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Pathophysiology of severe traumatic brain injury and management of intracranial hypertension

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Abstract. It is well recognized that severe traumatic brain injury causes major health and socioeconomic burdens for patients their families and society itself. Over the past decade, understanding of secondary brain injury processes has increased tremendously, permitting implementation of new neurocritical methods of care that substantially contribute to improved outcomes of such patients. The main objective of current treatment protocols is to optimize different physiological measurements that prevent secondary insults and reinforce the ability of the brain to heal. The aim of this literature review is to uncover the pathophysiological mechanisms of severe traumatic brain injury and their interrelationship, including cerebral metabolic crisis, disturbances of blood flow to the brain and development of edema, putting emphasis on intracranial hypertension and its current management options.

Key words: traumatic brain injury, head injury, head trauma, critical care, intracranial hypertension.

Sunkios galvos smegenų traumos patofiziologija ir intrakranijinės hipertenzijos gydymas

Santrauka. Gerai žinoma, jog sunki galvos smegenų trauma yra didelė našta pacientams, jų artimiesiems ir, apskritai, visuomenei. Per paskutinį dešimtmetį mūsų suvokimas apie antrinio smegenų pažeidimo procesus smarkiai išaugo. Tai leido sukurti naujų neurokritinių ligonių gydymo metodų, kurie svariai prisidėjo prie geresnių išeičių po sunkių galvos smegenų traumų. Pagrindinis gydymo tikslas – optimizuoti skirtingus fiziologinius parametrus, kurie sumažintų antrinį smegenų pakenkimą ir palengvintų smegenų galimybę gyti pačioms.

Pristatomos apžvalgos tikslas – atskleisti sunkios galvos smegenų traumos patofiziologinius mechanizmus ir jų sąveiką, įskaitant smegenų metabolinę krizę, kraujotakos sutrikimus ir edemos vystymąsi, daugiau dėmesio skiriant intrakranijinei hipertenzijai ir jos gydymo galimybėms.

Reikšminiai žodžiai: galvos smegenų trauma, smegenų pažeidimas, intensyvus gydymas, intrakranijinė hipertenzija.

Introduction

Traumatic brain injury (TBI) could be simply defined as an alteration in brain function due to external forces and is considered as one of the leading cause of death and disability worldwide, especially among young adults and the elderly. Current estimates imply that annual incidence of TBI is 50–60 million worldwide, and specifically for Europe and USA, 0.5% of Europeans and 1.1% of Americans are experiencing a TBI each year [1]. Fortunately, about 85% of those injuries are classified as mild. In case of severe TBI, there is a 40% mortality rate regardless of age [2]. TBI is commonly classified according to Glasgow Coma Scale (GCS) scores as mild (GCS 13–15), moderate (GCS 9–12), or severe (GCS 3–8). This scale, however, only helps to

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frame the degree of injury, but the extent of brain damage itself is not comparable between different cases of the same GCS, mainly because of the complexity and heterogeneity in each particular situation.

Following a traumatic event, a cascade of interrelated biochemical processes occurs, and understanding them is critical for the implementation and rationale of treatment strategies. Fundamental and clinical studies in the field of neurocritical care provide us with greater insight than ever before and help toestablish appropriate therapeutic guidelines that, as evidence suggests, significantly improve outcomes. Management of intracranial hypertension (IHT) is one of the key treatment priorities, particularly due to life-threatening complications such as cerebral herniation and ischemia.

Pathophysiological features of TBI and cerebral edema

TBI is one of the most complex conditions affecting even more complex organ, and it is very important to understand the pathophysiological mechanism behind it in order to successfully pursue the treatment. Primary injury occurs at the moment of trauma due to direct impact, rapid acceleration/deceleration, forces or any other mechanical insult, leading to the disruption of white matter axons, neuronal/glial cells bodies, and cerebrovascular structures. Consequently, this initiates a secondary injury resulting in a cascade of interrelated molecular processes that occur in a delayed manner and cause further gradual damage to the brain parenchyma [3]. The key events of secondary injury include excitotoxicity, ionic imbalances, shift towards anaerobic metabolism, vascular dysfunction, oxidative stress, development of edema, and neuroinflammation [4]. All those molecular events contribute to the development of cerebral metabolic crisis, ischemia, increased intracranial pressure (ICP) and consequently decreased cerebral blood flow (CBF) and cerebral perfusion pressure (CPP), which in fact further promote the aforementioned processes, establishing a positive feedback loop [5]. In addition, the development and progression of extracerebral complications such as pneumonia, sepsis, multiple organ failure secondary to central dysregulation, systemic inflammation, and catecholamine surge lead to worsening of clinical condition and contribute to a poor outcome [6, 7].

Cerebral metabolic crisis

Within minutes following TBI, the cerebral metabolic rate of oxygen ($CMRO_2$) dramatically decreases, and the extent of this drop has been shown to correlate with a poor neurological outcome [8]. This is mainly attributed to inadequate CBF, hypoxia, and mitochondrial failure, shifting ATP-generating processes to an anaerobic state [9]. Excessive lactate production in fact leads to cerebral acidosis and concurrent disturbances in electrolytes levels, impairment of metabolic autoregulation, and denaturation of vital proteins [9, 10]. A recent cerebral microdialysis cohort of 223 patients showed that an increase in the lactate-pyruvate ratio, reflecting the anaerobic activity of cells, was associated with worse outcomes at 6 months [11]. Moreover, hyperglycemia is an important predictor of increased mortality and poor neurological outcomes in severe TBI [12–14]. Elevated levels of blood glucose not only promotes cerebral acidosis, but is also linked with disruption of the blood-brain barrier, contributing to ischemia and vasogenic edema [15, 16]. This led to clinical trials investigating the effectiveness of intensive insulin therapy, but patients in such treatment groups had a higher rate of adverse outcomes, primarily due to frequent hypoglycemic episodes [17, 18]. A cerebral microdialysis study showed correlation between optimal cerebral glucose levels and the lactate-pyruvate ratio with arterial blood glucose levels in a range of 6–9 mmol/L, suggesting a potentially ideal range of glycemia for neurocritical patients [19].

Cerebral blood flow disturbances

One of the most significant mechanisms of secondary brain injury is ischemia, which has been estimated to occur within the first 12 hours of post-severe TBI in up to 33% of patients and is an independent predictor

of a poor neurological outcome [20]. In an arterial occlusion model, it was shown that ischemic damage occurs at a CBF threshold of <18 ml/100 g/min, leading to hypoxic conditions that interfere with normal mitochondrial functions, causing failure of energy-dependent ionic pumps, and accumulating excessive amounts of sodium and calcium ions intracellularly. This results in cytotoxic edema, oxidative damage, and activation of apoptotic mechanisms, finally contributing to increased ICP and loss of functional cerebral tissue [21–23]. After severe TBI, this threshold for ischemic insults decreases to approximately 20 ml/100 g/min, increasing brain vulnerability to both the duration and extent of CBF impairments. This is likely to result from a combination of excitotoxicity, ionic imbalances and metabolic crisis [20, 24].

In addition to ischemic injury, impairment of cerebrovascular autoregulation is another important factor to consider, and at least to some degree it occurs in up to 87% of severe TBI cases [25]. Early decrease in $CMRO_2$ is not always followed by proportional decrease in CBF causing metabolic uncoupling, which was estimated to occur in up to 55% of severe TBI cases [26]. This defect in metabolic autoregulation leads to higher CBF than metabolic demand, inducing hyperemia, which is most prevalent within the first 5 days after injury and is firmly linked with diffuse cerebral swelling and increased ICP [27]. The change towards anaerobic metabolism is held responsible for this metabolic dysautoregulation primarily due to cerebral acidosis [10].

Similar to metabolic uncoupling, the ability of the brain to maintain adequate CBF in a context of mean arterial blood pressure (MABP) fluctuations might be impaired as well. Under physiological conditions, optimal CBF is maintained in the range of 50 to 150 mmHg of MABP, mainly due to intrinsic myogenic mechanisms. Following severe TBI, the capacity of pressure autoregulation shrinks and leaves the brain more vulnerable to systemic MABP changes, leading to hypo- and hyper-perfusion, which greatly contributes to ischemic events or cerebral hyperemia, respectively [25]. This is particularly prevalent during the first week after severe TBI and is estimated to occur in half of the cases, correlating with better outcomes among those with intact pressure autoregulation [28, 29]. The cause of disturbances in pressure autoregulation remains poorly understood: current theories suggest brainstem dysfunction and/or endothelial damage that follow severe TBI [30, 31].

Cerebral edema and increased ICP

The formation of cerebral edema following primary injury is a significant element contributing to the evolution of secondary brain damage. Grossly speaking, there are two main mechanisms responsible for the development of cerebral edema. Firstly, the mechanical disruption of the blood-brain barrier and concurrent secretion of permeability factors from injured structures results in vasogenic edema, permitting the exudation of plasma proteins and blood-borne cells, eventually drawing fluids into the brain extracellular space [32, 33]. Secondly, most often as an outcome of ischemia or hypoxia, the dysfunction of ionic channels and failure of membrane potential maintenance ensue and cells begin to swell, resulting in cytotoxic edema [34]. However, cellular swelling does not increase brain volume and ICP itself, but rather generate an osmotic gradient that reinforces vasogenic edema, because solutes and water are diffusing intracellularly, setting the stage for further extravasation into the extracellular space of the brain [35, 36]. Therefore, cerebral edema should be seen as an entirety of pathologic processes reinforcing one another with vascular and cytotoxic components.

The primary issue of cerebral edema is that it results in an exponential rise in ICP once the cranial compensatory mechanisms are exceeded, in turn leading to proportionally decreased CPP and eventually ischemic damage, which establishes a positive feedback loop due to the further development of edema [37]. In addition, generation of a pressure gradient across different intracranial compartments may lead to further neurological injury due to different herniation syndromes.

Management of intracranial hypertension

The management of IHT following severe TBI has been of major importance for decades: general principles involve the promotion of cerebral venous return by placing the patient's head into neutral position of 30 degrees and ensuring that cervical collar or endotracheal tube restraints do not compress jugular veins. The use of sedation, analgesia, and osmotic therapy are well-known methods for their potential to control ICP. If indicated by the patient's current neurological status and radiological findings, removal of intracranial mass lesions and/or cerebrospinal fluid (CSF) drainage are very important interventions to execute. Additionally, in case of conservative-treatment refractory IHT, more radical approaches such as decompressive craniectomy should be employed. Finally, somewhat controversial and generally considered as the last resort measures when previously mentioned therapies fail, hypothermia and barbiturate coma might be of benefit to reduce ICP.

Neuromonitoring and optimal CPP

Historically, the maintenance of ICP <20 mmHg was shown to significantly improve outcomes after severe TBI, but recently treatment guidelines have shifted from target ICP-oriented methods towards an individualized approach with the aim of establishing patient-specific optimal CPP (CPPopt) values at which the cerebrovascular pressure reactivity mechanisms operate best [38, 39]. Both, intraparechymal and intraventricular ICP monitoring techniques are generally congruent and applicable for sustained measurements, even though CSF drainage in certain situations can be an attractive option of intraventricular device [40].

Continuous monitoring of ICP and recording its changes in real time based on MABP fluctuations allow one to evaluate cerebrovascular pressure autoregulation capacity and have led to a derivation of the pressure reactivity index (PRx): a moving correlation coefficient between the slow waves of MABP and ICP measured in a minute-to-minute fashion. PRx values in a range of [–1; 0] reflect normal pressure reactivity, whereas positive PRx measurements are in a linear relationship with the severity of cerebrovascular autoregulation dysfunction [41]. This is reflected in a clinical setting, in which a threshold of mean PRx value >0.25 is strongly linked with a fatal outcome [42]. However, the averaged value might not be that reliable clinically, since it does not take a time-dependent component into account. A recent study showed that the impact of a single prolonged elevated PRx event (for example, PRx >0.7 for 40 minutes) was associated with worse outcomes at 6 months, even though mean PRx value might be below a critical threshold [43]. In addition to its prognostic value, PRx can be plotted against CPP to identify CPPopt or a CPP at which PRx turns out to be lowest. This reflects the patient-specific CPP at which cerebrovascular pressure autoregulation functions optimally, setting a therapeutic goal for CPP maintenance as close as possible to this value – deviations below or above CPPopt are associated with adverse outcomes [44].

In recent clinical studies it was shown that superior clinical outcomes are achieved when CPPopt of 60–80 mmHg is kept at gentle hyperperfusion of <10 mmHg above the ideal value. However, better outcomes when CPPopt is >80 mmHg are observed while maintaining CPP fluctuations within the range of ±5 mmHg of optimum [45, 46].

Analgesia and sedation

Continuous sedation and analgesia are generally considered as the standard strategy to manage IHT. The reasoning is that analgetics permit control of pain and agitation, managing arterial hypertension and patient-ventilator asynchrony, whereas sedatives reduce cerebral metabolic demand and therefore in a coupled manner decreases CBF, eventually diminishing cerebral blood volume (CBV). All those factors contribute to a decrease in ICP [47]. Propofol is a routinely used sedative in TBI cases, primarily due to its dose-dependent action on cerebral metabolism, preservation of cerebral autoregulation, and antiepileptic effect, but care should be

taken to avoid potential side effects such as hypotension, cerebral hypoperfusion, and respiration distress [48]. However, propofol does not provide analgesia and is typically used in combination with opioids, preferably fentanyl/remifentanil, because morphine is linked to unpredictable effects on ICP, though the mechanisms remain unclear. Common opioids-induced adverse effects include respiratory depression and hypotension, which increase the risk of further brain ischemia, especially in the context of impaired cerebral autoregulation [48, 49].

Hyperosmolar therapy

One of the key treatment strategy employed in the management of intracranial hypertension is hyperosmolar therapy. The establishment of increased blood osmotic gradient relative to the brain parenchyma leads to the efflux of cerebral interstitial water back into circulation. In addition to that, a decrease in blood viscosity improves CBF, which is balanced out by cerebral vasoconstriction, eventually diminishing CBV [50]. Those two mechanisms explain decrease in ICP following osmotherapy. Popular agents currently include mannitol and hypertonic saline. Mannitol is a non-metabolizable sugar that has potent diuretic properties. The effect on ICP is typically seen within 15 minutes after recommended bolus administration of 0.25 g to 1 g/kg [39]. Yet, nephrotoxicity and hydroelectrolytic derangements (namely hypovolemia/hyperkalemia) following mannitol therapy should be anticipated and managed accordingly via fluid therapy [51]. Hypertonic saline (HTS) works by inducing a state of serum hyperosmolarity without significant diuresis. The onset of the effect on ICP is within minutes following administration of a NaCl solution with concentrations ranging from 3.5% to 23.4%. Generally, less concentrated solutions are recommended for continuous ICP management, whereas in the case of acute increase in ICP or suspected cerebral herniation, administration of 23.4% HTS can rapidly reduce cerebral edema [51, 52]. Still, concerns associated with HTS treatments involve systemic fluid overload, hypernatremia, hyperchloremic acidosis, thrombophlebitis, or even pontine myelinolysis [53].

To compare the two hyperosmolar agents, there is not enough statistically significant evidence to state the superiority of one approach over the other [54]. There is some data suggesting that HTS-based management groups have fewer ICP treatment failures with stronger and longer effects as opposed to mannitol. However, those findings are inconsistent between different studies and as of this year (2018), are not implemented into guidelines for the management of severe TBI [39, 55, 56]. A large, well-designed randomized clinical trial is necessary in order to conclude whether there is difference in outcomes with different osmotherapeutic agents employed.

Neurosurgical intervention

In certain cases of severe TBI, conservative treatment may not be sufficient to achieve desired ICP levels and neurosurgical procedures might turn out lifesaving. Surgical interventions generally involve the evacuation of an intracranial hematoma, decompressive craniectomy, or CSF drainage.

The role of surgery when there is an intracranial space-occupying lesion is to prevent further brain injury due to a hematoma expansion or mass effect and to reduce ICP, which if not fixed in time would ultimately lead to fatal cerebral herniation. There is a lack of reliable evidence to guide clinical decision-making about whether conservative or surgical management is superior, especially for mid-sized lesions. Each situation should be assessed in a case-specific manner, and current recommendations are based on the presence of neurological deficits, pupillary abnormalities, the degree of midline shift and the size of the lesion [57–59]. Conservative management of traumatic mass lesions consists of intensive monitoring of a patient's neurological status, serial imaging of the brain, and medical treatment of secondary brain injury [39].

- Epidural hematomas greater than 30 mL or >15 mm thick should be evacuated regardless the neurological status of the patient. Conservative management is advised if the size of the hematoma is <30 mL, there is <5 mm midline shift, and the GCS score >8 [57].
- Patients with acute subdural hematomas of >10 mm in thickness, >5 mm midline dislocation, mental deterioration by 2 or more points in the GCS score after admission or with anisocoria are good candidates for craniotomy and hematoma removal. Observation is preferable if the patient does not meet the criteria for surgery [58].
- Traumatic intracerebral hematomas located in the forebrain should be removed in case of progressive mental status deterioration with treatment-refractory IHT and mass effect, hematoma volume of >50 ml or GCS of 6 to 8 with frontal/temporal contusions of >20 mL that causes >5 mm midline shift and/or basal cisterns compression. Non-operative approach is indicated if the patient lack neurological deficits, ICP is controlled adequately, and there is no evidence of significant mass effect [59].

Decompressive craniectomy (DC) is a surgical procedure involving partial removal of the skull: it creates space for intracranial contents to expand and thus reduce ICP. It is done either following mass lesion evacuation when swelling is anticipated or as a rescue measure if earlier medical therapies to control edema have failed. Due to limited evidence, there is a continuous debate regarding the effectiveness of DC in the setting of IHT following severe TBI. A randomized clinical trial of 155 patients published in 2011 compared standard treatment versus DC groups. The results showed that the surgical group indeed had lower ICP levels but also had significantly worse outcomes at 6 months [60]. Anyway, the limitations of the study include inadequate randomization of patients and use of bilateral hemicraniectomy, which according to the current guidelines is inferior to unilateral hemicraniectomy [39, 61]. Another randomized clinical trial of 398 patients published in 2016 compared unilateral DC and medical treatment groups. The study demonstrated a reduction in mortality in the DC group at 6 and 12 months at the expense of slightly higher rates of vegetative state and poor functional outcome compared to standard medical treatment [62]. The results of this study verify that unilateral DC is a life-saving procedure with its own risks of potentially worse functional outcome. For reduced mortality and improved neurological outcomes, a large unilateral DC of at least 12x15 cm is recommended over the smaller craniectomies [39].

In addition to the measurement of ICP, an external ventricular drain also allows drainage of CSF, permitting control of IHT at the bedside [39]. Unfortunately, simultaneous drainage and ICP evaluation is not possible, raising uncertainty whether the continuous or intermittent drainage of CSF should be used: constantly open system prevents ICP monitoring and poses a risk of over-draining, which can potentially lead to ventricular collapse, whereas transient drainage exposes patients to unnoticed periods of IHT [63]. The decision about whether an open or closed system is better should be based on the particular situation of each individual case. Placement of an extraventricular catheter carries minimal but significant risks of post-operative bleed and infection [64].

Hypothermia

Experimental studies with TBI animal models laid the basic foundation for understanding the effects of hypothermia during the process of secondary brain injury. Those effect include a reduction in cerebral edema and $CMRO_2$, seizure control, and neuroprotection. Those mechanisms theoretically appear very compelling due to potential of ICP control and healthy brain tissue preservation [65]. This fundamental knowledge led to multiple low-evidence investigations that yielded conflicting results, primarily due to different methodological protocols used and small sample sizes [66]. Although there is some proof that hypothermia reduces ICP, outcomes after such treatment do not improve. A recent prospective randomized clinical trial of 387 patients concluded that the outcomes of hypothermia plus standard care groups were worse than standard

care alone in case of refractory IHT [67]. Further investigations are necessary to establish clear indications with optimal target temperature, length of the treatment, and rate of rewarming. As of 2018, hypothermia is not recommended as a treatment option in case of severe TBI [39].

Barbiturates

If initial methods used to reduce ICP have no success, a pharmacologic coma might be considered as a last resort. Barbiturates decrease $CMRO_2$, which is coupled with diminished CBF, consequently leading to lower CBV and ICP. Pentobarbital is used widely for this purpose but such treatment increases the risk of hypotension and cardiac depression, which could potentially lead to severely reduced CPP and cerebral ischemia [68]. Barbiturates should be used only in hemodynamically stable patients undergoing continuous EEG, loading the dose of barbiturate until burst suppressions appear or ICP is controlled [69]. Even though some smaller studies indeed show better functional outcomes among survivors, current systematic reviews do not support this approach to improve patient results [68, 70]. Current guidelines recommend high-dose barbiturate treatment as the very last resource when maximal medical and surgical interventions failed to control IHT [39].

Conclusions

Traumatic brain injury is a very complex and heterogeneous condition with complicated pathophysiological mechanisms that can be efficiently modified. This opens a therapeutic window that if used correctly, significantly improves functional outcomes and mortality rates. The development of cerebral edema and intracranial hypertension is one of the most common complications that occur following severe TBI. It can, however, be successfully managed by implementing different evidence-based methods that allow us not only to cut the potential risks of IHT, but also to adjust ICP in order to maintain optimal CPP, permitting an individualized, patient-specific approach to secondary brain injury treatment.

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