
Animal Models of Traumatic Brain Injury

Tavleen Kaur, Sumit Jamwal and Puneet Kumar Bansal

1 Introduction

Traumatic brain injury (TBI) is defined as the damage to the brain as a result of mechanical forces like crush, violent blow, or jolt to the head from blunt or penetrating object into the skull like a bullet or a sharp object. TBI may or may not alter the consciousness of person, but it is one of the leading factors responsible for impairment of cognitive ability or physical functioning. It is well depicted in clinical reports that around 10 million of deaths and hospitalizations annually are directly attributable to TBI. Head injuries are mainly of two types, i.e., primary head injury is an injury sustained by the brain at the time of impact, e.g., brain laceration, brain contusion whereas secondary head injury may be delayed neuronal damage or cell loss over a period of hours, days, weeks, or months. This injury involves biochemical and molecular changes in the distant tissues lead to secondary injuries (such as hypoxia, hypotension, seizures, or repeated TBI).

TBI is one of the leading causes of death and disability among the children's and young adults. Researchers discerned that TBI is a frequent injury occurs in the victims of sports, and during motor vehicle clashes. This also produces short- and

T. Kaur · S. Jamwal · P.K. Bansal (✉)

Department of Pharmacology, ISF College of Pharmacy, Moga 142001, Punjab, India
e-mail: punnubansal79@gmail.com

T. Kaur

e-mail: prtavleen@gmail.com

S. Jamwal

e-mail: jamwalisf@gmail.com

P.K. Bansal

Department of Pharmaceutical Sciences and Technology, Maharaja Ranjit Singh Punjab
Technical University (State Govt. University), Bathinda, Punjab, India

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long-term physical, cognitive, behavioral, and emotional impairments. Even though after the availability of extensive literature on the brain trauma, there is no reliable curative drug available for the treatment of patients suffering from TBI till date. TBI patients frequently suffer from long-term personality changes, cognitive deficits, and motor performances (post-concussion syndrome), making it need of hour for novel therapeutic interventions. Worldwide, motor vehicle accidents and military combats are the prevalence factors responsible for TBI in developing nations. TBI contributes a third (30.5%) of all the injury-related deaths in the USA. According to Centers for Disease Control and Prevention 2014 reports, 1.7 million Americans sustain a TBI/year out of which 27.5 thousand hospitalizations, 80 thousand disabilities, and 52 thousand deaths, creating a significant socioeconomic and emotional burden on the families and society.

The mechanical insult to the brain may lead to decreased cerebral blood flow (CBF) and thus produces ischemia-like condition. This ischemia is thought to be the first step in pathology of TBI (Fig. 1). Similarly, in anaerobic glycolysis, lactate accumulates and there is reduction in oxygen metabolism, increased membrane permeability leading to edema and decreased glucose uptake in the affected area of the brain. Altered metabolic function in the cells may initiate glutamate-induced excitotoxicity and neuronal cell death. Also, altered calcium homeostasis increases the reactive oxygen species, and generation of inflammatory mediators may also lead to the cell death.

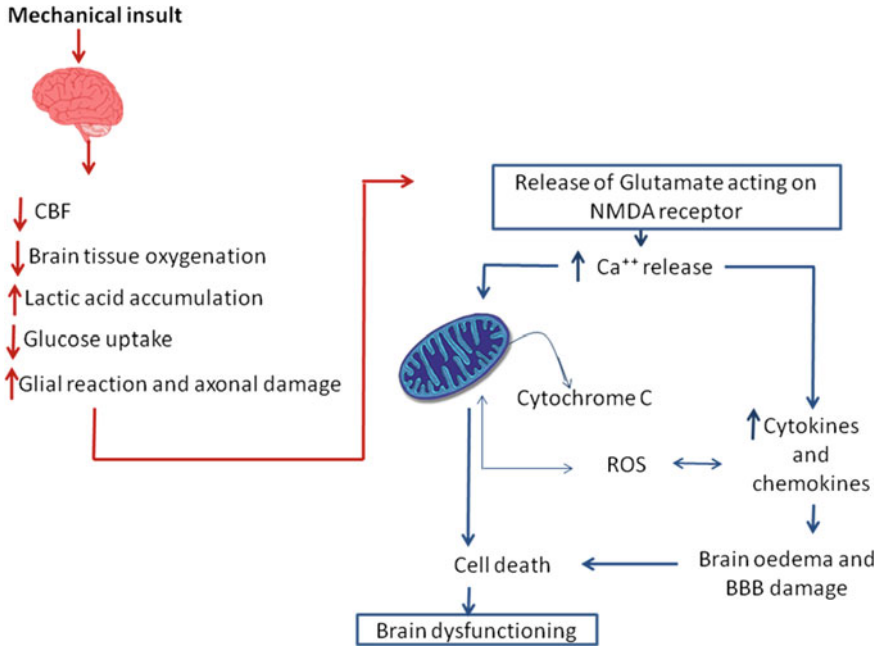


Fig. 1 Molecular mechanism involved in TBI

2 Types of Traumatic Brain Injury (TBI)

Depending upon the degree of severity, TBI can range from mild to severe with an extended period of unconsciousness. TBI occurs when an outside force impacts the head causing the brain to move, a direct blow to the head or a rapid acceleration and deceleration of the head mainly caused by motor vehicle accidents, sporting or leisure, workplace injuries, assaults, blasts, etc.

Traumatic brain injuries (TBIs) are classified into many types depending upon the tools used for analysis such as CT scans and magnetic resonance imaging (MRI). These techniques easily help to differentiate the multiple types of brain injury and variety of host factors and other confounders that might influence the yield of clinical trials (Fig. 2).

Based on severity of traumatic brain injury

| Injury | GCS | PTA | LOC |
|-----------------------------|-------|---------------|----------------------------|
| Mild TBI | 13–15 | <1 day | 0–30 min |
| Moderate TBI | 9–12 | >1 to <7 days | >30 min to <24 h |
| Severe TBI | 3–8 | >7 days | >24 h |
| Vegetative state | <3 | – | Coma |
| Persistent vegetative state | <3 | – | Coma longer than one month |
| Brain death | – | – | – |

where *GCS* Glasgow Coma Scale; *PTA* post-traumatic amnesia; *LOC* loss of consciousness

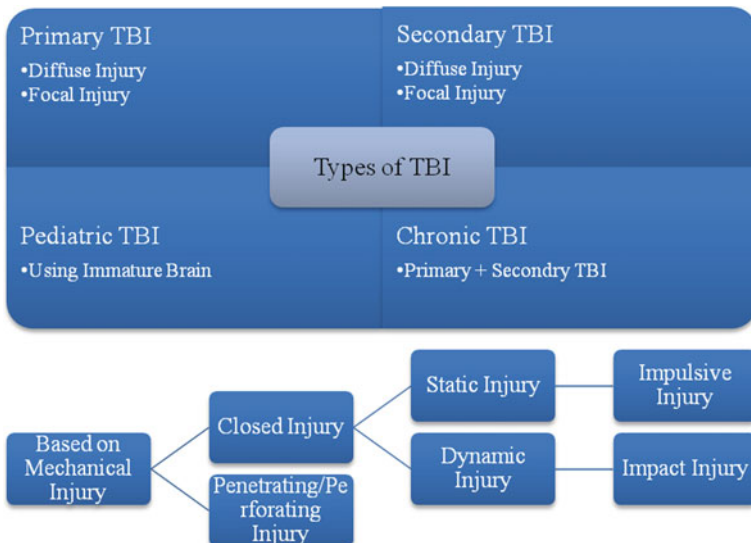


Fig. 2 Classification of TBI

The human head injury is very heterogeneous, and it is very hard to conduct controlled studies on human beings according to ethical guidelines. So the animal models are the powerful tools help to determine the typical patterns of dysfunction, perceive neurobiological mechanisms, and explore potential therapeutic interventions. Still at present, no FDA-approved pharmacological treatment available for the detrimental consequences (e.g., cognitive, emotional, behavioral impairment) is occurred due to TBI. However, the neuroprotective drugs, which were earlier identified to be effective in animal models of TBI, had not shown significant effectiveness in phase II or phase III of clinical trials. This failure in the preclinical studies highlights a compelling need to revisit the current status of animal models of TBI and therapeutic strategies.

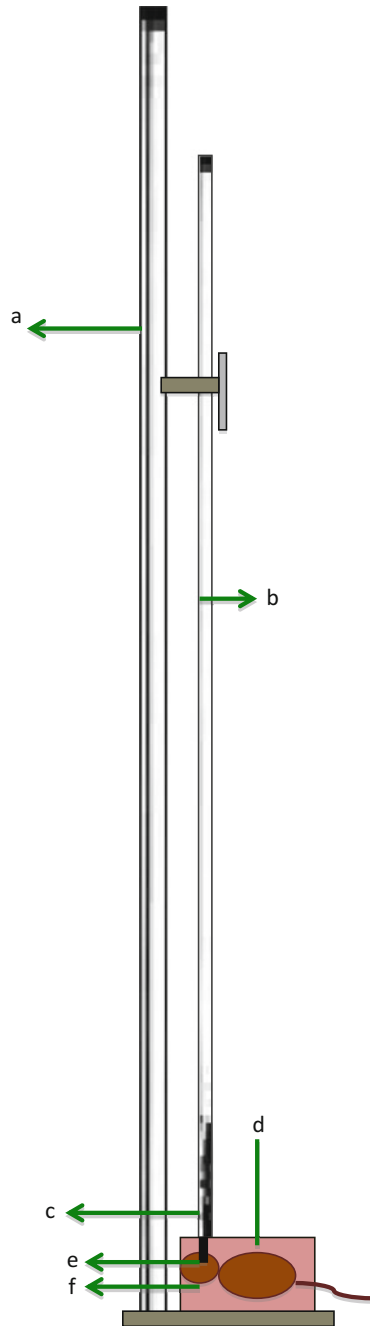
However, many mild TBIs have functional effects that last for a considerable amount of time and the underlying factors remain to be established. In most models, the mechanical input is controlled and results in injury that is reproducible, quantifiable, and clinically relevant. No single animal model is reliable for providing the full spectrum of human TBI, so that is why different models with different pathologies were proposed to know the underline mechanism.

3 Classification of TBI Models

The classification of TBI based on GCS for trial inclusion and targeted therapies is important, but mechanistic classification has great utility in modeling injuries and developing preventive measures. The most commonly used TBI models are described below:

| Injury/mechanism | Animal model |
|--|---|
| Acceleration/deceleration TBI | <ul style="list-style-type: none"> • Feeney's weight-drop model • Shohami's weight-drop model • Marmarou's weight-drop model • Maryland's model |
| Impact acceleration (direct brain deformation models) | <ul style="list-style-type: none"> • Fluid percussion injury model • Controlled cortical impact model |
| Penetrating TBI models (skull perforation by missile, impact energy) | <ul style="list-style-type: none"> • Penetrating ballistic brain injury model • Pellet accelerated penetrating trauma model |
| Blast TBI models (high velocity, impact brain injury) | <ul style="list-style-type: none"> • Open-field blast • Blast tubes for explosive • Shock tubes with compressed air or gas • Fragment penetration model |
| Miscellaneous | <ul style="list-style-type: none"> • Cell culture system • Cranium only blast injury apparatus |

Fig. 3 Design of Weight-drop model assembly where: **a** Clamp stand; **b** Guide pipe 1–2 m; **c** Cylindrical slotted weights 450 gm; **d** Anesthetized rat lying on foam bed; **e** Metallic disk surgically adhered between bregma and lambda; **f** Foam bed of (10 cm thick)



3.1 Models for Acceleration/Deceleration TBI

Weight-drop TBI model: Weight-drop TBI model closely resembles with the real-life injuries and symptoms as observed in mild traumatic brain injury patients; therefore, weight-drop model is considered as original TBI model and is commonly used to deliver a traumatic brain injury to rodents like rats/mice. TBI patients often experience cognitive, behavioral, and emotional disturbances which are closely mimicked by this model (Fig. 3).

Procedure:

- In weight-drop model, firstly animal is anesthetized, and then, skull is exposed for the free-falling weight to generate a direct focal cortical compression.
- The apparatus consists of a guide pipe of length 1–2 m, either made up of Plexiglas or metal through which weights (composed of either metal or acrylic) are passed.
- For the induction of a mild injury, the weight should be less than 50 g, while for moderate, it should be 51–99 g weight; severe trauma corresponds to a 100–149 g weight, and for induction of ultra-severe injury, weights greater than 150 g should be used.
- Usually, a metal plate is fixed to the cranium or by craniotomy directly into the brain to reduce the risk of skull fracture.
- The animals are placed on non-flexible platforms for inducing focal brain injury in order to reduce loss of energy whereas flexible platforms like foam or platforms with elastic springs are used for inducing a diffuse brain injury so that impact is distributed over the skull.
- The induced brain injury such as hemorrhages, neuronal cell death, astrogliosis, diffuse axonal injury, or cytotoxic brain edema is purely dependent upon the severity of the impact. Weight-drop models of TBI vary with regard to the method of induction of injury and location of impact.

3.1.1 Feeney's Weight-Drop Model

It is consisted of a rat model in which craniotomy is induced prior to TBI resulting in a cortical contusion with hemorrhage and damage to the blood–brain barrier. This leads to activation of microglia and astrocytes with activation of the complement system and invasion of neutrophils and macrophages. Cortical spreading depression and delayed microcirculatory disturbances have also been reported in this model. The severity of injury determines the pattern of post-traumatic cell death (Feeney et al. 1981).

3.1.2 Shohami's Weight-Drop model

This rodent model is mostly used for closed head injury (CHI), consisting of a weight-drop impact delivered to one side of an unprotected skull by the head on the hard surface. The height and mass of the falling weights determine the severity of injury in this model. Therefore, heavier weights or increased falling height produces

an ipsilateral cortical brain contusion and blood–brain barrier disruption followed by brain edema and finally cell death. Recently, neurobehavioral deficits, activation of microglia and astrocytes, neurodegeneration, and morphological changes detected by MRI have been demonstrated in this mouse CHI model indicating this model resembles the clinical condition in human CHI.

3.1.3 Marmarou’s Weight-Drop Model

The impact acceleration model of diffuse traumatic brain injury (DTBI), commonly referred to as the “Marmarou” weight-drop model. This model depicts the clinical aspects of DTBI a type of TBI in humans, which is mainly caused by falls or motor vehicle accidents. The device consists of sectioned weights set that fall freely from a designated height through a Plexiglas tube.

Procedure:

- In this, surgical procedure is performed with anesthesia given to the rats and are subjected to a midline incision to expose their skull.
- A metallic disk is adhered surgically between lambda and bregma so as to prevent skull fracture.
- The rats are then placed on a foam bed and subjected to the impact by dropping the sectioned weight onto the metallic disk.
- The impact that is induced by a falling of a 450-g weight from a 2-m height causes a mortality rate of 44% with 12.5% incidence of skull fracture.
- The mortality in this model is primarily caused by respiratory depression; therefore, mechanical ventilation after the impact greatly reduces the mortality rate after severe injury (Foda and Marmarou 1994).

3.1.4 Maryland’s Model

In this model, TBI can be produced by applying the impact force to the anterior part of the cranium, causing anterior–posterior plus sagittal rotational acceleration of the brain inside the intact cranium. The characteristics of animals are absence of mortality, absence of cortical contusions, skull fractures, prolonged apnea, but the chances of hemorrhages and diffuse axonal injury are more. Also, the neurobehavioral dysfunction is manifested as reduced spontaneous exploration persists for more than 1 week. However, there is a need of more studies for exploring the pathological causes (Xiong et al. 2013).

Advantages:

- This model is useful to investigate mild to severe diffuse brain injuries.
- This model provides ease to perform and is able to produce graded diffuse axonal injury similar to human TBI.
- Weight-drop model produces variable brain injury and is used to assess focal to diffuse brain injuries as seen clinically.
- This model does not produce any structural damage to the mouse’s brain as confirmed by MRI.

- It has been widely used in preclinical settings to assess the effect of pharmacological intervention to treat diffuse brain injury.
- This model produces irreversible learning and memory deficits, escorted by a depression-like behavior in mice as evidenced even 90 days post-injury.

Disadvantages:

- Weight-drop models show high variability in producing brain injury.
- Unintended skull fractures and imprecision with regard to the impact site is commonly seen in this model.
- These models have been criticized in the past due to their reduced level of impact control and measurement.

3.2 Impact Acceleration Models (Direct Brain Deformation Models)

The direct brain deformation models (through craniotomy) and penetrating head injury (through skull perforation by a missile) are caused by the impact energy.

3.2.1 Fluid Percussion Injury Model

Principle: The model of closed head injury with fluid pressure is an important model of cerebral concussion. It was first developed by Lindgren and Rinder (1969) in order to produce an “experimental brain concussion.” The model was originally developed in rats and has been modified for use in mice to create similar injuries related to focal injury models. Thompson et al. (2005) concluded that it is currently the most widely employed animal model of TBI which appropriately elicits the human TBI. As a result of fluid percussion, this model corresponds to mortality rate 20–25% in animals after the acute post-traumatic period (15 min). Generally, the common features are respiratory failure and pulmonary edema which replicates (Fluid Percussion Injury) FPI clinically like TBI without skull fracture.

Procedure:

- Firstly, anesthetize the animals and then apply fluid pulse to the intact dura mater through a craniotomy made centrally around the midline between bregma and lambda or laterally over the parietal bone between bregma and lambda in a stereotaxic frame for inducing diffuse brain injury.
- A reservoir cylinder filled with sterile solution of either saline or distilled water is attached to the cap cemented on the craniotomy of the animal’s skull.
- Now with the help of pendulum, generate a rapid (~ 20 ms) fluid pulse which causes an insult, through the craniotomy onto the intact dura following the inner curvature of the skull and creates an elastic decompression of the brain.
- The mechanical forces disrupt cell membrane, blood vessels, and neuronal processes.

- The severity of the injury depends on the strength of the pressure pulse, which can be adjusted by selecting the angles of the pendulum. The brain injury caused by this model replicates human TBI without skull fracture mixed with diffuse injury characteristics (Thompson et al. 2005).

Traumatic pathology involves:

- Cortical contusion, hemorrhage, and brain edema (cytotoxic or vasogenic) typically either bilateral for central FP injury or ipsilateral for lateral fluid percussion injury.
- Changes in the blood pressure, elevated craniocerebral pressure, decreased cerebral perfusion pressure, reduced cerebral blood flow directly promote respiratory arrest, and increased cerebral vascular resistance have been shown to produce fluid percussion.
- Neuronal cell death, necrosis, and apoptosis are found to be major hallmarks which improve the reproducibility of fluid percussion model.

Advantages:

- FPI has been regarded as the best model to represent intracerebral hematoma.
- The model provides graded level of injury severity by adjusting the force of the fluid pressure pulse.
- The model increases the relevance as the recovery period after surgery returns the animals to a condition that more closely resembles the human condition.
- FPI significantly alters the cognitive dysfunction irrespective of the location of injury; hence, it can be a useful model for post-traumatic dementia.
- It is widely accepted in neurotrauma research for both mechanistic studies and for drug screening because it can reproduce intracranial hemorrhage, brain swelling, and progressive gray matter damage that are all pathophysiological hallmarks of human TBI.
- This model induces the injury which directly replicates the clinical contusion without skull fracture.

Disadvantages:

- Fluid percussion at high velocity levels produces an injury primarily associated with the brain stem which may also result in histopathological changes that are not typically characteristic of severe human TBI.
- Fluid percussion model is complicated in terms of clinical aspects because the pressure from injection of the fluid pulse is not directly associated with mechanical impact to the brain.
- This model includes the fluid pulse that disperses diffusely within the epidural space, making the tissue displacement difficult to compute, along with the lack of a cortical contusion.

- It increases the severity or morbidity mainly due to disproportional involvement of the brainstem and development of neurogenic pulmonary edema.
- The fluid flow characteristics (i.e., direction, displacement, and velocity) are dependent on brain geometry and the species so it is difficult to achieve the accurate biomechanical analyses after injury.
- High mortality rate due to apnea is evident.

3.2.2 Controlled Cortical Impact Injury Model (CCI)

Principle: This model was the first to be developed by Lighthall (1988) with the use of ferrets. The CCI model is widely used in TBI research because of its simplicity and high reproducibility. CCI is an invasive impact method that causes a measurable brain displacement using a solid percussion device applied through a cranial opening.

Procedure:

- It consisted of a rigid impactor to generate the mechanical energy to the intact dura with the head of the animal usually for delivering the good impact.
- The compressed air mechanically drove the actuated piston which is rigidly mounted on a crossbar in either an angled or vertical position to control the velocity and depth of cortical impact causing deformation in the parenchyma with an intact dura.
- The impactor is attached to the lower end of the metallic piston, and pressurized air acts as the source of the mechanical energy.
- A typical penetration depth for this device is 2.6–2.8 mm with a velocity of 4.0 m s^{-1} and a dwell time of 50–150 ms consistently produces an injury of moderate severity. However, it is useful for producing controlled focal or cortical deformations in the rodents that mimic histological, physiological, neurochemical, and functional aspects of human traumatic brain injury.

Advantages:

- The model is reproducible and induces varying severity of brain injury.
- This model provides high level of correlation between the degree of cortical distortion and histological damage.
- This model provides ease to control various mechanical factors such as time, velocity, and intensity of impact.
- This model minimizes the risk of a rebound injury.
- This model does not produce stem deformation and has very less mortality rate.
- This model replicates similar neurobehavioral and cognitive deficits as seen clinically.

Disadvantages:

- This model fails to produce symptoms of pure diffuse brain injury.

3.3 Penetrating TBI Models

Missile injuries, such as gunshot wounds, are a common cause of military TBI. The injury occurs when an object with high velocity penetrates the skin, skull, and meninges directly injured to the brain tissue. These injuries are of two types penetrating and perforating depending on how the missile traverses the head. When the object enters and dwells within the cranial cavity, it is called penetrating injury, but when the object passes through the cranial cavity and leaves an exit wound, it is called perforating injuries. The severity of the injury depends upon missile shape and mass and also the direction and velocity. At present, no high-speed penetrating rodent injury model has been available except a ballistic brain injury model using a balloon inflation technique. At current, there are only two rodent penetrating TBI models.

3.3.1 Penetrating Ballistic Brain Injury Model (PBB)

The PBB model in rats was developed by Williams et al. (2005), in which bullet-like round inflatable penetrating probe is used to produce a large temporary cavity in the brain. The model reflects the features both the permanent injury and large temporary injury. For the permanent injury, the tract is created by selecting the specific path of the bullet itself, but the large temporary cavity or injury is generated by energy dissipation from the bullet. The procedure utilizes the probe with balloon, which is to be inserted in the brain at the desired location and with rapid inflation commonly mimics the temporary cavity.

Advantage:

- The model has been characterized in a large number of studies and can presumably generate important knowledge about cavity formation during fragment penetration.

Disadvantages:

- The major obstacle with this model is high mortality rate in high-speed penetrating TBI.

3.3.2 Pellet Accelerated Penetrating Trauma Model

Principle: This is a recently developed penetrating TBI model (Plantman et al. 2012), in which the object penetrates in the brain parenchyma at approximately 90 m/s after being hit by a pellet of an anesthetized rat. The pellet which hits the probe is accelerated by a modified air rifle. The speed and the depth of penetration are adjustable and highly reproducible (Plantman et al. 2012). Neurodegeneration occurs in the injured cortex 24 h after injury. After a period of 14 days, the injury develops into a large cavity. It also produces extracellular perivascular edema.

Advantage:

- The biomechanics of this TBI model enables survival of the animals following a high-speed penetration of brain tissue.
- The model produces motor disturbances with severe memory impairment.

3.4 Models for Blast (High Velocity, Impact Brain Injury)

Traumatic brain injuries (TBI) related to high velocity is more common among the military personnel worldwide. However, the mechanism how the blast waves affect the brain is not well understood. Experimental animal models provide significant correlation by mimicking mild TBI due to blast and also provide an insight pathological mechanism of the injury. Single or multiple blast exposures have been commonly seen in association with chronic neurological and psychiatric sequelae including persistent cognitive impairment, post-traumatic stress disorder (PTSD), and depression. Blast injuries occur through multiple mechanisms that may be related to the effects of the primary blast wave, or by the individual being knocked down or thrown into solid objects.

3.4.1 Open-Field Exposure

This experiment determined the thresholds for mortality and injuries such as bleeding in air-filled organs such as the lungs and intestines. The potential effects on the central nervous system are, however, difficult to assess.

Advantages:

- Open-field experiments may allow for more realistic experiments with large animals that are more similar in size to humans.

Disadvantages:

- These types of experiments require large amounts of explosives and difficult to perform at every experimental laboratory.

3.4.2 Blast Tubes for Explosives

Earlier these large size blast tubes were created to study the effects of wave forms relevant to nuclear detonations. Later on, these blast tubes were modified for their utilization in rodents in around 1990s. Now presently while experimentation, the anesthetized animals are mounted in the blast tube at a distance of 1 m from the charge. Five grams of plastic explosives PETN (pentaerythritol tetranitrate) results in a peak pressure exceeding 10 bars during detonation. The animals are mounted in metallic nets or fixed to a body protection in order to limit acceleration

movements. The secondary and tertiary blast effects are very difficult to perform in this model. However, smoke and gas emission contribute with quaternary blast effects.

Advantages:

- The equipment can be used in laboratory.
- The quality and quantity of blast waves can be controlled easily.

Disadvantages:

- Short duration and very simple form of the blast wave.

3.4.3 Shock Tubes with Compressed Air or Gas

Procedure:

- In this procedure, the animals are firstly anesthetized and then exposed to high-blast waves with peak reflected overpressures for inducing blast trauma.
- Helium under high pressure is utilized by placing the rats were at certain distances, i.e., 39 and 17 cm, from the shock tube opening for the low- and high-blast shockwave exposure conditions, respectively.
- Pressure sensors depict the typical reflected pressures (either 100 or 450 kPa referred to the low-blast and high-blast conditions, respectively).
- However, the exhaust gasses, or blast wind, can lead to considerable head acceleration; animals were placed 40° and 20° lateral to the shock tube axis to limit blast wind exposure for the low- and high-blast conditions, respectively (Budde et al. [2013](#)).

Advantage and Disadvantage:

- The duration of the pulse is usually longer, and the peak pressure is much lower than in the Clemmedson tube. Also, quaternary blast effects as well as other disadvantages of explosives are absent. However, this advantage can also be regarded as a disadvantage.

3.4.4 Model for Fragment Penetration

This model can be used to mimic the more severe blast TBI, where shrapnel fragments penetrate the skull and brain tissue. The velocity of such fragments is assumed to be less than 300 m/s, depending on the presence and effectiveness of helmets.

Procedure:

- Firstly, anesthetize the rats and then place in a stereotaxic frame for performing craniotomy. A lead bullet is accelerated by air pressure in a specially designed rifle and impacts a secondary projectile.
- Now, allow the pin of the secondary projectile, guide by a narrow tube penetrates the surface of the brain with a speed of 100 m/s.
- The base of the projectile is surrounded by a compressible ring that helps to control the penetration (depth) into the brain, which is usually set to 5 mm.
- The speed and shape of the penetrating secondary projectile can be changed to obtain a variation of physical properties.

Advantages:

- This penetrating TBI results in a central cavity corresponding to the actual penetration. A zone of reactive tissue, which contains a mixture of dying cells, reactive cells, and invading inflammatory cells, surrounds this cavity.
- Electron microscopy has demonstrated mainly extracellular perivascular edema.

Disadvantages:

- This method gains less success due to high mortality rate in animals.

Ethical Statement

All institutional guidelines, national guidelines, state and local laws and regulations with professional standards for the care and use of laboratory animals should be followed. Studies involving animals must state that the institutional animal ethical committee has approved the protocol. For authors using experimental animals, a statement should be made that the animals' care is in accordance with institutional guidelines and animals used have been treated humanely and with regard to the alleviation of suffering. Researchers should treat animals as sentient and must consider their proper care and use and the avoidance or minimization of discomfort, distress, or pain as imperatives. Animal experiments should be designed only after due consideration of animal health. It should be ensured that all researchers who are using animals have received instruction in research methods and in the care, maintenance, and handling of the species being used. All the surgical procedures should be performed under appropriate anesthesia and followed only those procedures which avoid infection and minimize pain during and after surgery.

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