WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 10, 269-278. Review Article ISSN 2277– 7105

RECENT ADVANCEMENTS IN THE TREATMENT OF TRAUMATIC BRAIN INJURY

Kolekar Utkarsha U.[1]*, Kasar Poonam S.[2], Chaudhari Pooja S.[3] and Kanse Apeksha S.[4]

[1,3,4]Samarth Institute of Pharmacy, Belhe, Pune Maharashtra, India.

[2]Department of Quality Assurance,

Samarth Institute of Pharmacy, Belhe, Pune Maharashtra, India.

Article Received on
25 May 2022,

Revised on 15 June 2022,
Accepted on 05 July 2022

DOI: 10.20959/wjpr202210-24838

***Corresponding Author**
Kolekar Utkarsha U.
Samarth Institute of Pharmacy, Belhe, Pune Maharashtra, India.

ABSTRACT

Traumatic brain injury (TBI) presents in several forms ranging from mild alterations of consciousness to not in determination 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 the context of the situation and cannot be used in every individual circumstance.

KEYWORDS: Intracranial hypertension; management; Traumatic brain injury; Treatment strategies, Recent advances in TBI.

INTRODUCTION

Traumatic brain injury is defined as damage to the brain resulting from the external mechanical force, such as rapid acceleration or deceleration impact, blast waves, or penetration by a projectile, leading to temporary or permanent impairment of brain function.

Traumatic brain injury (TBI) has a dramatic impact on the health of the nation: it accounts for 15–20% of deaths in people aged 5–35 yr. old and is responsible for 1% of all adult deaths. TBI is a major cause of death and disability worldwide, especially in children and young adults. Males sustain traumatic brain injuries more frequently than do females. This has a

severe financial, emotional, and social impact on survivors left with lifelong disabilities and on their families. It is well established that the major determinant of outcome from TBI is the severity of the primary injury, which is irreversible. However, secondary injury, primarily cerebral, occurring in the post-injury phase, may be due to intracranial hypertension, systemic hypotension, hypoxia, hyperpyrexia, hypocapnia, and hypoglycemia, all of which have been shown to independently worsen survival after TBI. Traumatic brain injuries (TBI) are a steadily increasing and major cause of morbidity, mortality, and loss of migration, altering traditional methods of living and working.

Mechanism of injury

The type, direction, intensity, and duration of forces all contribute to the characteristics and severity of TBI. Forces that may contribute to TBI include angular, rotational, shear, and translational forces.

Even in the absence of an impact, significant acceleration or deceleration of the head can cause TBI; however, in most cases, a combination of impact and acceleration is probably to blame. Forces involving the head striking or being struck by something, termed contact or impact loading, are the cause of most focal injuries, and movement of the brain within the skull, termed noncontact or inertial loading, usually causes diffuse injuries.

Explosive Blasts and Other combat injuries

Explosive blasts are a common cause of traumatic brain injury in active-duty military personnel. Although how the damage occurs isn't yet well understood, many researchers believe that the pressure wave passing through the brain significantly disrupts brain function.

Traumatic brain injury also results from penetrating wounds, severe blows to the head with shrapnel or debris, and falls or bodily collisions with objects following a blast.

Classification of traumatic brain injury

There are various classification determinants utilized to classify traumatic brain injury. The clinical presentation and prognosis depend on the individual nature of the injury with often coexisting types of traumatic brain injury. The classification is important for acute management, treatment, and prognosis as well as neurorehabilitation requirements.

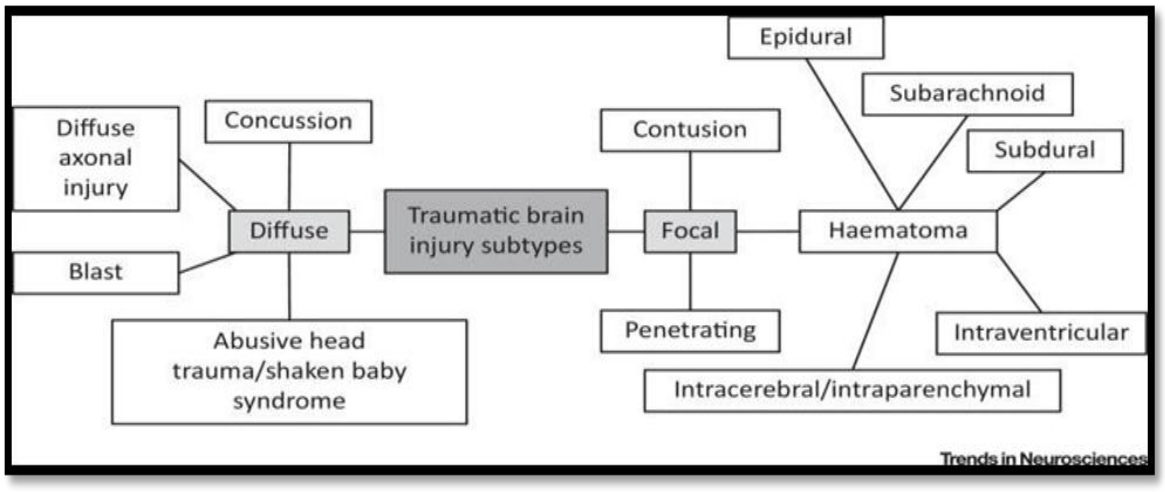


Fig. no. 1: Traumatic brain injury subtypes.

Primary v secondary injuries

Dependent on the timing and impact nature, i.e., mechanical or non-mechanical, and accompanying pathophysiological processes.

Primary and Secondary

Primary Injury:

- Occurs at the time of injury and is decreased by mechanical forces. Two main mechanisms that cause primary injury are:
- Contact i.e., an object striking the head or the brain striking the inside of the skull
- Acceleration – Deceleration
- the Primary injury because of acceleration-deceleration results from unrestricted movement of the head and leads to shear, tensile, and compressive strains. These forces can cause intracranial hematoma, diffuse vascular injury, and injury to cranial nerves and the pituitary stalk.

Secondary Injury:

- A secondary injury is not mechanically increased. It may be delayed from the moment of impact, and it may superimpose injury on a brain already affected by a mechanical injury.
- The secondary damage is caused by care, ,a cade of processes impacting "cerebral blood flow (hyper or hypoperfusion), impaired cerebrovascular autoregulation, cerebral metabolic dysfunction and impaired cerebral oxygenation."

Focal v diffuse injuries

Focal Injury	Diffuse Injury
Usually due to contact and causing scalp injury, it might present as skull fracture, contusions and/or intracranial hemorrhage. Those injuries are detectable by CT, MRI or PET scans.	Usually due to acceleration/deceleration injury and concussion resulting in diffuse axonal injury (DAI) and brain swelling.
This mechanism is related to the moving of intracranial content in the skull and impinging on in the internal surface of the skull. Commonly observed injury is coup-contrecoup injury presenting with a contusion on opposite sides of the brain.	A diffuse axonal injury might be accompanied by some focal lesions, but again only diagnosable microscopically. The tearing of the nerve tissue disrupts the brain's regular communication metabolic processes.

Opened v closed injuries

Table no. 1: Open and Closed injuries.

Open/Penetrating Injury	Closed/Non-Penetrating Injury
Open/ Penetrating Injury occurs from the effect of a bullet, knife, or another sharp object that forces hair, skin, bone ,and fragments from the object into the brain and the dura mater is breached.	A closed injury is an injury to the brain caused by an outside force without any penetration of the skull. The more serious complication is that brain edema within constrained space of the skull and resultant induces the intracranial pressure and compression of brain structures and cranial nerves.

Risk factors

Traumatic brain injury common risk factors

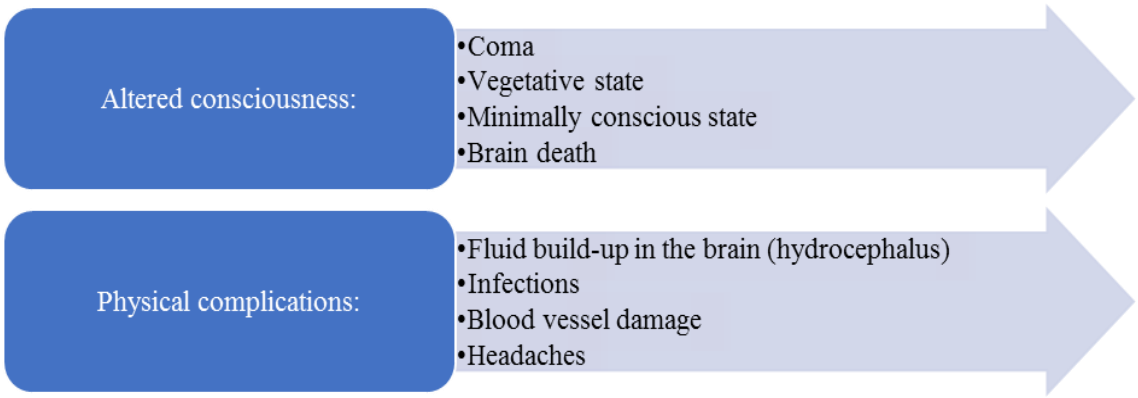
Your brain is well protected within your skull. For example, fluid surrounds your brain that cushions it from ever making contact with the hard inside of the skull. After all, a jarring blow to your body or head can cause your brain to move around, which rise the chance of a traumatic contact between skull and brain. Even if anyone can suffer a brain injury, there are certain risk factors of which you should be aware.

Table no. 2: Risk factor.

1	Newborns	Delivery head injury Intracranial hemorrhages Cephalic hematoma Subgaleal hematoma	Caused by head compression and traction through the birth canal (vaginal delivery) with obstetric instruments. A low birth mass and hypoxemia are risk factors for intracranial hemorrhage.
2	Infants	Accidental head injury Abusive Head Trauma	Caused by inappropriate childcare practices. If the mechanism of injury is not clear, careful consideration for the diagnosis of child abuse is required. AHT is the frequent cause of TBI-related hospitalization and death.
3	Toddlers and School children	Accidental head injury	Causes of accidents increase as children develop motor ability. With an increase in the use of child safety seats, the severity of the injury and the deaths has dropped. The pedestrian injury also rises in this age group.
4	Adolescents	Bicycle and motorcycle-related accidents Sports-related head injuries	Awareness of prevention must be raised. Trainers and players those convoluted in contact sports (i.e., judo, rugby, American football) will require education about concussions.

Complications

Moderate to severe traumatic brain injury can result in prolonged, or permanent changes in a person's state of consciousness, awareness or responsiveness. Different states of consciousness include:



Recent advances in traumatic brain injury

1. Refining neurocritical Care and Monitoring

The concept of primary and secondary injuries arose more than 25 years ago from an appreciation that alongside the initial insult at the time of trauma, additional insults such as hypotension and hypoxia could supervene and exacerbate brain injury. This simple concept has shaped TBI management in two ways: first, pre-hospital care protocols that ensure airway protection, systemic oxygenation, and adequate systemic perfusion, and, second the use of monitoring and goal-directed therapy of neuronal physiology in the neurosciences critical care unit.

2. Brain multi-modality monitoring

Brain multi-modality monitoring (MMM) is the use of multiple overlapping monitors to allow early disclosure of physiological derangements and provide personalized targets for NCCU interventions. Real-time data acquisition software functioning as ICM+, CNS Monitor, and Bed master Ex allows both visualization and analysis of these parameters at the bedside. The explanation of pathological targets for these monitors and determining the optimal method of correcting the physiological parameters have derived the advances in NCCU treatment of moderate and severe TBI. The two most widely used monitoring inquiries in addition to intracranial pressure monitors are brain tissue oxygenation and microdialysis monitors.

3. Cerebral micro dialysis (CMD)

Cerebral microdialysis is protruding monitor that allows sampling of the brain extracellular fluid for cerebral metabolites over a semi-permeable blind-ended intraparenchymal catheter. It is all off for direct measurement and trend profiling of various analytes of which the better essential are glucose, lactate, and pyruvate [allowing calculation of the lactate pyruvate ratio (LPR)] typically at hourly intervals. The Consensus Statement from the 2014 International Microdialysis Forum, which thoroughly reviewed the literature on CMD in TBI, recommends a tiered clinical approach to CMD analytes. This Consensus Statement identified LP ratio > 25 and low brain glucose < 0.8 mmol/L as pathological thresholds associated with unfavorable outcomes and necessitating intervention.

While these are parameters well recognized as an independent predictors of outcome over and above clinical parameters and ICP, there is no clearly defined intervention to correct a deranged LP ratio. This reflects the complexity of the underlying pathophysiology such that raised LP ratio can arise from a diverse range of pathologies including classical ischemia, cortical spreading depression, mitochondrial dysfunction, microvascular collapse, and diffusion-limited hypoxia. Prospective protocols that address these issues sequentially are currently being assessed; however, no universally accepted treatment paradigm exists. Nonetheless, CMD has a key advantage over other monitoring tools as it directly determines the biochemical derangements that occur following TBI, at the cellular level, giving sensitive monitoring of metabolic dysfunction, even if there are various pathological routes to this derangement. Overall, there is still low-level evidence supporting the association of CMD analyte levels with functional, neurophysiological, and tissue outcomes as highlighted by a recent systematic review on the topic. Huge prospective studies with a multimodal approach are warranted to good profile normal and pathologic values of CMD analytes, and to evaluate associations with patient and tissue outcomes.

4. Intracranial pressure (ICP) monitoring

ICP is the most necessary goal-directed parameter in the clinical management of severe TBI. Increased intracranial pressure decreased cerebral perfusion (cerebral perfusion pressure = mean arterial pressure − ICP) risking ischemia and, when severe and sustained brain herniation. The Brain Trauma Foundation (BTF) has provided evidence-based guidelines (4th edition, 2016) that summarize the NCCU interventions available for controlling ICP in a staged fashion, with a goal-directed target of 20–25 mmHg. Despite the widespread use of

ICP monitoring and acceptance in the TBI community, a recent randomized control trial of ICP monitoring (BEST: TRIP, 2012) was unable to show any benefit. This trial has been extremely criticized in addition to two key lines: first, the trial was carried out in units that did not have previous experience of ICP monitoring (to allow ethical clinical equipment) before the trial. Second, both groups of patients had aggressive ICP *therapies* regardless. Therefore, the trial did not test the utility of ICP interventions but whether the so many figures from the monitor provided a benefit over 'blind' management in units with no practice of using the monitors.

5. Brain tissue oxygenation monitoring

The main benefit of brain tissue oxygen tension (PbtO2) monitoring PRIM is primarily building as a method for evading cerebral ischemia during therapeutic hyperventilation for the control of the ICP. The commonest method for monitoring PbtO2 is using an invasive probe using a modified Clark electrode, with a typical pathological threshold of 20 mmHg. In multivariate analysis of outcome, PbtO2 has continuously been shown to impact the outcome. This has led to prospective trials of PbtO2 targeted therapy in addition to standard ICP-driven care. A phase II trial (BOOST-II, Brain Tissue Oxygen Monitoring, and Management in Severe Traumatic Brain Injury) has demonstrated a significant reduction in hypoxia burden (74%) during hospitalization in the PbtO2-targeted treatment group with no substantial safety issues. Depending on the study group, directed interventions were used for ICP management (if > 20 mmHg for > 5 min), PbtO2 control (if < 20 mmHg for > 5 min) or both. The third phase of the randomized study (BOOST-III) will evaluate the clinical adequacy of "a treatment protocol based on PbtO2 monitoring compared to treatment fixed on ICP monitoring alone" and will enroll patients in the United States.

6. Biomarkers

Sustained efforts have in made to identify biomarkers of the injury that results from TBI to detect ongoing injury, to flake the need for monitoring and interventions, and to approve prognostic information. Several biological portions have been assessed including serum, cerebrospinal fluid, cerebral micro dialysate from brain extracellular fluid, and brain tissue. Biomarkers are currently not framed routinely outside of clinical research background Noteworthy biomarkers in TBI include glia-related biomarkers (GFAP, S100B), neuron/axon-related biomarkers (neuron-specific enolase [NSE], neurofilament light polypeptide [NFL], ubiquitin carboxy-terminal hydrolase [UCH-L1], tau, amyloid β, αII-

Sceptrin breakdown products among others) and other inflammation-related biomarkers (high mobility group box protein 1 [HMGB1], various cytokines and autoantibodies). To date, only S100B is part of a consensus guideline pathway (by the Scandinavian Neurotrauma Committee) for stratification of mild TBI patients at presentation for CT imaging. No guidelines regarding the use of biomarkers in severe TBI exist.

Protein biomarkers with a shorter serum half-life (*t*1/2), e.g., S100B (*t*1/2 ~ 24 h) are likely more useful than proteins with a longer serum half-life, e.g., NSE (*t*1/2 ~ 48–72 h). A longer half-life provides a longer post-injury window for the detection of secondary neurological insults in severe TBI.

CONCLUSION

Advances in critical care, imaging, and the reorganization of trauma systems have led to a pronounced reduction in deaths and disability resulting from traumatic brain injury. This improvement has resulted largely from early recognition and treatment of cerebral hypoperfusion.

Variability in trauma systems and critical care led to the development of scientific, evidence-based guidelines for management which serve as the basis for standardizing in hospital acute care. The next advance in prevention of secondary brain damage will arrive with improved prehospital recognition and treatment of traumatic brain injury.

ACKNOWLEDGMENT

We excess our thanks and gratitude to the Trustee of Samarth Rural Educational Institute and Samarth Institute of Pharmacy, Belhe for their valuable guidance and support.

REFERENCES

1. Timofeev I, Santarius T, Kolias AG, Hutchinson PJA. *Decompressive craniectomy—operative technique and perioperative care. Advances and technical standards in neurosurgery*. New York: Springer, 2012; 115–136. [PubMed] [Google Scholar]
2. Faul M, Wald MM, Xu L, Coronado VG (2010) Traumatic brain injury in the United States; emergency department visits, hospitalizations, and deaths, 2002–2006.
3. Patel HC, Bouamra O, Woodford M, King AT, Yates DW, Lecky FE. Trends in head injury outcome from 1989 to 2003 and the effect of neurosurgical care: an observational

study. *Lancet (London, England),* 2005; 366(9496): 1538–1544. [PubMed] [Google Scholar]

4. Chesnut RM, Marshall LF, Klauber MR, Blunt BA, Baldwin N, Eisenberg HM, et al. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma,* 1993; 34(2): 216–222. [PubMed] [Google Scholar]
5. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GWJ, Bell MJ, et al. Guidelines for the management of severe traumatic brain injury. *Neurosurgery,* 2017; 80(1): 6 15. [PubMed] [Google Scholar]
6. Chesnut RM, Temkin N, Carney N, Dikmen S, Rondina C, Videtta W, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med,* 2012; 367(26): 2471–2481. [PMC free article] [PubMed] [Google Scholar]
7. Smielewski P, Lavinio A, Timofeev I, Radolovich D, Perkes I, Pickard JD, et al. ICM+, a flexible platform for investigations of cerebrospinal dynamics in clinical practice. *Acta Neurochir Suppl,* 2008; 102: 145–151. [PubMed] [Google Scholar]
8. Moberg (2019) CNS Monitor 2019. https://www.moberg.com/products/cns-monitor. Accessed, 2019; 1.
9. Anandic Medical Systems (2019) Bed Master Ex, 2019. https://www.bedmaster.net/en/products/bedmasterex. Accessed 1 July2019
10. Okonkwo DO, Shutter LA, Moore C, Temkin NR, Puccio AM, Madden CJ, et al. Brain oxygen optimization in severe traumatic brain injury phase-II: a phase II randomized trial. *Crit Care Med,* 2017; 45(11): 1907–1914. [PMC free article] [PubMed] [Google Scholar]
11. Hill CS, Coleman MP, Menon DK. Traumatic Axonal Injury: Mechanisms and Translational Opportunities. Trends in Neuroscience, 2016; 39(5): 311-324. doi.org/10.1016/j.tins.2016.03.002
12. Hill CS, Coleman MP, Menon DK. Traumatic Axonal Injury: Mechanisms and Translational Opportunities. Trends in Neuroscience, 2016; 39, 5: 311-324. doi.org/10.1016/j.tins.2016.03.002
13. Jump up to:5.0 5.1 Silver JM, McAllister TW, Yodofsky SC, editors. Textbook of Traumatic Brain Injury. Arlington, Va: American Psychiatric Publishing, 2005; 27-39.
14. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. British Journal of Anaesthesia, 2007; 99(1): 4-9. DOI: 10.1093/bja/aem131

15. Hill CS, Coleman MP, Menon DK. Traumatic Axonal Injury: Mechanisms and Translational Opportunities. Trends in Neuroscience, 2016; 39(5): 311-324. doi.org/10.1016/j.tins.2016.03.002
16. Centola Grassi D, Macedo da Conceição D, da Costa Leite C, Santos Andrade C. Current contribution of diffusion tensor imaging in the evaluation of diffuse axonal injury. Arq. Neuro-Psiquiatr, 2018; 76(3): 189-199. doi.org/10.1590/0004-282x20180007