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Effect of Vitamin E on Lipid Peroxidation and Oxidative Stress in Traumatic Brain Injury-Induced Rats

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Objective: A traumatic brain injury (TBI) is a significant contributor to both death and disability globally. This research was formulated to explore the potential impact of antioxidants in the management of experimentally induced TBI in albino rats.
Methodology: Adult albino rats were subjected to traumatic brain injury using the weight drop method. The rats were divided into three sets, each consisting of ten rats. In Group I, the rats were exposed to trauma and then received treatment (referred to as the traumatized-treated group, TT). In Group II, the rats were neither traumatized nor treated (referred to as the non-traumatized, non-treated group, TNT). Lastly, Group III comprised the normal control group. The treatment group (TT) was administered a dose of 67.5mg/kg of vitamin E (VE). Treatment commenced 30 minutes after

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the traumatic event and persisted for a duration of 21 days. To assess oxidative stress (OS), various antioxidant enzymes including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), as well as malondialdehyde (MDA) levels in serum tissue, were analyzed.
Results: The group that received treatment exhibited a significant ($p<0.05$) rise in the levels of antioxidant enzymes (SOD, CAT, GPx), while there was a notable ($p<0.05$) reduction in the MDA concentration when compared to the non-traumatized, non-treated (TNT) group.
Conclusion: The findings of this study indicate that the utilization of the antioxidant vitamin E (VE) could serve as a valuable neuroprotective approach in the management of traumatic brain injuries (TBI).

Keywords: Antioxidant; catalase; glutathione peroxidase; traumatic brain injury; superoxide dismutase; oxidative stress.

1. INTRODUCTION

Traumatic brain injury (TBI) is described as a modification in brain function or instant mechanical disruption of brain tissue due to an external force and followed by biochemical events that can aggravate the injury [1]. Though the extent of damage is not always immediately apparent, it depends on whether the external force is accidental or deliberate, direct hit or indirect acceleration/deceleration or blast forces, and penetrating or non-penetrating. The degree of brain damage may range from minor/mild to severe/critical [2]. Life threatening complications can develop even after mild injuries [3]. Mortality in developed countries is 20-30% and reaches up to 90% in developing countries [4]. Traumatic brain injury is expected to be the world wide leading cause of morbidity and mortality in the near future, especially in under developed and developing countries [5] Predictable estimates of TBI in Africa are great, with a weight of approximately 6 to 14 million new cases in 2050 [4, 5]. Its socioeconomic impact is particularly significant because it is one of the most frequent reasons of mortality and morbidity in young adults [4]. In Africa, head injury represents a significant risk for morbidity and mortality of which road traffic accident (RTA) increases injury severity. Due to stressed health systems in Africa, 30% of all head injured patients have poor prognosis, and those with severe head injury have nearly double the risk of dying compared to those in high-income countries [6]. Survivors usually have lifelong disabilities such as cognitive and sensory motor deficits based on the pathophysiology [7].

The primary and secondary injury processes in the pathophysiology of TBI are responsible for the reported neurodegeneration and disabilities following trauma. The primary injury may be simple hematomas or more complex and diffuse lesions. However, it then sets off a cascade of molecular events that lead to secondary injury. These include a wide variety of processes such as depolarization, disturbances of ionic homeostasis, and release of neurotransmitters (such as excitatory amino acids), mitochondrial dysfunction, initiation of inflammation and release of free radicals and eventually may be responsible for a significant component of the chronic neurodegeneration and neurological impairment following TBI [8].

One of the extensively researched and firmly established facets of secondary damage to brain tissue is the production of free radicals that occurs after a traumatic brain injury (TBI). [9]. A free radical is defined as any chemical entity capable of existing independently, possessing one or more unpaired electrons that are accountable for its reactivity. [10]. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) encompass both free radicals and substances that can break down to form free radicals. Following traumatic brain injuries (TBI), ROS and RNS are often generated through various mechanisms. These reactive species play a role in the development of TBI by exacerbating other secondary injury mechanisms and triggering oxidative stress [11].

Oxidative stress has been implicated as a possible factor in the development of acute injuries to the central nervous system. In the aftermath of a brain injury, the natural production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) gives rise to tissue damage through diverse cellular and molecular mechanisms. These radicals can inflict harm on lipids, proteins, and nucleic acids, such as DNA, ultimately leading to oxidative stress and subsequent cell demise [9]. Mammalian cells are equipped with internal or inherent antioxidants, like superoxide dismutase, catalase, or

glutathione peroxidase, to shield the cells from an excess of free radicals [12].

Antioxidants are substances that inhibit the oxidation of other compounds. They safeguard vital cellular components by neutralizing the harmful impact of free radicals [13].

The primary and most crucial line of defense against reactive oxygen species (ROS) consists of enzymatic antioxidants like SOD, CAT, and GPx [14]. Although these internal antioxidants enhance their activity following a traumatic brain injury (TBI), the extent of the rise in free radicals challenges the antioxidant system's ability to effectively counteract the detrimental effects of these free radicals [12].

Nonetheless, the external introduction of substances possessing antioxidant qualities, such as vitamins, minerals (like selenium and zinc), or other agents like albumin, can offer supplementary safeguarding [15]. These natural antioxidants or other compounds capable of counteracting free radicals may play a pivotal role in averting oxidative stress.

Vitamin E, a strong scavenger of peroxyl radicals, serves as a chain-breaking antioxidant that hinders the spread of free radical harm within biological membranes [16, 17]. Vitamin E plays a significant role in enhancing immune function, managing stress, and increasing disease resistance. The objective of this research is to substantiate the neurochemical impact of vitamin E in traumatic brain injuries (TBI).

2. MATERIALS AND METHODS

2.1 Animals

All the thirty male adult rats tested were seemingly healthy albino rats weighing between 200 to 250 grams. These rats were procured from the Animal House of the Biological Sciences Department at the University of Maiduguri in Nigeria for the purposes of this research. Prior to experimentation, the rats were allowed for 2 weeks to adapt to the laboratory environment, and they were maintained on a 12-hour light and 12-hour dark cycle. They were provided with vital® feed in the form of growers' mash and had unrestricted access to clean drinking water.

2.2 Experimental Design

The experimental animals were randomly allocated into three categories. Group I comprised animals that were subjected to induction and treated with vitamin E (VE), while Group II consisted of animals that were subjected to trauma but not treated (TNT). Group III served as the normal control group, meaning they were neither traumatized nor treated (NTNT). The treatment period spanned 21 days. This research received approval from the University of Maiduguri's board, adhering to both national and international standards. The care and handling of the animals were conducted in compliance with institutional guidelines.

2.3 Induction of TBI

Head injury was induced in the entire experimental animals except in the negative control group by weight drop method using an acceleration impact device of Marmarou [18].

2.4 Sample Collection

The rats were anesthetized using chloroform in a glass jar and brain tissue was extracted from the skull for biochemical analysis.

2.5 Analysis of Oxidative Stress

Biomarkers for oxidative stress markers were assayed in the brain tissue after homogenization. The antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX) and lipid peroxidation by-product malondialdehyde (MDA) were assayed using Cayman’s Assay Kits, with batch number 706002 for SOD, 707002 for CAT, 703102 for GPX and 700870 for MDA. The manufacturer’s instructions were meticulously adhered to.

2.6 Statistical Analysis

The data obtained from the experiments were subjected to statistical analysis using SPSS version 22. The results were presented as means with their corresponding standard deviations (means ± SD). To assess the data, a one-way analysis of variance (ANOVA) was conducted. Duncan Multiple Range Test (DMRT) for multiple comparison between the different groups was employed and differences of values less than or equal to 0.05 ($P \leq 0.05$) were considered significant.

3. RESULTS

3.1 Effect of Supplementation of TBI Rats with Vitamin E on the Activity of SOD in the Brain Tissue

The results presented in Fig. 1 shows the activity of SOD in brain tissue of TBI rats treated with

VE. The result indicated that TBI caused significant (P<0.05) decrease in the activities of the enzyme. Supplementation with VE significantly increased the activity of SOD.

3.2 Effect of Supplementation with Vitamin E on the Activity of Catalase in the Brain Tissue

Fig. 2 shows the result of the effect of VE on brain tissue level of CAT. The result indicated that TBI caused significant (P<0.05) decrease in the activity of the enzyme. Supplementation of the antioxidant (67.5 mg/kg body weight) increased the activity significantly (P<0.05).

3.3 Effect of Supplementation with VE on the Activity of GPx in the Brain Tissue

The results in Fig. 3 showed that TBI caused significant (P<0.05) decrease in the activity of the enzyme while administration at 67.5mg/kg BW of the antioxidants significantly (P<0.05) increased the activity of the enzyme.

3.4 Effect of Supplementation with VE on MDA Concentration in the Brain Tissue

The results in Fig. 4 indicated that TBI caused significant (P<0.05) increase in the level of MDA in the brain of TNT group. After administration of the antioxidant, the concentration of MDA decreased significantly (P<0.05).

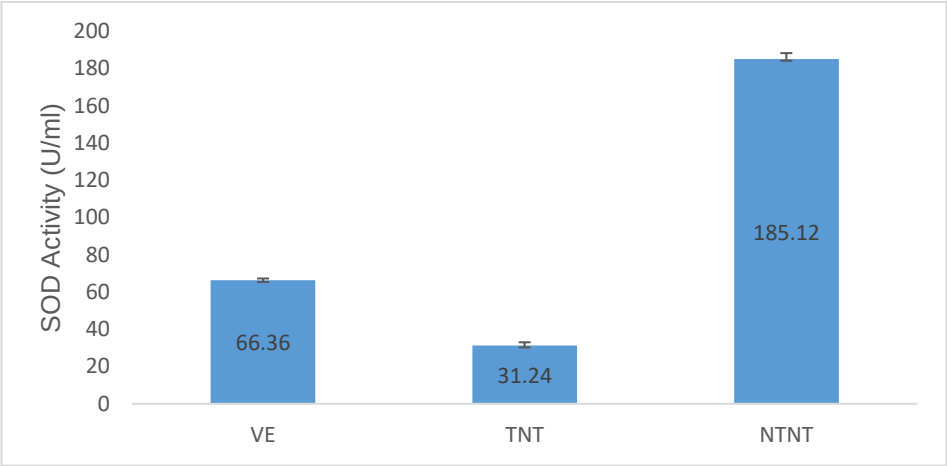

Fig. 1. Effects of VE on the Activity of Superoxide dismutase in Brain Tissue

*-SOD- Superoxide dismutase, TNT- Traumatized non- treated, NTNT- Non-traumatized non- treated, VE – Vitamin E *(p<0.05) (n=10).*

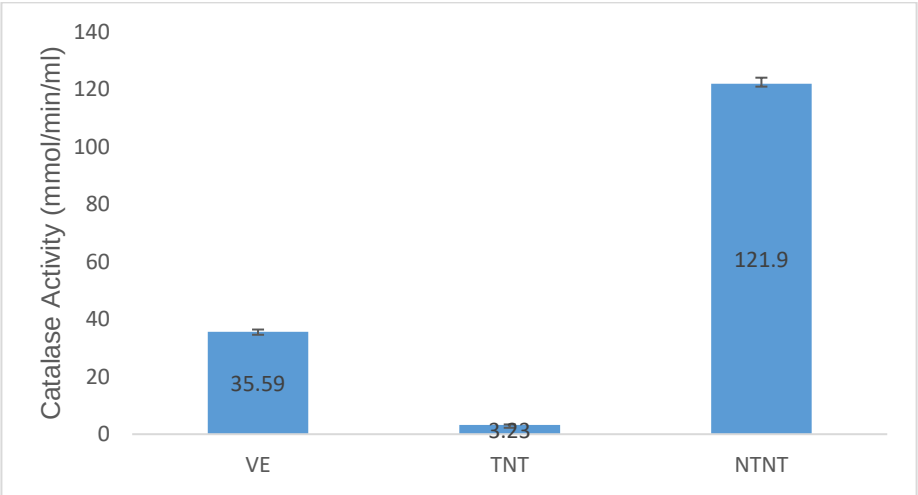

Fig. 2. Effects of VE on the Activity of CAT in the Brain Tissue

CAT- Catalase, TNT- Traumatized non- treated, NTNT- Non-traumatized non-treated, VE – vitamin E Values with asterisk are significantly different (p<0.05) (p<0.05), (n=10)*

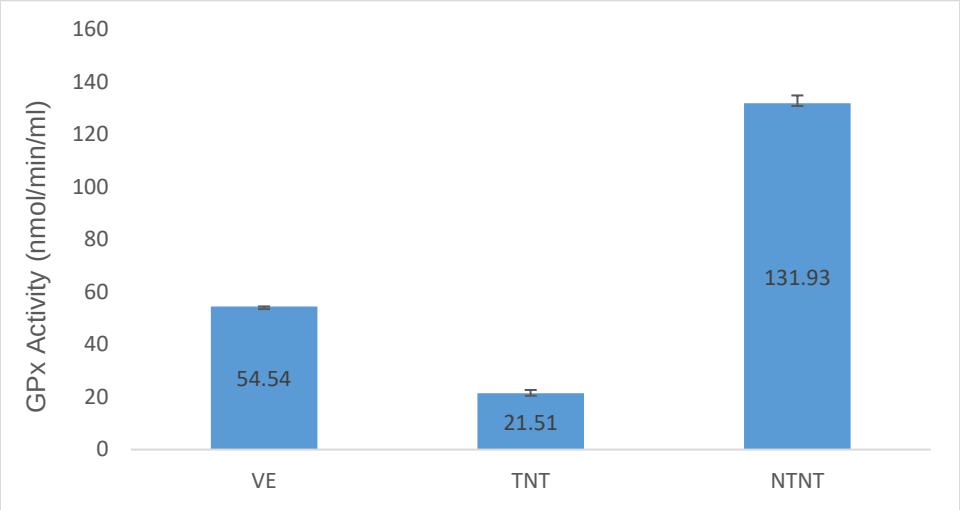

Fig. 3. Effects of VE on the Activity of GPX in Brain

GPX- Glutathion peroxidase, TNT- Traumatized non- treated, NTNT- Non-traumatized non- treated, VE – vitamin E (p<0.05), (n=10)

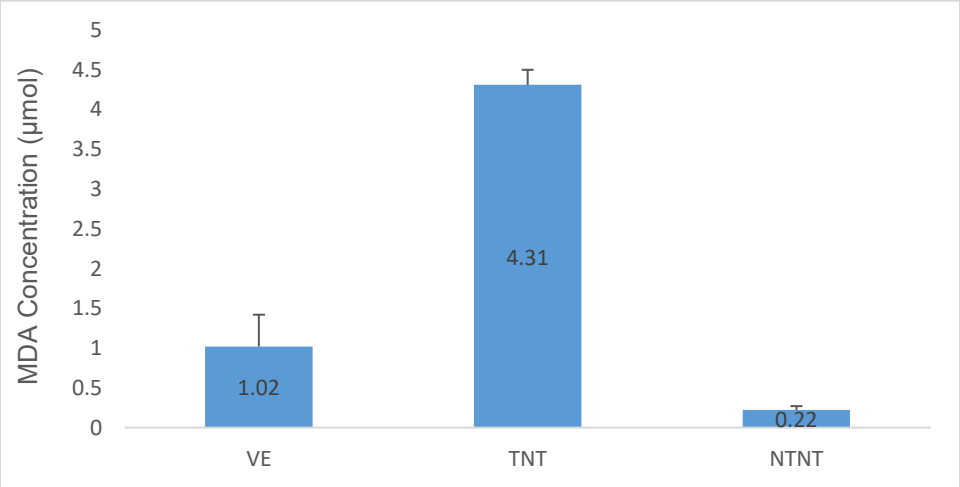

Fig. 4. Effects of VE on the Concentration of MDA in the Brain Tissue of experimental rats

MDA- Malondialdehyd, TNT- Traumatized non treated, NTNT- Non-traumatized non- treated, VE – vitamin E. (p<0.05), (n=10)

4. DISCUSSION

In this study, oxidative stress was assessed by measuring the levels of SOD, CAT, GPx, and MDA, which serve as indicators for enzymatic antioxidant activity and lipid peroxidation. A notable decrease in the activities of SOD, CAT, GPx, and an increase in MDA concentration were observed in the brain tissue of TNT-exposed rats compared to those not exposed; NTNT rats (refer to Figs. 1-4). This indicates the presence of oxidative stress resulting from the induced traumatic brain injury (TBI). The supplementation with VE, effectively mitigated the induced oxidative stress (Figs. 1-4).

Treatment of TBI-induced rats with 67.5 mg/kg of VE indicated significant increase (P< 0.05) in the activities of SOD, CAT and GPx and decrease concentration of MDA in the brain tissue of the treated group compared to the TNT group (Figs. 1 – 4). This might be due to the ability of VE to quench free radicals and reduce their oxidative activity on lipids, proteins and nucleic acid which leads to the suppression of the antioxidant system and accumulation of MDA.

This could also be attributed to the regenerative properties of vitamin E and glutathione, which are highly effective against reactive oxygen species (ROS) according to Heidi and colleagues

[19]. The effectiveness may stem from vitamin E's role as a prominent chain-breaking antioxidant, coupled with its abundance in cellular and mitochondrial membranes, where ROS are generated. Dysfunction in these areas can lead to an excessive release of free radicals. Therefore, vitamin E may have acted by inhibiting lipid peroxidation and oxidative stress at these crucial sites of free radical production, as reported by Inci and colleagues [20]. Zingg [21] noted that vitamin E, being lipid-soluble, hinders the formation of lipid peroxides. Moreover, numerous animal studies have reported on vitamin E's modifying effect on oxidative stress pathways, ultimately improving neurological outcomes [20]. It is also recognized that, beyond its direct impact on ROS, vitamin E can interact with various antioxidants like vitamin C, GSH, and β-carotene to produce a synergistic effect. Consequently, these antioxidants contribute to the regeneration of vitamin E, thereby enhancing its effectiveness [22].

The findings of this work revealed that the group treated with VE have significantly ($P<0.05$) increased activities of the antioxidants enzymes and significantly ($P<0.05$) decreased level of MDA compared to the TNT counterpart (Figs. 1– 4).

5. CONCLUSION

Following the induction of traumatic brain injury (TBI), there was a notable reduction in the activities of antioxidant enzymes, accompanied by an increase in the level of MDA, indicating the presence of oxidative stress. Oxidative stress stands as the principal pathological mechanism responsible for secondary injury, which can lead to neuronal degeneration and functional deficits. Interventions aimed at mitigating this harmful process offer neuroprotection and support the restoration of neuronal function. The administered antioxidants have exhibited its potential in both protecting and restoring neurological function by enhancing antioxidant capabilities and inhibiting lipid peroxidation. These encouraging findings suggest that vitamin E may hold promise in the management of TBI. Though, in rats vitamin E can be given preventively as shown in this experiment but in humans this is not the case. Therefore, more of such study is needed in human model.

ETHICAL APPROVAL

The research outlined in this study adhered to the ethical guidelines established by the World Medical Association's Code of Ethics (Declaration of Helsinki) for experiments involving animals. Furthermore, this study received approval from the University of Maiduguri's governing board, ensuring compliance with both national and international standards. The care and handling of the animals followed the guidelines set forth by the institution.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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