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REVIEW
SEVERE TRAUMATIC BRAIN INJURY

Standard of care, controversies, and innovations in the medical treatment of severe traumatic brain injury

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ABSTRACT

Severe traumatic brain injury (STBI) is characterized by a primary injury which cannot be reversed and a secondary injury that can be prevented or reversed. Management of STBI patients in intensive care mainly aims at preventing the secondary injury. Treatment aims to: reducing ICP pressure (that can result in an ischemic insult); avoiding hypotension, hyperthermia, or hypoxemia; maintaining a normal electrolytes homeostasis; treating the autonomic dysfunction syndrome, coagulopathies, acute kidney injury and maintaining an adequate nutrition. Many treatment protocols are already well established, while many others are still debated. Moreover, new frontiers in STBI management are represented by the neurovascular regeneration and neurorestoration which are showing very promising results even if most of them still need a clinical validation. In this paper we review standard of care, controversies and innovations in the medical treatment of STBI.

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Guidelines for severe traumatic brain injury (STBI) management have been developed in order to standardize the assessment and treatment and to improve clinical outcomes.¹

Management of STBI patients in acute care focuses on preventing the secondary injury, which can result mainly from ischemic insult due to increased intracranial pressure, hypotension, hyperthermia, or hypoxemia.²

Although primary brain injury cannot be reversed, secondary brain injury can be prevented or reversed. Particularly, acute treatment is based on stabilization of the patient and optimization of cerebral hemodynamic.

The cornerstone of severe TBI management is represented by monitoring and treating intracranial pressure (ICP) as an indicator of injury severity.

In-hospital practical and critical care approach in pa-

tients with suspected TBI starts in the emergency department. In this phase, treatment and diagnostic assessment is done according to the Advanced Trauma Life Support (ATLS) protocol: rapid primary and secondary survey through evaluation of airways, breathing, and circulation should be performed as soon as possible during cervical spine immobilization and concomitant systemic traumatic injuries assessment.

Adequate oxygenation (PaO₂ >60 mmHg) avoiding hypercapnia or hypocapnia and BP support (systolic blood pressure [SBP] >90 mmHg) are priorities^{3,4} for adequate management of ICP and consequent neuroprotection.

Other measures for physiologic neuroprotection include prevention/treatment of sodium balance disorders, recognition and adequate treatment of autonomic dysfunction syndrome and prophylaxis or treatment of seizures.

However, it is also necessary to perform adequate management of trauma-related coagulopathy complications, adequate nutrition and a prevention/treatment of acute kidney injury.

ICP monitoring and medical treatment

ICP monitoring is recommended to reduce in-hospital and 2-week post-injury mortality (Level IIb). A combination of ICP monitoring, clinical findings and CT scan is helpful in management decisions (Level IIb).¹

ICP monitoring after severe TBI is indicated:

- in all salvageable patients with a TBI GCS 3-8 after resuscitation and an abnormal CT (hematomas, contusions, swelling, herniation or compressed basal cistern) (Level IIb);¹
- with GCS 3-8 and a normal CT if 2 of the following factor are present (age > 40 yo, unilateral or bilateral motor posturing, SBP < 90 mmHg) (Level IIb).¹

Invasive and non-invasive ICP monitoring devices are now available but intraventricular catheter (IVC) zeroed at the midbrain actually remains the gold standard for its possibility of measuring and treatment at the same time. Its use is specially indicated to lower ICP during the first

12 hours after STBI (Level III). A continuous drainage of CSF is more efficient than the intermittent one (Level III).¹

The optimal ICP at which to begin treatment is still object of study; nonetheless, treating ICP > 22-25 mmHg is recommended (Level III).¹

Medical treatment is commonly divided into three different levels of intensity (Table I).¹

The last TBI guidelines (IV) update treatment recommend:

- elevate HOB to 30-45°;
- heavy sedation (*e.g.* fentanyl 1-2 mL or magnesium sulfate [MgSO₄] 2-4 mg IV every 1 hour) and/or paralysis (*e.g.* vecuronium 8-10 mg IV);
- propofol drip: 0.5 mg/kg test dose, then 20-75 µg/kg/min IV drip;
- high-dose barbiturate (pentobarbital 100 mg slow IV or thiopental 2.5 mg/kg IV administration) to control elevated ICP refractory to maximum standard medical and surgical treatment. Hemodynamic stability is essential before and during barbiturate therapy (Level IIb);
- mannitol at doses of 0.25 to 1 g/kg body weight and it can be alternated with furosemide (Lasix®) (adult 10-20 mg IV every 6 hours); however, arterial hypotension (SBP < 90 mmHg) should be avoided;

TABLE I.—Medical treatment algorithm for raised intracranial pressure (ICP) (Level Ia).

Treatment	Rationale
<i>First level of intensity</i>	
Head-up positioning 30-45°	ICP decreases by enhancing venous outflow
Cerebral perfusion pressure 50-70 mmHg avoiding hypotension (SBP < 90 mmHg)	
PaO ₂ > 60 mmHg, preferably > 75 mmHg	Hypoxia may cause ischemic brain injury
PaCO ₂ between 34-38 mmHg	
Normothermia (36-37.5 °C)	Prophylactic hypothermia is not recommended to improve final outcome Lev IIb
Prevent hyperglycemia	It can aggravate cerebral edema
Light sedation: codeine 30-60 mg IM every 4 hours or Lorazepam 1-2 mg IV	
Intubation	If GCS < 8 or respiratory distress
<i>Second level of intensity</i>	
Heavy sedation and paralysis: Fentanyl 1-2 mL vecuronium 8-10 mg IV, MgSO ₄ 2-4 mg/hour IV	To reduce sympathetic tone and spontaneous movements if patients is agitated
IVC: drain 3-5 mL	To reduce intracranial volume
Hyperventilation: PaCO ₂ 30-35 mmHg	In neurological deterioration, a reduction of CO ₂ may reduce ICP
Mannitol 0.25-1 g/kg, then 0.25 mg/kg every 6 hours	Mannitol draws out fluid from the brain with a reduction of ICP
Hypertonic saline bolus 10-20 mL of 23.4% or continuous infusion 3%.	If refractory to mannitol
Consider EEG and anticonvulsant prophylaxis	
<i>Third level of intensity</i>	
IVC drainage 3-5 mL of CSF	
Bolus of mannitol 1 g/kg IV	
Bolus of hypertonic saline 23.4% 10-20 mL	
Hyperventilation: PaCO ₂ until 25 mmHg	Prolonged hyperventilation is not recommended (Level IIb), if it is used it must be associated to monitor oxygen delivery (Level IIb)
Pentobarbital 100 mg IV or Thiopental 2.5/kg IV over 10 min, if hemodynamically stable	If intracranial hypertension is refractory to maximal medical ICP lowering therapy

- hyperventilation is indicated as a temporary measure to reduce ICP, but its prophylactic use is contraindicated (Level IIb).

High doses of propofol are associated with high morbidity (Level IIb) and are therefore not recommended. Steroids have demonstrated no benefit in the treatment of acute brain injury. A 2004 European multicenter randomized trial included 10008 adults with head injury and a GCS of 14 or less treated with infusion of methylprednisolone or placebo: this study found a higher mortality after only 2 weeks in the steroid-treated patients⁵ (Level I).

Airways and ventilation: hypoxemia, hypercapnia, or hypocapnia

Patients with severe TBI are usually intubated and mechanically ventilated. Conventionally, in brain trauma, urgent intubation to secure airways should be considered in any patient who presents with a Glasgow Coma Score (GCS) <8. However, the GCS score has some limitations and should not be determinant for a definitive airway protection.⁶

Ventilation management should be focused on maintenance a PaCO₂ within a normal range of 34-38 mmHg avoiding hypoventilation.

Hypocapnia can lead to cerebral hyperemia with an increase in blood volume and ICP. Conversely, hyperventilation can cause vasoconstriction increasing tissue hypoxia. In addition, high PaO₂ should be avoided because of the increased risk of hyperoxic cerebral vasoconstriction.

Brain Trauma Foundation Guidelines recommend performing early tracheostomy in order to reduce ventilation days (Level IIA).¹

However, recent randomized controlled trial showed that early tracheostomy is not associated with a decrease in ventilator-associated pneumonia rates but there is a decrease in ventilator/intensive care unit days (Table II).⁷

Hemodynamics

Hypotension represents one of the most important predictors of mortality together with hypoxemia. A single episode of hypotension just in the prehospital setting can dramatically worsen the outcome.⁸

There is no consensus concerning the lower limit to define hypotension in patients with isolated head injury. Several guidelines define hypotension as SBP <90 mm Hg and provide corresponding treatment recommendations.^{9, 10} Brenner *et al.* defined higher thresholds (closer to 120 mmHg) than traditionally defined (110 mmHg).¹¹

Fluid resuscitation can be necessary but not necessarily helps, because it could exacerbate bleedings. Aggressive fluid resuscitation is harmful as showed from emerging evidence.

The choice of fluids is still a matter of debate. Isotonic crystalloids seem to be a safer choice and are cost-effective as well (Table II).⁸

Colloids should not be used as first choice and do not provide further benefit. Moreover, SAFE Trial showed increased mortality in patients receiving albumin compared to saline.¹²

Concerning vasopressors, the existing data are of very low quality, according to the Grading of Recommendations, Assessment, Development and Evaluation methodology. A recent systematic review concluded that the balance between benefits and harms of vasopressor therapy during the early phase of resuscitation following traumatic injury is uncertain.¹³

A physiological response that indicates a brain impairment can be represented by hypertension, which must be treated only in the presence of systolic blood pressure above 180-200 mmHg. In this case, short-acting beta blockers (Metoprolol 0.2 to 0.3 mg/kg/24 hours IV) that do not cause cerebral vasodilation can be used.¹⁴

CPP should be maintained between 60 and 70 mmHg as indicated by the 4th Edition of brain trauma foundation guidelines (Level III).¹

Sodium balance disorders

Hyponatremia, defined as serum sodium ([Na⁺]) <135 mEq/L, is the most common electrolyte abnormality and an independent predictor of poor neurologic outcome in patients with STBI,¹⁵ with an incidence that ranges from 9.6% to 51%.^{16, 17}

Symptoms of mild ([Na⁺] <130 mEq/L) hyponatremia include: anorexia, headache, irritability, weakness. Severe hyponatremia (<125 mEq/L) or a rapid drop (>0.5 mEq/hour) can cause neuromuscular excitability, cerebral edema, confusion, seizures, respiratory arrest and delayed ischemic damage and/or osmotic demyelination leading to disability and increased mortality.¹⁸

Diagnostic workup consists of: serum [Na⁺], serum osmolality, urine osmolality, clinical assessment of volume status.

Recent guidelines about hyponatremia indicate the management strategy depends on the speed of its onset.^{19, 20}

Common etiologies are:

- hypopituitarism and inadequate salt dietary intake

TABLE II.—Evidences on different kind of treatment.

Parameters	Strictly recommended	Possible efficacy	Not recommended
Airways and ventilation	Urgent intubation when GCS<8, PaCO ₂ within 34-38 mmHg	Early tracheostomy	High PaO ₂
Hemodynamics	Short-acting beta blocker (Metoprolol 0.2 to 0.3 mg/kg/24 hours IV) for hypertension (180-200 mmHg)	Vasopressors	Aggressive fluid resuscitation Colloids
Sodium balance disorders SIADH	Hypertonic saline (3%, starting infusion 1-2 mL/kg body weight per hour), furosemide (20 mg IV every 6 hours), Vaptans, water restriction	Active sodium supplementation, mineralocorticoids, vasopressin 2 receptor antagonists	
CSWS	Hypertonic saline (0.9% NS at 100-125 mL/hour), Salt replacement		Vaptans
Hyponatremia	Fluid replacement, desmopressin (DDAVP®, 0.1 mg PO every 12 hours, adjust up or down on the urine output or nasal spray 0.025 mL every 12 hours)		
Autonomic dysfunction		Morphine, benzodiazepines, propranolol, bromocriptine, intrathecal baclofen, gabapentin	
Coagulopathy		Tranexamic acid, rFVIIa, prothrombin complex, platelets, DDAVP	Fresh frozen plasma
Nutrition	Early use of enteral nutrition	Probiotic supplementation, small bowel feeding	
AKI	Continuous renal replacement therapy		Intermittent hemodialysis
Seizures prophylaxis	Phenytoin (300-600 mg/day divided BID or TID)	Levetiracetam (start with 500 mg <i>per os</i> twice a day; increment by 1000 mg/day every 2 weeks PRN to a maximum of 3000 mg/day)	

which can be easily diagnosed respectively with a low urine spot sodium (below 20 mEq/L) and biochemical evaluation of pituitary hormones;

- the syndrome of inappropriate antidiuretic hormone secretion (SIADH): excess water retention due to inappropriate ADH secretion causes hyponatremia with hypervolemia (occasionally with euvolemia), inappropriately high urine osmolality (>100 mOsm/L) and no evidence of renal or adrenal dysfunction;

- the cerebral salt wasting syndrome (CSWS): renal loss of sodium produces hyponatremia and a decrease in extracellular fluid volume (hypovolemia). The cause of the kidneys failure to retain sodium in CSWS is not known. It could be an unidentified natriuretic factor or a direct neural control mechanism.

No definite consensus concerning the proportion of patients with hyponatremia caused by SIADH and CSWS, the panels of laboratory and clinical tests, and practical management protocols exist.^{20, 21} Differential diagnosis is a challenge because both syndromes present hyponatremia and concentrated urine with natriuresis (urine spot [Na⁺] >40 mEq/L).²²

However, CSWS is usually characterized by hypovolemia.

Emergent treatment for SIADH consist of: hypertonic saline (3% saline, starting infusion 1-2 mL/kg body weight

per hour) and furosemide 20 mg IV every 6 hours. In refractory cases, Tolvaptan (loading dose 20 mg IV over 30 minutes, followed by infusions of 20 mg over 24 hours ×3 days), an arginine vasopressin antagonist, can be administered (Table II).^{23, 24}

Goal of treatment in CSWS are volume replacement and positive salt balance. The patient can be hydrated with 0.9% NS at 100-125 mL/hour. Salt replacement can be administered orally. Vaptans are contraindicated in CSWS (Table II).²²

Concerning the treatment of hyponatremia in general, the European guidelines¹⁹ and recommendations of an American Expert panel²⁰ have come to similar conclusions. The European guidelines recommend rapid infusion of two 150-mL boluses of 3% saline each over 20 minutes for severe or moderately severe symptoms (nausea without vomiting, confusion, or headache), measuring serum sodium between infusions, and repeating this regimen if necessary to correct by 5 mEq/L. The American expert panel also recommended aggressive therapy with a 10-minute 3% saline for seizures and coma, repeated three times as needed.

The optimal treatment for hyponatremia in TBI patients has not been established. Further studies examining the use of active sodium supplementation, mineralocorticoids, and/or vasopressin 2 receptor antagonists, are needed.

Hyponatremia, defined as serum [Na⁺] >150 mEq/L,

may occur in TBI too. This could be due to a variety of mechanisms, including hyperosmotic fluids, limitation of free water, or diabetes insipidus (DI). As shown by recent meta-analysis, the role for hypernatremia for the management of patients with TBI but also the dose, duration, and serum sodium target of the intervention remains unclear in order to avoid complications related to mannitol or hypertonic solution administration.²⁵

When DI is present (dilute urine with osmolality <200 mOsm/L or specific gravity <1.003, the inability to concentrate urine to >300 mOsm/L in the presence of clinical dehydration, urine output >250 cc/hour), treatment is based on fluid replacement and desmopressin (DDAVP®, 0.1 mg PO every 12 hours, adjust up or down on the urine output or nasal spray 0.025 mL every 12 hours).

Autonomic dysfunction syndrome

The autonomic dysfunction syndrome (ADS), also known as autonomic storms, is characterized by hypertension, fever, tachycardia, tachypnea, pupillary dilation, and extensor posturing. A decrease in baroreflex sensitivity correlates with an increased risk of cardiac complications such as ventricular tachyarrhythmias and sudden cardiac death.²⁶

ADS has an incidence of 8% and typically presents 1-2 weeks after severe TBI, especially in patients with diffuse axonal injury.²⁷

Diagnostic criteria by Jennett *et al.*²⁸ are: heart rate >120 bpm, respiratory rate >30 breaths/min, temperature >39 °C and blood pressure above 160 mmHg.

Treatment is based on the maintenance of normal core temperature and beta-blockers administration. Although beta blockers are able to control hypertension and tachycardia during ADS, cerebral perfusion is poorly regulated and increased brain temperature can increase metabolic load without a compensatory increase in blood flow, worsening brain injury. Bromocriptine is helpful for hyperthermia and diaphoresis. Prolonged diaphoresis may result in dehydration and in electrolytes abnormalities.

Frequently, dysautonomic patients are significantly more likely to receive neurologically active medications such as morphine, midazolam, chlorpromazine or gabapentin (Table II).²⁹

Unfortunately, lack of a standardized nomenclature and diagnostic tests represent a limit to improve the management. Further studies are needed concerning the pharmacological management of dysautonomia after severe TBI in order to minimize disability.

Coagulopathy

The true incidence of coagulopathy is difficult to be defined, due to the lack of standardization of studies in terms of patient selection criteria, injury severity, diagnostic criteria of coagulopathy, clotting tests used. Routine coagulation tests should be performed in all patients with traumatic brain injury. Penetrating TBI is more likely associated with coagulopathy than blunt TBI.³⁰

Prolongations in PT and aPTT, increase of D-dimer, and decrease of fibrinogen have all been seen within minutes of injury, with peak derangements occurring by around 6 hours before reversing. As alternatives/adjuncts to conventional tests, the use of viscoelastic tests of coagulation function, namely thromboelastography (TEG) and rotational thromboelastometry (ROTEM) can be helpful. Talving *et al.* in their prospective study of 436 adult patients with traumatic brain injury showed a statistically significant association between development of coagulopathy and a lower GCS score. In addition, the development of TBI coagulopathy is associated with longer ICU length of stay and an almost tenfold increased risk of death. Independent risk factors for coagulopathy in isolated head injuries include GCS score of ≤8, Injury Severity Score ≥16, hypotension upon admission, cerebral edema, subarachnoid hemorrhage, and midline shift.³¹

Lustenberger *et al.* found in their study that coagulopathy occurred 23.1±2.2 hours after admission and early coagulation abnormalities occurred within 12 hours of admission.³²

Antifibrinolytic agents used in polytrauma have shown some promising results. The large randomized controlled CRASH-2 trial showed a survival benefit from early administration of anti-fibrinolytic agent tranexamic acid (TXA). Jokar *et al.* in a smaller 80-patient single-blinded study administered TXA showing a reduction of hematoma expansion without any consideration about clinical outcome.³³ In literature, results from clinical trials are still pending (Table II).

Recombinant factor VIIa (rFVIIa) can be used off label for the management of traumatic intracerebral hemorrhage.

Yuan *et al.* found in their prospective study that low-dose rFVIIa (20 µg/kg) is effective for correcting coagulopathy without an increase in thromboembolic events (Table II). A benefit was seen in prevention of hemorrhage progression, but no significant survival benefit was observed.³⁴

There are still doubts concerning the appropriate man-

agement of coagulopathy in patients taking antiplatelet or anticoagulant drugs. Data about empiric platelet transfusion for patients on antiplatelet therapy as well as the administration of desmopressin did not show a conclusive clinical benefit.³⁵ Transfusion of fresh frozen plasma carries distinct disadvantages, particularly related to the large volume necessary to normalize INR.

On the contrary, concentrated prothrombin complex has significantly improved the reversibility of coagulopathy related to warfarin with a reduced time to normalization of INR and has also reduced the incidence of hemorrhage expansion.³⁶

Further studies are still needed to completely define the pathogenesis of traumatic coagulopathy and finally to achieve its effective treatment.

As traumatic brain injury may alter coagulation, this can increase the risk of venous thromboembolism. Reiff *et al.* reported an increased risk of deep venous thrombosis of 15% if no pharmacologic prophylaxis was given within the first 48 hours.³⁷ Therefore, the benefits of thromboembolism prevention should be balanced with the risk of intracranial bleeding extension. Some reports suggest that early prophylaxis with enoxaparin or heparin within the first 3 days did not increase intracranial hemorrhage progression.³⁸

Nutrition

Patients with severe TBI often present a metabolic disorder with a reduced immune function and higher risks of nosocomial infections as a result of decreased energy and increased protein catabolism. There is a paucity of epidemiological data that describe nutrition practices in sTBI patients and previous studies are generally retrospective and included cohorts of relatively small numbers.

High energy and protein deficits are associated with adverse outcomes and can persist after ICU discharge. Particularly, Chapple *et al.* showed that patients ingesting nutrition orally are at particular risk of energy deficit (which seems to be almost twice as great as tube-fed).³⁹

Brain Trauma Foundation guidelines recommend the early use of enteral nutrition to optimize recovery following TBI¹ with a lower rate of nosocomial infections.⁴

Probiotic supplementation has been associated with significantly lower rates of infection in TBI. In addition, supplementation with omega 3 fats, vitamin D, N-Acetylcysteine, branched chain amino acids, and zinc may be helpful for recovery.⁴⁰ The ASPEN⁴¹ recommend enteral feeding be started early, within the first 24-48 hours of ad-

mission, and advanced toward optimal nutrition goals over the next 48-72 hours. However, there are no data to document improvement in relevant outcome parameters associated with early enteral feeding.

The Working Group on Gastrointestinal Function within the Metabolism, Endocrinology and Nutrition (MEN) Section of the European Society of Intensive Care Medicine (ESICM) elaborated evidence-based guidelines for early enteral nutrition (EEN) during critical illness. Concerning TBI, they suggest using EEN in critically-ill adult patients with traumatic brain injury (conditional recommendation based on expert opinion = Grade 2D). Existing evidence did not allow determining or excluding any benefit or harm of EEN, therefore this recommendation is based on expert opinion.⁴²

However, the enteral route is often neglected for patients with severe TBI due to increased incidence of gastrointestinal complications, particularly gastric residuals because of trauma itself and because of the therapeutics used to control intracranial hypertension and patient support.⁴

Results of a recent systematic review and meta-analysis showed that, although with limited evidence, in patients with severe TBI small bowel feeding, compared with gastric feeding, is associated with a lower risk of pneumonia, gastroesophageal reflux and subsequent aspiration pneumonia (Table II).⁴³

No best practice guidelines for nutrition and TBI currently exist. Further research is necessary to optimize and standardize the nutrition therapy concerning the nutrient provision, timing, size, and route of administration.

Acute kidney injury

Brain injury can influence kidney function by the following mechanisms: hypothalamo-pituitary axis imbalance, neuroinflammation and increased neuro-sympathetic activity. Particularly, due to exaggerated sympathetic activity and increased catecholamine levels, systolic blood pressure increases and renal blood flow decreases.⁴⁴

Urea and other solutes tend to increase with worsening of renal function and reach the brain through a breakdown of the blood-brain barrier (BBB). This influx is initially compensated by astrocytes taking up additional ions and water. Progressively, this compensation is disrupted, worsening cerebral edema.⁴⁵

Adequate hydration avoiding hypotension, minimizing multiple contrast exposure and nephrotoxic drugs should be performed.⁴⁴

There is limited information on the incidence of acute kidney injury (AKI) in patients with TBI. An AKI is suspected in presence of:

- oliguria (urine output <200 mL/12 h) or anuria (urine output: 0-50 mL/12 h);
- blood urea >35 mmol/L (>98 mg/dL);
- serum creatinine >400 mmol/L (>4.5 mg/dL);
- uncompensated metabolic acidosis (pH<7.1);
- serum K⁺ >6.5 mmol/L or rapidly rising values;
- serum Na⁺ <110 and >160 mmol/L;
- pulmonary edema unresponsive to diuretics

Renal replacement therapy (RRT) plays a significant role in the treatment of patients with renal failure. The fundamental principle is the removal of unwanted solutes and water through a semi-permeable membrane. Different techniques can be used, such as intermittent hemodialysis, hemofiltration, hemodiafiltration, peritoneal dialysis, etc.

If RRT can improve encephalopathy through removal of azotemia, retention products and toxics, a rapid fall in serum urea may paradoxically cause cerebral edema (Table II). Particularly, intermittent hemodialysis can worsen cerebral edema while continuous renal replacement therapy (CRRT) is the preferred treatment with a better cardiovascular stability. Park *et al.* suggested to perform early CRRT before urine output is reduced to less than 500 mL/day.⁴⁶

The absence of a shared approach and the lack of diagnosis of subclinical AKI through the early identification of damage markers may compromise the earlier initiation of AKI treatment, mitigating the adverse effects of AKI until renal function recovery.

Wu *et al.* performed a nationwide population-based cohort study of 32,152 TBI patients and 128,608 propensity score-matched control showing that TBI patients had higher incidence rate of chronic kidney disease (CKD) than the control cohort. Particularly, in subgroup analysis, TBI patients under 65 years were at a greater risk to develop CKD.⁴⁷

Further well-designed studies should be focused on diagnosis of clinical AKI on the basis of Kidney Disease – Improving Global Outcomes (KDIGO) criteria, subclinical AKI, and on definition of therapeutic advantages of early CRRT in TBI patients.

Seizure prophylaxis and treatment

The incidence of clinical seizures after severe TBI is about 12%, while subclinical seizures demonstrated by EEG are 20-25%.⁴⁸

Post-traumatic seizures (PTS) are classified as “early”

when they occur within 7 days of injury or “late” when they occur after 7 days. 10% of early seizure patients are at risk of status epilepticus. PTSs after TBI may increase the risk of posttraumatic epilepsy.⁴⁹

Routine seizure prophylaxis has the potential benefits of preventing acute seizures after TBI, the development of chronic epilepsy, bleeding and herniation.⁵⁰

Current evidence supports the use of antiepileptic drugs (AEDs) to prevent early PTS when the overall benefits is thought to outweigh the complications associated with such treatment. However antiepileptics seem not to prevent late PTS¹ (Level IIA).⁵⁰

PTS prophylaxis is recommended only during the first seven days after TBI, especially if risk factors for early PTS are present (GCS<10, depressed skull fractures, hematomas as subdural extradural or intracerebral or cortical contusion, age <65 years, alcoholism).⁴⁸ There is no evidence to support PTS prophylaxis for longer than seven days after TBI, even if risk factors are present.⁵¹

Phenytoin^{50, 52} (300-600 mg/day divided BID or TID) has historically been the drug of choice; nowadays, Levetiracetam (start with 500 mg PO BID, increment by 1000 mg/day every 2 weeks PRN to a maximum of 3000 mg/day) is the most used for seizure prophylaxis after STBI with its low side effect profile (Table II).¹

However, comparative studies are still insufficient to compare efficacy and safety of Phenytoin vs. Levetiracetam (Level IIA).^{1, 53, 54}

Controversies, new perspectives, and experimental models

While hypothermia may decrease ICP, a randomized study including 392 patients with brain injury demonstrated that it did not improve outcome.⁵⁵ Another trial including 232 patients treated with early hypothermia was interrupted for futility.⁵⁶

Drugs not commonly used in the standard protocols for STBI medical management are showing interesting results. Among these, Amantadine (a dopamine agonist used for Parkinson's disease) acts as an NMDA receptor antagonist avoiding glutamate excitotoxicity in the acute phase of STBI. Sawyer *et al.*⁵⁷ demonstrated that in doses of 200-400 mg/day, amantadine appears to safely improve arousal and cognition in patients with TBI.

Nowadays, new frontiers in STBI management are represented by the neurovascular regeneration and neurorestoration.⁵⁸ Most of the related studies on these issues are experimental and still need a clinical validation; however,

these strategies could represent a real improvement in the outcome of STBI.

Brain recovery after trauma could be improved by neuronal and vascular regeneration.

S100B is a calcium binding neurotrophic protein which is involved in cell morphology regulation and apoptosis prevention. Kleindienst *et al.*⁵⁹ showed a beneficial effect of S100B on neurogenesis and cognitive function following TBI.

They demonstrated in animal models that intraventricular infusion of S100B may augment innate repair mechanisms of the brain, may induce neurogenesis within the hippocampus and promote memory consolidation after TBI. Unfortunately, S100B has not been used for clinical treatment of TBI yet.

The effects of neurogenesis, angiogenesis and increase in neuroblast migration after brain injury induced by nitric oxide (NO) in the central nervous system, have recently been discovered. ¹³NO induces the production of cyclic GMP (cGMP), a second messenger involved in different cellular processes, in particular in vascular regeneration, which lays the foundations for neural plasticity and functional recovery.

In experimental models, treatment with NO donors promoted survival of the newly generated cells in the hippocampus after TBI.⁶⁰ Although there are many animal studies showing the benefic effects of Sildenafil (a phosphodiesterase type-5 inhibitor who increases cGMP level) for ischemic injury,^{61, 62} clinical human trials still lack. A study by Silver *et al.*⁶³ shows Sildenafil (25 mg daily for 2 weeks) is safe in a group of patients with mild to moderately severe stroke. However, further clinical studies are needed in order to test its effect in patients suffering from STBI.

Mesenchymal, stem or progenitor cells use, could represent a promising approach for treatment of STBI sequelae, although their use is often limited by ethical issues.

There is an increasing evidence indicating a benefit of mesenchymal stem cells (MSCs) transplantation in various disorders characterized by cell injuries, such as stroke⁶⁴ or Parkinson's disease.⁶⁵

MSCs are present in bone-marrow and can also differentiate in neuronal cells.⁶⁶ When in culture under specific conditions they create neurospheres. These neurospheres, if cultured with astrocytes, can differentiate into neurons.⁵¹ Again, different animal models showed the improvement in functional recovery after STBI in animals treated with MSCs infusion.^{64, 67} The dose of MSCs ranges from 0.1 to 20 million cells per kg body weight.⁶⁸

The mechanism hypothesized is not only based on their

differentiation in neuronal cells (which appears to be limited), but mainly on their ability of producing growth factors able to mediate the repair and replacement of damaged tissue.⁶⁴ TBI-conditioned MSCs cultures demonstrated a time-dependent increase of BDNF, NGF, VEGF, and HGF.⁶⁴ The global effects of MSCs transplantation are: the enhancement of angiogenesis and vascular stabilization in the lesion boundary zone, the decrease of glial scar formation and the increase of glial-axonal remodeling.¹³

Few clinical studies are available for the evaluation of MSCs transplantation in humans. Zhang *et al.*⁶⁹ administered MSCs through a combined procedure of direct application on the injured brain parenchyma followed by an intravenous boost. MSCs differentiation and the secretion of neurotrophic factors promoted tissue recovery. Neurologic function was significantly improved at 6 months after cell therapy without immediate or delayed toxicity.

Different cerebral areas have been shown to be sites of neurogenesis like the dentate gyrus and the subventricular zone.⁵⁸ Neuronal progenitor and stem cells (NPCs/NSCs) within these regions can proliferate and differentiate into neurons.^{70, 71} Moreover, this kind of response can be regulated by mitogenic and neurotrophic factors released in the injured brain.

Nowadays, no clinical trials on NPCs/NSCs transplantation exist for TBI recovery, however a study in traumatic cervical spinal cord injury demonstrated safe outcomes.⁷²

Transplantation of embryonic stem cells (ESCs) in rats has provided cures for the damaged nervous system, improving neurological outcomes. However, this may cause tumors.⁷³

Cell based therapies are a very promising approach for STBI sequelae; however, a clinical clear validation on humans is still lacking and risk, benefits and costs need to be further analyzed.

Conclusions

Medical management of STBI requires several treatment approaches. All strategies are aimed to preventing secondary injury in the acute phase and improving neurorestoration in the subacute phase. After immediate assessment and stabilization of airways and circulation, mean arterial pressures should be kept above 90 mmHg, ICP should be maintained below 20-25 mmHg (with Mannitol, hyperventilation and eventually high-dose barbiturates) and CPP should be maintained at least at 70 mmHg. Coagulopathy, sodium balance, seizures and kidney function should be strictly monitored and corrected in the acute phase.

New frontiers are opening with neurovascular regeneration and neurorestoration; however, a clear clinical validation on humans is still lacking and the relationship of benefits and costs needs to be carefully evaluated.

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