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# MODELING OF CRANIOSKELETAL TRAUMA IN THE EXPERIMENT (REVIEW)

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**Abstract. Aim.** To determine the existing models of craniocerebral and skeletal trauma to improve the modeling of combined polytrauma in the experiment.

**Methods.** The search for scientific publications was carried out in NCBI PubMed for 2018-2023 using the keywords "TBI", "Traumatic brain injury", "model", "animal model". As a result, 583 original studies were obtained with a detailed indication of the TBI or fracture model used. All models were divided into 7 types according to Xiong: controlled cortical impact, weight drop, fluid percussion injury, blast injury, repetitive mild trauma, ballistic trauma, and rotational acceleration.

**Results.** The most commonly used model for modeling TBI is the controlled cortical impact model, which was used in 307 cases. While most researchers consider cortical impact model easy to reproduce and affordable, craniotomy is an crucial element to localize the injury.  A less commonly used model in terms of frequency of use in published sources is the weight drop model, which was used in 91 papers (15.6%). The severity of the injury is regulated by the weight and height of the dropped object, as well as the area of the impactor. The most commonly used among them are the model proposed by Feeney, the Shohami model, and the Marmarou model. The fluid percussion model is used to study diffuse unilateral axonal lesions, although the frequency of its use is lower - 60 (10.3%) cases. The model allows studying diffuse axonal lesions in the absence of a skull fracture. A unique aspect of the model is the ability to study such elements of TBI as increased intracranial pressure and intracerebral haemorrhage 43 studies (7.4%) described the use of the model with the use of single-event multiple mild TBI. To model blast-related TBI, 34 studies (5.8%) used explosive elements of different strengths and at different distances from animals. The use of explosive chamber with separation of explosive from the test animal by a diaphragm allows for standardisation of the impact. In 23 (4%) studies, a penetrating ballistic model was used to study TBI resulting from gunshot wounds to the head. Subsequent neurodegeneration is also caused by hypoxia due to haemorrhagic shock and activation of endogenous enzymes. The rotational acceleration model is used both for modelling acute stage of TBI and for repetitive mild TBI. For assessment of TBI, the neurological severity score (NSS) and its modification (mNSS) are mostly used. There is a close morphological relationship between the severity of TBI and the degree of neurological deficit according to the mNSS. The simplest and with the highest reproducibility is the three-axis bending trauma of femoral fracture followed by intramedullary fixation. If the aim is to study the bone healing in the absence of stabilisation, no fixation is performed. Open osteotomy increases both fracture pattern reproducibility and surgical complications rate.

**Conclusion.** The main possible disadvantages of the existing models of traumatic brain injury are the frequent need for craniotomy, their reproducibility and lethality. It is advisable to use a controlled cortical impact, or a weight drop device as the most reproducible and available models. Among the models of skeletal trauma, the closest to clinical conditions is a closed three-axis bending model. The quality of modeling of combined polytrauma depends on careful consideration of all aspects of the chosen model.

**Keywords:** animal model, polytrauma, traumatic brain injury, fracture.

**Introduction.** Polytrauma is a major cause of mortality and disability in developed countries under the age of 45 [1]. The term "polytrauma" is usually used to describe cases of damage to two or more areas of the human body with a total score on the Injury Severity Scale(ISS) of more than 15 [2, 3]. Among all cases of polyfocal injuries, the most common (19%) is head and limb injury, which is called combined cranio-skeletal injury (CSI) [4].

Isolated traumatic brain injury (TBI) is one of the leading causes of death worldwide [5]. More than 31% cases of in-patients TBI are lethal [6]. The vast majority of TBIs are closed and occur as a result of road traffic accidents, falls from a height, and blunt trauma [7, 8]. TBI results in a complex pathophysiological process with primary and secondary damage to brain structures [9]. However, not all molecular and physiological aspects of TBI are studied [10], so modelling TBI in experimental animals remains necessary not only to determine the safety and efficacy of neuroprotective drugs, but also for further research on both isolated TBI and polytrauma [9, 11, 12].

Several methods are available to model TBI in the experiment, according to the type of lesion (focal, diffuse or mixed) and the severity of the injury (mild, moderate or severe) [10]. However, having a similar modelling goal, the methods can differ significantly in terms of the representativeness and reproducibility of each model [10].

According to statistics, fractures of the femur and lower leg bones are the most common among all structures of the musculoskeletal system in polytrauma [13]. That is why polytrauma is most often modelled in combination with TBI and tubular fracture with soft tissue injury and blood loss[14]. There are methods for modelling fractures of tubular bones in animals with simultaneous internal or external fixation of the fracture [15,16]. Femur fracture is more commonly modelled from the skeleton because of its adequate soft tissue coverage [15].

Modelling of polytrauma remains essential for studying the black dots in the bone healing under the influence of the local and systemic immune response that occurs during the "genomic storm" [17, 18].

**Objective.** To improve the modelling of a combined type of polytrauma by analysing existing models of TBI and skeletal trauma.

**Materials and methods.** We searched for scientific publications in the NCBI PubMed database for 2018-2023 using the combined keywords "Traumatic brain injury", "model", "animal model", "skeletal trauma", "fracture". Duplicates, in vitro studies, and review articles were removed from the 907 search results. As a result, 583 original studies were obtained with a detailed description of the used TBI or fracture model.

All models were divided into 7 types according to the classification proposed by Xiong [9]: controlled cortical impact, weight drop, fluid percussion injury, blast injury, repetitive mild trauma, ballistic trauma, and rotational acceleration.

**Results and discussion.**

**Controlled cortical impact (CCI).** The most used model for modelling TBI is the CCI model, which was used in 307 (52.7%) studies related to TBI. This model is based on the use of a commercial or self-developed device to deliver a single point standardised impact to the brain tissue. The model is used both with and without craniectomy. However, the craniotomy is an important element of localizing the injury. In order to strike the planned structures, it is necessary to take into account the stereotactic map of the projections of the brain structures [9]. The diameter of the impactor determines the area, type, and strength of the lesion: subdural haematoma, local axonal lesion, contusion, or coma.

Most researchers consider CCI easy to reproduce and affordable [19]. There are even commercially available electromagnetic and pneumatic devices for simulating CCI [20]. The severity of TBI clearly depends on the force of impact [21]. The necessary physical parameters for modelling different degrees of TBI severity are clinically and histologically confirmed and described in detail in existing studies [9, 21].

**Weight drop(WD).** The less commonly used model in terms of frequency of use in published sources is the WD model, which was used in 91 studies (15.6%). The model is based on a targeted weight injury under the acceleration of free fall. The severity of the injury is regulated by the weight and height of the dropped object, as well as the area of the impactor. The most commonly used WD is the one proposed by Feeney [22].

There are several modifications of the WD. The Feeney model involves craniectomy and a blow to the dura mater [22]. The traumatic agent is a compressive subdural haematoma that occurs as a result of the impact, with a predicted recovery of neurological deficit from 2 to 12 weeks, depending on the severity of the injury [23]. The Shohami model is a variant of modelling closed TBI due to impact on the bare skull [9]. Several clinical and experimental studies have confirmed the representativeness of the Shohami model and its correlation with clinical data in humans [24]. The model proposed by Marmarou is used to simulate diffuse axonal damage that occurs in road traffic accidents (RTAs) or falls from a height [9]. To do this, after exposing the skull bones, a disc or metal helmet is fixed to them with glue, which is hit by a WD, causing diffuse damage to brain tissue, the area and depth of which depends on the width of the disc [25]. The Maryland WD modification involves modelling one of the most common types of road traffic injuries - frontal cortex injury [25]. This model of injury occurs in the form of anterior-posterior and diffuse brain damage in the absence of a skull fracture [9, 26].

**Fluid percussion injury (FPI)** is a simultaneous sharp increase in intracranial pressure because of the jet injection of a predetermined amount of fluid into the epidural space with an intact dura mater. Since this mechanism is used to study mostly diffuse unilateral axonal lesions, the frequency of using the model is lower - 60 (10.3%) studies with FPI. The model allows studying diffuse axonal lesions in the absence of a skull fracture, however, its mandatory element is a craniotomy [27]. The craniotomy site determines the location of the lesion. A unique aspect of the model is the ability to study such elements of TBI as increased intracranial pressure and intracerebral haemorrhage [28]. The reproducibility of this model has been demonstrated in rats and other mammals [9, 29]. The number of studies indicates a concomitant high mortality of the model compared to others [30].

**Repetitive mild TBI.** Since mild TBI is common in sports, there are models that mimic a similar injury in animals. Moreover, 70 to 90% of all TBIs are mild [31]. There is reliable evidence that repetitive TBI has a cumulative long-term effect, causing irreversible neurodegeneration [31]. There is also a correlation between repetitive mild TBI and the onset of post-traumatic stress disorder, which is relevant for military personnel [21, 32]. 43 studies (7.4%) describe the use of these models using both single-event repeated mild TBI and series of mild TBI over a period of time in animals under sedation. There are several ways to model repetitive mild TBI: a series of impacts due to a fall from a height, controlled cortical impacts, or a series of low-energy explosions [32].

**Blast model.** To model blast injury as well as TBI, 34 studies (5.8%) used explosive elements of different strengths and at different distances from animals. These studies revealed an increase in axonal damage when using body armour that directs the blast wave towards the head [33], as well as due to temporary short-term hypoxia caused by lung and heart contusion [9]. When modelling TBI due to an explosion, both standard models with explosive elements of different strengths and shock tubes are used, where the explosive chamber is separated from the test animal by a diaphragm of the required strength, which allows for standardisation of the impact [34]. Given the high military value of such studies, there is a NATO standard (STO-TR-HFM-234) for modelling pathologies caused by blast [35].

**Penetrating ballistic-like brain injury (PBBI)** was used in 23 (4%) studies to study TBI resulting from

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gunshot wounds to the head and from trauma with small elements of high kinetic energy. Similar patterns occur in non-lethal shots with high-energy objects through the anatomical structures of the brain with the formation of a primary defect zone(permanent cavity) and a temporary(stretch) cavity [36]. Studies indicate diffuse brain damage in areas that were not involved in the initial trauma with damage to both cellular and subcellular structures [36, 37]. In addition to neurotrauma, subsequent neurodegeneration is also caused by hypoxia due to haemorrhagic shock and activation of lysosomal enzymes [38]. The model allowed us to identify potential neuroprotective properties of drugs such as glibenclamide and dextromethorphan in penetrating brain injuries, but, as the authors point out, further research is needed [32, 39].

Models using **rotational acceleration** (CHIMERA - Closed-head impact model of engineered rotational acceleration) are a new non-surgical method of modelling TBI occurring in road accidents due to whiplash trauma. Over the past 5 years, 25 (4.3%) publications have described the results of applying this model. The model is qualitatively representative and easy to use, causing diffuse axonal damage [40]. This model is used both for modelling TBI of varying severity [41] and for repetitive mild TBI [42, 43]. Repetitive trauma by a similar mechanism, in addition to memory impairment, long-term neurodegeneration, and coordination disorders, causes visual impairment in experimental animals due to secondary immune damage [44]. Similar injuries can occur in people whose profession is associated with overloads due to rotational force: fighter pilots and astronauts [41].

**Assessment of TBI.** In addition to invasive morphological analysis, there are several scales for assessing the neurological status of experimental animals, similar to the Glasgow Coma Scale, to determine the required force of injury that causes different types of TBI severity [45]. In addition, there are a number of techniques for assessing the dysfunction of individual elements of the neurological state: motor function and cognitive function [45].

The Morris water maze is the most widely used and researched method for assessing memory in animals, with proven cross-species reproducibility in humans and rodents [46]. Briefly, the maze consists of a 150 cm wide water basin with an invisible underwater platform and one or more visual landmarks. The animal is placed at one or more predetermined points in the pool, each time recording the duration of the platform search, the length of the path, and the speed of movement [47].

To assess motor function, rotating rods, walking tests with sticks of different widths and balancing platforms are used–[45]. A more reproducible assessment is based on the analysis of gait in experimental animals after TBI, where the injury causes a slower gait, shorter distance between steps and a disturbed walking pattern.

For assessment of TBI severity, the neurological severity score (NSS) and its simplified modification (mNSS) are most commonly used [48]. The NSS is a comprehensive assessment of motor, sensory, reflex and cognitive function based on several tests: time to find the exit from the circle maze, paresis, gait disturbance, clap reflex, pole balancing, beam test and beam balancing test [48]. Each of these elements corresponds to a certain number of points: from 1 to 6 points corresponds to mild TBI, from 7 to 12 points to moderate TBI, and more than 13 points to severe TBI [49]. The disadvantage of the scale is the inability to distribute the degree of damage to individual components of neurological status, so additional scales should be used for this purpose [50]. There is a close morphological relationship between the severity of TBI and the degree of neurological deficit according to the mNSS [51].

**Modelling of skeletal trauma.** The model of closed skeletal trauma is most used to study the mechanisms and impairment of bone repair, as closed fractures of the axial skeleton account for the majority of skeletal trauma in humans [52]. Experimental models of skeletal trauma allow the identification and testing of potential treatment strategies for nonunions [52]. There are several options for modelling fractures of both metaphyseal and diaphyseal bone regions [53]. However, the simplest and, at the same time, the closest to real conditions with a high reproducibility is the three-axis bending model, where there is an adequate damage to the soft tissues, which is important in the context of modelling polytrauma [15], or its guillotine modification [54]. The model consists of placing the hip of a anaesthetised animal under a mechanism where there are two points of support in the area of the femoral metaphysis, and the fracture is caused by controlled pressure or impact in the intermediate area between them [54]. In such cases, fracture stabilisation is performed intramedullary [55]. For better reproducibility of the model, intramedullary fixation is performed before the injury, which contributes to a more controlled and expected fracture pattern [55]. Fractures of the proximal bone are stabilised with external fixation devices or plates [56]. If the aim is to study the bone healing in the absence of stabilisation, no fixation is performed [57]. The presence of a fracture and the position of the fixator are determined clinically or/and by X-ray [54].

The open model involves an osteotomy with or without additional trauma to the muscles or other soft tissues [16]. The osteotomy procedure involves soft tissue trauma that affects healing, but the procedure mimics standard surgical practice for hard to closed reposition fractures [58]. The advantage of the model is the reproducibility of the fracture pattern and the degree of soft tissue injury during the trauma [59]. However, the additional trauma to the intramedullary canal by osteotomy should be taken into account when interpreting the results [58]. The risks of bone infection due to exposure of the fracture zone to the environment can also affect the results [60].

**Conclusions.** The main possible disadvantages of traumatic brain injury models are the need for craniotomy, their reproducibility and lethality. Craniotomy is an additional forcing factor osteogenesis, which should be considered while interpret study results. Since the majority of TBIs are closed and not accompanied by skull fracture, it is advisable to use a controlled cortical impact, or a weight drop device as the most reproducible and available models with the most realistic conditions of injury.

Further improvement of existing models of TBI is needed to reduce their mortality and increase their reproducibility.

Among the models of skeletal trauma, the three-axis bending model is the closest to clinical conditions. However, to improve the reproducibility of skeletal trauma, further modification of existing models and development of new ones is necessary.

The quality of simulation of combined polytrauma depends on careful consideration of all aspects, advantages, and disadvantages of the existing models to mimic a specific clinical situation.

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## МОДЕЛЮВАННЯ КРАНІОСКЕЛЕТНОЇ ТРАВМИ В ЕКСПЕРИМЕНТІ (ОГЛЯД ЛІТЕРАТУРИ)

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**Резюме. Мета.** Визначити існуючі моделі черепно-мозкової та скелетної травми для покращення моделювання поєднаного виду політравми в експерименті.

**Методи.** Пошук наукових публікацій здійснювали в NCBI PubMed за 2018-2023 роки за ключовими словами «TBI», «Traumatic brain injury», «model», «animal model». В результаті отримали 583 оригінальних дослідження з детальним зазначенням використаної моделі ЧМТ або перелому. Усі моделі поділено на 7 типів згідно робори проведеної Xiong.

**Результати дослідження.** Найчастіше для моделювання ЧМТ використовується модель контрольованого кортикального удару, яку використали в 307 випадках. Менш вживаною моделлю за частотою використання в опублікованих джерелах є модель вільного падіння (weight drop), яку використали в 91 роботі (15,6%). Найбільш часто вживаною серед них є модель, запропонована Feeney, модель Shohami та модель Marmarou. Для вивчення дисфузного унілатерального аксонального ураження використовується рідинна струменева модель, хоча частота її використання є меншою – 60 (10,3%) випадків. Модель дозволяє вивчати дифузне аксональне ураження за відсутності перелому кісток черепа. У 43 дослідженнях (7,4%) описано використання моделі із застосуванням одномоментної багаторазової легкої ЧМТ. Для моделювання акубаротравми, а також ЧМТ при вибухових ураженнях у 34 дослідженнях (5,8%) використовувались вибухові елементи різної сили та на різній відстані від тварин. В 23 (4%) дослідженнях для вивчення ЧМТ, що виникає внаслідок вогнепальних уражень голови використовували проникаючу балістичну модель. Найпростішою і з найвищим показником відтворюваності є трьохосьовий згинальний механізм формування перелому стегнової кістки.

**Висновок.** Основними можливими недоліками існуючих моделей черепно-мозкової травми є часта необхідність краніотомії, їх відтворюваність та летальність. Серед моделей скелетної травми найбільш наближеною до клінічних умов є закрита трьохосьова згинальна модель. Якість моделювання поєднаної політравми залежить від ретельного врахування всіх аспектів обраної моделі.

**Ключові слова:** тваринна модель, політравма, черепно-мозкова травма, перелом.

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