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Editorial

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Traumatic Brain Injury: An Update

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Traumatic brain injury (TBI) remains one of the leading causes of trauma-related mortality and morbidity in the United States.[1] An estimated 2.5 million TBI occur annually resulting in 282,000 hospitalization and 50,000 deaths with an estimated economic burden of $141 billion.[2] While TBI accounts for 30% of all injury related deaths, survivors face physical and cognitive disabilities together with an increasing risk for neurodegenerative diseases and lasting effects on the individual, the family and the community. The association between TBI and depression, aggressive behavior, attention and memory deficits, cognitive deficit, suicide, premature death, progressive dementia, seizures and even neurodegenerative diseases is well founded.[3-6]

Primary TBI sets a series of compensatory adjustments including stress and inflammatory responses largely driven by hypoxia and ischemia to cause secondary brain injury. This injury occurs hours to days after the primary insult and manifests as systemic hypertension, intracranial hypertension, cerebral edema, and hypo-perfusion. With the pre-existing primary injury, the secondary brain injury contributes to the mortality and morbidity of TBI.[7] Therefore, the quality of the clinical recovery after TBI depends on the severity of the primary insult, the presence or absence of a TBI-associated coagulopathy and the prevalence, sustainability and progression of the secondary brain injury.[8-11] The direct mechanical brain injury is generally expressed as concussion, contusion, intracranial hemorrhage, or diffuse axonal injury. This primary brain injury cannot be influenced therapeutically, and therefore, the main goal of TBI management is to minimize and halt the progression of the secondary brain injury. Although, guidelines have been established for the management of TBI, the optimal therapeutic management of secondary brain injury in TBI patients remains unclear.[12] Also, since the publication of the Brain Trauma Foundation (BTF) guidelines a decade ago, today's TBI management has not changed significantly and still comprise of tiered management of intracranial pressure (ICP) using sedation, hyperosmolar therapy, and/or craniotomy.

Surgical management of TBI is often a life-saving intervention particularly for mass lesion evacuation; neurosurgical decompression to control an ICP that is refractory to medical treatment or an intractable cerebral hypertension; and in some cases, a depressed skull fracture that is compounded by gross contamination or infection, or by disruption of the dura mater that results in pneumocephalus or an underlying hematoma. Although, there is no consensus as to the optimal timing to intervene surgically, and which surgical technique to use, the neurosurgical techniques that are commonly used in TBI are craniotomy, burr holes operation and craniectomy.[13,14]

Secondary brain injury results from delayed biochemical, metabolic, immunologic, and cellular changes that are triggered by the primary TBI. As this injury is amenable to therapeutic intervention, preclinical research has focused in the development and discovery of potentially effective neuroprotective agents. Specifically, this effort has focused on the mitigation of the role of various pathways involved in the pathogenesis of the secondary brain injury. Among others, the potential neuroprotective roles of calcium-channel antagonists[13]; steroids[14]; N-methyl-D-aspartate (NMDA) antagonists[15,16]; glutamate agonists[17]; oxygen free-radical scavengers[18]; immune-modulators[19,20]; statins[21]; progesterone[22,23]; and hypothermia[24] were evaluated. Although, most of these developmental neuroprotective agents have shown promising results in the preclinical evaluation phase, their translations for clinical use have been disappointing.[13,25,26]

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This is likely to be explained by the complexity of the pathophysiology of TBI and the inability of these developmental agents to modulate the single critical element in the pathogenesis of secondary brain injury, which is cerebral blood flow. The brain has the lowest tolerance to ischemic-hypoxia, making it vulnerable to injury and loss of function even at a relative ischemia due to fluctuations in cerebral blood flow. TBI invariably decreases cerebral blood flow by altering one or more of the mechanisms that regulate and optimize a steady cerebral blood flow to meet neuronal functions and metabolic demands.[27] Preclinical as well as clinical data confirm that TBI-induced neurovascular uncoupling, cerebral blood flow-metabolism uncoupling, and impaired cerebral blood flow autoregulation are determinants of the clinical outcome after TBI.[27-31] Based on this premise, interventions that selectively restore a steady cerebral blood flow are more likely to be effective neuroprotective agents against the secondary brain injury. Procedures that can directly influence cerebral blood flow after TBI are: 1) remote ischemic conditioning (RIC); and 2) β-adrenoceptors blockade.

Remote ischemic conditioning (RIC) is a procedure in which non-injured tissues are subjected to short cycles of non-lethal ischemia and reperfusion in order to exert protection against ischemia reperfusion injury in remote tissues/organs. RIC is easy to apply, safe, non-invasive and cost effective intervention, which can be applied in pre-hospital settings or during transport. RIC activates the body's natural protective pathways against the tissue damage caused by low oxygen levels (ischemia) and reperfusion.[32] The molecular mechanisms underlying the protective effect of RIC are not fully understood, but thought to involve complex interactions of intrinsic protective pathways and mediators, protein transporters and ion channels.[33-39] Brief cycles of non-lethal ischemia and reperfusion in the non-injured organ generate endogenous factors that can protect the target (remote) organs from injury. The transmission of this protective signal is multifactorial, comprising of blood-borne factors, neuronal mechanisms and systemic responses. These then activates a cascade of events in the target organ or tissue, which confers the protective effect. Although, the protective effects of RIC were first demonstrated in acute myocardial infarction, its beneficial effects are also observed in other organs like the lung, the liver, the kidney.[40-42] Recent advances in neurosciences have explored the use of RIC in non-traumatic brain disorders like aneurysmal subarachnoid hemorrhage and ischemic stroke and have shown promising results.[43-46] Joseph and colleagues conducted the first-in-humans randomized trial on RIC in patients with severe TBI.[47] The study demonstrated that specific neuronal markers of TBI such as S100B and NSE were significantly reduced in patients who underwent brief periods of RIC upon arrival in the ED.

TBI sets in motion a host-adaptive neuroendocrine, immune, metabolic and inflammatory response that is integrated by increased sympathetic drive and exaggerated catecholamine surge. An unopposed host stress response exaggerates inflammation, impairs host immunity, and accelerates metabolism and tissue injury, which constitute a secondary brain injury. The concept of opposing this host stress response through neutralization of the catecholamine actions early after TBI is a viable option for neuroprotection against the secondary brain injury. Numerous preclinical studies, retrospective reviews, and meta-analysis data have confirmed the beneficial effects of β-adrenoceptors blockade in the management of TBI.[48-57] In particular, studies have shown that β-Blockers improve in-hospital survival of TBI patients.

Management of TBI is changing towards a personalized approach of early diagnosis, early assessment of associated risk factors that contribute to morbidity and mortality, and early interventions to protect neurons against further damage. Preclinical studies are required to elaborate on the pathophysiology of TBI, and in particular, the pathogenesis of the secondary brain injury that is associated with TBI. Prospective evidence on the short- and long-term benefits of RIC and β-Blockers in the management of TBI is warranted.

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