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Traumatic Brain Injury: Current Treatment Strategies and Future Endeavors

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Abstract

Traumatic brain injury (TBI) presents in various forms ranging from mild alterations of consciousness to an unrelenting comatose state and death. In the most severe form of TBI, the entirety of the brain is affected by a diffuse type of injury and swelling. Treatment modalities vary extensively based on the severity of the injury and range from daily cognitive therapy sessions to radical surgery such as bilateral decompressive craniectomies. Guidelines have been set forth regarding the optimal management of TBI, but they must be taken in context of the situation and cannot be used in every individual circumstance. In this review article, we have summarized the current status of treatment for TBI in both clinical practice and basic research. We have put forth a brief overview of the various subtypes of traumatic injuries, optimal medical management, and both the noninvasive and invasive monitoring modalities, in addition to the surgical interventions necessary in particular instances. We have overviewed the main achievements in searching for therapeutic strategies of TBI in basic science. We have also discussed the future direction for developing TBI treatment from an experimental perspective.

Keywords

traumatic brain injury, management, intracranial hypertension, treatment strategies

Epidemiology of Traumatic Brain Injury (TBI)

TBI continues to plague millions of individuals around the world on an annual basis. According to the Centers for Disease Control, the total combined rates for TBI-related emergency department visits, hospitalizations, and deaths have increased in the decade 2001–2010.[1] However, taken individually, the number of deaths related to TBIs has decreased over this same period of time likely secondary in part to increased awareness, structuralizing management and guidelines, and significant technological advancements in current treatment regimens. We should also acknowledge that there is a certain percentage of TBIs that never reach medical care, hence, the overall rates for TBIs are likely underreported.[2] The highest rates of TBI tend to be in a very young age-group (0–4 y) as well as in adolescents and young adults (15–24 y). There is another peak in incidence in the elderly (>65 y). The 2 leading causes of TBI overall are falls and motor vehicle accidents.[3] As a result of an overall increased number of TBIs, but lower rate of related deaths, we have a growing population of individuals living with significant disabilities directly related to their TBI.

Pathophysiology of TBI

TBI pathogenesis is a complex process that results from primary and secondary injuries that lead to temporary or permanent neurological deficits. The primary deficit is related directly to the primary external impact of the brain. The secondary injury can happen from minutes to days from the primary impact and consists of a molecular, chemical, and inflammatory cascade responsible for further cerebral damage. This cascade involves depolarization of the neurons

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with the release of excitatory neurotransmitters such as glutamate and aspartate that lead to increased intracellular calcium. Intracellular calcium activates a series of mechanisms with the activation of enzymes caspases, calpases, and free radicals that results in degradation of cells either directly or indirectly through an apoptotic process. This degradation of neuronal cells is associated with an inflammatory response that further damages neuronal cells and incites a breach in the blood brain barrier (BBB) and further cerebral edema. This entire process is upregulated and downregulated as well through several mediators. After the second injury phase follows the recovery period, which consists of reorganization in an anatomical, molecular, and functional level.

The volume of the intracranial compartment is comprised of 3 separate contents: the brain parenchyma (83%), cerebrospinal fluid (CSF, 11%), and blood (6%).[4] Each of these contents relies on one another for a homeostatic environment within the skull. However, when intracranial volume exceeds that of its normal constituents, a cascade of compensatory mechanisms takes place. An increase in intracranial volume can take place in the traumatized brain via mass effect from blood, both cytotoxic and vasogenic edema, and venous congestion. Brain tissue is incompressible. As a result, edematous brain tissue will initially cause an extrusion of CSF to the spinal compartment. Eventually, blood, especially that of venous origin, is also extruded away from the brain. Without proper intervention, and sometimes even with maximal intervention, the compensatory mechanisms fail and the end result is pathological brain compression and ensuing death.[5]

Concussion

Concussive injuries are often viewed as mild TBIs without any gross structural damage secondary to a nonpenetrating TBI.[6] They usually follow direct blows to the head with subsequent acceleration/deceleration forces taking place. A concussive injury typically leaves the individual with varying levels of transient altered mental status, ranging from slight confusion to an actual state of unconsciousness for a few minutes. Routine neuroradiographic imaging such as computerized axial tomography scan (also called computerized tomography [CT] scan) and magnetic resonance imaging (MRI) do not show any immediate abnormalities. However, newer imaging techniques using MRI such as diffusion tensor imaging and functional MRI may result in earlier diagnosis of concussion. It has been postulated that mild degrees of axonal damage take place even in the face of a mild TBI.[7]

A very rare condition seen most often in athletes is second impact syndrome. The inciting event is often a concussion, however, the player may return to play prematurely and sustain a second concussive event amid continued recovery from their initial injury. The mechanism typically involves the rapid evolution of malignant cerebral edema, ensuing over a short-time course after the second injury takes place often on the playing field. The mortality rate ranges from 50% to 100%.[8]

Chronic Traumatic Encephalopathy (CTE)

Repetitive mild TBI may lead to a delayed manifestation known as CTE. This entity has gained popular attention in the media as one of the unfortunate consequences of CTE is psychiatric disturbances, ultimately leading to suicidal behavior in a number of high-profile athletes in professional sports. Other clinical manifestations of CTE include dysarthric speech, tremors, difficulty with attention, deficits in memory and executive functions, and incoordination and pyramidal signs.[5] CTE likely results from evolution of progressive neuronal loss.[9,10]

Extra-axial Hematomas

Extra-axial hematomas consist of both epidural hematomas (EDH) and subdural hematomas (SDH). EDH classically result from a direct blow to the temporal region, at times causing a skull fracture, with resultant disruption of the middle meningeal artery. However, venous injuries, such as disruption of the transverse sinus, have also accounted for more posteriorly oriented EDH. EDH can rapidly grow in size, causing an individual to present with essentially normal mentation, followed by deterioration down the cascade of herniation syndromes once a critical level of intracranial pressure (ICP) is reached.[11]

While EDH are almost always encountered in the acute setting, SDH have varying presentations based on the age of the patient and the chronicity of blood products. SDH in the setting of trauma often take place via acceleration/deceleration of the surface of the brain against the undersurface of the skull, causing shearing injuries to the bridging veins.[12] Acute SDH can be quite dangerous for the patient in the context of trauma, as they generally involve a much higher degree of underlying brain injury than does an EDH. The underlying cerebral edema is often a significant contributing factor to ensuing midline shifting of structures and progression of herniation syndromes if left untreated. There are some SDH that go unnoticed to the patient for a period of time. As acute blood in the subdural space liquefies over time, subacute and chronic SDH can be encountered. In the subacute and chronic setting of subdural hematoma, the clinical presentation is not nearly as rapid and progressive as in the acute phase. More chronic-appearing SDH tend to be encountered in the elderly population, many times while they are on antiplatelet agents or anticoagulants. The usual presentation for subacute and chronic SDH's tends to be more insidious, with headaches, hemiparesis, speech problems, confusion, and altered mentation being most common. On rare occasion, a patient will present with significant neurological deterioration due to untreated unilateral or bilateral chronic SDH.

Contusions and Traumatic Subarachnoid Hemorrhage

Contusions generally take place as a result of coup and contrecoup forces. Coup injuries occur at the site of impact, while contrecoup injuries typically take place on the contralateral side of impact, most often causing injury to the frontal lobe and anterior temporal lobe. Subarachnoid hemorrhage is most often caused by trauma and takes place when small capillaries tear and ultimately spill blood transiently into the subarachnoid space. Generally, traumatic subarachnoid hemorrhage is not as severe a brain injury as is spontaneous aneurysmal subarachnoid hemorrhage,[13] given the fact that in the latter, blood is projected into the subarachnoid space under arterial pressure.

Diffuse Axonal Injury (DAI)

DAI is the ultimate form of axonal shearing injury. Significant rotational acceleration/deceleration forces are generally required for such an injury to take place.[14] Radiographically, it is often picked up on T2 and gradient echo sequences as subtle hemorrhagic foci seen in areas such as the corona radiata, corpus callosum, internal capsule, brainstem, and thalamus.[15] Depending on where the axonal shearing takes place, patients can have varying degrees of clinical presentations. A subset of patients with DAI may have altered conscious for a few days, while others present with hemiparesis from internal capsule involvement. Others never regain consciousness due to loss of axonal integrity in parts of the reticular activating system.

Neurological Exam in the Brain-injured Patient

In the assessment of the brain-injured patient, a detailed neurological exam must be completed after the primary and secondary surveys have been completed by the trauma or emergency room staff. An adequate understanding of the Glascow Coma Scale (GCS)[16] is paramount in this setting, as it often dictates management based on current guidelines. In the nonintubated, nonsedated patient, a basic survey of neurological symmetry should be undertaken once a GCS score is established. Pupil size should be compared, as should motor strength and sensation. Other nuances of the neurological exam, although important, do not play a significant role in the immediate decision-making of the traumatic brain-injured patients. Although eye opening is one individual component of the GCS grading, clinicians tend to put more weight on this finding, as it often suggests a more reassuring neurological status in our experience if a patient opens his or her eyes spontaneously. Assessment of the intubated patient with a much lower GCS score can be more challenging. A quick method of examining the intubated, potentially sedated brain-injured patient entails establishing a GCS score as soon as possible. Checking for pupil reactivity, symmetry, as well as cough/gag, and corneal reflexes are also important. Intubated patients are usually sedated to some degree and pharmacologically paralyzed for placement of the endotracheal tube. This is also the case in patients intoxicated with alcohol and/or recreational drugs. These pharmacological factors play a significant role in the neurological exam at face value but are generally unaccounted for in basic grading scales such as the GCS. In these circumstances, it is of the utmost importance to gather data in a brisk fashion, such as the sedative/paralyzing medications used, the timing of administration, their half-lives, and any other potential confounding factors to the neurological exam. Without these details, untoward decisions may be made based on a GCS score alone, which may not be in the best interest of the patient. A full neurological exam of sedatives should be the primary goal of the neurosurgeon once airway, breathing, and circulation have been addressed.

Medical Interventions for TBI

Head Elevation

Raising the head of a traumatic brain-injured individual generally has rapid effects. ICP is reduced by displacement of CSF from the intracranial compartment as well as promotion of venous outflow.[5] Although the mean carotid pressure is reduced during head of bed elevation, ICP is reduced and cerebral blood flow (CBF) is unaffected.[17]

Hyperventilation

Hyperventilation lowers ICP by reducing the intraarterial carbon dioxide partial pressure (PaCO2), which subsequently results in vasoconstriction. This pattern of events ultimately results in the reduction of cerebral blood volume.[18] Prophylactic hyperventilation is not generally recommended, as vasoconstriction lowers CBF. In areas of preserved autoregulation, focal areas of ischemia can occur.[19] The use of hyperventilation in the setting of severe TBI is usually only used for brief periods during acute neurological deterioration.[5]

Seizure Prophylaxis

Current TBI guidelines state that 1 wk of prophylactic antiepileptics is acceptable to help prevent early seizures. However, there has not been any proven benefit in prevention of late-term seizures after a TBI, and hence, the antiepileptic is generally discontinued after 7 d.[20]

Hyperosmolar Therapy

Hyperosmolar therapy in the setting of a TBI can be administered in the form a bolus or an infusion. It has been shown that the immediate effects of mannitol are actually due to alterations in blood rheology. As blood rheology improves and blood becomes less viscous, an increase in CBF takes place.[21] The body's autoregulatory

response to this is transient vasoconstriction, which ultimately limits the degree of CBF. Mannitol also does have osmotic diuretic properties, but this mechanism of decreasing ICPs is not thought to take place until after the primary effect.

Medically Induced Comatose State

One of the last steps of maximal management is placing a patient in a medically induced comatose state usually by infusion of a benzodiazepine such as midazolam or infusion of a barbiturate such as pentobarbital. These medications are titrated to burst suppression on the continuous electroencephalogram. They work by significantly decreasing the metabolic demand in the brain. Prophylactic use of barbiturates for burst suppression is not currently recommended. It is, however, recommended for severe refractory intracranial hypertension after maximal medical and surgical ICP-lowering therapy have been exhausted.[5,18] Oftentimes, medically induced comatose states are used once a form of invasive intracranial pressure monitoring has been undertaken. Medications such as midazolam and pentobarbital pose a potential risk of altering blood pressure to patients.

Therapeutic Cooling

It is thought that oxidative stress is a secondary effect of TBI. Therapeutic hypothermia has been shown in infants and children to decrease oxidative injury.[22] As the body's temperature cools, the cerebral metabolic demand decreases. This type of therapy also comes with risks such as alterations in blood sugar, platelet count, and coagulation factors. Platelet count and coagulation factors must be checked before any invasive procedure when an individual is brought to a hypothermic state. Therapeutic cooling in the context of severe TBI has had mixed results and is currently a second-tier therapeutic modality.[23]

ICP Monitoring

Certain indications have been put forth as guidelines in regard to ICP monitoring in brain-injured patients. Some patients clinically present with signs of significant neurological compromise but without clear indications for emergent surgical intervention. Level II evidence exists for placing an ICP monitor in patients with a severe TBI, a GCS between 3 and 8, and an abnormal CT scan of the head. Level III evidence also suggests placing an ICP monitor in patients with a severe TBI and a normal CT scan of the head, if 2 or more of the following are noted upon admission: age over 40 y, unilateral or bilateral posturing, or systolic blood pressure <90 mm Hg.[24] The rationale behind placing an ICP monitor exists, because it is now known that secondary injuries to the brain have the ability to potentiate further deterioration.[24] If the primary impact, such as a subdural hematoma, does not warrant immediate surgical intervention, both cytotoxic and vasogenic edema, as well as resulting cerebral hypoperfusion, may ensue. These secondary impacts may cause the abrupt demise of a patient, if the ICP is not closely monitored. Other parameters such as brain oxygen tension are now able to be monitored as well, giving clinicians another means of monitoring the injured brain.[25] The mainstay of ICP monitoring continues to be the external ventricular drain, which can be utilized for both therapeutic and diagnostic purposes.[26] If the patient's ventricles are too small and do not accommodate a ventricular drain, another option is to place a diagnostic fiberoptic ICP monitor.[27] New models are now being used on a more routine basis to monitor brain oxygen tension, as evidence exists that this parameter falls in cases of severe TBI. These different modalities help neurosurgeons decide on which patients can safely be managed with medical management alone and which patients will ultimately need neurosurgical intervention.

Surgical Intervention

Craniotomy: Evacuation of Extra-axial Hematoma/ Contusion

Surgical intervention is generally warranted when there is significant mass effect from either an epidural or subdural hematoma or a contusion with a significant volume of blood.[28] The underlying brain injury associated with an EDH is usually quite minor, however, the rapidity with which an EDH can expand often makes this a neurosurgical emergency. The mainstay of treatment of an EDH is a craniotomy over the desired region, with evacuation of the hematoma and cauterization of the bleeding vessel, often the middle meningeal artery. Acute SDH are usually associated with a much more significant underlying brain injury. Not only does the extra-axial blood cause mass effect on the brain, but the underlying cerebral edema is often what pushes the patients over the edge to clinical deterioration. As a result of the oftentimes severe brain injury associated with an acute SDH, a decompressive craniectomy (DC) is performed. Standalone evacuation of the subdural hematoma without temporary removal of the bone flap in a patient with significant associated underlying cerebral edema can result in further delayed deterioration after the initial surgery has taken place. However, if the underlying brain injury is minimal and mass effect is mainly due to the hematoma itself, it may be reasonable to perform a craniotomy, with hematoma evacuation and duraplasty.[28]

SDH vary in age from acute (the most severe form) to subacute, chronic, and mixed. After a number of days, acute SDH generally enter into a process of liquefaction, making them amenable to minimally invasive surgical evacuation. While acute SDH's are actual clotted blood, subacute and chronic SDH's have a liquefied component. A bedside subdural bolt evacuating system can be placed once blood is out of the acute phase and has liquefied to a significant degree.

A very small incision is made over the area of the SDH, a handheld twist drill is then used to make a burr hole, the durra is opened, and the metal bolt is secured into the burr hole. A tube connected to a small suction device is then attached to the bolt and allowed to drain via self-suction. A limitation to this device is when there are multiple subdural septations and loculations, allowing chronic blood to be evacuated from only the pocket the bolt is overlying. In the case of a symptomatic mixed-density SDH, surgical intervention may be undertaken whereby a craniotomy is performed, followed by the SDH evacuation, and finally clearing of the subdural membranes responsible for the recurrent "leakage" of blood from neovascularized blood vessels.[29]

Most contusions that occur can usually be watched clinically and radiographically to ensure that they do not significantly expand. However, a small percentage of brain contusions do "blossom" to the point of requiring surgical intervention with a craniotomy and clot evacuation.

DC for Cerebral Edema

Radiographically, some severe TBIs do not yield significant hemorrhages. However, upon close inspection, it can be noted that there is blurring of the gray–white junction, effacement of the ventricles, and obliteration of normally visible cisterns. Obliteration of the basal cisterns is an ominous sign that there is impending distal herniation, ultimately leading to the demise of the patient. If the edema is localized to one side of cerebral hemispheres, surgical intervention may consist of a hemicraniectomy, whereby a large bone flap is removed from the surrounding skull, and the durra is opened. Severe bilateral diffuse cerebral edema may warrant bilateral DC as a last resort surgical option to salvage the patient.[30]

Synopsis

The clinical aspects of TBI can be quite complex, as is evidenced by the wide array of presentations and treatment strategies. Of utmost importance in the management of TBI patients is obtaining neuroradiographic imaging as well as a baseline neurological examination. The decision-making process for therapeutic maneuvers will essentially be based upon critical deviations from the initial scan and neurological status. Therapies for TBI range from medical management alone with frequent neurological exams, to invasive intracranial monitoring, and as a last resort to radical decompressive surgical interventions.

Therapeutic Studies in Animal Models of TBI

TBI is a combination of anatomical and functional damage to the brain after direct mechanical insult from external forces. TBI-induced cerebral injury is a mixture of structural, cellular, and vascular injury. Reaction with a complex molecular and cellular cascade is activated as a result of the structural damage from the initial impact.

In order to minimize the cerebral injury after the TBI, therapeutic intervention is directed to prevent the first impact damage and to restrict the molecular and cellular cascade of the continuous cell damage. So far, there are no effective treatments for the first impact damage. Numerous studies have been carried out in an effort to search for treatment to prevent further neuronal damage after TBI and to enhance neural network reorganization and functional recovery. Unfortunately, these experimental studies have not been successfully translated into clinical therapies. Many questions have been raised through these years such as whether we fully understand the pathological dynamics after TBI and whether TBI models are clinically relevant.

Animal Models of TBI

Several animal models for TBI have been proposed and each of them has tried to mimic clinical TBI. Animal models of TBI that have been frequently used for research include fluid percussion injury (FPI), control cortical impact injury (CCI), weight drop impact acceleration injury (WDIAI), and blast injury model.[31]

FPI. FPI produces a TBI that is characterized by cerebral edema, intraparenchymal hemorrhage, and cortical neuronal injury. Lately, FPI model has been modified to lateral FPI model, which creates not only focal cortical contusion but it also transmits the traumatic injury into subcortical structures such as hippocampus and thalamus. The neuronal loss starts immediately after the impact and progresses up to 7 d post-TBI. The cascade of the molecular changes continues for months in the subcortical structures such as septum pellucidum, thalamus, amygdala, and striatum. This TBI model produces similar symptoms to humans and manifests severe neurobehavioral deficits that persist more than 1 y after TBI.[31,32]

Control CCI. Control CCI is a TBI model that provides a more controlled injury in terms of velocity force, time, and depth of injury as compared to the FPI model. This model creates cortical injury, SDH, axonal injury, and subcortical injury in the thalamus and hippocampus. The CCI model-induced brain injuries cause long-term neurobehavioral deficits that persist more than a year and are associated with cortical atrophy and reduced brain perfusion.[31,33]

WDIAI. WDIAI is a model that generates an open or closed head injury. The result of the first impact is cortical contusion with possible subcortical intracerebral hemorrhage. This leads to the formation of a necrotic cavity within 2 wk after injury. In this model, the recovery phase is ranged from 2 wk to 3 mo. The closed head injury of this model causes neurologic deficits, neurodegeneration, inflammatory response with microglial activation, BBB breakdown, and

DAI. The pathology features of this model contain similar components as seen in human TBI that is caused by motor vehicle accidents or sport injury.[31]

Blast injury. Blast injury model is created by high-velocity ballistic penetration or a stub of a blast. The anatomical and morphological characteristics of the blast injury are related to trajectory of the injury with intraparenchymal hemorrhage and subsequent cavity formation. Moreover, this model also generates additional TBI components such as inflammation with BBB breakdown, cerebral edema, neurodegeneration, tauopathy, and axonal degeneration.[31,34]

Exploration of Therapeutic Strategies in Animal Models of TBI

Animal model not only helps us understand the pathological progression after TBI, but it also allows us to develop putative interventions for preventing secondary injury, enhancing brain repair and improving recovery after TBI.[31] Neuroprotection, neurovascular regeneration, and neurorestoration have been proposed to be therapeutic strategies for TBI. As mentioned earlier, TBI leads to a cascade of primary and secondary neuron loss, which is clinically manifested with different degrees of neurological deficits depending on the location and the severity of the neuron loss. Numerous studies have targeted the reduction or prevention of the TBI-induced neuronal loss. Treatment that shows neuroprotective effects on TBI in animal models requires intervention within a few hours after the first impact.[35–37] However, a large number of clinical trials using neuroprotective treatment have not shown promising results. The therapeutic potential of neuroprotection, therefore, has become questionable in TBI research. Several neuroprotective approaches that have been used for TBI clinical trials or animal models are outlined below.

Calcium channel blockers. Increased intracellular calcium is a very important element in the cascade of the cellular damage after TBI. Using 2 types of calcium channel blockers (L-type and N-type) to neutralize intracellular calcium has shown benefits in preventing TBI-induced cellular death.[38–41]

The neuroprotective effect of nimodipine was reported in 1984[38] based on the regulation in brain perfusion and prevention of further neuronal damage. Nimodipine is an L-type calcium channel blocker and has been shown to improve outcomes in the patients with spontaneous subarachnoid hemorrhage.[39] However, a systematic review contradicted those results and revealed that the mortality and morbidity displayed no significant difference between placebo and nimodipine treatment in TBI patients.[40]

Ziconotide (SNX-111) is an N-type calcium channel blocker. It has been shown that administration of ziconotide during the period of 15 min to 6 h after TBI improves mitochondrial function in patients[41]; however, significant side effects such as hypotension were also observed. Another N-type calcium channel blocker, SNX-185, was reported to show neuroprotective effects when directly injected to hippocampal CA2 and CA3, 24 h after TBI.[41]

Osmotherapy. Hyperosmolar agents are used in patients with severe TBI to control ICP. Hyperosmolar saline injection displayed beneficial effects in TBI patients. Mannitol, one of hyperosmolar agents, has been shown as having a significant effect on reducing ICP in TBI patients in a dose-dependent manner. Mannitol treatment also resulted in improvement of blood perfusion and reduction of inflammatory response after the TBI.[41]

Amantadine. Amantadine is a dopamine agonist used for Parkinson's disease. Amantadine can distribute in frontal lobes and acts as an N-methyl-D-Aspartate (NMDA) receptor antagonist. It has been proposed that amantadine may protect the neurons against glutamate excitotoxicity in the acute phase of TBI. Many studies have demonstrated that amantadine in dose of 100–400 mg/d may increase the arousal and improve cognitive function when given within 12 wk after the TBI.[37,42]

Erythropoietin (EPO). EPO is a secreted glycoprotein with a molecular weight of 30-kD. The role of EPO in the regulation of erythropoiesis has been initially identified in the hematopoietic system.[43] EPO may also play a role in the central nervous system as the expression of both EPO and its receptor, EpoR, are widespread in the brain.[44,45]

Although the molecular weight of EPO is larger than the molecular threshold of the BBB, exogenous EPO has been found in the brain parenchyma where it may play a role in neuroprotection after brain injury.[46] Several studies have demonstrated that EPO shows antiexcitotoxic, antioxidant, antiedematous, and antiinflammatory effects in TBI.[47–50] Brain injury causes upregulation of EpoR expression.[45] Reduced number of neural progenitor cells (NPCs) and increased apoptosis has been found in the mice lacking the EPO receptor.[51]

EPO/EpoR signal pathway has been shown to be involved in neuroprotection in pathological conditions.[50,52] Expression of the receptors for EPO is significantly increased in neurons, glia, and endothelial cells after TBI.[41] EPO appears to promote neuroprotection through binding to EpoR and activating JAK-2/NF-kB and PI3K signaling pathway.[41,53] Additionally, JAK-2 phosphorylation activates PI3K/AKT and Ras/MAPK pathways and promotes STAT-5 homodimerization, which has been shown to have antiapoptotic and neurotrophic effects.[54–56] However, a recent double-blind randomized controlled clinical trial has revealed that EPO does not reduce the number of patients with severe neurological dysfunction and that the effect of EPO on mortality remains uncertain in moderate or severe TBI.[57] Clearly, more clinical trials need to be performed to confirm the results collected from the experimental studies.

S100B protein. S100B protein is a calcium-binding protein produced by glial cells. S100B protein has been detected in serum after the opening of the BBB after brain injury. S100B shows a dose-dependent dual effect in neurons. In small doses, S100B acts as a neurotrophic factor for neuroprotection. However, in high doses, S100B increases neuroinflammation and worsens the neural survival.[41]

Hypothermia. In 1945, Fay reported possible benefits of hypothermia on severe cerebral trauma.[58] Since then, many studies have shown that hypothermia improves outcome in animal models of TBI.[59–64] Temperature management in the brain is very important after cerebral injury.[65,66] Deep hypothermia (below 30 °C) appears to show no benefits for TBI while mild to moderate hypothermia (32 to 35 °C) displays neuroprotective effects.[67,68] However, the neuroprotective mechanisms of hypothermia after TBI remain poorly understood. Several beneficial effects of hypothermia have been determined, including the effects on regulation of metabolism, excitotoxicity, inflammatory mediators, or autophagy.[68–74] Neuroprotective effects of hypothermia have been proposed to be associated with the reduction of brain oxygen consumption and glucose metabolic rate, preservation of high-energy phosphate compounds, and maintaining of tissue pH in the brain.[75] Recent studies have shown that therapeutic hypothermia significantly alters genomic transcripts and microRNA responses and regulates protein synthesis and translation in rat models of TBI.[76–78] The hypothermia-induced changes in gene, microRNA, and protein responses following TBI may target the delayed responses that regulate the secondary brain damage. Although the robust neuroprotective effects of therapeutic cooling have been demonstrated in animal models of TBI, it still remains controversial whether hypothermia treatment could really provide permanent protection or delay the injury processes.[69]

DC. DC is a neurosurgical procedure, which allows a swelling brain to expand without being compressed. DC has been used to reduce ICP in the conditions of brain tumor, stroke, and severe TBI.[79] DC as a treatment of TBI was originally reported by Emil Theodor Kocher.[80] However, due to the controversial findings in both clinical and experimental studies, DC is recommended as a third-tier therapy for the treatment of elevated ICP by most national and international guidelines.[80,81] The role of DC on brain edema formation and secondary injury after TBI has been examined in animal models of TBI. Using a controlled cortical impact model of TBI in mice, Zweckberger and coworkers reported that early craniectomy prevented secondary brain damage and significantly reduced brain edema formation.[82] A recent study suggested that DC might affect AQP4 expression and reduce brain edema formation after TBI.[83] However, Szczygielski and coworkers reported opposite findings. They found that surgical decompression promoted brain edema formation and contusional blossoming and exacerbated functional impairments in mice with closed head injury.[84] The different results may be attributed to different injury severity from different TBI models. The outcomes of craniectomy application are highly correlated with the severity of the initial injury.[79] Although the results of experimental studies are controversial, DC still exhibits an important role to save the lives of patients with TBI and improve neural functional outcomes. Further studies need to be performed to confirm which kind of TBI is suitable for DC and which physiological and pathological mechanisms are related to functional outcomes after DC in TBI patients.

Neurovascular Regeneration

Neuronal and vascular regeneration have been proposed to play a role in brain recovery after brain injury. Neurogenesis in adult brain has been shown to occur in the subgranular zone in the dentate gyrus (DG) of the hippocampus and subventricular zone. In animal models, it has been described that TBI induces the neurogenesis in cerebral cortex, DG, and CA3. Thymosin β 4 (Tβ4) is an important G-actin-sequestering molecule in cells. In animal models, Tβ4 injection increases proliferation of NPCs. Moreover, Tβ4 also enhances angiogenesis and promotes NPC differentiation.[35]

In the subventricular zone and subgranular zone, there is a particular group of astrocytes that can go through division and differentiation into new neurons. These newborn neurons have been proposed to play a role in replacing the neurons in the olfactory bulb or in the cortex and hippocampus after TBI. In animal models, it has been shown that the number of regenerated neurons in young animals is greater than those of aged animals. The process of NPC proliferation and differentiation has a peak at 2 to 5 d after TBI, while some studies extend this time frame to 14 d.[85]

TBI causes changes in vascular density in the cortex, DG, and CA3 in animal models. Tβ4 treatment increases the vascular density in the cortex, DG, and CA3. This increased vascular density is associated with neurogenesis and synaptogenesis. The entire process of angiogenesis, neurogenesis, and synaptogenesis may contribute to TBI recovery.[35] Recently, Zhang et al.[86] reported that a Tβ4 active peptide fragment, N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP), enhanced angiogenesis and neurogenesis, and increased the number of dendritic spines in the injured brain.

S100B appears to be a stimulator for neurogenesis after TBI. Using animal models of TBI, a number of studies have shown that intraventricular administration of S100B in the acute or subacute phase of TBI promotes neurogenesis in the hippocampus and subventricular area and improves cognitive function and spatial learning.[41,87] It has been shown that nitric oxide enhances neurogenesis and angiogenesis through the mediation of guanylyl cyclase and formation of guanylate cyclase.[88] Induced neurovascular regeneration lays the foundations for neural plasticity and functional recovery.

Neurorestoration

Cell-based therapy for TBI recovery. In the past few decades, stem cell-based therapy opened a new therapeutic avenue for neurological disorders and Central Nervous System (CNS) injuries. Preclinical studies utilizing stem cells and progenitor cells as treatment for spinal cord injury,[89–91] stroke,[92,93] and brain injury[94,95] have shown beneficial effects in improving recovery. Currently, different cell types have been used as putative therapies for TBI recovery. It has been revealed that enhancing neurogenesis, angiogenesis, and immunoregulation by secreting chemokine and growth factors are involved in the functional recovery induced by stem cell/progenitor cell-based interventions.[96–99] Several clinical trials in cell-based treatment for TBI recovery have demonstrated safety of this therapeutic approach.[100,101] However, the administration route, dose, and time window still remain controversial.

The therapeutic effects of mesenchymal stem cell (MSC) transplantation in TBI recovery have been demonstrated in animal models. MSCs were mainly isolated from the bone marrow, umbilical cord, and adipose tissue.[99,101,102] The administration dose of MSCs ranges from 0.1 to 20 million cells per kg body weight.[96] The approaches of lateral ventricle and intravenous injection have been utilized.[96] The timing for MSC transplantation in experimental animal models has been intensively studied within 24 h after TBI. Recently, a clinical study has showed significant improvements in neurological function of patients with sequelae of TBI after umbilical cord MSC transplantation.[101] Although it remains to be fully understood how MSCs transplantation improves functional recovery after TBI, emerging evidence has suggested that neurorestoration is most likely the mechanism underlying the MSCs transplantation-induced TBI recovery rather than neuroreplacement. It has been shown that MSCs release growth factors such as Fibroblast growth factor 2 (FGF-2), Vascular endothelial growth factor (VEGF), Brain-derived neurotrophic factor (BDNF). These growth factors enhance neurogenesis, angiogenesis, and synaptogenesis.[41,103] The efficacy of MSCs transplantation in the acute phase of TBI is contradictory. Extensive studies are needed to further validate the therapeutic effects of MSCs transplantation in the acute phase of TBI in animal models before this approach is translated into clinical trials.

Neural stem cells (NSCs)/NPCs are also most frequently used in experimental TBI. NSCs/NPCs reside in the mammalian brain at the ependymal lining, subventricular zone, and hippocampus.[104] Recently, promoting endogenous NSCs or NPCs proliferation and differentiation have been shown to stabilize the cortical microenvironment and enhance post-TBI functional recovery.[105–108] Exogenous NSC transplantation also promotes neuroprotection, enhances hippocampal neurogenesis, and improves functional outcomes.[109] In animal models, the number of cells for transplantation ranges from 0.15 to 25 million cells per kg body weight.[96] The most common delivery method used for NSC transplantation is stereotactic injection to the brain. Although the timing for transplantation ranges from immediately after TBI to a few weeks later,[110–112] Shear et al.[113] reported that NSC transplantation at 2 d after TBI showed better outcome than at 2 wk after TBI. It has been shown that the benefits of NSC/NPC transplantation may attribute to differentiating into functional neurons and replacing lost neurons.[114,115] Recent studies have shed new light on the interaction between NSCs/NPCs and immune system. The cross-talk between immune cells and transplanted NSCs/NPCs not only enhances endogenous regenerative responses, but it also promotes functional integration of grafted NSCs/NPCs.[116] Gao et al. reported that grafted human NSCs promoted the switch of microglia/macrophages into an anti-inflammation phenotype which may contribute to stem cell-mediated neuroprotective effects after severe TBI in mice.[117] Although there is no clinical trial concerning NSC transplantation for TBI recovery, the clinical study in traumatic cervical spinal cord injury has shown the safe outcomes.[118]

Transplantation of embryonic stem cells (ESCs) in TBI has also been studied. Molcanyi et al.[119] reported that post-traumatic inflammatory response inhibited the survival and integration of transplanted ESCs after TBI. Riess et al.[120] revealed that ESC transplantation improved neurological outcomes but it had the risk of tumorigenesis.

Although preclinical studies indicate stem cell-based interventions may be a promising approach for TBI, long-term risks and benefits of this approach still need to be further investigated.

Enriched environment (EE) intervention for TBI recovery. Neurorehabilitation plays a crucial role in integrating TBI patients into a functional lifestyle. TBI survivors are often left with long-term depression. Exposure to positive environments plays a significant role in improving emotional well-being for TBI patients.

Numerous studies have examined the effects of exposing animals to EEs after neurological insults. An EE consists of housing animals in a larger cage and allowing animals to have more opportunities for social interaction, sensory stimulation, and exploratory behavior.[121] Rats exposed to an EE have shown benefits in both neurobehavior and neuroanatomy.[121–131] Using animal models of TBI, multimodal interventions including exposure to an EE have yielded positive results.[132,133] It has been shown that EE exposure improves spatial memory recovery after cerebral ischemia.[134] In olfactory bulbectomized rats, exposure to an EE results in antidepressant effects.[135] In rats with striatal lesion, EE has also proven beneficial for neural graft function and morphology.[136] It has also been reported that visually defected rats may regain some degree of visual acuity after exposure to an EE.[17] The prophylactic effects of EE exposure prior to undergoing a TBI has also shown positive results.[137] Spinal cord-injured rats also display functional recovery once exposed to an EE.[126]

Translating the research on EEs to the clinical arena in humans has significantly positive implications in

neurorehabilitation. Individuals sustaining TBIs are known to have a high incidence of depression. EE intervention plays a key role in rehabilitative motivation for the individuals.

Conclusive Remarks

Although there is lack of effective treatment for TBI recovery today, the efforts for developing therapeutic strategies on TBI recovery have been continuously made over the past several decades. Standard medical and surgical interventions always play a significant role in the acute management for TBI patients. Given increased population of TBI survivors due to the advent of better acute management guidelines in the acute phase of TBI, the number of TBI survivors with various disabilities has risen. This calls for major research of TBI to be shifted into the area of neurorestoration and neurorehabilitation.

Authors' Note

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References

1. Centers for Disease Control and Prevention. Injury prevention & control: traumatic brain injury & concussion [accessed 2016 Jan 22]. http://www.cdc.gov/traumaticbraininjury/data/rates.html.
2. Levin HS, Shum D, Chan RC. Understanding traumatic brain injury: current research and future directions. New York (NY): Oxford University Press; 2014.
3. Rutland-Brown W, Langlois JA, Thomas KE, Xi YL. Incidence of traumatic brain injury in the United States, 2003. J Head Trauma Rehabil. 2006;21(6):544.
4. Smith M. Monitoring intracranial pressure in traumatic brain injury. Anesth Analga. 2008;106(1):240–248.
5. Greenberg MS, Arredondo N. Handbook of neurosurgery. 6th ed. New York (NY): Thieme Medical Publishers; 2006.
6. Kelly JP, Rosenberg JH. Diagnosis and management of concussion in sports. Neurology. 1997;48(3):575–580.
7. Povlishock JT, Katz DI. Update of neuropathology and neurological recovery after traumatic brain injury. J Head Trauma Rehabil. 2005;20(1):76–94.
8. Bey T, Ostick B. Second impact syndrome. West J Emerg Med. 2009;10(1):6–10.
9. McKee AC, Cantu RC, Nowinski CJ, Hedley-Whyte ET, Gavett BE, Budson AE, Santini VE, Lee H-S, Kubilus CA, Stern RA. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. J Neuropath Exp Neurol. 2009;68(7):709–735.
10. Maxwell WL, Domleo A, McColl G, Jafari SS, Graham DI. Post-acute alterations in the axonal cytoskeleton after traumatic axonal injury. J Neurotrauma. 2003;20(2):151–168.
11. Bullock MR, Chesnut R, Ghajar J, Gordon D, Hartl R, Newell DW, Servadei F, Walters BC, Wilberger JE. Surgical management of acute epidural hematomas. Neurosurgery. 2006;58(3):S2–S7.
12. Bešenski N. Traumatic injuries: imaging of head injuries. Eur Radiol. 2002;12(6):1237–1252.
13. Lee JJ, Segar DJ, Asaad WF. Comprehensive assessment of isolated traumatic subarachnoid hemorrhage. J Neurotrauma. 2014;31(7):595–609.
14. Gennarelli TA, Thibault LE, Adams JH, Graham DI, Thompson CJ, Marcincin RP. Diffuse axonal injury and traumatic coma in the primate. Ann Neurol. 1982;12(6):564–574.
15. Medscape: diffuse axonal injury imaging. New York (NY): Medscape; 2016 [accessed 2016 Sep 23]. http://emedicine.medscape.com/article/339912-overview.
16. Sternbach GL. The Glasgow coma scale. J Emerg Med. 2000;19(1):67–71.
17. Feldman Z, Kanter MJ, Robertson CS, Contant CF, Hayes C, Sheinberg MA, Villareal CA, Narayan RK, Grossman RG. Effect of head elevation on intracranial pressure, cerebral perfusion pressure, and cerebral blood flow in head-injured patients. J Neurosurg. 1992;76(2):207–211.
18. Grubb RL, Jr, Raichle ME, Eichling JO, Ter-Pogossian MM. The effects of changes in PaCO2 cerebral blood volume, blood flow, and vascular mean transit time. Stroke. 1974;5(5):630–639.
19. Darby JM, Yonas H, Marion DW, Latchaw RE. Local "inverse steal" induced by hyperventilation in head injury. Neurosurgery. 1988;23(1):84–88.
20. Torbic H, Forni AA, Anger KE, Degrado JR, Greenwood BC. Use of antiepileptics for seizure prophylaxis after traumatic brain injury. Am J Health Syst Pharm. 2013;70(9):759–766.
21. Burke AM, Quest DO, Chien S, Cerri C. The effects of mannitol on blood viscosity. J Neurosurg. 1981;55(4):550–553.
22. Bayir H, Adelson PD, Wisniewski SR, Shore P, Lai Y, Brown D, Janesko-Feldman KL, Kagan VE, Kochanek PM. Therapeutic hypothermia preserves antioxidant defenses after severe traumatic brain injury in infants and children. Crit Care Med. 2009;37(2):689.
23. Sandestig A, Romner B, Grände P-O. Therapeutic hypothermia in children and adults with severe traumatic brain injury. Ther Hypothermia Temp Manag. 2014;4(1):10–20.
24. Bullock M, Povlishock J. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, AANS/CNS Joint Section on Neurotrauma and

Critical Care. Guidelines for the management of severe traumatic brain injury. J Neurotrauma. 2007;24(Suppl 1):S1–S106.
25. Keddie S, Rohman L. Reviewing the reliability, effectiveness and applications of Licox in traumatic brain injury. Nurs Crit Care. 2012;17(4):204–212.
26. Srinivasan VM, O'Neill BR, Jho D, Whiting DM, Oh MY. The history of external ventricular drainage. J Neurosurg. 2014; 120(1):228–236.
27. Chambers IR, Kane PJ, Choksey MS, Mendelow AD. An evaluation of the Camino ventricular bolt system in clinical practice. Neurosurgery. 1993;33(5):866–868.
28. Bullock MR, Chesnut R, Ghajar J, Gordon D, Hartl R, Newell DW, Servadei F, Walters BC, Wilberger JE. Surgical management of acute subdural hematomas. Neurosurgery. 2006;58(3 Suppl):S16–S24; discussion Si–Siv.
29. Tanaka Y, Ohno K. Chronic subdural hematoma-an up-to-date concept. J Med Dent Sci. 2013;60(2):55–61.
30. Walcott BP, Nahed BV, Sheth SA, Yanamadala V, Caracci JR, Asaad WF. Bilateral hemicraniectomy in non-penetrating traumatic brain injury. J Neurotrauma. 2012;29(10):1879–1885.
31. Xiong Y, Mahmood A, Chopp M. Animal models of traumatic brain injury. Nat Rev Neurosci. 2013;14(2):128–142.
32. Thompson HJ, Lifshitz J, Marklund N, Grady MS, Graham DI, Hovda DA, McIntosh TK. Lateral fluid percussion brain injury: a 15-year review and evaluation. J Neurotrauma. 2005;22(1):42–75.
33. Hall ED, Sullivan PG, Gibson TR, Pavel KM, Thompson BM, Scheff SW. Spatial and temporal characteristics of neurodegeneration after controlled cortical impact in mice: more than a focal brain injury. J Neurotrauma. 2005;22(2):252–265.
34. Goldstein LE, Fisher AM, Tagge CA, Zhang X-L, Velisek L, Sullivan JA, Upreti C, Kracht JM, Ericsson M, Wojnarowicz MW. Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. Sci Transl Med. 2012;4(134):134ra60.
35. Xiong Y, Mahmood A, Meng Y, Zhang Y, Zhang ZG, Morris DC, Chopp M. Neuroprotective and neurorestorative effects of thymosin β4 treatment following experimental traumatic brain injury. Ann NY Acad Sci. 2012;1270(1):51–58.
36. Hagg T. Molecular regulation of adult CNS neurogenesis: an integrated view. Trends Neurosci. 2005;28(11):589–595.
37. Marklund N, Hillered L. Animal modelling of traumatic brain injury in preclinical drug development: where do we go from here? Br J Pharmacol. 2011;164(4):1207–1229.
38. Kostron H, Twerdy K, Stampfl G, Mohsenipour I, Fischer J, Grunert V. Treatment of the traumatic cerebral vasospasm with the calciumchannel blocker nimodipine: a preliminary report. Neurol Res. 1984;6(1–2):29–32.
39. Langham J, Goldfrad C, Teasdale G, Shaw D, Rowan K. Calcium channel blockers for acute traumatic brain injury. Cochrane Database Syst Rev. 2003;(4):Cd000565.
40. Vergouwen MD, Vermeulen M, Roos YB. Effect of nimodipine on outcome in patients with traumatic subarachnoid haemorrhage: a systematic review. Lancet Neurol. 2006;5(12):1029–1032.
41. Xiong Y, Mahmood A, Chopp M. Emerging treatments for traumatic brain injury. Expert Opin Emerg Drugs. 2009; 14(1):67–84.
42. Sawyer E, Mauro LS, Ohlinger MJ. Amantadine enhancement of arousal and cognition after traumatic brain injury. Ann Pharmacother. 2008;42(2):247–252.
43. Jelkmann W. Erythropoietin: structure, control of production, and function. Physiol Rev. 1992;72(2):449–489.
44. Ott C, Martens H, Hassouna I, Oliveira B, Erck C, Zafeiriou MP, Peteri UK, Hesse D, Gerhart S, Altas B, et al. Widespread expression of erythropoietin receptor in brain and its induction by injury. Mol Med. 2015;21(1):803–815.
45. Hasselblatt M, Ehrenreich H, Siren AL. The brain erythropoietin system and its potential for therapeutic exploitation in brain disease. J Neurosurg Anesthesiol. 2006;18(2):132–138.
46. Brines ML, Ghezzi P, Keenan S, Agnello D, de Lanerolle NC, Cerami C, Itri LM, Cerami A. Erythropoietin crosses the blood-brain barrier to protect against experimental brain injury. Proc Natl Acad Sci USA. 2000;97(19):10526–10531.
47. Cerami A, Brines ML, Ghezzi P, Cerami CJ. Effects of epoetin alfa on the central nervous system. Semin Oncol. 2001;28(2 Suppl 8):66–70.
48. Bramlett HM, Dietrich WD, Dixon CE, Shear DA, Schmid KE, Mondello S, Wang KK, Hayes RL, Povlishock JT, Tortella FC, et al. Erythropoietin treatment in traumatic brain injury: operation brain trauma therapy. J Neurotrauma. 2016;33(6): 538–552.
49. Peng W, Xing Z, Yang J, Wang Y, Wang W, Huang W. The efficacy of erythropoietin in treating experimental traumatic brain injury: a systematic review of controlled trials in animal models. J Neurosurg. 2014;121(3):653–664.
50. Ponce LL, Navarro JC, Ahmed O, Robertson CS. Erythropoietin neuroprotection with traumatic brain injury. Pathophysiology. 2013;20(1):31–38.
51. Yu X, Shacka JJ, Eells JB, Suarez-Quian C, Przygodzki RM, Beleslin-Cokic B, Lin CS, Nikodem VM, Hempstead B, Flanders KC, et al. Erythropoietin receptor signalling is required for normal brain development. Development. 2002;129(2): 505–516.
52. Ghezzi P, Brines M. Erythropoietin as an antiapoptotic, tissue-protective cytokine. Cell Death Differ. 2004;11(Suppl 1): S37–S44.
53. Digicaylioglu M, Lipton SA. Erythropoietin-mediated neuroprotection involves cross-talk between Jak2 and NF-kappaB signalling cascades. Nature. 2001;412(6847):641–647.
54. Jia Y, Mo SJ, Feng QQ, Zhan ML, OuYang LS, Chen JC, Ma YX, Wu JJ, Lei WL. EPO-dependent activation of PI3K/Akt/FoxO3a signalling mediates neuroprotection in in vitro and in vivo models of Parkinson's disease. J Mol Neurosci. 2014; 53(1):117–124.
55. Sattler MB, Merkler D, Maier K, Stadelmann C, Ehrenreich H, Bahr M, Diem R. Neuroprotective effects and intracellular signaling pathways of erythropoietin in a rat model of multiple sclerosis. Cell Death Differ. 2004;11(Suppl 2): S181–S192.
56. Byts N, Samoylenko A, Fasshauer T, Ivanisevic M, Hennighausen L, Ehrenreich H, Siren AL. Essential role for Stat5 in the neurotrophic but not in the neuroprotective effect of erythropoietin. Cell Death Differ. 2008;15(4):783–792.

57. Nichol A, French C, Little L, Haddad S, Presneill J, Arabi Y, Bailey M, Cooper DJ, Duranteau J, Huet O, et al. Erythropoietin in traumatic brain injury (EPO-TBI): a double-blind randomised controlled trial. Lancet. 2015;386(10012):2499–2506.
58. Fay T. Observations on generalized refrigeration in cases of severe cerebral trauma. Res Publ Assoc Nerv Dis. 1945;4: 611–619.
59. Mullan S, Raimondi AJ, Suwanwela C. Effect of hypothermia upon cerebral injuries in dogs. Some observations made in cases of experimental injury at 28-30 centigrade. Arch Neurol. 1961;5(5):545–551.
60. Clifton GL, Jiang JY, Lyeth BG, Jenkins LW, Hamm RJ, Hayes RL. Marked protection by moderate hypothermia after experimental traumatic brain injury. J Cereb Blood Flow Metab. 1991;11(1):114–121.
61. Tisherman SA, Safar P, Radovsky A, Peitzman A, Marrone G, Kuboyama K, Weinrauch V. Profound hypothermia (less than 10 degrees C) compared with deep hypothermia (15 degrees C) improves neurologic outcome in dogs after two hours' circulatory arrest induced to enable resuscitative surgery. J Trauma. 1991;31(8):1051–1061; discussion 1061–1062.
62. Fujita M, Wei EP, Povlishock JT. Effects of hypothermia on cerebral autoregulatory vascular responses in two rodent models of traumatic brain injury. J Neurotrauma. 2012;29(7): 1491–1498.
63. Gu X, Wei ZZ, Espinera A, Lee JH, Ji X, Wei L, Dix TA, Yu SP. Pharmacologically induced hypothermia attenuates traumatic brain injury in neonatal rats. Exp Neurol. 2015;267: 135–142.
64. Lee JH, Wei L, Gu X, Wei Z, Dix TA, Yu SP. Therapeutic effects of pharmacologically induced hypothermia against traumatic brain injury in mice. J Neurotrauma. 2014;31(16): 1417–1430.
65. Dietrich WD. The importance of brain temperature in cerebral injury. J Neurotrauma. 1992;9(Suppl 2):S475–S485.
66. Dietrich WD, Bramlett HM. Therapeutic hypothermia and targeted temperature management in traumatic brain injury: clinical challenges for successful translation. Brain Res. 2016; 1640(Pt A):94–103.
67. Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. Lancet. 2008;371(9628):1955–1969.
68. Badjatia N. Hypothermia in neurocritical care. Neurosurg Clin N Am. 2013;24(3):457–467.
69. Yenari MA, Han HS. Neuroprotective mechanisms of hypothermia in brain ischaemia. Nat Rev Neurosci. 2012; 13(4):267–278.
70. Jin Y, Lin Y, Feng JF, Jia F, Gao GY, Jiang JY. Moderate hypothermia significantly decreases hippocampal cell death involving autophagy pathway after moderate traumatic brain injury. J Neurotrauma. 2015;32(14):1090–1100.
71. Tomura S, de Rivero Vaccari JP, Keane RW, Bramlett HM, Dietrich WD. Effects of therapeutic hypothermia on inflammasome signaling after traumatic brain injury. J Cereb Blood Flow Metab. 2012;32(10):1939–1947.
72. Suh SW, Frederickson CJ, Danscher G. Neurotoxic zinc translocation into hippocampal neurons is inhibited by hypothermia and is aggravated by hyperthermia after traumatic brain injury in rats. J Cereb Blood Flow Metab. 2006;26(2):161–169.
73. Darwazeh R, Yan Y. Mild hypothermia as a treatment for central nervous system injuries: positive or negative effects. Neural Regen Res. 2013;8(28):2677–2686.
74. Truettner JS, Suzuki T, Dietrich WD. The effect of therapeutic hypothermia on the expression of inflammatory response genes following moderate traumatic brain injury in the rat. Brain Res Mol Brain Res. 2005;138(2):124–134.
75. Erecinska M, Thoresen M, Silver IA. Effects of hypothermia on energy metabolism in mammalian central nervous system. J Cereb Blood Flow Metab. 2003;23(5):513–530.
76. Knight JR, Willis AE. Control of translation in the cold: implications for therapeutic hypothermia. Biochem Soc Trans. 2015;43(3):333–337.
77. Feng JF, Zhang KM, Jiang JY, Gao GY, Fu X, Liang YM. Effect of therapeutic mild hypothermia on the genomics of the hippocampus after moderate traumatic brain injury in rats. Neurosurgery. 2010;67(3):730–742.
78. Truettner JS, Alonso OF, Bramlett HM, Dietrich WD. Therapeutic hypothermia alters microRNA responses to traumatic brain injury in rats. J Cereb Blood Flow Metab. 2011;31(9): 1897–1907.
79. Bohman LE, Schuster JM. Decompressive craniectomy for management of traumatic brain injury: an update. Curr Neurol Neurosci Rep. 2013;13(11):392.
80. Plesnila N. Decompression craniectomy after traumatic brain injury: recent experimental results. Prog Brain Res. 2007;161: 393–400.
81. Kunze E, Meixensberger J, Janka M, Sorensen N, Roosen K. Decompressive craniectomy in patients with uncontrollable intracranial hypertension. Acta Neurochir Suppl. 1998;71: 16–18.
82. Zweckberger K, Eros C, Zimmermann R, Kim SW, Engel D, Plesnila N. Effect of early and delayed decompressive craniectomy on secondary brain damage after controlled cortical impact in mice. J Neurotrauma. 2006;23(7):1083–1093.
83. Tomura S, Nawashiro H, Otani N, Uozumi Y, Toyooka T, Ohsumi A, Shima K. Effect of decompressive craniectomy on aquaporin-4 expression after lateral fluid percussion injury in rats. J Neurotrauma. 2011;28(2):237–243.
84. Szczygielski J, Mautes AE, Muller A, Sippl C, Glameanu C, Schwerdtfeger K, Steudel WI, Oertel J. Decompressive craniectomy increases brain lesion volume and exacerbates functional impairment in closed head injury in mice. J Neurotrauma. 2016;33(1):122–131.
85. Richardson RM, Singh A, Sun D, Fillmore HL, Dietrich III DW, Bullock MR. Stem cell biology in traumatic brain injury: effects of injury and strategies for repair: a review. J Neurosurg. 2010;112(5):1125–1138.
86. Zhang Y, Zhang ZG, Chopp M, Meng Y, Zhang L, Mahmood A, Xiong Y. Treatment of traumatic brain injury in rats with N-acetyl-seryl-aspartyl-lysyl-proline. J Neurosurg. 2017; 126(3):782–795.

87. Kleindienst A, McGinn MJ, Harvey HB, Colello RJ, Hamm RJ, Bullock MR. Enhanced hippocampal neurogenesis by intraventricular S100B infusion is associated with improved cognitive recovery after traumatic brain injury. J Neurotrauma. 2005;22(6):645–655.
88. Chen J, Chopp M. Neurorestorative treatment of stroke: cell and pharmacological approaches. NeuroRx. 2006;3(4): 466–473.
89. Qiu XC, Jin H, Zhang RY, Ding Y, Zeng X, Lai BQ, Ling EA, Wu JL, Zeng YS. Donor mesenchymal stem cell-derived neural-like cells transdifferentiate into myelin-forming cells and promote axon regeneration in rat spinal cord transection. Stem Cell Res Ther. 2015;6:105.
90. Zeng X, Qiu XC, Ma YH, Duan JJ, Chen YF, Gu HY, Wang JM, Ling EA, Wu JL, Wu W, et al. Integration of donor mesenchymal stem cell-derived neuron-like cells into host neural network after rat spinal cord transection. Biomaterials. 2015;53:184–201.
91. Al-Zoubi A, Jafar E, Jamous M, Al-Twal F, Al-Bakheet S, Zalloum M, Khalifeh F, Radi SA, El-Khateeb M, Al-Zoubi Z. Transplantation of purified autologous leukapheresis-derived CD34+ and CD133+ stem cells for patients with chronic spinal cord injuries: long-term evaluation of safety and efficacy. Cell Transplant. 2014;23(Suppl 1):S25–S34.
92. Taguchi A, Sakai C, Soma T, Kasahara Y, Stern DM, Kajimoto K, Ihara M, Daimon T, Yamahara K, Doi K, et al. Intravenous autologous bone marrow mononuclear cell transplantation for stroke: phase1/2a clinical trial in a homogeneous group of stroke patients. Stem Cells Dev. 2015;24(19):2207–2218.
93. Wang Y, Zhao Z, Rege SV, Wang M, Si G, Zhou Y, Wang S, Griffin JH, Goldman SA, Zlokovic BV. 3K3A-activated protein C stimulates postischemic neuronal repair by human neural stem cells in mice. Nat Med. 2016;22(9):1050–1055.
94. Haus DL, Lopez-Velazquez L, Gold EM, Cunningham KM, Perez H, Anderson AJ, Cummings BJ. Transplantation of human neural stem cells restores cognition in an immunodeficient rodent model of traumatic brain injury. Exp Neurol. 2016; 281:1–16.
95. Luan Z, Qu S, Du K, Liu W, Yang Y, Wang Z, Cui Y, Du Q. Neural stem/progenitor cell transplantation for cortical visual impairment in neonatal brain injured patients. Cell Transplant. 2013;22(Suppl 1):S101–S112.
96. Gennai S, Monsel A, Hao Q, Liu J, Gudapati V, Barbier EL, Lee JW. Cell-based therapy for traumatic brain injury. Br J Anaesth. 2015;115(2):203–212.
97. Duan H, Li X, Wang C, Hao P, Song W, Li M, Zhao W, Gao Y, Yang Z. Functional hyaluronate collagen scaffolds induce NSCs differentiation into functional neurons in repairing the traumatic brain injury. Acta Biomater. 2016;45:182–195.
98. Liu SJ, Zou Y, Belegu V, Lv LY, Lin N, Wang TY, McDonald JW, Zhou X, Xia QJ, Wang TH. Co-grafting of neural stem cells with olfactory en sheathing cells promotes neuronal restoration in traumatic brain injury with an anti-inflammatory mechanism. J Neuroinflammation. 2014;11:66.
99. Hu W, Liu J, Jiang J, Yang F. Effect of bone marrow mesenchymal stem cells on angiogenesis in rats after brain injury. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2016;41(5): 489–495.
100. Tian C, Wang X, Wang X, Wang L, Wang X, Wu S, Wan Z. Autologous bone marrow mesenchymal stem cell therapy in the subacute stage of traumatic brain injury by lumbar puncture. Exp Clin Transplant. 2013;11(2):176–181.
101. Wang S, Cheng H, Dai G, Wang X, Hua R, Liu X, Wang P, Chen G, Yue W, An Y. Umbilical cord mesenchymal stem cell transplantation significantly improves neurological function in patients with sequelae of traumatic brain injury. Brain Res. 2013;1532:76–84.
102. Mastro-Martinez I, Perez-Suarez E, Melen G, Gonzalez-Murillo A, Casco F, Lozano-Carbonero N, Gutierrez-Fernandez M, Diez-Tejedor E, Casado-Flores J, Ramirez-Orellana M, et al. Effects of local administration of allogenic adipose tissue-derived mesenchymal stem cells on functional recovery in experimental traumatic brain injury. Brain Inj. 2015; 29(12):1497–1510.
103. Qu C, Xiong Y, Mahmood A, Kaplan DL, Goussev A, Ning R, Chopp M. Treatment of traumatic brain injury in mice with bone marrow stromal cell-impregnated collagen scaffolds. J Neurosurg. 2009;111(4):658.
104. Gritti A, Bonfanti L, Doetsch F, Caille I, Alvarez-Buylla A, Lim DA, Galli R, Verdugo JM, Herrera DG, Vescovi AL. Multipotent neural stem cells reside into the rostral extension and olfactory bulb of adult rodents. J Neurosci. 2002;22(2): 437–445.
105. Patel K, Sun D. Strategies targeting endogenous neurogenic cell response to improve recovery following traumatic brain injury. Brain Res. 2016;1640(Pt A):104–113.
106. Jiang S, Chen W, Zhang Y, Zhang Y, Chen A, Dai Q, Lin S, Lin H. Acupuncture induces the proliferation and differentiation of endogenous neural stem cells in rats with traumatic brain injury. Evid Based Complement Alternat Med. 2016; 2016:2047412.
107. Chang EH, Adorjan I, Mundim MV, Sun B, Dizon ML, Szele FG. Traumatic brain injury activation of the adult subventricular zone neurogenic niche. Front Neurosci. 2016;10:332.
108. Dixon KJ, Theus MH, Nelersa CM, Mier J, Travieso LG, Yu TS, Kernie SG, Liebl DJ. Endogenous neural stem/progenitor cells stabilize the cortical microenvironment after traumatic brain injury. J Neurotrauma. 2015;32(11):753–764.
109. Blaya MO, Tsoulfas P, Bramlett HM, Dietrich WD. Neural progenitor cell transplantation promotes neuroprotection, enhances hippocampal neurogenesis, and improves cognitive outcomes after traumatic brain injury. Exp Neurol. 2015;264:67–81.
110. Ma H, Yu B, Kong L, Zhang Y, Shi Y. Neural stem cells overexpressing brain-derived neurotrophic factor (BDNF) stimulate synaptic protein expression and promote functional recovery following transplantation in rat model of traumatic brain injury. Neurochem Res. 2012;37(1):69–83.
111. Harting MT, Sloan LE, Jimenez F, Baumgartner J, Cox CS. Subacute neural stem cell therapy for traumatic brain injury. J Surg Res. 2009;153(2):188–194.
112. Zhang C, Saatman KE, Royo NC, Soltesz KM, Millard M, Schouten JW, Motta M, Hoover RC, McMillan A, Watson DJ.

Delayed transplantation of human neurons following brain injury in rats: a long-term graft survival and behavior study. J Neurotrauma. 2005;22(12):1456–1474.
113. Shear DA, Tate CC, Tate MC, Archer DR, LaPlaca MC, Stein DG, Dunbar GL. Stem cell survival and functional outcome after traumatic brain injury is dependent on transplant timing and location. Restor Neurol Neurosci. 2011; 29(4):215–225.
114. Kobeissy FH. Brain neurotrauma: molecular, neuropsychological, and rehabilitation aspects. 1st ed. Boca Raton (FL): CRC Press/Taylor & Francis; 2015.
115. Wallenquist U, Brannvall K, Clausen F, Lewen A, Hillered L, Forsberg-Nilsson K. Grafted neural progenitors migrate and form neurons after experimental traumatic brain injury. Restor Neurol Neurosci. 2009;27(4):323–334.
116. Kokaia Z, Martino G, Schwartz M, Lindvall O. Cross-talk between neural stem cells and immune cells: the key to better brain repair? Nat Neurosci. 2012;15(8):1078–1087.
117. Gao J, Grill RJ, Dunn TJ, Bedi S, Labastida JA, Hetz RA, Xue H, Thonhoff JR, DeWitt DS, Prough DS, et al. Human neural stem cell transplantation-mediated alteration of microglial/macrophage phenotypes after traumatic brain injury. Cell Transplant. 2016;25(10):1863–1877.
118. Shin JC, Kim KN, Yoo J, Kim IS, Yun S, Lee H, Jung K, Hwang K, Kim M, Lee IS, et al. Clinical trial of human fetal brain-derived neural stem/progenitor cell transplantation in patients with traumatic cervical spinal cord injury. Neural Plast. 2015;2015:630932. doiI:10.1155/2015/630932.
119. Molcanyi M, Riess P, Bentz K, Maegele M, Hescheler J, Schafke B, Trapp T, Neugebauer E, Klug N, Schafer U. Trauma-associated inflammatory response impairs embryonic stem cell survival and integration after implantation into injured rat brain. J Neurotrauma. 2007;24(4): 625–637.
120. Riess P, Molcanyi M, Bentz K, Maegele M, Simanski C, Carlitscheck C, Schneider A, Hescheler J, Bouillon B, Schafer U, et al. Embryonic stem cell transplantation after experimental traumatic brain injury dramatically improves neurological outcome, but may cause tumors. J Neurotrauma. 2007;24(1):216–225.
121. Sozda CN, Hoffman AN, Olsen AS, Cheng JP, Zafonte RD, Kline AE. Empirical comparison of typical and atypical environmental enrichment paradigms on functional and histological outcome after experimental traumatic brain injury. J Neurotrauma. 2010;27(6):1047–1057.
122. Berrocal Y, Pearse DD, Singh A, Andrade CM, McBroom JS, Puentes R, Eaton MJ. Social and environmental enrichment improves sensory and motor recovery after severe contusive spinal cord injury in the rat. J Neurotrauma. 2007;24(11): 1761–1772.
123. Briones TL, Rogozinska M, Woods J. Environmental experience modulates ischemia-induced amyloidogenesis and enhances functional recovery. J Neurotrauma. 2009;26(4):613–625.
124. Buchhold B, Mogoanta L, Suofu Y, Hamm A, Walker L, Kessler C, Popa-Wagner A. Environmental enrichment improves functional and neuropathological indices following stroke in young and aged rats. Restor Neurol Neurosci. 2007; 25(5, 6):467–484.
125. Dahlqvist P, Rönnbäck A, Bergström SA, Söderström I, Olsson T. Environmental enrichment reverses learning impairment in the Morris water maze after focal cerebral ischemia in rats. Eur J Neurosci. 2004;19(8):2288–2298.
126. Fischer FR, Peduzzi JD. Functional recovery in rats with chronic spinal cord injuries after exposure to an enriched environment. J Spinal Cord Med. 2007;30(2):147.
127. Hamm RJ, Temple MD, O'dell DM, Pike BR, Lyeth BG. Exposure to environmental complexity promotes recovery of cognitive function after traumatic brain injury. J Neurotrauma. 1996;13(1):41–47.
128. Hicks R, Zhang L, Atkinson A, Stevenon M, Veneracion M, Seroogy K. Environmental enrichment attenuates cognitive deficits, but does not alter neurotrophin gene expression in the hippocampus following lateral fluid percussion brain injury. Neuroscience. 2002;112(3):631–637.
129. Johansson BB, Ohlsson A-L. Environment, social interaction, and physical activity as determinants of functional outcome after cerebral infarction in the rat. Exp Neurol. 1996;139(2): 322–327.
130. Kline AE, Wagner AK, Westergom BP, Malena RR, Zafonte RD, Olsen AS, Sozda CN, Luthra P, Panda M, Cheng JP. Acute treatment with the 5-HT 1A receptor agonist 8-OH-DPAT and chronic environmental enrichment confer neurobehavioral benefit after experimental brain trauma. Behav Brain Res. 2007;177(2):186–194.
131. Passineau MJ, Green EJ, Dietrich WD. Therapeutic effects of environmental enrichment on cognitive function and tissue integrity following severe traumatic brain injury in rats. Exp Neurol. 2001;168(2):373–384.
132. Dunkerson J, Moritz KE, Young J, Pionk T, Fink K, Rossignol J, Dunbar G, Smith JS. Combining enriched environment and induced pluripotent stem cell therapy results in improved cognitive and motor function following traumatic brain injury. Restor Neurol Neurosci. 2014;32(5):675–687.
133. Nudi ET, Jacqmain J, Dubbs K, Geeck K, Salois G, Searles MA, Smith JS. Combining enriched environment, progesterone, and embryonic neural stem cell therapy improves recovery after brain injury. J Neurotrauma. 2015;32(14):1117–1129.
134. Pereira LO, Arteni NS, Petersen RC, da Rocha AP, Achaval M, Netto CA. Effects of daily environmental enrichment on memory deficits and brain injury following neonatal hypoxia-ischemia in the rat. Neurobiol Learn Mem. 2007;87(1):101–108.
135. Hendriksen H, Meulendijks D, Douma TN, Bink DI, Breuer ME, Westphal KG, Olivier B, Oosting RS. Environmental enrichment has antidepressant-like action without improving learning and memory deficits in olfactory bulbectomized rats. Neuropharmacology. 2012;62(1):270–277.
136. Döbrössy MD, Dunnett SB. Environmental enrichment affects striatal graft morphology and functional recovery. European J Neurosci. 2004;19(1):159–168.
137. Johnson EM. Environmental enrichment protects against functional deficits caused by traumatic brain injury. Front Behav Neurosci. 2013;7:44.