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Review Article

Criteria to define mild, moderate, and severe traumatic brain injury in the mouse controlled cortical impact model

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ABSTRACT

Traumatic brain injury (TBI) is a major health concern in the United States resulting in a substantial number of hospitalizations and in a broad spectrum of symptoms and disabilities. In the clinical setting, neurological responsiveness and structural imaging are used to classify mild, moderate and severe TBI. To evaluate the complex secondary and severity-specific injury response, investigators have relied on pre-clinical rodent models. The controlled cortical impact (CCI) model in mice is a widely used to study TBI. The CCI method has demonstrated consistent intra-laboratory outcomes due to precise control of cortical depth penetration, dwell time and speed of impact. While the CCI method results in control of injury severity, there is no consensus regarding the injury parameters or behavioral and histological endpoints that constitute a mild, moderate or severe TBI in this model. This discrepancy has resulted in considerable variability across laboratories in the outcomes of CCI-induced mild, moderate, and severe TBI. Inconsistent with clinical evaluation, injury severity in the CCI model has predominately relied on the extent of tissue damage. In the present review, we discuss variations in surgical parameters for injury induction as well as the criteria used to determine injury severity. Additionally, we propose guiding principles for the induction and defining of mild, moderate and severe TBI in the craniectomy-dependent experimental mouse CCI model.

1. Introduction

Traumatic brain injury (TBI) is a major health concern in the United States resulting in a substantial number of hospitalizations and a broad spectrum of symptoms and disabilities. TBI is not only a personal tragedy due to chronic motor, cognitive, and emotional deficits but also results in a familial and economic burdens. With over 2 million occurrences and approximately 50,000 deaths annually, TBI is the leading cause of death in young adults (< 45 years of age) and is associated with $76.5 billion in direct and indirect medical costs (Finkelstein et al., 2006; Faul & Coronado, 2015; Patel et al., 2005). Of importance, TBI can result in lifelong complications and at present the therapeutic options are non-existent. Heightened public awareness of the devastating impact of TBI along with advances in neuroimaging and other clinical tools for diagnosing the chronic impact of TBI has led to an increase in studies investigating the mechanisms underlying these deleterious effects with the hope of developing effective therapeutic options.

TBI results from an initial insult to the brain referred to as the primary injury. The primary injury can be produced by a penetrating, blast injury or an impact of the brain against the skull as a result of falls and motor vehicle collisions. The heterogeneous primary injury is then followed by a complex secondary response. This includes changes in cell proliferation and differentiation (Gao & Chen, 2013; Bye et al., 2011; Susarla et al., 2014), neuronal cell death (Clark et al., 1997; Sabirzhanov et al., 2016), mitochondrial dysfunction (Miller et al., 2015; Wu et al., 2016), multifaceted immune responses (White et al., 2013; Scherbel et al., 1999; Laird et al., 2014; Weaver et al., 2015), glutamate-induced excitotoxicity (Amorini et al., 2017; Katayama et al., 1990; Bullock et al., 1998; Hinzman et al., 2012), and cerebrovascular dysfunction and repair (Jullienne et al., 2016; Salehi et al., 2017; Obenaus et al., 2017). In order to study these complex phenomena following TBI and due to limitations in the clinical setting, pre-clinical research has relied heavily on rodent models. The three most widely used rodent TBI models include the fluid percussion injury, controlled

Abbreviations: TBI, Traumatic Brain Injury; CCI, Controlled Cortical Impact; GCS, Glasgow Coma Scale; MRI, Magnetic Resonance Imaging; CT, Computed Tomography; VA/DoD, Department of Veterans Affairs and the Department of Defense; NSS, Neurological Severity Score; MWM, Morris Water Maze; ICP, Intracranial pressure; RR, Righting Reflex; AHRQ, Agency for Healthcare Research and Quality

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Table 1
Attributes of commonly used TBI models.

Model	Injury type	Strengths	Weaknesses	Major pathological features
Weight-drop	Diffuse and focal subtypes	Injury mechanism closely resemble human TBI injury biomechanics Low technical skill needed for implementation	Low reproducibility High mortality rate	Concussion, traumatic axonal injury
Fluid percussion	Mixed	Highly reproducible	Requires craniotomy which may reduce ICP pathology High mortality rate Requires surgical skilled technician No immediate post-injury neuroscoring	Contusion
Controlled cortical impact	Mainly focal	Highly reproducible Low mortality rate[a]	Requires craniotomy which may reduce ICP pathology Requires surgical skilled technician No immediate post-injury neuroscoring	Contusion, hemorrhage
Blast injury	Mainly diffuse	Injury mechanism closely resemble human military TBI injury biomechanics	Needs standardization	Concussion, traumatic axonal injury

Table modified from (Xiong et al., 2013).
[a] Differential mortality rates seen primarily in severe forms of injury induction.

cortical impact (CCI) and weight-drop model. For a review of these models, see Xiong et al. [22]. Each model replicates specific attributes of clinical TBI and has been used in both mice and rats (Table 1). The CCI model is the most commonly used model and is well-recognized for inducing both moderate and severe TBI. Importantly, while the model is well-recognized in the field of TBI, there are currently no guidelines to grade the severity of injury following a mouse CCI resulting in considerable variation across different laboratories. Variations include surgical parameters such as depth of cortical depression and velocity of impact as well as behavioral and histological endpoints. These variations often lead to opposing or conflicting findings that are difficult to reconcile across studies.

In the clinical setting, TBI is classified into mild, moderate, and severe injury using clinical practice guidelines. A number of guides have been developed including, Department of Veterans Affairs and the Department of Defense (VA/DoD), Center for Disease Control (CDC), Agency for Healthcare Research and Quality (AHRQ) and World Health Organization (WHO) (Report to Congress on Traumatic Brain Injury in the United States: Epidemiology and Rehabilitation, 2015; T.B.I.W.G, 2009; Brasure et al., 2012; Holm et al., 2005). All aforementioned clinical practice guidelines incorporate structural imaging, duration of loss of consciousness and post-traumatic amnesia, and the Glasgow Coma Scale (GCS) in their criteria for classifying injury severity. The GCS is a 15-point behavioral observation scale that defines severity based on eye, verbal, and motor response (Gomez et al., 2017). Individuals with a score of 3–8 are classified as severe, 9–12 as moderate, and those between 13 and 15 as mild TBI. Mild TBIs are defined as momentary changes in consciousness as a result of an external force to the skull and contribute to over 70% of reported brain injuries and include concussions (Cassidy et al., 2004). Most individuals experience complete symptom resolution within 3 months after mild TBI despite evidence for chronic pathological changes in brain tissue (Cassidy et al., 2004). In contrast to mild, severe TBI is associated with sustained loss of consciousness (> 24 h) and a 24% mortality rate with 43% of surviving patients exhibiting chronic physical and emotional disabilities (Selassie et al., 2008; Steppacher et al., 2016). Along with the GCS, the extent of morphological damage via MRI or CT scan is also used to evaluate severity and injury progression. According to clinical practice guidelines developed by the VA/DoD and the CDC, abnormal structural imaging results in the classification of a moderate to severe TBI (T.B.I.W.G, 2009). While the presence of abnormal structural imaging excludes the classification of mild TBI, normal structural imaging can be present in mild, moderate, and severe TBI. Under these circumstances, a patient may be classified as having a moderate to severe TBI based on neurological assessment alone. Neurological assessments include length of time patients exhibit post-traumatic amnesia, alterations of consciousness, duration of loss of consciousness and their GCS within the first 24 h (Report to Congress on Traumatic Brain Injury in the United States: Epidemiology and Rehabilitation, 2015; T.B.I.W.G, 2009). The VA/DoD guidelines state that if criteria are met in multiple classifications of injury, the classification with the highest severity is assigned (T.B.I.W.G, 2009). Ongoing research continues to evaluate the potential structural damage that has clinically relevant predictive value for functional recovery (Shakir et al., 2016). Another area of ongoing research is that of blood and cerebrospinal fluid biomarkers for both prognostic and diagnostic purposes (see review (Agoston et al., 2017)). The FDA recently approved a blood test detecting glial fibrillary acidic protein (GFAP) and ubiquitin c-terminal hydrolase L1 (UCHL1) in patients with head injuries as an indicator of potential intracranial lesions and the necessity of neuroimaging (FDA authorizes marketing of first blood test to aid in the evaluation of concussion in adults, 2018). S100-beta (Egea-Guerrero et al., 2012), neuron-specific enolase (NSE) (Costine et al., 2012; Zurek & Fedora, 2012), myelin basic protein (MBP) (Beers et al., 2007), tau (Gabbita et al., 2005), H-FABP (Lagerstedt et al., 2017) and neurofilament heavy chain protein (NF-H) (Gatson et al., 2014) continue to be potential candidates in the evaluation of acute injury severity and progression.

While formal guidelines (VA/DoD) for clinical characterization of injury severity exist, there are presently no guidelines for grading injury severity in the mouse CCI model. A major difficulty in assigning the categorical severity of mild, moderate, and severe injury to the mouse CCI model is the differing responses to TBI between mice and humans. The direct translation of neurological assessments used in clinical settings, including alterations of consciousness, post-traumatic amnesia, and the GCS (eye, verbal, and motor response), to preclinical settings has been challenging. In the rodent models of TBI, motor response, cognitive deficits, and depression- or anxiety-like behavior are the most frequently used neurological assessments. However, neurological assessments are rarely used to define injury severity in preclinical models. Taking into account the guidelines set forth by the VA/DoD for clinical evaluations, definitions for injury severity in the CCI mouse model should include specific time-points for recovery, neurological assessments, and structural alterations following injury induction. To date, most mouse CCI studies use only histological outcomes as their evidence for defining injury severity, often referencing the extent of cortical and hippocampal lesion sizes as the predominant factor (Brickler et al., 2016; Wang et al., 2016).

In the present review, we discuss the criteria used to determine injury severity in the mouse CCI model. The CCI model was originally developed to investigate moderate to severe TBI and is infrequently used to mimic mild TBI because of the necessity of a craniectomy (Dixon et al., 1991). Modified versions of CCI have now been developed