Current Opinions on Epidemiology, Treatment and Outcome After Traumatic Brain Injury

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Abstract

Objective: The objective of this article is to provide an overview on current incidences of traumatic brain injury (TBI) with special focus on current surgical and non-surgical treatment options as well as outcome.

Method: A Medline database search was performed using various combinations of the search terms "traumatic brain injury", "TBI", "treatment", "outcome", "pediatric", "intracranial hypertension", "epidemiology" and "incidence".

Results: We found an incidence of TBI of 332/100,000 inhabitants in Germany per year and 219-345/100,000 TBI occurring in children. TBI is still the leading cause of mortality and morbidity worldwide. The overall mortality after TBI is described with 1%.

Typical symptoms of TBI represent headache, nausea and vomiting, dizziness, blurred vision, paresis, aphasia, seizures and impaired coordination on the physical side. Cognitive impairments include attention, memory and concentration disorders or decreased processing speed whereas behavioural symptoms present as depression, anxiety, agitation or aggression. Persistence of these symptoms results in a vicious circle of impaired skill acquisition and an adaptive deficit with increased academic failure, unemployment and loss of salary, social and behavioural dysfunction and isolation.

The injury severity of TBI is commonly classified according to the established Glasgow Coma Scale (GCS) and the TCDB classification in CT-Scans.

Established non-surgical treatment of intracranial pressure after TBI emphasizes on hyperventilation, hypothermia as well as application of mannitol, hypertonic saline solution or barbiturates. Recently, neuroprotective effects of erythropoietin (EPO) have been demonstrated. Surgical therapy consists of lumbar drainage of cerebrospinal fluid, decompressive craniotomy, and the evacuation of mass lesions.

Conclusion: While scientific data concerning the classification of TBI, treatment and outcome prediction has significantly progressed over the last two decades identifying risk factors and treatment options, further research is needed consolidating first-, second- and third-tier treatment. Identifying treatment pathways based upon potential predictive factors and rehabilitative outcome is thought to improve family support of patients concerned and to optimize health care requirements.

Keywords: Traumatic brain injury; Outcome; Morbidity; Treatment; Paediatric TBI

Traumatic Brain Injury

Traumatic Brain Injury (TBI) continues to be the major cause of disability and death throughout the world despite improvements of research and medical treatment [1]. Consequently, an overview on the current incidence of TBI as well as current treatment options and outcome seems considerably relevant.

With 332 Traumatic Brain Injuries per 100,000 inhabitants in Germany every year [2], TBI is still the leading cause of mortality and morbidity worldwide [3] resulting in prolonged rehabilitation and long-term care [4]. In multiple traumatized patients, head injuries are evaluated as the most frequent injury, followed by lower and upper extremity trauma [5]. Examining current data, two major gender- and age-related incidences of TBI can be found: one occurs in the late teens to twenties [6] commonly due to motor vehicle accidents [4] with males being three times as often affected compared to females [7]. The second major incidence occurs in the geriatric population caused by falls due to geriatric co-morbidities [6]. While mortality decreased during the last decades based on medical improvements, the World Health Organization (WHO) predicts that TBI will be the third greatest cause of disease and injury by 2020 [8].
Emphasizing on an adequate classification of the injury severity, the established Glasgow Coma Scale (GCS) is most commonly used [12,13]. According to this score, three commonly used TBI severity groups are defined as mild (GCS 13–15), moderate (GCS 9–12) and severe TBI (GCS 3–8) [14,15]. However, the Department of Defense and Veterans Affairs (DOD/VA) of the United States of America stratifies TBI by loss of consciousness, alteration of consciousness and post-traumatic amnesia in addition to the aforementioned GCS-based classification [9]. Beside these descriptive clinical differentiations, further diagnostics include computed tomography (CT) and magnetic resonance imaging (MRI) [1]. Analysing CT-diagnostics as established standard after TBI, the TCDB classification has been elucidated (Table 1): This classification identifies six groups of patients’ TBI differentiating between mass lesions and permitting further differentiation of patients with diffuse injuries into 4 categories, taking into account signs of intracranial pressure [15]. The predictive value of this classification has been repeatedly confirmed [16-18].

**Paediatric TBI**

Special interest is displayed towards paediatric TBI resulting in sizable scientific research over the last few years [19-24]. 219-345/100,000 TBI occur in children commonly caused by traffic accidents resulting in 53 deaths per 100,000 children every year [25]. Consequently, mortality rate of 15% during the first 15 years of age has been elucidated [26]. Increasing clinical experiences and improved treatment algorithms reduced mortality of paediatric TBI during the last decades [20]. Similar to adult TBI, prediction of outcome in survivors is described to be complex, with several factors like the injury severity [27,28], rehabilitation and social support interacting to determine the extent of residual impairments [28]. Anatomic variances in adults like a disproportional large and heavy head with weak neck muscles as well as greater flexibility of cranial bones minimize focal brain injuries but increase the risk of diffuse brain injuries [20,29-36]. In the past, a child’s brain has been suggested to be capable of adapting to considerable TBI impacts, while currently several studies indicate that younger age is associated with minimal recovery after injury in comparison to older children [35-37]. In pre-school children, the brain is rapidly developing with considerable cognitive skill maturation, and might be most vulnerable to disruptions caused by TBI compared to older children [20,28,38,39]. Differences referring to outcome were demonstrated between pre-school aged children (0 to 7 years) and school-aged children (8 to 17 years). Due to an immature brain in pre-school aged children, TBI is expected to influence the development of potential coping mechanisms considerably [19]. Consequently, significant differences after rehabilitation of pre-school children compared to school-aged children referring to increased social and behavioural impairment have been analysed [20,40]. In contrast to this assumption, the association of injury severity and outcome deficits diminishes with increasing time since injury [28,36,41], suggesting other influencing factors like social and family environment [37,42].

**Therapeutic Options**

The overall mortality after TBI is described with 1% [43]. However, severe TBI is known to result in increased on-scene mortality due to severe cerebral injuries [44]. These injuries are caused by direct impact, rapid acceleration or deceleration with shearing damage of white-matter tracts, rupturing of blood vessels followed by hematoma, focal contusions and diffused swelling [1]. In addition, primary ischemic brain damage can be caused by systemic complications resulting in reduced cerebral perfusion and oxygenation or toxic brain damage. Beside these impacts, 60% of patients with severe TBI commonly sustain additional extracranial injuries increasing on-scene mortality considerably [43]. During resuscitation or clinical course so-called “secondary brain injuries” might occur [45,46] increasing the risk of an unfavourable outcome. The development is based upon the known inflammatory response to trauma with free radical and calcium mediated cell necrosis and astrocytic swelling caused by neurotransmitter stimulation [1]. Increased autophagy is postulated to play a pivotal role in secondary injuries as well [47]. However, once the critical phase has been passed, mortality has been analysed almost similar between TBI patients compared to a normative population [48,49].

While mild TBI requires minor treatment focusing short term supervision and analgesia, the individualized treatment of moderate to severe TBI is described to be more complex [2,4,14,50-61]. It has been shown that hypoxia and hypotension are strongly associated with secondary insults leading to poor outcome in TBI [62]. Consequently, pre-hospital care is emphasized to prevent hypoxia and hypotension during primary resuscitation [1]. Hyperglycaemia and hypertension resulting in impaired autoregulation of cerebral perfusion have also been associated with poor mid-term outcome [23,24,63]. During clinical course various treatment options are available focusing on reduction of cerebral swelling, minimizing intracranial pressure and optimizing systemic co-morbidities [2,4,51-53,56-58]. There is general agreement that optimized cerebral perfusion via oxygenation, glycemic control, temperature adjustment, balanced anaesthesia, as well as nutritional and electrolyte homeostasis should be preferred [1,64]. Referring to specialized neurointensive care invasive monitoring of intracranial pressure (ICP) is described as major priority: an ICP >20 mmHg has been found to be strongly related to short-term mortality with almost 18% during the initial 6-months [65,66].

Therefore, non-surgical treatment reducing an increased ICP emphasizes on hyperventilation, hypothermia, as well as application of mannitol, hypertonic saline solution or barbiturates [3,49]. Recently, neuroprotective effects of erythropoietin (EPO) have been demonstrated [53,55] and clinical application is currently under review [67]. Therapeutic hyperventilation has been performed continuously during the last decades [68]. However, its potential benefit is still discussed controversially [50,52,61,69,70]. While hyperventilation

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**Table 1: TCDB classification of TBI severity.**

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Diffuse injury I (no visible pathology)</td>
<td>No visible intracranial pathology seen on CT scan</td>
</tr>
<tr>
<td>Diffuse injury II</td>
<td>Cisterns are present with midline shift of 0–5 mm and/or lesions densities present; no high or mixed density lesion &gt;25 cm² may include bone fragments and foreign bodies</td>
</tr>
<tr>
<td>Diffuse injury III (swelling)</td>
<td>Cisterns compressed or absent with midline shift of 0–5 mm; no high or mixed density lesion &gt;25 mm</td>
</tr>
<tr>
<td>Diffuse injury IV (shift)</td>
<td>Midline shift &gt;5 mm; no high or mixed density lesion &gt;25 cm²</td>
</tr>
<tr>
<td>Evacuated mass lesion</td>
<td>Any lesion surgically evacuated</td>
</tr>
<tr>
<td>Non-evacuated mass lesion</td>
<td>High or mixed density lesion &gt;25 cm²; not surgically evacuated</td>
</tr>
</tbody>
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with a pCO\textsubscript{2} between 32 and 35 mmHg reduces intracranial pressure via vasoconstriction, long-term therapy has recently been suggested to result in reactive vasodilatation due to pH-changes [53]. Furthermore, depletion of bicarbonate levels [71] within the cerebrospinal fluid might potentially increase the risk of cerebral ischemia [1,71,72].

Prophylactic hypothermia with 32-34°C [4] is demonstrated to reduce the cerebral metabolic rate (6-7% reduction for each 1°C decrease in temperature [73]) and appears to decrease the systemic inflammatory response [74,75]. However, the risk of a “rebound” intracranial hypertension during patients’ rewarming increases in strong correlation with the overall therapeutic duration of hypothermia [76]. In addition, hypothermia also inhibits physical coagulation and therefore might cause uncontrollable bleeding [4,50]. Consequently, the risk-benefit-analysis recommends hypothermia as the second line therapeutic option with intervals shorter than 72 hours [77].

Intravenous application of mannitol creates an osmolar gradient via an intact blood-brain barrier reducing intracerebral pressure [1]. The onset is described quickly usually within five minutes after infusion lasting between one and six hours achieving a maximum level after 60 minutes [58]. By drawing water into the blood vessels, blood viscosity is reduced, further increasing perfusion [68]. Besides its cerebral therapeutic mechanism mannitol is known as diuretic agent [78]. Therefore, volume replacement might commonly be required increasing potential risks of rebound ICP increase due to a reversed osmolar gradient [78]. Hyperosmolar saline acts similar to mannitol (3-3.4%), as it also creates an osmolar gradient across the blood brain barrier [58,78]. Several studies indicate that its effect is even enhanced compared in mannitol [79,80].

The mechanism of barbiturates decreasing intracranial pressure remains unclear. It has been proposed that cerebral dysautoregulation is reduced resulting in improved oxygenation [51] while other studies indicate a neuroprotective effect [81,82] via membrane hyperpolarization and electrolyte balancing [83]. However, due to the potential risk of severe hypotension barbiturates are considered as second-tier medication [79].

Application of EPO, on a cellular level, attenuates brain injury reducing neuronal apoptosis and systemic inflammation while cerebral cells are protected from secondary impacts due to hypoxemia and ischemia [60]. In addition to these microscopic effects, EPO induces macroscopic protective effects (reduction of post-traumatic cerebral oedema, contusion volume and infarct area) [84]. A level III prospective study has been proposed to verify these effects [4] also examining the increased risk of thrombosis due to EPO therapy [54].

A semi-operative procedure to reduce intracranial pressure is offered through lumbar drainage of cerebrospinal fluid (CSF). Not until recently, CSF-drainage has been contraindicated in patients with TBI due to risk of potentially lethal transtentorial or cerebellar tonsillary herniation [50]. Recently it has been shown that in absence of supratentorial mass lesions and discernible basal cisterns [85], lumbar drainage is a quick and safe option to reduce intracranial pressure [69].

Surgical therapy consists of decompressive craniotomy and the evacuation of mass lesions [86]. In case of surgical craniotomy, a considerable decrease of intracerebral pressure has been reported [87,88]. Nevertheless, the potential risks of significant complications like infection, hygroma, oedema, haemorrhage and hydrocephalus [56] imply surgical treatment of intracranial hypertension in absence of mass lesions as last resort [59]. In case of cerebral mass lesions like epidural or subdural hematomas, surgical evacuation has been demonstrated to be potentially vital referring to a favourable outcome [64]. However, the surgical indication to decompress subcortical lobar bleedings is currently under close investigation [57].

Outcome

While most investigations analysing “outcome” as key parameter have examined patients after TBI between one and three years [7,27,57,69,89], only few studies have investigated long-term outcome [7,20,21,30,90,91]. Interestingly, these studies focused severe TBI almost exclusively.

Outcome can be differentiated between somatic and psychosocial parameters, though both are intertwined [87] as personal and economic burdens arise for the patient, for a family and for the community [20].

Somatic deficits include persisting headaches, concentration and cognition deficits, attention disorders and impaired executive cerebral function as well as somatic complaints [20,92]. Complaints present at 1-year examination usually persist until 3-year examinations and some authors postulate permanent [7,91]. Other long term studies indicate an improvement as employment rates increase during the post-3-year interval [88].

Psychosocial deficits are usually evaluated by the Glasgow Outcome Scale (GOS) [93] or the Glasgow Outcome Scale extended (GOSE) [94]. It has been shown that a reduced GOS and GOSE at time of hospital discharge is strongly correlated with poor mid-term outcome [91]. Depression and anxiety are known as most common psychiatric problems in patients sustaining TBI [7]. 26% of TBI victims develop a depression between the first and second year after injury [95]. Patients suffering from severe TBI tend to be socially isolated according to measured increased divorces and more “singles” three years after trauma [88,91].

While somatic complaints may result in impaired skill acquisition and adaptive deficits, and thus creating a vicious cycle of academic failure, unemployment and loss of salary [7,91], worsening depression and anxiety.

In addition, psychological impairments may result in social and behavioural dysfunction and thus denying patients of social support networks that are vital for retaining and refining cognitive and social skill sets [90].

Since 47% of patients with severe TBI are not capable of living independently [4], supportive environments for long-term rehabilitation seem particularly required [6]. This seems to meet current assumptions of increased divorce rates and increased social isolation [89] resulting in a downward spiral creating vast demands on national health care systems [4,95]. In support of this suggestion, Colantionio et al. revealed improved rehabilitation after three years in patients supported by functioning social networks [90].

The same implications apply for children affected by TBI, though social and behavioural deficits seem to be more important compared to adults [87]. On the other hand cognitive outcome tends to be much better due to closer family networks [20,88].

Conclusion

While scientific data concerning the classification of TBI, treatment and outcome prediction has significantly progressed over the last two decades identifying risk factors and treatment options, further research is needed consolidating first-, second- and third-tier treatment. Identifying treatment pathways based upon potential predictive
patients concerned and to optimize health care requirements.

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**References**


