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The Neurobehavioral Response in a Rat Model of Brain Injury Using the Weight Drop Method

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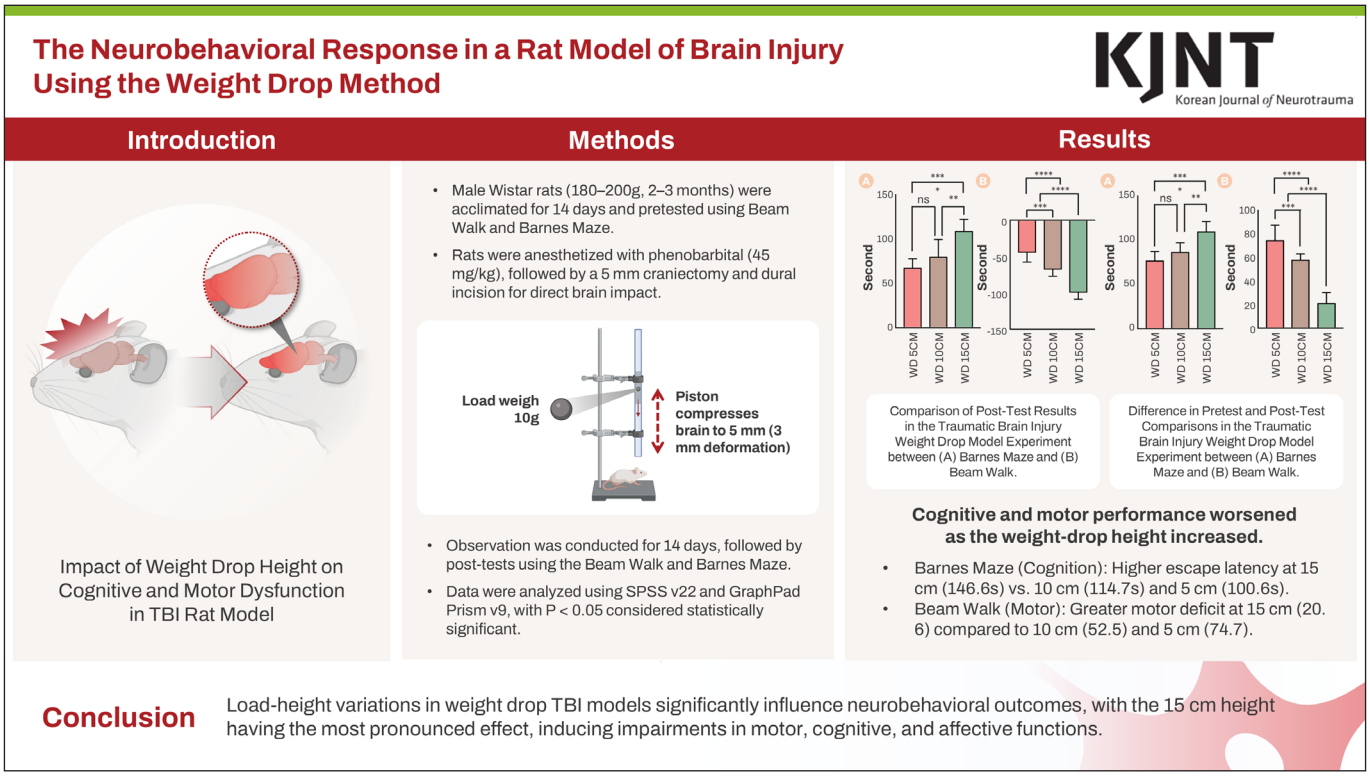
ABSTRACT

Objective: To evaluate the effects of high-impact loads in a weight drop (WD) model of traumatic brain injury (TBI) on sustained neurobehavioral dysfunction over a 14-day period.
Methods: The experimental treatment involved craniotomy of rats, exposing the brain to a load applied via the WD method. Loads of 10 g were dropped from heights of 5, 10, and 15 cm. Neurobehavioral assessments included the Barnes maze for cognitive and affective function evaluation and the beam walking test for motor function assessment. Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 22 and GraphPad Prism version 9 software. Statistical significance was set at $p<0.05$.
Results: In the Barnes maze test, an increase in WD height was directly proportional to the post-test mean score, indicating poorer cognitive performance, with WD 15 cm yielding the highest mean score (146.6±16.8), followed by WD 10 cm (114.7±22.7) and WD 5 cm (100.6±18.6). Conversely, in the beam walk test, an increase in WD height contributed to a decline in motor performance, with the lowest mean score observed at WD 15 cm (20.6±9.84), while WD 10 cm (52.5±9.79) and WD 5 cm (74.7±12.5) showed less impairment.
Conclusion: Load-height variations in WD TBI models significantly influence neurobehavioral outcomes, with the 15 cm height having the most pronounced effect, inducing impairments in motor, cognitive, and affective functions.

Keywords: Models, animal; Neurobehavioral manifestations; Maze learning; Motor activity; Brain injuries, traumatic

GRAPHICAL ABSTRACT



Funding
No funding was obtained for this study.

Conflict of Interest
The authors have no financial conflicts of interest.

Informed Consent
This type of study does not require informed consent.

Ethics Approval
This study was conducted with ethical approval from the Research Ethics Committee of the Faculty of Medicine, Universitas Brawijaya (No. 246/EC/KEPK-S3/11/2022).

INTRODUCTION

Traumatic brain injury (TBI) is a major global health concern. In the United States, more than 1.7 million cases of TBI occur each year.[21] In Indonesia, the incidence and mortality rates of TBI remain high, particularly among males aged 15–24 years, who are often involved in motor vehicle accidents.[27] TBI is not a degenerative or congenital condition, but rather a result of mechanical external forces that can cause either permanent or temporary impairment of cognitive, physical, and psychosocial functions.[5]

TBI can manifest in various forms ranging from mild alterations in consciousness to prolonged coma or even death. In cases of severe brain injury, the entire brain tissue may sustain damage accompanied by cerebral edema.[8] The severity of TBI is typically assessed using the Glasgow Coma Scale (GCS), with mild (GCS 13–15), moderate (GCS 9–12), and severe (GCS 3–8) categories.[16,22]

TBI consists of primary brain injury resulting from direct mechanical impact, and secondary brain injury due to the primary injury or cellular and molecular metabolic processes that ultimately lead to neuronal cell death, tissue damage, glial scar formation, and atrophy.[26] Clinical manifestations include decreased consciousness, neurobehavioral deficits, and cognitive impairment.

Given the high prevalence and extensive impact of TBI, effective therapies are urgently required to mitigate tissue damage and prevent secondary injury. However, to date, no optimal

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treatment exists, and research is ongoing through *in vitro*, *in vivo*, and clinical trials. *In vitro* testing lacks relevance owing to the absence of living organisms, whereas *in vivo* testing is suitable for observing therapeutic responses to neural injury. Direct testing in humans poses high risks; thus, animal models are employed to better understand the pathophysiology.

Over the past 80 years, numerous animal models have been developed to replicate distinctive human features, including emotional, cognitive, and biomechanical aspects.[2] Rats are a commonly selected model in TBI research due to their small size, cost-effectiveness, and physiological similarities to humans. Several widely used TBI models in rats include weight drop (WD) injury, fluid percussion injury, controlled cortical impact, and blast injury.[26]

From a patho-anatomical perspective, TBI can be classified into focal and diffuse brain injuries. In this study, we used a TBI model with the WD method, as previous research has shown that the WD model effectively represents focal brain injury with characteristics of localized axonal damage.[10,17] Specifically, the Shohami WD injury model is clinically relevant for inducing traumatic axonal injury in small animal models, such as rats.[11,26] Additionally, this model is advantageous in producing neurobehavioral deficits pertinent to the development of TBI therapies. In the WD model, craniotomy is performed to minimize the bias arising from differences in skull and scalp thicknesses in rats. The injury severity can be adjusted according to the weight and drop height of the impactor.

In a previous study by Shohami's group, as cited in Flierl et al.[7], a WD model was used, employing weights ranging from 333 g to 1,600 g at a drop height of 2 cm, which correlated with mild injury, while a drop height of 3 cm was linked to severe injury. In contrast, Feeney et al.[6] used a WD device to induce graded focal cortical contusion. A low impact force (50 g/cm^2) did not produce surface hemorrhage, whereas higher forces (200–1,000 g/cm^2) resulted in surface bleeding and cortical disorganization in some.

Neurobehavioral responses investigated in rats subjected to TBI induced by the WD model include impairments in cognitive, motor, and affective functions.[2] In alignment with these findings, this study aimed to develop a model of TBI caused by blunt trauma that is valid, straightforward, cost-effective, and easily applicable. This model was intended to produce posttraumatic neurobehavioral deficits while ensuring the survival of experimental animals for a 14-day observation period, thereby maximizing the timeframe for evaluating therapeutic efficacy.

MATERIALS AND METHODS

Experimental design and study framework

This study employed a true experimental design with an *in vivo* approach. A pre-test and post-test control group research design was applied, in which assessments were conducted both before and after the intervention to evaluate the impact of varying drop heights on rats subjected to TBI. This study was conducted with ethical approval from the Research Ethics Committee of the Faculty of Medicine at Universitas Brawijaya (No. 246/EC/KEPK-S3/11/2022).

Experimental animals and selection criteria

The experimental animals used in this study were male Wistar strain *Rattus norvegicus* rats aged 2–3 months and weighing 180–200 g. Rats were sourced from a breeder at Universitas

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Brawijaya, Malang. Prior to treatment, the rats were acclimated to the laboratory for 14 days to ensure stability. Only healthy rats, identified by active movement, thick white fur, and clear eyes, were included in this study. Rats displaying congenital abnormalities or signs of illness, such as sluggish movements or narrowed eyes, and those that died during the experiment were excluded from the study. However, none of the rats died during the experiment, and all subjects survived until the neurobehavioral test was conducted on day 14. Therefore, no animals were excluded on the basis of mortality, and the consistency of injuries across all subjects was maintained.

WD apparatus and protocol

The WD apparatus used in this study was an innovative adaptation of the Feeney model (**FIGURE 1**). It consisted of a metal platform to hold the rat in place, fitted with pins to secure the rat's head, and a safety strap to stabilize the body during the procedure. The front of the platform had a cylindrical projectile holder attached to a 25 cm transparent glass tube. This tube was marked with a centimeter scale for a precise WD onto the rat's head from predetermined heights. The glass tube could be rotated 360° to allow precise positioning of the weight over the rat's head as required for the study. To ensure sterility, the WD apparatus, including the weights, was sterilized using a central sterilization machine (autoclave), following the same protocol as for surgical instruments. This sterilization procedure was performed before each experiment to maintain a sterile environment and prevent contamination.

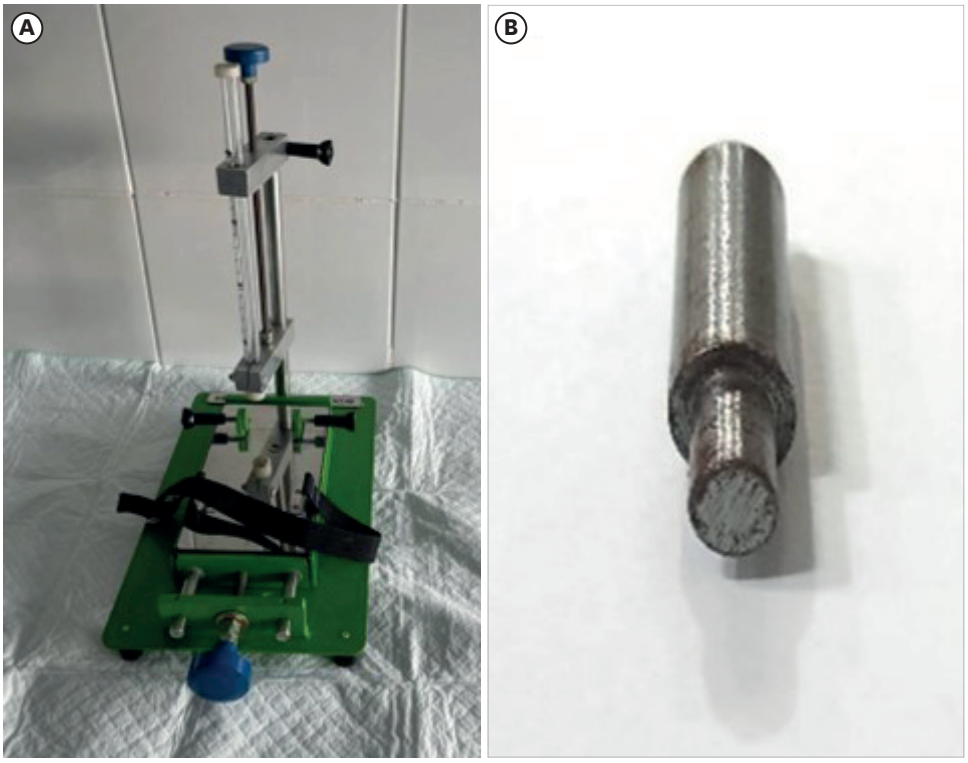

FIGURE 1. The weight-drop model used to induce TBI in rats includes a transparent load delivery tube, 25 cm in length, which allows for controlled adjustments to the drop height. This setup facilitates precise simulation of TBI in experimental rats. (A) The full apparatus view; (B) A 10-g weight being dropped onto the exposed brain of a rat to induce TBI.
TBI: traumatic brain injury.

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TBI induction in experimental animals

The TBI procedure involved dropping a 10-g weight from various heights. According to a study by Xiong et al.,[26] the injury severity in these models (WD models) can be altered by adjusting the mass of the weight and the height from which it falls. Each rat group was impacted from a specific height of 5 cm (group 1), 10 cm (group 2), and 15 cm (group 3). Based on a study by Nyanzu,[17] the WD method showed high variability in injury severity. To reduce this, drop heights of 5, 10, and 15 cm were chosen, with 5 cm being the lowest, to ensure consistency and reproducibility and produce moderate-to-severe injuries, as observed in previous studies.

Craniotomy and brain injury procedure

In this study, brain exposure was implemented during the WD procedure to minimize any potential bias from the dura mater, which may reduce the force transmitted to the brain, resulting in diffuse injury. By opting for brain exposure, we aimed to induce a more direct and focal cortical injury. This approach ensured consistency in the injury model across all subjects and enhanced the accuracy of the experimental outcomes. The rats were administered an intraperitoneal injection of phenobarbital (45 mg/kg body weight) for anesthesia and secured on a surgical table using a stereotactic apparatus. The scalp was shaved and disinfected with 10% povidone-iodine solution. The aseptic technique was followed throughout the procedure, and a local anesthetic, lidocaine HCl (2%), was applied. A 5 mm craniectomy was performed on the left side, positioned 3 mm posterior to the bregma and 2 mm lateral to the midline for all groups, as a modification of the approach described by Hua et al.,[9] considering the use of a smaller size for rats in our study. The dura was incised using a No. 11 blade, and a 10-g weight was dropped from each respective height of 5 cm, 10 cm, and 15 cm directly onto the exposed brain. The contact surface area of the weight with the exposed brain tissue was 2 mm. This ensured accurate alignment with the brain exposed through the 5 mm craniectomy, allowing for precise delivery of the impact to the target area. The rats were randomly assigned to one of 3 groups: group 1 (5 cm height), group 2 (10 cm height), and group 3 (15 cm height). The piston compressed the brain tissue to a maximum depth of 5 mm, with a brain deformation of 3 mm. The scalp was then sutured using 5-0 monofilament interrupted sutures. Post-procedure, the rats were returned to their cages and maintained at room temperature (23°C±1°C).

Neurobehavioral function assessment

The rats that underwent treatment and sustained brain injury were observed for 14 days to assess any neurobehavioral dysfunction that may occur during the observation period. We chose a 14-day follow-up period as it allowed the inflammatory phase to subside and the proliferative phase to begin, ensuring the viability of the animals for further treatment evaluation. Motor function was assessed using the beam walking test, which measures the time taken by each rat to traverse a narrow beam (**FIGURE 2**). The beam used in the beam walking test had a length of 1 m and width of 1 cm. We selected the beam walking test because it offers ease of setup and requires less observation time to efficiently evaluate motor abilities. In the Barnes maze test, we measured escape latency, defined as the time taken by the rats to locate the escape hole, as a primary parameter for evaluating cognitive performance (**FIGURE 3**). Cognitive and affective functions were evaluated using the Barnes maze test, in which rats were required to navigate through a maze to locate an exit. The Barnes maze test was chosen for its simplicity in construction and its ability to assess cognitive and affective functions simultaneously in a short period. These assessments were conducted both before (pre-test) and after (post-test) treatment to evaluate neurobehavioral changes due to TBI. Each rat

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FIGURE 2. Beam walking test setup.

FIGURE 3. Barnes maze test setup.

underwent a training session before the pre-WD test assessments. The day before the pre-test, the rats were trained for 15 minutes each in both the Barnes maze and beam walk tests to familiarize them with the apparatus and procedures. Additionally, to ensure animal health and exclude signs of infection or fever, the body temperature was monitored daily using a thermogun throughout the study. Temperature readings were recorded, and any significant deviations were promptly addressed.

Statistical procedure and data analysis

Data collected from the pre-test and post-test assessments are presented in tables and bar charts. An analysis of variance (ANOVA) test was performed to analyze the differences among the treatment groups, followed by a *post hoc* test to identify significant differences. All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) version 22 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 9 software (GraphPad Software Inc., San Diego, CA, USA). Statistical significance was set at $p<0.05$.

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RESULTS

The results of this study were divided into 2 sections, a comparison of post-test outcomes and the difference between pre-test and post-test scores, utilizing 2 testing methods: the Barnes maze and beam walk. The post-test results for both methods at each WD level (5, 10, and 15 cm) are presented in **TABLE 1**.

In the Barnes maze test, an increase in WD height was directly proportional to the post-test mean score, with WD 15 cm yielding the highest mean score (146.6±16.8), followed by WD 10 cm (114.7±22.7) and WD 5 cm (100.6±18.6). Conversely, in the beam walk test, an increase in WD height contributed to a decline in performance, with the lowest post-test mean observed at WD 15 cm (52.5±9.79), while WD 10 cm (20.6±9.84) and WD 5 cm (74.7±12.5) showed comparatively less decline in performance (**FIGURE 4**).

Statistical analysis using ANOVA revealed significant differences across both testing methods (p<0.0001). *Post hoc* analysis with Tukey's test indicated that in the Barnes maze test, there was no significant difference between WD 5 cm and WD 10 cm (p=0.1523).

TABLE 1. Comparison of post-test results in the traumatic brain injury model induced by WD between Barnes maze and beam walk

Testing method	WD (cm)	Mean	*p*-value
Barnez maze	5	100.6±18.6	<0.0001
	10	114.7±22.7	
	15	146.6±16.8	
Beam walk	5	74.7±12.5	<0.0001
	10	52.5±9.79	
	15	20.6±9.84	

WD: weight drop.

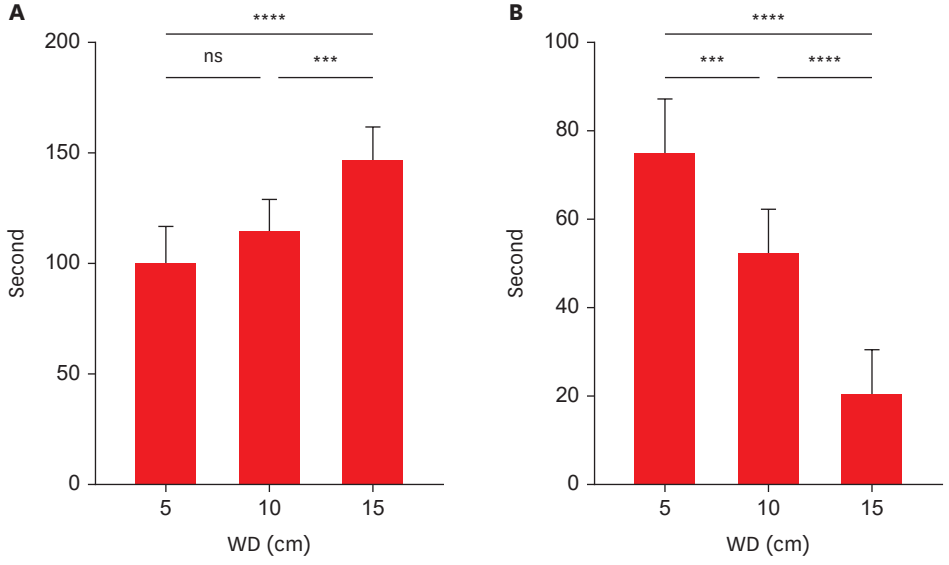

FIGURE 4. Comparison of post-test results in the traumatic brain injury weight drop model experiment between (A) Barnes maze and (B) beam walk. Data are presented as mean ± standard deviation. Statistical analysis was conducted using analysis of variance.
WD: weight drop, ns: not significant.
An asterisk (*) indicates a statistically significant difference between the 2 treatment groups (***p< 0.001, ****p<0.0001), while (ns) denotes no statistically significant difference.

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TABLE 2. Difference in pre-test and post-test comparisons in the traumatic brain injury weight drop model experiment using the Barnes maze and beam walk tests

Testing method	Delta (cm)	Pre-test–post-test difference (mean ± SD)	*p*-value
Barnez maze	5	67.11±10.9	<0.0001
	10	79.89±19.7	
	15	108.55±14.5	
Beam walk	5	−45.22±12.53	<0.0001
	10	−67.44±9.779	
	15	−99.33±9.84	

SD: standard deviation.

However, a significant difference was observed between WD 5 cm and WD 15 cm (p<0.0001) and between WD 10 cm and WD 15 cm (p=0.0006). In the beam walk test, all pairwise comparisons of WD height demonstrated statistically significant differences (p<0.0001), with a more substantial decline in performance associated with increasing WD height.

The results of the pre-test and post-test comparisons in the TBI WD model experiment using the Barnes maze and beam walk tests at each WD level (5 cm, 10 cm, and 15 cm) are shown in **TABLE 2**.

The pre-test-post-test difference in the Barnes maze test indicated a significant improvement in performance with increasing WD height. The greatest mean increase was observed at WD 15 cm (108.55±14.5), followed by WD 10 cm (79.89±19.7) and WD 5 cm (67.11±10.9). ANOVA revealed a significant difference across all WD groups (p<0.0001). *Post hoc* Tukey's test indicated no significant difference between WD 5 cm and WD 10 cm, whereas WD 15 cm was significantly different from both (p<0.0001) (**FIGURE 5**).

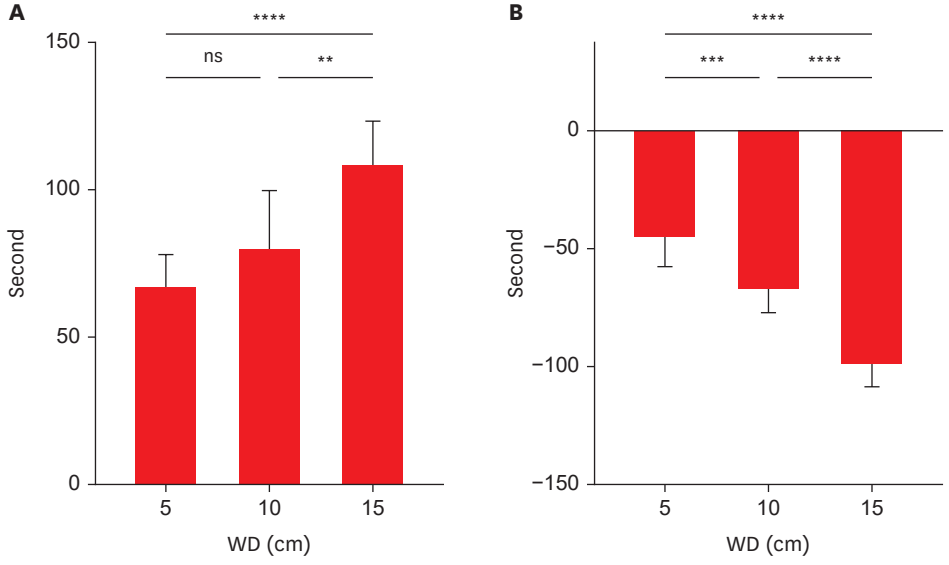

FIGURE 5. Difference in pre-test and post-test comparisons in the traumatic brain injury WD model experiment between (A) Barnes maze and (B) beam walk. Data are presented as mean ± standard deviation. Statistical analysis was conducted using analysis of variance.
WD: weight drop, ns: not significant.
An asterisk (*) denotes a statistically significant difference between the 2 treatment groups (**p< 0.01, ***p< 0.001, ****p<0.0001), and (ns) indicates no statistically significant difference.

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In the beam walk test, the pre-test-post-test difference revealed a progressively larger decline in performance with increasing WD height. The greatest decline was observed at WD 15 cm (−99.33±9.84), followed by WD 10 cm (−67.44±9.779) and WD 5 cm (−45.22±12.53). ANOVA also indicated a significant difference among the 3 WD groups (p<0.0001), and *post hoc* Tukey's test revealed that all pairwise comparisons between WD levels were statistically significant (p<0.0001).

DISCUSSION

The weight drop model of traumatic brain injury in reducing neurobehavioral function

A commonly used model to induce TBI in rodents is the WD model.[26] This model induces brain injury by dropping a weighted object directly onto the target area (e.g., the brain), with the severity of injury adjusted by varying the weight and the height from which it is dropped. In this study, the WD method was applied to induce TBI by dropping a 10-g weight from heights of 5, 10, and 15 cm. The results indicated that a 10-g weight dropped from a height of 15 cm successfully induced significant brain injury in rats. These findings are consistent with those reported by Wardhana et al.,[25] where a 10-g weight dropped from 5 to 10 cm caused brain injury in rats, with a 10 cm drop height leading to substantial injury. Similarly, another study conducted by Toklu et al.[23] also demonstrated that a 10-gram weight dropped from 10 cm effectively produced brain injury in rats.

The WD method for inducing brain injury has been shown to produce injury severity dependent on both the weight and the drop height of the object.[1] Differences in brain injury severity are associated with variations in trauma height, where greater weight and height result in more severe brain injury, subsequently impacting the inflammatory cell response within the brain.[20] In a study by Chakraborty et al.,[4] an aluminum weight of 500 g was dropped from heights of 100 cm and 120 cm onto rat brains, revealing that the 120 cm drop height yielded the most optimal injury effect due to higher impact energy (0.588 joules) compared with the 100 cm drop (0.49 joules). Similarly, another study reported that TBI in rats can be induced by a 250-g object dropped from a height of 2 cm.[11] Based on these findings, it can be concluded that the WD model, specifically using a 10-g weight dropped from a height of 10 cm, is sufficient to induce TBI in rodent test subjects.

This study also assessed neurobehavioral responses, including motor, cognitive, and affective functions, in rats using the beam walking test and Barnes maze. Neurobehavioral evaluations were conducted before and after the WD intervention to determine any differences in neurobehavioral responses. The results of the beam walk test showed a significant difference in pre- and post-intervention performance in the intervention group, with a decline in average beam walk scores post-intervention. ANOVA revealed that the most substantial decline occurred in rats subjected to a 10-g WD from a height of 15 cm, as they exhibited limited time to maintain balance, resulting in difficulties in coordination and increased falls. Delta analysis further confirmed a highly significant difference between the control and intervention groups, as indicated by a negative delta value following the WD intervention.

Assessment of motor impairment via beam walk evaluation

The beam walking test is widely used to detect subtle deficits in motor skills and balance that may not be identifiable through other motor coordination tests.[14] Findings from this

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study indicated that rats subjected to a WD intervention, specifically a 10-g weight from a height of 15 cm, exhibited motor dysfunction, evidenced by the limited ability to maintain balance before ultimately falling. These results are consistent with those of Martínez-Tapia et al.,[15] who reported that rats with TBI displayed a statistically significant reduction in latency. Reed et al.[19] also documented altered gait patterns in rats resulting from TBI. Based on these findings and the supporting literature, it can be concluded that rats exposed to a 10-g WD from a 15-cm height experience neurobehavioral disturbances, particularly in motor function.

A more substantial decline in performance with an increased drop height suggests that heightened brain trauma progressively impairs motor abilities, as evidenced by the beam walk test. This finding emphasizes the increasing severity of neurobehavioral deficits as trauma increases, underscoring the critical role of drop height in evaluating the impact of physical stressors on motor function.

The clinical manifestations commonly observed in patients with TBI are frequently associated with neurological and cognitive deficits. The Barnes maze is a widely employed method to assess cognitive impairment and learning deficits in rodents with TBI.[24] Findings from this study indicated that the Barnes maze performance, pre- and post-intervention in the treatment group, revealed significant differences in the mean time taken by the rats to complete the maze by locating the escape route. Post-intervention ANOVA showed that the most pronounced delay occurred in rats subjected to a 10-g WD from a height of 15 cm, where the animals required substantially longer time to navigate the maze. Delta analysis further substantiated these findings, demonstrating a statistically significant difference in task completion between the control and intervention groups, as indicated by a negative delta value after WD, signifying an increased time requirement for the rats to locate the exit in the Barnes maze.

Assessment of cognitive and affective disorders using the Barnes maze

The Barnes maze has become a widely used method for evaluating spatial working memory, spatial reference memory, and cognitive flexibility in rodents.[12] The results of this study align with findings indicating that animals with severe TBI may experience cognitive impairments detectable 1 week post-injury, whereas animals with mild TBI show no cognitive deficits on the seventh day post-injury.[10] Conversely, other studies have reported that rodents subjected to repeated mild TBI exhibit significant cognitive deficits compared with those without injuries.[3]

Rodents with TBI exhibit reduced behavioral flexibility when seeking an escape route in the Barnes maze, along with delayed performance compared with non-injured controls. Observations from the Barnes maze assessment suggest that these deficits extend beyond cognitive functions such as learning and memory; careful observation, coupled with supplementary tests, is necessary to evaluate potential anxiety-related behaviors.[18] Additional studies indicate that, compared with mild TBI, moderate to severe TBI poses a higher risk for chronic and persistent cognitive impairment.[13]

The results of this study showed that the 15 cm condition exerted the most pronounced effect on reducing the time to balance loss in rats, suggesting the existence of a threshold at which physical stressors may induce substantial impairment in neurobehavioral function. This observation reinforces the idea that TBI severity plays a crucial role in the extent of post-injury cognitive and motor deficits. Both empirical evidence and theoretical frameworks highlight that TBI can result in neurobehavioral disturbances, notably cognitive deficits.

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Limitations and suggestions for future research

This study has several limitations, including the absence of magnetic resonance imaging (MRI), lack of determination of inflammatory markers, and omission of histopathological examinations. In addition, an ideal control group was not included. Future studies should address these limitations by incorporating MRI to assess anatomical changes, determining inflammatory markers, and performing histopathological examinations to gain a deeper understanding of the underlying biological processes. Furthermore, employing an ideal control group such as rats undergoing craniotomy without the WD test would enhance the study design.

CONCLUSION

This study concludes that variations in the load-height combination in brain injury models using the WD method significantly influence neurobehavioral outcomes. The combination of a 10-g weight dropped from a height of 15 cm had the most pronounced effect, causing brain injury in rodents accompanied by neurobehavioral dysfunction. Neurobehavioral responses in rats after brain injury demonstrated impairments in motor, cognitive, and affective functions. Therefore, further investigations are warranted to explore variations in weight and drop height using the WD method. Future research should investigate the recovery processes following traumatic injury and evaluate effective management strategies for neurobehavioral impairment in rodent brain injury models after WD treatment.

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