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Serum Dynamics of Electrolytes, Lipid profile, and Neuro-Behavioral Severity Score in Traumatic Brain Injury-induced Albino Rat Models

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ABSTRACT

Traumatic brain injury (TBI) is a pervasive public health concern globally, with millions of reported cases annually. This study investigates the impact of TBI on neurobehavioral deficits, electrolytes and lipid metabolism in albino rat models at different time points within 24 hours. Twenty-eight albino rats were randomly divided into four groups of seven rats each; Group I (Non traumatized, Control), Group II (Traumatized and sacrificed at 0 minute), Group III (Traumatized and sacrificed at 30 minutes), Group IV (Traumatized and sacrificed at 1hour), Group V (Traumatized and sacrificed at 24 hours). TBI was induced using a weight drop method after anesthesia with xylazine and ketamine at 5mg/kg and 80mg/kg respectively. A neurological severity test was carried out to determine the neurobehavioral deficits of rats in all the experimental groups. Blood sample was collected after sacrifice at 0 hour, 30 minutes, 1hour, and 24hours respectively in plain sample bottle, and serum was collected for electrolyte and lipid profiles. A mild neurological impact at 30 minutes, 1 hour, and 24 hours post-injury was recorded as indicated by the lack of progression in the NSS-R score. There was a significant increase in sodium, potassium and chloride after TBI.Lipid profile analysis showed a significant increase in total cholesterol levels, while triglyceride levels remain stable post-TBI. High-density lipoprotein cholesterol (HDL-c) was significantly decreased post-TBI, while Low-density lipoprotein cholesterol (LDL-c) levels had no significant change post-TBI. Induction of traumatic brain injury can result in profound electrolyte imbalance and dyslipidemia within 24 hours, thus serving as baseline data for proposed therapeutic interventions.

Keywords: Albino rats; Electrolytes; Lipid profile; Neuro-behavioral severity score; Traumatic brain injury

INTRODUCTION

Traumatic brain injury (TBI) remains a significant public health concern worldwide, contributing to substantial morbidity and mortality rates annually (de Souza *et al.,* 2015; Maas *et al.,* 2022). TBI encompasses a spectrum of injuries ranging from mild concussions to severe traumatic insults, often leading to devastating neurological consequences (Chauhan, 2014; Gupta and Sen, 2016; Pearn *et al.,* 2017). The intricate pathophysiological mechanisms underlying TBI involve a cascade of events, including cellular damage, neuroinflammation, oxidative stress, and alterations in serum electrolytes and lipid profiles, which collectively contribute to the neurobehavioral deficits observed in affected individuals (Pathak and Sriram, 2023).

Serum electrolytes, comprising ions such as sodium, potassium, chloride, and calcium, play crucial roles in maintaining cellular homeostasis, neuronal excitability, and synaptic transmission within the central nervous system (Jomova *et al.,* 2022; Munteanu *et al.,* 2022). Disturbances in serum electrolyte levels have been extensively documented following TBI and have been

associated with adverse clinical outcomes. For instance, hypernatremia and hyponatremia have been linked to increased intracranial pressure and cerebral edema, exacerbating secondary brain injury in TBI patients (Hale *et al.,* 2019). Similarly, alterations in serum potassium levels have been implicated in the pathogenesis of neuronal hyperexcitability and seizure activity post-TBI (Zeng *et al.,* 2020). Understanding the dynamics of serum electrolytes in TBI-induced animal models is essential for

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elucidating their role in the pathophysiology of injury and identifying potential therapeutic targets.

Lipid metabolism also undergoes significant perturbations following TBI, with alterations in serum lipid profiles observed in both clinical and experimental settings (Hogan *et al.,* 2018; Bowman *et al.,* 2019; Allen *et al.,* 2023). Dyslipidemia, characterized by elevated levels of total cholesterol, triglycerides, and low-density lipoprotein cholesterol (LDL-C), coupled with decreased high-density lipoprotein cholesterol (HDL-C), has been reported in TBI patients and animal models (Wang *et al.,* 2018). These lipid abnormalities are thought to contribute to neuroinflammation, blood-brain barrier dysfunction, and neuronal cell death, thereby exacerbating TBI pathology. Investigating the temporal changes in serum lipid profiles in TBI-induced animal models can provide valuable insights into the underlying mechanisms driving lipid dysregulation and its impact on neurological outcomes.

Furthermore, assessing neurobehavioral deficits is integral to characterizing the severity and progression of TBI in animal models. Neurobehavioral assessment tools, such as the Neurological Severity Score (NSS), provide quantitative measures of motor function, sensory responses, and reflex activity following experimental TBI induction. Elevated NSS scores correlate with increased injury severity and impaired functional recovery, reflecting the complex interplay between neuronal damage, inflammation, and behavioral dysfunction in TBI (Chen *et al.,* 2019). Monitoring changes in NSS scores alongside serum electrolyte and lipid dynamics offers a comprehensive approach to evaluating the neuroprotective efficacy of therapeutic interventions in preclinical TBI research. This study was designed to investigate the serum dynamics of electrolytes, lipid profile, and neurobehavioral severity scores in TBI-induced albino rat models, with the aim of providing findings that can inform the development of targeted therapeutic strategies aimed at mitigating secondary brain injury and improving clinical outcomes in TBI patients.

MATERIALS AND METHODS

Experimental Animals

This investigation involved the acquisition of twenty-eight (28) healthy albino rats with weights ranging from 150-200g. The rats were obtained from the Faculty of Veterinary Medicine animal house, University of Maiduguri, Nigeria. The rats were given a period of three weeks to adapt to the environmental circumstances of the research facility and were provided with ad-libitum access to growers' mash of vital® feed and were also supplied with water.

Experimental Design

A cohort of 28 apparently healthy albino rats, with weights ranging from 150g to 200g, were randomly allocated into four groups, each consisting of seven animals.

Grouping of Experimental Animal

Group I: Non-Traumatized (control)

Group II: Traumatized and sacrificed at 30 minutes.

Group III: Traumatized and sacrificed at 1 hour.

Group IV: Traumatized and sacrificed at 24 hours.

Induction of Traumatic Brain Injury

The experimental animals, except for those in the negative control group, were subjected to head injury using the weight drop method. This approach involved the use of an acceleration impact device developed by Marmarou *et al*. (1994). The experimental rats were appropriately immobilized and anaesthetized using xylazine and ketamine combination at a dosage of 5mg/kg and 80mg/kg body weight, respectively. The animals were classified using the following designations: Neck, Back, RFL, RHL, Tail, LFL, and LHL. After the rats have lost consciousness, their scalp was shaved using a razor blade and subsequently sterilized with an antiseptic solution (Dettol). The cranium was surgically exposed by a midline incision measuring 1cm, utilizing a scalpel blade and a blade holder. Subsequently, a stainless-steel disk with dimensions of 10mm in diameter and 3mm in depth was affixed to the center of the frontal bone. The experimental animals were immobilized in a supine position on a foam bed with a depth of 10cm. The injury was caused by releasing a brass ball, weighing (120g) through a guide from a vertical distance of one meter. The stainless-steel disc was promptly removed from the cranium, while the lacerated skin was sutured utilizing chromic catgut size 3.0 in a simple interrupted suture pattern. The animal was permitted to recuperate within the confines of the enclosure.

Neurological Severity Score for Rats

The scoring was done at intervals within 24 hours using the methods described by Yarnell *et al*. (2016). Two vacant containers were positioned with approximately 25cm between them, a linear balance beam was positioned on top of the containers. Subsequently, a rat was positioned at the initial point of the beam to carry out a series of neurobehavioral assessments while accounting for the element of time. These assessments encompassed various tests, namely the general balance test, landing test, sound reflex, tail raise test, drag test, righting reflex, ear reflex, eye reflex, and paw flexion reflex. The findings are documented in the following manner.

0 = rat was able to do each of the above tests successfully without any hindrance.

1 = the rat had some difficulties while undergoing those tests.

2= rats did not respond. The scale has a total of 0 to 20 scores with higher scores indicating an increase in severity.

Data Analysis

The data obtained were presented in the format of mean ± standard deviation (SD). One-way analysis of variance (ANOVA) was used with turkey post hoc to detect significant differences between groups. Significance was attributed to differences in p values that were less than or equal to 0.05 ($P \leq 0.05$).

Ethical Statement

The Animal Use and Ethic Committee of the Faculty of Veterinary Medicine University of Maiduguri has approved the work, with AUP number AUP-R001/2022

RESULTS

Neurological Severity Score (NSS) of Albino Rat Induced with TBI within 24 hours

Table 4.1 showed the result of the neurological assessment (NSS) of all the experimental groups with the severity score being from 0 to 2, where 0 indicates normal response, 1 indicates abnormal response and 2 indicates no response TBI. There was a varied neurological response among the groups as indicated by their NSS-R score from 30 minutes to 24 hours.

Table 1. Neurological Severity Score in Post Traumatic Brain Injury-induced Rats

Groups	General Balance	Landing Test	Tail Raise test	Drag Test	Righting Test	Ear Reflex Test	Eye Reflex Test	Sound Reflex Test	Tail Reflex Test	Paw flexion Reflex
I	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
II	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
III	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
IV	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

Values are mean of seven rats per group. Normal response: 0, abnormal response: 1, No response: 2
Group I (NC) = Normal control (Non-traumatized), Group II =, Traumatized and sacrificed at 30 minutes, II = Traumatized and sacrificed at 1hr and IV = Traumatized and sacrificed at 24hr

Effect of Traumatic brain injury on serum electrolyte values of albino rats at different time points within 24 hours.

The results of this study showed significant changes in serum electrolytes levels between the groups. An increase in sodium (138.0±5.57, 144.0±5.51) at 30 minutes and 24 hours, potassium (7.93±1.51) after an hour, and chloride (99.3±1.53) after 24 hours, were observed in groups II, III and IV compared to the basal (normal) control group as shown in table 2. However, there was a decrease in sodium and chloride (133.0±7.00, 95.7±2.52), and an increase in potassium levels (7.93±1.51) in group III when compared to the control and other groups.

Table 2. Effect of Traumatic brain injury on serum electrolytes values of albino rats at different time points within 24 hours.

Groups	Timing	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)
Group I (NC)	0 minutes	136.7±8.08	6.90±1.47	97.3±6.43
Group II	30minutes	138.0±5.57	7.93±1.51	97.0±1.00
Group III	1HR	133.0±7.00	6.97±0.66	95.7±2.52
Group IV	24HRS	144.0±5.51	6.23±0.57	99.3±1.53

Value are expressed as mean ± SD (n=7).Group I (NC)= Normal control (Non-traumatized), Group II =Traumatized and sacrificed at 30minutes, III Traumatized and sacrificed at 1hr and IV Traumatized and sacrificed at 24hr.

Effect of traumatic brain injury on lipid profile values of albino rats at different time points within 24 hours

The results for lipid profiles change in response to traumatic brain injury in albino rats, over different time intervals, with the baseline represented by the normal group (Group 1) is shown in table 2. There was an increase in total cholesterol levels from 30 minutes (2.06 ± 0.30), with a significant increase ($p \leq 0.05$) observed at 1 hour (2.60 ± 0.65) post induction of traumatic brain injury when compared to the 0 hour (1.90 ± 0.45), while the triglyceride had no significant change in all traumatic brain injury induced rats compared to the control. There was a significant increase ($p \leq 0.05$) in HDL-cholesterol levels after 30 minutes (1.00 ± 0.05), and a decrease after an 1hour (0.83 ± 0.20) post induction of traumatic brain injury when compared with group I and group IV. There was not any notable significant change in LDL-Cholesterol level in all traumatic brain injury induced rats compared to the control (0 hour).

Table 3. Effect of Traumatic brain injury on lipid profile values of albino rats at different time points.

Groups	Timing (Hours)	T. Cholesterol (mmol/L)	Triglycerides (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)
Group I (NC)	0 hour	1.90 ± 0.45	0.7 ± 0.10	0.96 ± 0.05	1.26 ± 0.50
Group II	30 minutes	2.06 ± 0.30	0.93 ±0.15	1.00 ± 0.00[b]	1.46 ± 0.20
Group III	1 hour	2.60 ± 0.65[a]	0.70 ± 0.34	0.83 ± 0.20[b]	1.73 ± 0.86
Group IV	24 hours	1.96 ± 0.40	0.73 ± 0.11	0.86 ± 0.15	1.46 ± 0.20

Superscript in the same column represents statistical significance at ($p \leq 0.05$).Group I (NC)= Normal control (Non-traumatized), Group II, III and IV Traumatic brain injury-induced rats, HDL-c -High density lipoprotein cholesterol, LDL-c -Low density lipoprotein cholesterol.

DISCUSSION

The complicated role of electrolyte imbalance and dyslipidemia is delineated in severe cranial trauma and maybe essential investigations for its therapeuticmanagements. This study was designed touncover the pathophysiological changes in neurological response, lipid profile and electrolyte values in traumatic brain injury-induced rats, at different time points within 24hours.

The induction of traumatic brain injury showed clear signs of brain injury in all the traumatized rats, with marked changes in behaviour, motor activity, and level of consciousness. They were non-responsive to pinching, auricular, visual and auditory stimuli during the first 30 minutes and after 1 hour of induction. At 24hrs post TBI, they started responding but abnormally. Damage to cells caused by TBI results in neurological dysfunction. Source of the damage can be oxidative cell damage caused by free radicals, and inflammation-induced cell damage (Bulama *et al*., 2024).

The risk associated with the development of electrolyte disturbance in TBI patients depends on the severity of head injury, underlying disease, age, and primary therapeutic strategy such as the choice of resuscitation fluid, administration of mannitol or diuretics, and hyperventilation (Carney *et al.,* 2017). The most common electrolyte subject to imbalance in TBI patients is serum sodium (Suman *et al* 2016) and (Rafiq *et al.,* 2011). The reported most common electrolyte imbalance condition in TBI was hypernatremia followed by hyponatremia and hypokalemia (Rhoney *et al.,* 2006). An increase in serum sodium was observed in group II (138.0±5.57) and group IV (144.0±5.51) respectively between 30 minutes and 24 hours post traumatic brain injury compared with group I (136.7±8.08).

Potassium is the most common electrolyte which undergoes derangement during TBI. An increase in serum potassium was observed in group II (7.93±1.51) and group III (6.97±0.66) after 30mins and 1hour of TBI respectively. This is in accordance with the study conducted by (Pomeranz *et al* 1989; Bulama *et al* 2024). These changes may be because of large amount of catecholamine, which has been recorded during severe head trauma with resultant beta 2-adrenergic stimulation of the Na^+-K^+ pump (Pomeranz *et al.,* 1989). Potassium is released into the extracellular space by damaged cells, such as neurons and glial cells, which causes hyperkalemia, a secondary cause of TBI brought on by reduced cerebral perfusion and tissue hypoxia. As sodium is excreted, the body tries to maintain a balance by increasing potassium excretion in the urine which results in decreased potassium level as observed 24hours post TBI induction.

Chloride is an important component of diagnostic tests in many clinical situations and plays a key role in the regulation of body fluids, electrolyte balance, the preservation of electrical neutrality, acid–base status and it is an essential component for the assessment of many pathological conditions including traumatic brain injury. An increase in chloride level was observed in group IV (99.3±1.53) rats 24 hours post TBI, which was slightly above the normal control group with chloride value of (97.3±6.43). This may be attributed to the fast recovery of the rats after 24 hours post induction which tallies with neurological severity score test.

The lipid profile results in this study showed a significant increase in total cholesterol levels post induction of traumatic brain injury from 30 minutes to 1 hour. This increase may be attributed to the cellular membrane damage, Inflammatory and stress responses, change in liver function, and metabolic activities that occur following induction of traumatic brain injury (Turkoglu *et al.,* 2009; Chen *et al.,* 2009; Lim *et al.,* 2017). The cell membranes in the brain and other tissues contain lipids, including cholesterol. Induction of traumatic brain injury can cause damage to cell membranes, leading to the release of lipids into the bloodstream, this can contribute to an elevation in serum total cholesterol levels (Adibhatla *et al.,* 2010; Chodobski *et al.,* 2011). TBI can triggers inflammatory response as part of the body's defense mechanism, this inflammation can impact lipid metabolism and lead to changes in lipid levels, including an increase in total cholesterol that can affect the liver and other organs involved in lipid regulation (Reis *et al.,* 2015; Palafox-Sánchez *et al.,* 2021).

Trauma induces a stress response in the body, and this can also influence lipid metabolism. Stress hormones, such as cortisol, can affect lipid synthesis and utilization. The body might respond to the stress of TBI by increasing the production and release of lipids, including cholesterol (Mellon *et al.,* 2018; Womersley *et al.,* 2022). The liver plays a key role in lipid metabolism, induction of TBI may also affect liver function, leading to altered synthesis and clearance of lipids. Changes in liver function can contribute to variations in lipid levels, including total cholesterol (Cartagena *et al.,* 2010; Dave and Peeples, 2021). Additionally, Traumatic brain injury can result in metabolic changes throughout the body. These changes may influence lipid metabolism, leading to alterations in cholesterol levels. Disruption of normal metabolic processes can contribute to an increase in circulating lipids (Marino *et al*., 2006; Li and Sirko, 2018).

Triglycerides are essential components of energy metabolism, serving as a major energy reservoir in the body. They are primarily stored in adipose tissues and released into circulation during periods of increased energy demand (Wang *et al.,* 2008; Arrese and Soulages, 2010). There was no significant change in triglyceride levels in all rat groups induced with traumatic brain injury compared to the control group. This result agrees with the study of Karve *et al*. (2016) where they documented no significant change in triglycerides and other lipid parameters using a controlled cortical impact model in rats.

The maintenance of triglyceride levels in the aftermath of TBI could be attributed to the body's ability to compensate for metabolic changes. Following a traumatic injury, there may be a shift in energy utilization, with the body adapting to the increased energy demands associated with the recovery process. This metabolic

compensation may involve the mobilization of stored triglycerides from adipose tissues to meet energy requirements without significantly altering circulating levels (Bowman *et al.,* 2019; Kurtz and Rocha, 2020).

Additionally, TBI induces a robust inflammatory and stress response, leading to the release of various cytokines and hormones. While inflammation is often associated with changes in lipid metabolism, triglyceride levels may remain stable due to the complex interplay between pro-inflammatory and anti-inflammatory signals. A study by Flierl *et al*. (2013) demonstrated that the inflammatory response post-TBI did not uniformly impact all lipid parameters, suggesting a nuanced regulation of lipid metabolism. Discrepancies in findings across TBI studies may be attributed to variations in animal models, injury severity, and the specific methodologies employed. The choice of injury model (controlled cortical impact, fluid percussion injury, and weight drop) and the use of different rat strains could contribute to the observed heterogeneity in triglyceride responses (O'Connor *et al.,* 2011; Marklund & Hillered, 2011).

High density lipoprotein cholesterol (HDL-c) plays a crucial role in lipid transport and metabolism, acting as a scavenger for excess cholesterol and promoting its reverse transport from peripheral tissues to the liver. In healthy individuals, higher HDL levels are associated with a lower risk of cardiovascular diseases (Gordon *et al.,* 1989), and the impact of TBI on HDL levels is essential, given the potential consequences on both lipid homeostasis and overall cardiovascular health.

There was a significant decrease in High density lipoprotein-cholesterol (HDL-c) levels post induction of traumatic brain injury in all experimental groups compared to the control. This can also be attributed to the inflammatory response characterized by the release of pro-inflammatory cytokines and activation of immune cells. This finding agrees with the study of Chander *et al*. (2019) who demonstrated that the acute inflammatory response triggered by TBI in rats led to a reduction in HDL through increased catabolism and decreased production.

Oxidative stress is a hallmark of TBI, leading to the generation of reactive oxygen species (ROS) and subsequent lipid peroxidation. The study by Shohami *et al*. (1997) revealed that oxidative stress in the brain following TBI contributed to alterations in lipoprotein metabolism, including a decrease in HDL. Oxidative modification of lipids within HDL particles could impair their functionality and lead to accelerated clearance from circulation. TBI often results in the disruption of the Blood-Brain Barrier, allowing the entry of inflammatory mediators and compromising the overall integrity of the central nervous system. This breach may directly influence lipid metabolism, as demonstrated by a study by Pan *et al*. (2016), where BBB disruption in a rat TBI model was associated with decreased HDL levels. The mechanisms behind this phenomenon are not fully elucidated but may involve altered hepatic production or enhanced peripheral clearance.

Low-Density Lipoprotein is primarily responsible for transporting cholesterol from the liver to peripheral tissues. It plays a crucial role in maintaining cellular membrane integrity and serving as a precursor for steroid hormones (Khosravi *et al*., 2018; Gu *et al*.,2022). There was no significant change in Low density lipoprotein-cholesterol (LDL-c) level in all traumatic brain injury induced rats compared to the control. This finding agrees with the study by Wang *et al*. (2019) who found no substantial alterations in LDL levels, despite significant changes in other lipid parameters using a rat model of controlled cortical impact.

The lack of change in LDL levels post-TBI could be attributed to the temporal dynamics of lipid metabolism following injury. Studies examining the acute phase of TBI may not capture potential delays or chronic alterations in LDL levels. Longitudinal studies tracking lipid profiles over extended periods could provide a more comprehensive understanding of the time course of lipid changes post-TBI (Carmichael, 2014; Nessel and Michael-Titus, 2021).

Lipid metabolism is a highly regulated process with different lipoproteins serving distinct functions. While HDL levels may be more responsive to acute inflammatory and oxidative stress post-TBI, LDL levels may remain relatively stable due to different regulatory mechanisms. A study by Greco *et al*. (2019) suggested that alterations in lipoprotein profiles following TBI are specific to certain subclasses and may not uniformly affect all lipoprotein fractions. The lack of change in LDL levels post-TBI may also be influenced by compensatory mechanisms within the body. The liver, a key organ in lipoprotein metabolism, may regulate LDL production and clearance to maintain cholesterol homeostasis. Additionally, adaptive changes in peripheral tissues could influence the uptake and utilization of LDL during the recovery phase from TBI (Royes *et al*., 2019; Jacquens *et al*.,2022).

Conclusion

In this study, it can be concluded that induction of traumatic brain injury in rats by weight drop method causes neurological deficits, electrolyte imbalance and dyslipidemia within 24 hours. This can serve as baseline data for frontline clinicians for a robust design in the management of TBI.

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Conflict of Interest

The authors have no conflicts of interest to declare.

Authors Contribution

BI, BU, and PAM conceptualized and designed the study; DD, YB, AM, collected samples, analyzed data and drafted the manuscript of this research; LSB and MBM provided critical advice on study design, data acquisition and skills on the laboratory activities; NS, MHT, and TTL carried out the acquisition of retrieved data, final review and editing of the manuscript; KAS, AW, and YBM,

supervised the study, interpreted data, analyzed data and reviewed the document. All authors have reviewed and given their approval of the final version of the work.

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