Review Article

Utility of Brain-on -a-chip Model in Traumatic Brain Injury: A Review

Usha Adiga[1*], Desy TM[2], Neha Martin Honnalli[3]

[1*]Professor, Nitte-DU, KS Hegde Medical Academy, Department of Biochemistry, Mangalore, India
[2]Senior Research Fellow, ICMR, Dept of Biochemistry, KS Hegde Medical Academy, Nitte- Deemed to be University, Mangalore, India
[3]Research Scholar, Dept of Biochemistry, KS Hegde Medical Academy, Nitte- Deemed to be University, Mangalore, India

***Corresponding Author: Usha Adiga**

* Professor, Dept of Biochemistry, KS Hegde Medical Academy, Nitte- Deemed to be University, Mangalore, India
ushachidu@yahoo.com
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Abstract

Traumatic brain injury (TBI), a form of acquired brain injury, occurs when a sudden trauma causes damage to the brain.There is a need to develop a panel of markers and their kinetics which help in predicting the outcome of TBI. The objective of the review is to discuss a brain on a chip device for the evaluation of the expression of markers of axonal injury (S-100B,GFAP) and neuronal injury (NSE,MBP and UCH-L1) as well as their kinetics as one compartment model. The kinetic study will give us an exact timing in which each marker attains a peak level after brain injury. This information is very important to decide the time of sampling after TBI, which is prognostic value. It may demonstrate that brain on a chip device can deliver a platform for the precision prognostic markers for traumatic brain injury, low resource or underserved settings with a sensitivity that is higher than that of the current diagnostic tests/imaging techniques used in the field . As this technique avoids the sacrifice of animals as brain-on-a-chip is an alternative model for animal studies.

Key words: brain -on-a chip ,microfluidic device,kinetic study, brain biomarkers

INTRODUCTION

Traumatic brain injury (TBI), a form of acquired brain injury, occurs when a sudden trauma causes damage to the brain.Traumatic brain injuries (TBI) are diverse and can manifest itself in a variety of ways. TBI can be categorized according to the mechanism of injury (e.g., sports injury, traffic accidents, falls, and assaults), clinical severity as measured by the Glasgow Coma Scale (GCS), or structural damage. Because of the disease's variability, determining the extent of trauma and predicting the clinical outcome for individual individuals is difficult[1,2]. Furthermore, the majority of initial injury characteristics do not always translate into long-term consequences. These factors have made developing an uniform and thorough TBI assessment protocol a difficult task in the medical industry. According to the GCS score (which utilizes motor, eye, and verbal responses to evaluate the patient's level of consciousness),duration of unconsciousness, and duration of post-traumatic amnesia, injuries are classed as mild, moderate, or severe [3,4-6]. TBI is characterized by an evolving pathology: time-dependent changes almost invariably follow the initial insult[3]. For this reason, biomarker-based methods for diagnosis and prognosis can only be interpreted in the context of an evolving pathology. The understanding of the role of biomarkers is confounded by the fact that many biomarkers have complex kinetics relating to release from brain cells, transfer across the blood–brain barrier (BBB), and clearance from the peripheral blood. These kinetic behaviors are at best indirectly related to the pathology of TBI.

TBI and its effects have been studied using serum and cerebrospinal fluid (CSF) markers as an alternative or synergistic addition to radiological examinations [4,7-9]. It is vital to appropriately diagnose acute cerebral disease and haemorrhage using a noninvasive biomarker-based technique. Surrogate markers of cerebral sequelae after TBI include glial fibrillary acidic protein (GFAP), S100B, and UCHL-1[4,7-9]. TBI biomarkers are frequently tested in bodily fluids. The majority of the evidence accessible today came from CSF or blood investigations [7,10-12].

MARKERS OF ASTROCYTE ACTIVATION

S100B: S100B is a calcium-binding protein secreted by astrocytes, Schwann cells, melanocytes, adipocytes, and chondrocytes. TBI patients with GCS of fifteen, after 6 hr of injury, serum levels of S100B at a cutoff of 0.130 ug/L diagnosed intracranial lesions with a sensitivity of 100 % and a specificity of 32.81 %[13].

GLIAL FIBRILLARY ACIDIC PROTEIN (GFAP):

Glial fibrillary acidic protein (GFAP) is an astrocyte specific intermediate filament. Among patients with severe TBI, the levels correlated with mortality [14]. In mild TBI, GFAP was elevated in patients who had CT scan abnormality, as well as in patients with axonal injury on MRI [15]. The GFAP levels were high in patients who had a late functional recovery.

So, it can be a promising marker of functional outcome.

MARKERS OF NEURONAL INJURY

Neuron-Specific Enolase (NSE):

NSE is a glycolytic enzyme which is found in neurons and neuroendocrine cells, such as adrenal, pituitary, and pineal, and non-CNS cells, such as erythrocytes. NSE levels estimated were sensitive to early injury and detectable within 6 h of injury. There are several studies demonstrating the elevations in serum NSE following moderate to severe TBI, but with limited sensitivity. Considering this limiting factor, it may be most useful in conjunction with other biomarkers. It was 100% elevated in CSF of patients with major head injury than the normal levels, and 47% had increased serum NSE [16].

Myelin Basic Protein (MBP):

Thirty percent of myelin in the CNS is composed of myelin basic protein. TBI is often associated with axonal injury. This often will lead to structural damage of the nearby myelin membrane, which ultimately leads to degradation of MBP. This can lead to demyelination and further axon vulnerability. MBP was elevated significantly on admission and remained high for 2 weeks among patients with severe intracerebral damage.

Ubiquitin C-terminal hydrolase-L1 (UCH-L1):

UCH-L, is found in abundance and is specific to neurons. It is a deubiquitinating protein. CSF levels of UCH-L1 were high in severe TBI when compared with control subjects and correlated to the severity of injury as indicated by GCS, lesions on CT, and 6- week mortality [17]. In a study of severe TBI patients, CSF and serum levels of this marker were correlated [18].

KINETICS OF BIOMARKERS

In the acute and chronic post-injury stages, many of these biomarkers are thought to have a patient-independent kinetic behavior, with variations in serum biomarker levels mostly based on source concentration and tissue of origin. However, it should be noted that these biomarkers do not always appear at the same time after injury, and that a biomarker's kinetic distribution is heavily influenced by the marker's biophysical properties such as molecular weight, as well as the anatomical and physiological characteristics of the individual (ie, glomerular filtration rate, age, gender, and skin pigmentation). S100B levels surge sharply within minutes of damage and revert to homeostatic levels around 1–2 hours later.

Abnormal serum GFAP levels, on the other hand, can last for days after the initial occurrence. It was demonstrated using a physiologically based pharmacokinetic model for biomarker distribution in blood that this time-dependent distribution is mostly reliant on the molecular weight of S100B and GFAP rather than the origin of the maker itself, as proposed by Maas et al. [3]. Because glomerular filtration rate is determined by a formula that takes into consideration age, gender, and ethnicity, these disparities in postinjury serum levels are further muddled by the anatomical and physiological qualities of individual individuals.

Markers of brain damage vs markers of BBB disruption

S100B was first discovered to be high even when no brain injury was evident. It was then discovered that families of soluble protein biomarkers, rather than brain injury, are also indicators of BBB breakdown [19,20]. This has substantial implications in a variety of clinical and preclinical models of systemic and brain disease. The traditional diagnostic definitions of "positive" and "negative" predictive values must also be rewritten. In fact, the markers report the condition of the BBB rather than "brain injury" in mTBI and in the absence of parenchymal lesions. As a result, a positive predictive value should refer to contrast MRI or other BBB malfunction detection sequences [4]. In TBI, there has never been a systematic comparison of blood markers and MRI. However, it has been studied in other pathologies [21-24].

Point of care CT scan and neurological status, particularly in mild TBI, cannot accurately predict outcome. There is a need to develop a panel of markers which help in predicting the outcome. The brain injury biomarkers promise to improve the patient diagnosis, management and outcomes, and aid in the development of novel therapeutics. Such prediction can help in prioritizing treatment. There are only a few studies on biochemical markers in TBI in Indian population. Currently there are no FDA-approved biomarkers for TBI or other acute brain injuries. A pilot study was conducted on these axonal injury markers (S-100B,GFAP) and markers of neuronal injury (NSE,MBP, UCH-L1) in the serum of 84 TBI patients. The samples were collected within 24 hours of injury. There was no significant correlation was seen between the markers and severity of injury in terms of Glasgow coma scale (GCS) as well as with the outcome in terms of Glasgow coma outcome scale (GOSE).This could be due to the varied kinetic properties of the markers. Studying the kinetics of biomarkers is essential to study as it gives an idea about ideal sampling time as well as its correlation with the severity of outcome. However, it is difficult to carry out kinetic studies in severe brain trauma patients. Hence brain on a chip model may be an alternative. A simple and user-friendly multi-layer silicone elastomer device will be designed, and optimized it for differentiation of pluripotent human cells into mixed population of mature neuronal and glial cells mimicking the CNS micro-environment. This is an attempt to demonstrate that this brain tissue model could be extended to incorporate the blood-brain barrier, making it an attractive platform for kinetic studies. This experimental platform is designed to analyze the kinetics of biomarkers of brain injury.

Future research perspectives

A study may be planned so as to develop a brain on a chip device for the evaluation of the expression of markers of axonal injury (S-100B,GFAP) and neuronal injury (NSE,MBP and UCH-L1) as well as their kinetics as one compartment model.

Applicability and novelty of the study

The study may demonstrate that brain on a chip device can deliver a platform for the precision prognostic markers for traumatic brain injury, underserved settings with a sensitivity that is higher than that of the current diagnostic tests/imaging techniques used in the field .This diagnostic devices may have a meaningful, positive impact on the provision of a panel of diagnostic markers for TBI .The study may demonstrate the feasibility of creating a one-compartment kinetic model of biomarker expression after traumatic brain injury. The one-compartment kinetic model may describe the observed levels of biomarkers, S100 B, GFAP, NSE,MBP and UCH-L1.after traumatic brain injury. The study may be able to establish the time intervals for raise of biomarkers, time taken to reach the peak and elimination. This may provide an idea about the timing of the blood/CSF sampling to be done in patients with TBI so that their association with severity of trauma can be predicted. In such scenario, the markers may serve as prognostic markers.

CONCLUSION

The Implications of this brain on a chip model from the patient's perspective would mean diagnosis and assessment of severity which has a crucial role in the management of TBI.Since we propose to use brain on a chip model in place of animal model, saves lives. It reproduces well mimicked micro-environment of human cells .The device will be easy to use, portable.

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