Brain Neurorehabil. 2022 Jul;15(2):e14
https://doi.org/10.12786/bn.2022.15.e14
pISSN 1976-8753·eISSN 2383-9910

Brain & NeuroRehabilitation

Review

Updates in Neurorehabilitation

Treatment and Rehabilitation for Traumatic Brain Injury: Current Update

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Received: Jun 15, 2022
Revised: Jul 20, 2022
Accepted: Jul 21, 2022
Published online: Jul 21, 2022

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HIGHLIGHTS

- Traumatic brain injury refers to the trauma caused to the brain by external forces.
- Earlier assessment of TBI symptoms leads to better prognosis and rehabilitation.

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Treatment and Rehabilitation for Traumatic Brain Injury: Current Update

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OPEN ACCESS

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Funding
This study was supported by a 2022 research grant from Pusan National University Yangsan Hospital.

Conflict of Interest
The authors have no potential conflicts of interest to disclose.

ABSTRACT

Traumatic brain injury (TBI) is an acquired injury to the brain caused by external mechanical forces, which can cause temporary or permanent disability. TBI and its potential long-term consequences are serious public health concerns. This review seeks to provide updated information on the current methods of management of patients with TBI to improve patient care.

Keywords: Traumatic Brain Injury; Rehabilitation; Treatment; Depression; Biomarker

INTRODUCTION

Traumatic brain injury (TBI) is defined as changes in brain function caused by an external force. It is an important cause of death or severe physical and mental dysfunction, leading to social and economic losses [1]. Approximately 69 million new TBI cases have been reported worldwide each year [2]. About 480,000 new cases of TBI occur annually in Korea, and the total medical cost of TBI has steadily increased over the past decade [3]. As the survival rate of patients with severe TBI increases owing to the development of medical technology for initial response and acute treatment, the need for long-term treatment and socioeconomic loss and deterioration in the quality of life of caregivers and families due to functional impairment are increasing. Therefore, it has become a social problem [4]. This has increased the need for appropriate acute to post-acute rehabilitation. This review article aims to discuss current trends regarding the treatment and rehabilitation of patients with TBI, especially focused on consciousness, mild TBI (mTBI), cognition, depression, post-traumatic headache, and biomarkers.

DISORDERS OF CONSCIOUSNESS (DOC)

DoC is a medical condition characterized by unconsciousness or reduced consciousness for at least four weeks after severe TBI [5]. With increase in the level of acute treatment and the survival rate of patients with severe TBI, the incidences of unresponsive wakefulness syndrome (UWS) and minimally conscious state (MCS) are increasing [6]. Therefore, DoC evaluation, management, and treatment are becoming increasingly important. However, treatments for DoC are limited, and DoC often become permanent.

In 2018, American Academy of Neurology and the American Congress of Rehabilitation Medicine presented 15 recommendations for patients with prolonged DoC (patients with a persistent DoC status of 28 days or longer) according to the practical guidelines [7]. Per the guideline, clinicians must use a structured and standardized assessment method for evaluating the accurate level of consciousness for diminished consciousness (Level B), and may use structural magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), and coma recovery scale-revised to assess prognosis (Level B). Specifically, in post-traumatic UWS, a disability rating scale scores < 26 (Level B), detectable P300 on event-related potentials (Level C), and reactive EEG at 2–3 months post-injury (Level C) suggest an increased likelihood of regaining consciousness within a year of the injury. Corona radiata injury, dorsolateral upper brainstem injury, or corpus callosal lesions observed on MRI 6–8 weeks after the injury are suggestive of a poor prognosis (Level B). For pharmacologic intervention, only amantadine is recommended as a treatment, and physiatrists should prescribe amantadine (100–200 mg BID) for adults with traumatic UWS or MCS (4–16 weeks post-injury) to accelerate functional recovery and reduce disability in the early stages of recovery (Level B).

Other known pharmacological treatments like zolpidem (non-benzodiazepine GABA agonist) [8-11], intrathecal baclofen (GABA agonist) [12,13], midazolam (benzodiazepine GABA agonist) [14], ziconotide (calcium channel blocker) [15], and other neurostimulants (bromocriptine, methylphenidate, etc.) [16] are mentioned in the review. Recently, a small number of additional studies have been conducted, but no evidence of new pharmacological effects has been reported.

Non-pharmacologic interventions for consciousness and arousal improvement include noninvasive brain stimulation (e.g., repeated transcranial magnetic stimulation [rTMS], transcranial direct current stimulation [tDCS], and low-intensity focused ultrasound pulse), invasive brain stimulation (e.g., deep brain stimulation [DBS]), and sensory stimulation programs. Among them, tDCS is the only stimulation method that has shown a clinical effect in patients in MCS [17]. tDCS applied to the dorsolateral prefrontal cortex (DLPFC) produced a clinical improvement in five randomized controlled trials (RCTs) (four class III, and one class II) in patients in MCS after TBI [18-22]. However, research has been highly heterogeneous in the protocols, and outcome measures. Accordingly, there is still insufficient evidence to identify the factors that may explain why some patients respond to the stimulation and others do not. In addition, most enrolled studies used a small sample size [23]. Studies involving large-scale RCTs that support the effectiveness of rTMS, DBS, and vagus nerve stimulation have not yet been reported.

A sensory stimulation program, familiar auditory stimulation training can facilitate recovery in patients with prolonged DoC [17]. In addition, head-up tilt and music therapy have been reported as sensory stimulation programs with insufficient evidence [24,25].

MTBI/POST-CONCUSSION SYNDROME

mTBI is the most prevalent form of TBI, also known as a concussion [26]. The World Health Organization Neurotrauma Task Force has defined mTBI as a head injury provoking an acute destruction of brain function, represented by a brief loss of consciousness (≤ 30 minutes), confusion, or post-traumatic amnesia (< 24 hours) [27]. It is known that mTBI

https://doi.org/10.12786/bn.2022.15.e14

is accompanied with physical, cognitive, or emotional symptoms, which often result in restricted physical/mental activity and can cause symptoms and disorders that last for more than a year. Therefore, the importance of management of mTBI is increasing [28].

Various clinical practice guidelines (CPGs) and expert consensus statements have been published for the management of mTBI [29-35]. Interdisciplinary professionals with common interests in brain injury (Brain Injury Interdisciplinary Special Interest Group Mild TBI Task Force of the American Congress of Rehabilitation Medicine) extracted evidence-based recommendations from the recent expert consensus statements and CPGs [36]. A narrative of the CPGs, expert consensus statements, and updated evidence is described in **Table 1**. The main symptoms after mTBI include cognitive dysfunction, anxiety, depression, and headache, which will be explained in detail in the next sections.

COGNITIVE IMPAIRMENT

The most debilitating and complex aspects of TBI are cognitive deficits that require management and treatment. The Cognitive Rehabilitation Task Force of the American Congress of Rehabilitation Medicine published an updated review of evidence-based cognitive rehabilitation related to TBI and stroke in 2019 [37]. **Table 2** summarizes the contents associated with TBI including the items corresponding to 'Practice Standards' with the highest level of evidence in the above study, which was published by adding updated contents to the systematic review of three previously published articles [38-40].

Table 1. The synthesis of management recommendations for concussion and mild TBI*

Management recommendations
- Prompt diagnostic evaluation is required.
- No clinical benefit of routine neuroimaging.
- The clinical utility of serum biomarkers is unclear.
- Rest for at least 1–3 days is recommended after injury.
- Guidance on gradual stepwise return to pre-injury activities must be provided.
- Patient/family early education should be provided.
- Requires validated symptom scales for initial evaluation and recovery follow-up.
- Requires follow-up of neuropsychological assessments to investigate persistent (> 30 days) cognitive symptoms.
- A referral to a specialist or higher-level treatment is required for patients with slow recovery (> 10–14 days for adult athletes, > 30 days for others).

TBI, traumatic brain injury.
*From Brain Injury Interdisciplinary Special Interest Group Mild TBI Task Force of the American Congress of Rehabilitation Medicine.

Table 2. Recommendations for cognitive rehabilitation for patients with TBI*

Cognitive domain	Intervention
Attention	Direct-attention training/Metacognitive strategy training - Increasing task performances - Accelerating activity of daily living functions
Memory	Memory strategy training - Improving prospective memory - Improving recall from performing daily tasks
Executive function	Metacognitive strategy training (self-monitoring and self-regulation) - Improving mild to moderate executive dysfunction and emotional self-dysregulation - Including protocols for goal management and problem-solving
Communication social cognition	Pragmatic conversational skills Recognition of emotions from facial expressions
Comprehensive-holistic neuropsychological rehabilitation	Comprehensive-holistic neuropsychological rehabilitation - Improving cognitive impairment and functional disability during post-acute rehabilitation

TBI, traumatic brain injury.
*From The Cognitive Rehabilitation Task Force of the American Congress of Rehabilitation Medicine.

https://doi.org/10.12786/bn.2022.15.e14

Methylphenidate is the best-known pharmacological intervention for cognitive impairment following TBI. Methylphenidate is known to help improve cognition through the blockade of the noradrenaline and dopamine transporters [41]. In 2019, Jenkins et al. [42] performed an RCT to measure the effect of the level of dopamine transporter using 123I-ioflupane SPECT on methylphenidate treatment in 40 patients with moderate-to-severe TBI. In patients with low caudate dopamine transporter binding on SPECT, there was a marked improvement in cognitive function after taking methylphenidate compared with the group with normal dopamine transporter binding. This result indicates that identifying patients with a hypodopaminergic state might help stratify the prescription of cognitive-enhancing therapy after TBI [42]. Amantadine, donepezil, and sertraline have also been reported to be effective for cognitive impairment after TBI, but additional large-scale RCT studies have not been reported to support this evidence [43,44].

Among non-pharmacologic interventions, the most recently studied are virtual reality (VR) and noninvasive brain stimulation, such as tDCS and rTMS. Manivannan et al. [45] reported a systematic review of 13 studies, including 4 RCTs that applied VR for cognitive improvement after TBI. According to the research results, VR intervention showed improvement in various cognitive domains such as attention, memory, and executive function in most studies. One study demonstrated post-intervention increase in blood oxygen level-dependent signal in several brain regions using functional MRI [46]. Two studies revealed the translation of improvements to the corresponding real-life tasks [47,48]. This results show a considerable evidence supporting the use of VR in cognitive rehabilitation of patients with TBI. However, several factors, such as standardized neuropsychological assessment tools and long-term follow-up, should be addressed in further studies.

Recently, the role of noninvasive brain stimulation for the cognitive rehabilitation in TBI has attracted significant interest. tDCS and rTMS are currently the most commonly used noninvasive brain stimulation methods in clinical applications [49]. According to the systematic review on noninvasive brain stimulation for cognitive impairment after TBI, some studies in which rTMS or tDCS was applied to the left DLPFC reported significant partial improvements in the cognitive domain compared to the control group [50]. The evidence for this is limited since the analysis involved only five studies (two studies of rTMS and three studies of tDCS), and it seems necessary to support the evidence with additional large-scale studies in the future.

DEPRESSION

Depression is a common psychological symptom after TBI [51]. The prevalence of depression after TBI ranges between 6% and 77% [52]. According to two recent nationwide longitudinal studies related to the risk of depression after TBI, the risk of depression post-TBI increased by 1.83 times in a study involving the US population (hazard ratio [HR], 1.83; 95% confidence interval [CI], 1.79–1.86) than in the matched controls without TBI [53], and it was found to increase by 1.19 times in a study based on data from the National Health Insurance Service in Korea (HR, 1.19; 95% CI, 1.18–1.20) than in the matched controls without TBI [54]. The male gender was identified as a common predictor of post-TBI depression in both the studies. In the US study, older adults were seen as a risk factor, but in the Korean study, younger adults were found to have a higher risk.

https://doi.org/10.12786/bn.2022.15.e14

In 2021, Cheng et al. [55] reported a network meta-analysis of the therapeutic benefits of pharmacologic and non-pharmacologic interventions for depressive symptoms after TBI. Ten RCTs analyzed the effects of pharmacological intervention, including seven treatment options (placebo/control, methylphenidate, sertraline, desipramine, melatonin, escitalopram, and atomoxetine), on depression in patients with TBI. Both pairwise and network meta-analyses indicated that only methylphenidate was more effective than placebo/control. There was a lack of superior efficacy of other antidepressants compared with placebo. It differs from the results of other meta-analyses reported earlier [56,57], suggesting that large-scale studies are needed to supplement this finding in the future.

Regarding non-pharmacologic interventions for depression after TBI, the Cochran review published in 2015 also mentioned psychological interventions (either cognitive behavior therapy [CBT] or mindfulness-based cognitive therapy) and rTMS [58]. However, none of these studies provided evidence for the treatment for depression after TBI.

Even in the meta-analysis of Cheng et al., [55] 17 RCTs that assessed the therapeutic effects of non-pharmacologic treatments against depressive symptoms in patients with TBI, including several treatment options: CBT, supportive psychotherapy, positive psychological CBT, mindfulness-based CBT, telephone supportive psychotherapy, motivational training plus CBT, enhanced supported employment, telephone CBT, social group training, psychotherapy with compensatory cognitive training, and etc. were included. However, none of the investigated non-pharmacologic interventions were more effective than the others.

In a recent meta-analysis, rTMS has a short-term effect on post-TBI depression, whereas the long-term efficacy of rTMS on post-TBI depression remained inconclusive [59]. In addition, there are meta-analysis reports which suggest that physical exercise and photobiomodulation using blue-wavelength light are effective for post-TBI depression, but further research is needed [60,61].

POST-TRAUMATIC HEADACHE

Post-traumatic headache (PTH) is the most common complaint following TBI, accounting for 30%–90% of total cases [62]. The clinical presentation of PTH is recurrent episodes of headache that can vary considerably in terms of frequency, duration, and pain intensity. Clinical features of PTH are often similar to those of primary headache disorders such as migraine and tension-type headaches [63]. In a review paper published by Ashina et al., [64] an algorithm for the pharmacologic treatment of PTH attributed to TBI was proposed (**Fig. 1**). Owing to the lack of large prospective cohort studies and RCTs on PTH management, the above algorithms might help in making clinical decisions.

BIOMARKERS

Recently, interest in biomarkers for the diagnosis and prognosis of TBI has been increasing. These biomarkers include not only protein measurements in biofluids, but also genes. It is believed that these biomarkers may be more cost-effective than other diagnostic tests. To date, biofluid-based biomarkers known to have diagnostic and prognostic potential in TBI include S100B, neuron-specific enolase, UCH-L1 (neuronal damage marker), and GFAP (astrocyte damage marker) [65].

https://doi.org/10.12786/bn.2022.15.e14

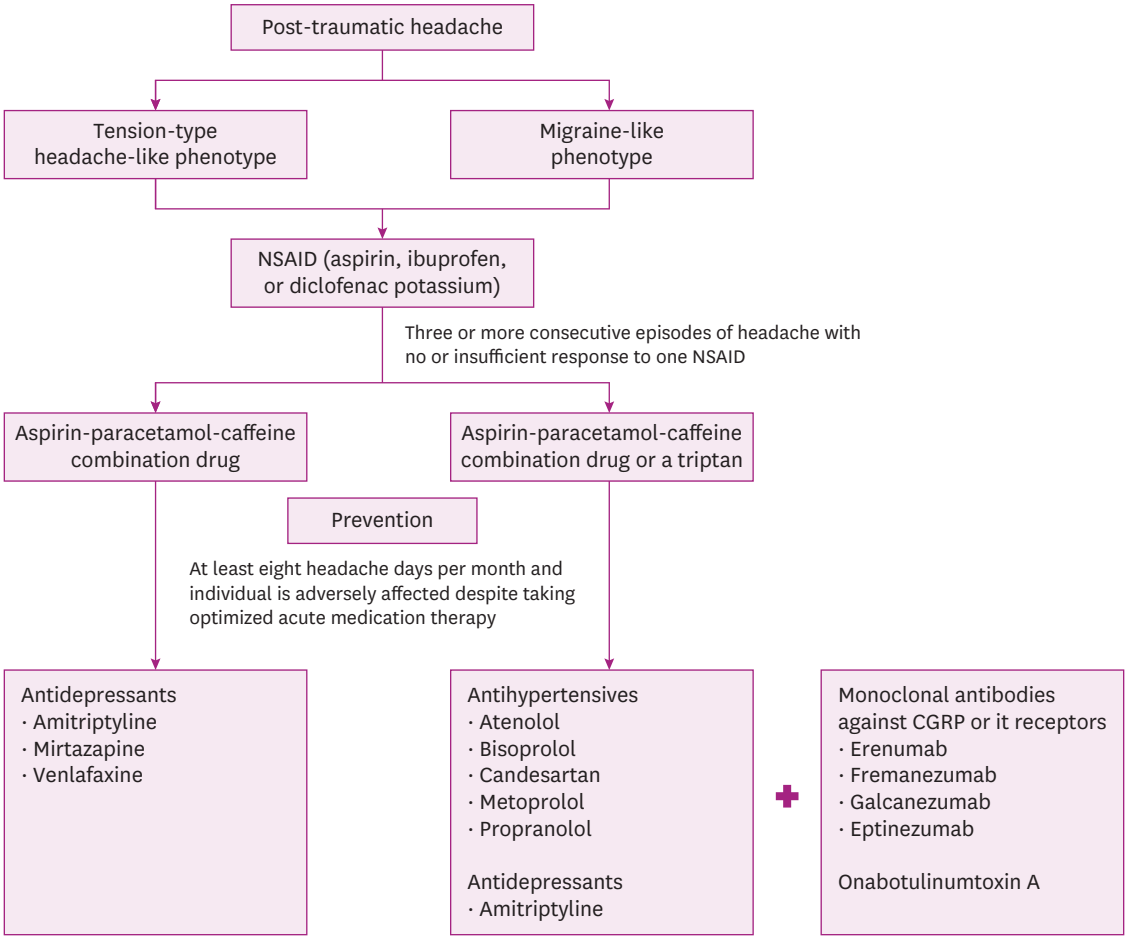

Fig. 1. Algorithm for pharmacological treatment and prevention of post-traumatic headache [58].
NSAID, non-steroidal anti-inflammatory drug; CGRP, Calcitonin gene-related peptide.

According to two recent studies by Shahim et al., [66,67] neurofilament light (NfL) is a useful biomarker of axonal injury that has been evaluated in TBI. In the first study [66], two groups of patients with TBI were recruited: a group of Swedish hockey players with lumbar puncture after sports-related TBI, and a clinic-based cohort with subacute or chronic TBI. In the first study, an important initial observation in hockey players was that the serum NfL level correlated well with the CSF level. Another key finding from the hockey players was that both CSF NfL and serum NfL were associated with incidence of concussions and severity of post-concussion symptoms after one year. The clinic-based group in this study showed that the serum NfL distinguished between mild, moderate, and severe TBI and declined over five years after TBI. The second report by Shahim et al. [67] used a clinic-based cohort to evaluate the utility of NfL in TBI diagnosis, with the main goal of comparing this biomarker with GFAP, UCH-L1, and tau. The results showed that NfL outperformed the other blood biomarkers.

Furthermore, according to a study by Shin et al., [68] elevated blood plasma acetylated tau (ac-tau) appears in TBI model mice and in patients with TBI, and the acceleration of ac-tau in the brains of patients with AD is significantly increased if they have a history of TBI. These findings suggest that ac-tau is a potential blood biomarker of TBI.

https://doi.org/10.12786/bn.2022.15.e14

CONCLUSION

Previous studies on TBI have made many developments in omnidirectional fields, such as evaluation and treatment, prevention, and prognostic assessment. The current updates related to TBI management described in this review show positive results, but evidence supporting these interventions is still lacking. To complement this evidence-based approach, addressing these shortcomings requires a concerted effort and should include large prospective cohort studies and RCTs. Overseas, large-scale cohort studies such as CENTER-TBI (ClinicalTrials.gov Identifier: NCT02210221) in Europe and TRACK-TBI (ClinicalTrials.gov Identifier: NCT02119182) in the United States are being conducted, and as a result, various evidences are being presented. Therefore, in Korea, long-term prospective studies with long-term assessments in large TBI patient populations are needed to add evidences for TBI management relevant to the domestic situation.

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