbiturates reduce ICP by decreasing cerebral metabolic demands and, due to the adaptation of CBF to cerebral metabolic needs, there is a reduction in cerebral blood volume and ICP. Therefore, the use of high doses of barbiturates (3-5 mg/kg/h of sodium thiopental) may be considered a recovery measure in patients with severe TBI who are hemodynamically stable and have ICH refractory to medical and surgical treatment, although there is no evidence that barbiturate therapy is associated with reduced mortality or functional disability. Experimental research has demonstrated that the level of neuroprotection conferred by the various barbiturates is not equal. A clinical trial showed that thiopental was more effective than pentobarbital in controlling refractory ICH in patients with severe TBI. There were no significant differences between the two groups with regard to the incidence of arterial hypotension or infection. The most frequent secondary effect of barbiturates is arterial hypotension and myocardial depression, with an incidence from 25 to 60%. Other adverse effects are hypothermia, paralytic ileus, and pupillary dilation, which is indistinguishable from that produced by cerebral structural injury and is the first sign to be recovered after treatment cessation.

As for the monitoring of barbiturate coma, measuring plasma levels is not useful, due to the great inter- and intra-individual variability resulting from enzyme induction and the existence of active metabolites. Continuous encephalographic recording showing the emergence of a wave suppression pattern is considered the “gold standard”. Other useful alternative to adjust barbiturate infusion is monitoring through BIS, which uses EEG principles to monitor hypnosis and sedation levels and allows for the proper quantification of the degree of EEG suppression. Additionally, SjO2 monitoring should be considered, since some patients may develop cerebral oligemic hypoxia. In a study that evaluated global cerebrovenous oxygenation before and after intravenous administration of pentobarbital for the management of refractory ICH, outcomes were significantly worse (p< 0.0001) in patients who developed decreases in SjO2 to levels below 45% than in those whose SjO2 remained at or above 45% (31% vs. 70% for full recovery/moderate disability, 40% vs. 16.5% for severe disability, 29% vs. 13.5% for vegetative state/death).

FUTURE ADVANCES

Although the present review focuses on the analysis of the treatments available in clinical practice, it is appropriate to present a brief consideration on future advances in the field of severe TBI management. Among the expected advances in severe TBI management, it is important to mention research on neuroprotection. Different neuroprotective agents have proven to be effective in animal models. However, clinical practice showed promising results only in some cases, which were focused on the prevention and/or reduction of cerebral edema induced by secondary injury and on brain remodeling. Several clinical trials reveal different neuroprotective strategies, such as promising and safe therapies that seem to improve neurological outcomes in patients with severe acute TBI, including the following: excitatory amino acid inhibitors (amantadine and dexamethasone), monoaminergic agonists (methylphenidate),...
progesterone, erythropoietine, and statins. Nonetheless, current evidence is not sufficient to recommend the routine use of these therapies in head trauma.

CONCLUSION

In patients with severe TBI, all conditions that worsen the initial brain injury should be avoided. The prevention of increased ICP and the maintenance of an adequate CPP are crucial to minimize brain ischemia. Therefore, initial management should be focused on optimizing oxygenation, ventilation and hemodynamics. The use of different monitoring systems allows for the early detection of situations of tissue hypoxia and helps to guide the implementation of staggered therapeutic measures for the treatment of ICH. In order for survival and functional results to continue to improve in TBI patients, it is necessary to implement therapeutic management protocols that incorporate recommendations from clinical practice guidelines. Additionally, research should continue to investigate potentially beneficial neuroprotective treatments.

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