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Oxidative Stress and Biochemical Alterations in Patients with Head and Multiple Organ Traumas

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ABSTRACT

AIM: The aim of this study was to evaluate paraoxonase (PON), total antioxidant status (TAS), total oxidant status (TOS), high-density lipoproteins (HDL), CRP, AST, ALT, GGT, ALP levels in patients with head and multiple organ traumas.

MATERIAL and METHODS: The study included 29 male patients undergoing treatment for head and multiple organ traumas. Blood sample analysis was performed on the first, third, and seventh days after trauma.

RESULTS: The mean age, duration of hospitalization in the intensive care unit, and intubation period of the study sample was 45 years (range: 9 to 81 years), 4.29 days, and 2.94 days, respectively. One patient died, and 13 underwent surgical intervention. Comparison of PON, TAS, TOS, and CRP levels showed statistically significant differences between the first day and the third and seventh days, although no such differences were seen in HDL levels. A moderately positive correlation was observed between CRP/AST, CRP/ALT and CRP/GGT, while a moderately negative correlation was seen between CRP/ALP.

CONCLUSION: The findings of this study suggest that some oxidative parameters may play a significant role in the prognosis and follow-up of intensive care patients. Moreover, biochemical markers can provide important information about patient response to trauma.

KEYWORDS: Biochemical alteration, Head trauma, Multiple traumas, Total antioxidant/oxidant level

ABBREVIATIONS: ANOVA: Analysis of variance, **CT:** Computed tomography, **GCS:** Glasgow Coma Scale, **HDL:** High-density lipoproteins, **ROS:** Reactive oxygen species, **SE:** Standard error, **TAS:** Total antioxidant status, **TBI:** Traumatic brain injury, **TOS:** Total oxidant status

INTRODUCTION

Trauma, a significant health issue affecting the working population, is a leading cause of death globally and can result in multiple injuries to one or more parts of the body. Traumatic injuries of the head are typically associated with significant neurological sequelae which prolong the recovery period and delay the patient's return to normal activities (9,32). Neurological damage caused by head trauma can be classified into primary (caused by the trauma itself) and secondary (caused by uncontrolled inflammation and post-traumatic stressors) damage, with the latter representing the target of treatment measures (18). Although previous studies have used experimental trauma models to demonstrate dramatic alterations in inflammatory marker levels over time and the benefits of antioxidant medications as treatment measures, there are a limited number of clinical studies on the subject (2,27).

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Reactive oxygen species (ROS) play a significant role in the etiology of complications such as infection and multiple organ failure in trauma patients (20), and severely affected patients often exhibit disruption of the antioxidant/oxidant balance in favor of oxidants, leading to oxidative stress (30).

Factors such as post-traumatic stressors, secondary damage, and inflammation can cause cessation and predominance of the anabolic and catabolic processes, respectively, while treatment measures such as intravenous access, urinary catheters, and endotracheal tubes can increase the patient's susceptibility to infections (3). It has been hypothesized that degradation of the antioxidant/oxidant balance, an inevitable process, may be reflected in various biochemical parameters. Considering this, the main aim of our study was to analyze the relationship between patient examination findings, trauma size, infection and biochemical parameters.

Secondary damage typically occurs on the first day of trauma and can act as a major stressor, leading to the development of various clinical symptoms in intensive care patients, particularly those requiring no surgical treatment (33). Therefore, the current study also aimed to determine response to treatment by evaluating changes in the total antioxidant/oxidant and biochemical marker levels in the blood serum of patients with head and multiple organ traumas over a follow-up period of one week.

MATERIAL and METHODS

Experimental Design

The study was approved by the General Secretariat of the Provincial Public Hospitals Union, Public Hospitals Institution of Tekirdağ/Turkey (Scientific Research Approval No. 42232655-605.01) and included 29 male patients diagnosed with head and multiple organ traumas in the Emergency Department of the State Hospital. Patients admitted to the intensive care unit on the first day of trauma following consultation with a neurosurgery clinic and those with no recent history of trauma, infection, or any other disease requiring hospitalization were included in the study. Female patients were excluded from the study as it was assumed that the stressor effects of their menstrual cycle may affect the study findings. Informed consent was collected from all patients prior to commencement of the study.

Radiological Analysis

Following diagnosis, the patient was stabilized, initial evaluation was carried out in the supine and neutral position, and they were referred to the computed tomography (CT) unit of the trauma board for whole-body imaging using the Aquilion Lightning™ system, a 16-row 32-section helical CT system manufactured by Canon Medical Systems. Damage to other organs was diagnosed via radiological evaluation using the DICOM PACS system.

Biochemical Analysis

Venous blood samples were collected in biochemistry tubes and centrifuged to separate the components. Some of these were stored at –20°C for up to 24 h for use in routine biochemical analyses (e.g., high-density lipoproteins (HDL), CRP, AST, ALT, ALP and GGT), while others were stored in a deep freezer at –80°C for use in the measurement of Paraoxonase (PON) activity, total antioxidant status (TAS), and total oxidant status (TOS). Serum PON activity was measured using the spectrophotometric method proposed by Eckerson et al., (13) while serum TAS and TOS levels were measured using the colorimetric and automatic methods developed by Erel (14,15). HDL and CRP levels and AST, ALT, ALP, and GGT activity were measured using an auto analyzer (Roche Diagnostics, Mannheim, Germany).

Statistical Analyses

All statistical analyses were carried out using the SPSS software (IBM SPSS Statistic 22). The one-sample Kolmogorov–Smirnov test was used to evaluate data distribution and the one-way analysis of variance (ANOVA) was used to compare the mean values of various biochemical markers on different days. Post-hoc analysis was carried out using the Anova-Duncan test upon observation of significant differences in mean values. The data have been presented as mean values ± standard error (SE), and a p-value of <0.05 was considered statistically significant.

RESULTS

Patient Demographics

The mean age, duration of hospitalization in the intensive care unit, and intubation period of the study sample was 45 years (range: 9 to 81 years), 4.29 days, and 2.94 days, respectively. One patient died, 13 underwent surgical intervention, and 9 developed infections that required antibiotic treatment. The Glasgow Coma Scale (GCS) score at the time of admission was severe in two patients (8>), moderate in 12 patients (9–12), and minor in 15 patients (13<) (24).

Radiological Findings

Patients who presented at the emergency room following a road traffic accident, occupational accident, or a fall from a great height underwent cranial imaging and further evaluation for diagnosis of traumatic injuries affecting multiple organs. A diagnosis of head trauma was made if cranial CT examination revealed a traumatic subarachnoid hemorrhage (Figure 1A), maxillofacial trauma (Figure 1B), linear fracture (Figure 1C), cerebral contusion (Figure 1D), compression fracture (Figure 1E), epidural hematoma (Figure 1F), intracerebral hematoma (Figure 1G), or a subdural hematoma (Figure 1H).

Biochemical Findings

Also examination for other systemic injuries showed presence of spinal traumas such as odontoid fractures (Figure 2A) and lower cervical (Figure 2B) or thoracolumbar fractures (Figure 2C). Additionally, hemothorax (Figure 2D), extremity fractures (Figure 2E), or pelvis fractures (Figure 2F) were also observed in some patients.

Routine blood tests and evaluation of PON activity and TAS, TOS, HDL, CRP, AST, ALT, ALP, and GGT levels was carried

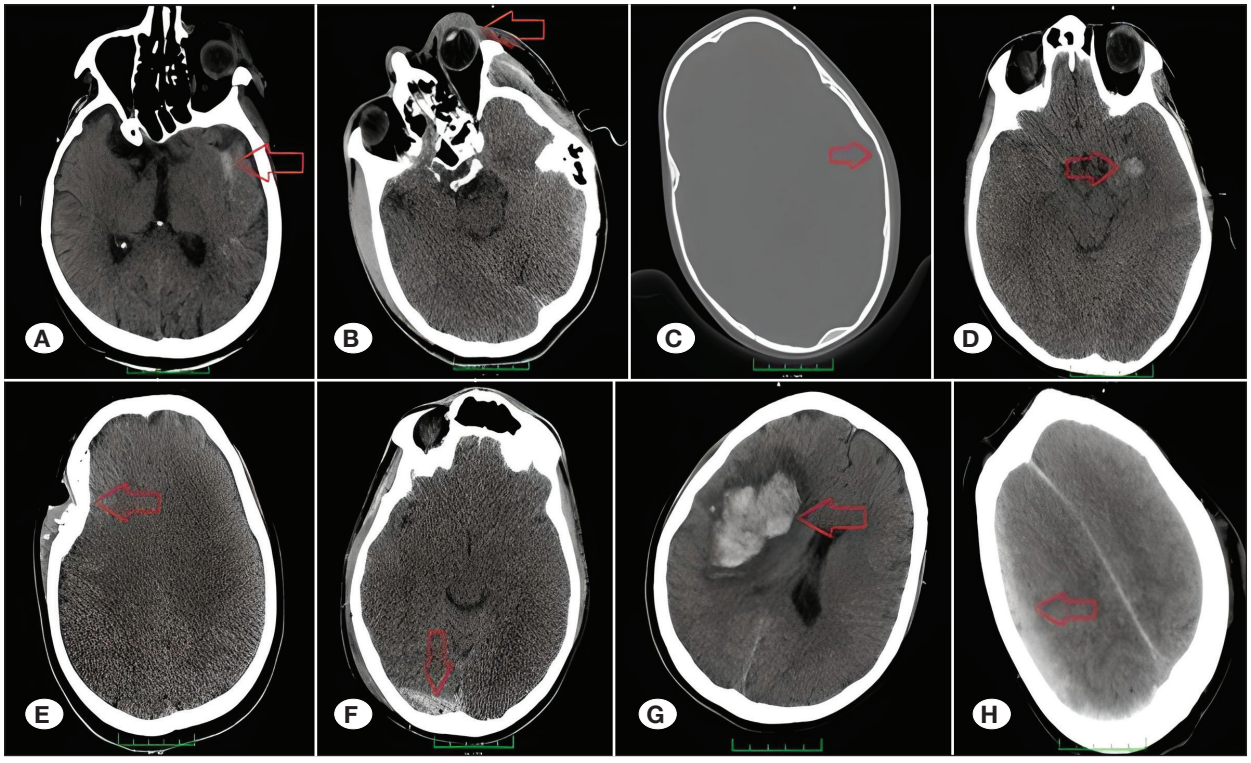

Figure 1: Axial section brain CT scan showing evidence of head trauma.

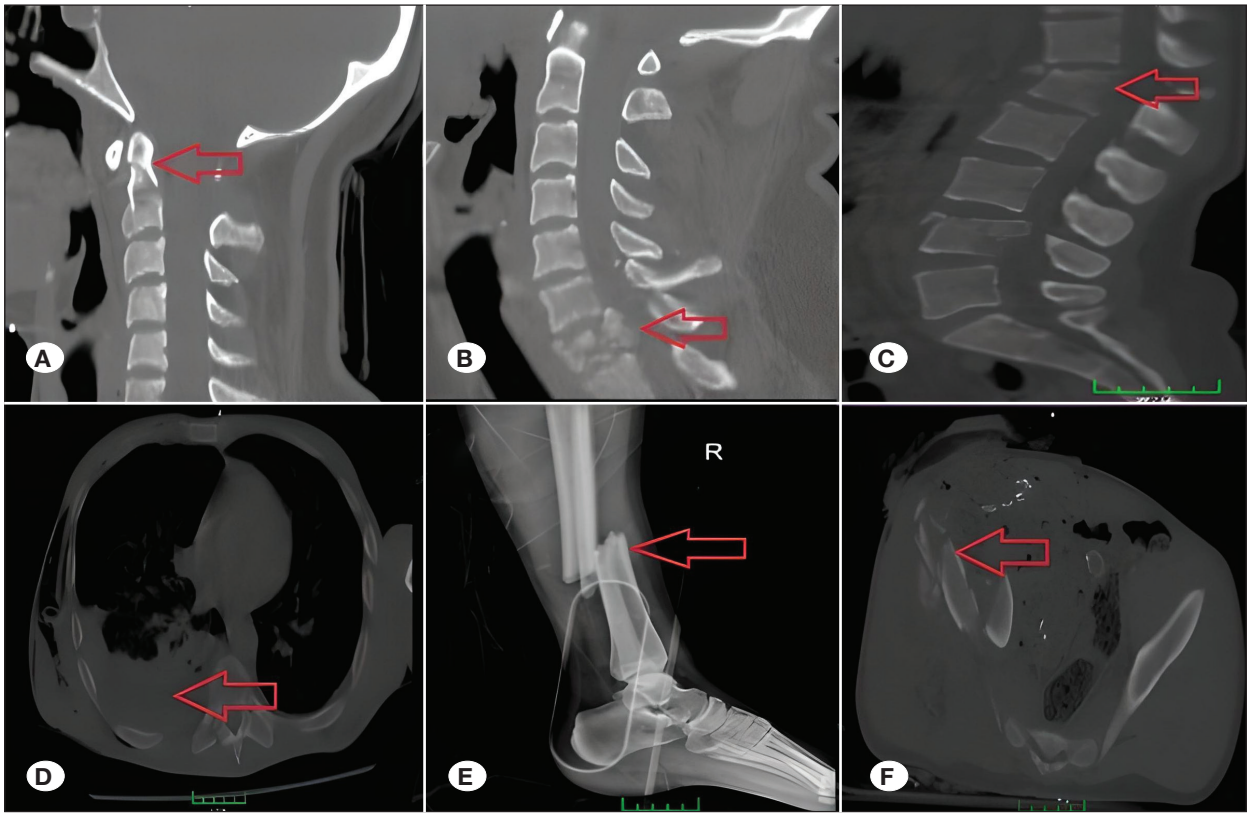

Figure 2: Radiological examination showing evidence of other organ injuries accompanying head trauma. Examination for other systemic injuries showed presence of spinal traumas such as odontoid fractures **(A)** and lower cervical **(B)** or thoracolumbar fractures **(C)**. Additionally, hemothorax **(D)**, extremity fractures **(E)**, or pelvis fractures **(F)** were also observed in some patients.

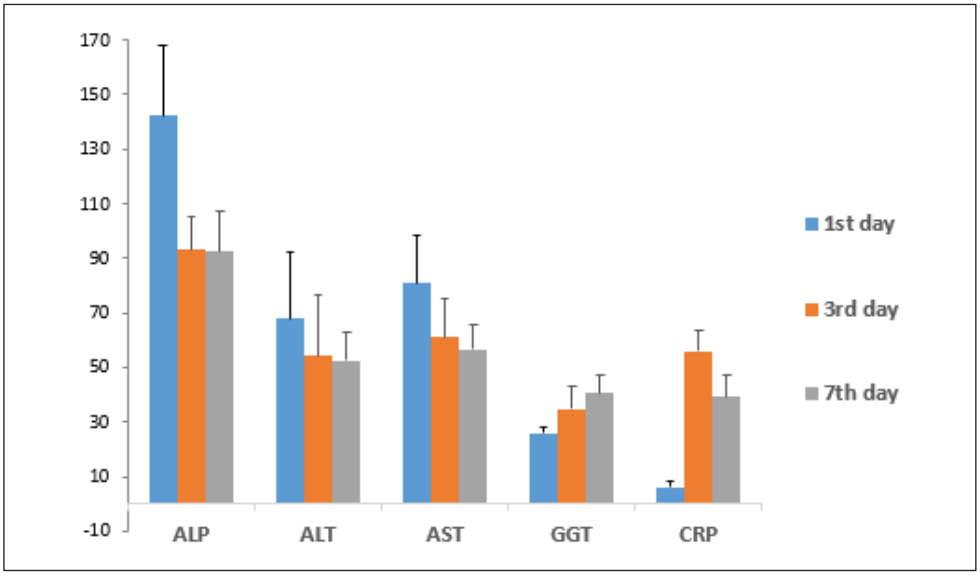

Figure 3: Biochemical parameter levels on different days in patients who were hospitalized in the intensive care unit.

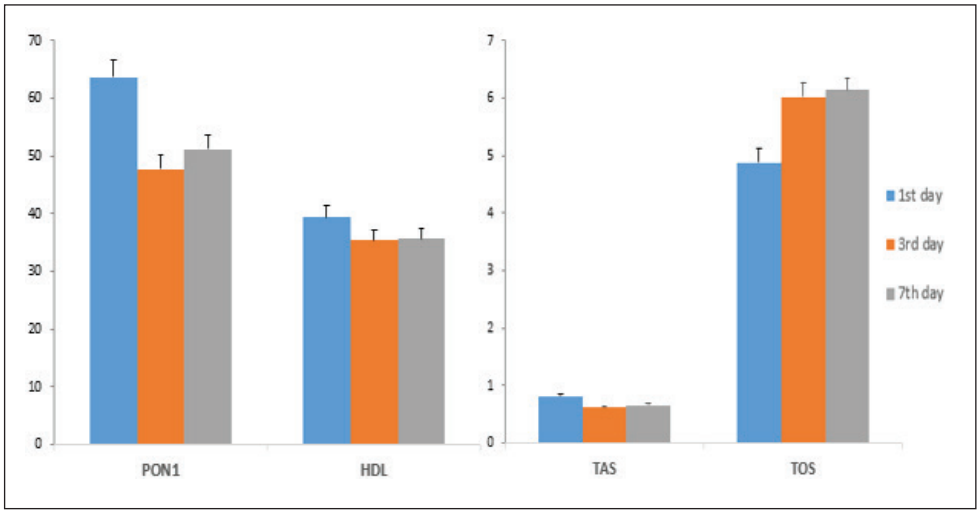

Figure 4: Serum PON, HDL, TAS, and TOS levels on different days in patients hospitalized in the intensive care unit.

out using blood samples on the first, third, and seventh days after trauma (Figures 3 and 4). Table I shows the mean ± SE values for the various parameters. The PON, TAS, and TOS levels were seen to significantly differ between the first day and the third and seventh days ($p<0.01$), while no such differences were seen between the third and seventh days. The mean HDL values did not significantly differ between the various days ($p>0.05$). The mean serum CRP values were 6.05, 55.95, and 39.8 on the first, third, and seventh days, respectively, and these were considerably higher than the normal limits (1–2 mg/L observed in healthy individuals) suggesting high infection rates. Moreover, the CRP values were seen to significantly differ between the first day and the third and seventh days ($p<0.01$), although no such differences were seen upon comparison of the third and seventh days. The mean AST values were 80.8 on the first day, 61.1 on the third day, and 56.7 on the seventh day, and these were considerably higher than the normal limit (15–50 IU/L in healthy individuals). Similarly, the mean ALT values were 67.8 on the first day, 54.1 on the third day, and 52.6 on the seventh day, and these were also above the normal limits (10–40 U/L in healthy individuals). The mean ALP values, known to be associated with age (normal values:25–100 U/L in healthy individuals over 16 years of age), were 142.3 on the first day, 93.1 on the third day, and 92.3 on the seventh day. In healthy individuals, the GGT value is 0–65 U/L. In our study, the values obtained day 1, 3 and 7 were 25.8, 34.6 and 40.5, respectively, which were below the normal limits. Comparison of the AST, ALT, ALP, and GGT values showed no statistically significant differences between the first, third, and seventh days ($p>0.05$). Upon examining the correlation between CRP, the most common marker of infection, and other parameters, the Pearson's correlation coefficient was seen to be 0.49 for CRP and AST; 0.40 for CRP and ALT; –0.31 for CRP and ALP; and 0.50 for CRP and GGT. Therefore, a moderately positive correlation was observed between CRP/AST, CRP/ALT and CRP/GGT, while a moderately negative correlation was seen between CRP/ALP.

Table I: Values of Biochemical Parameters, Obtained on Different Days

Parameters	Groups			p<
	1st day n=29 Mean ± SE	3rd day n=29 Mean ± SE	7th day n=29 Mean ± SE	
PON (U/L)	63.55 ± 2.99[a]	47.65 ± 2.20[b]	51.09 ± 2.41[b]	*
TAS (mmol Trolox Eqv./L)	0.81 ± 0.03[a]	0.61 ± 0.02[b]	0.65 ± 0.03[b]	*
TOS (μmol H_2O_2 Eqv./L)	4.88 ± 0.23[b]	6.01 ± 0.24[a]	6.13 ± 0.21[a]	*
HDL (mg/dL)	39.35 ± 1.40	35.29 ± 1.51	35.58 ± 1.43	**
CRP (mg/L)	6.056 ± 2.56[b]	55.956 ± 7.99[a]	39.80 ± 8.09[a]	*
AST (U/L)	80.81 ± 17.55	61.12 ± 14.27	56.75 ± 9.24	**
ALT (U/L)	67.81 ± 24.54	54.18 ± 22.28	52.68 ± 10.42	**
ALP (U/L)	142.37 ± 25.82	93.18 ± 11.81	92.37 ± 14.66	**
GGT (U/L)	25.87 ± 2.51	34.68 ± 8.78	40.56 ± 6.73	**

***:** p<0.01: Statistically significant difference, **a, b:** The difference between the means between different days in the same row is significant.*
***:** p>0.05=The difference between the values obtained on different days in the same row is insignificant, **n:** number of subjects in the group, **SE:** Standard error.*

DISCUSSION

Head trauma is often associated with secondary brain damage, and the post-traumatic inflammatory response represents the initial stages of this. Inflammation starts with infiltration of neutrophils into the tissues, and free radicals, and proteases produced by neutrophil activation cause deterioration of the blood-brain barrier and subsequent brain edema. The levels of amino acids such as glutamate and aspartate are elevated in the blood following a traumatic brain injury (TBI), and these can either decrease high-energy phosphate reserves or increase free radicals. Several clinical, epidemiological, and experimental studies have reported associations between free radicals and various diseases, such as cancer and neurodegenerative disorders (1,2). However, there is limited evidence on the serum antioxidant-oxidant balance following head trauma.

An increase in free radicals and oxidative stress has been shown to play a significant role in the pathophysiology of TBI (4,16,21). Paolin et al., found that lipid peroxidation induced by excessive production of free radicals played a critical role in the development of post-traumatic neuronal damage in humans (28). Crucial studies on molecular mechanisms of TBI pathology, as well as potential strategies and agents against pathological pathways have been carried out (16,21,28). Accordingly, we investigated few parameters related to oxidative stress and serum total antioxidant/oxidant levels in TBI and their results were evaluated in this study.

Head trauma patients typically exhibit central nervous system damage and an increase in intracranial pressure that is proportional to the severity of the trauma. Injuries to other organs can also induce peripheral nervous system damage and alterations in the autonomic nervous system. Therefore, patients with injuries of the head as well as other organs may exhibit significant systemic and local reactions (6,23). The participants were patients with head trauma as well as other system injuries. It was expected that the trauma would have a significant effect on the body due to central and peripheral nervous system damage.

Factors such as the duration of intubation, the patient's neurological scale, and incidence of surgical procedures are associated with an increased risk of infection (8). The GCS is a universal scale used for the assessment of neurological damage in patients (26), with a score ≤ 8 indicating severe injury, scores between 9 and 12 indicating moderate injury, and those between 13 and 15 indicating minor trauma (25). Based on this system, 2 patients in the current study were diagnosed with severe neurological damage, 12 patients were diagnosed with moderate damage, and 15 patients were diagnosed with minor damage. Nine patients were seen to develop infections within the first week, and the serum CRP and TOS values were seen to significantly increase on the third day in these patients.

Seifman et al. found that endogenous melatonin levels were seen to increase in patients with severe head trauma (e.g., compression fracture, traumatic cerebral hemorrhage), resulting in significant oxidative damage and metabolic dysfunction (31). Clausen et al. reported that Interstitial F_2-Isoprostane 8-Iso-$PGF_{2\alpha}$ was a biomarker of oxidative stress in patients exhibiting severe neurological damage and impaired parenchyma and bone integrity upon cranial imaging (7). The current study found that the increase in TOS levels was more pronounced in patients with lower GCS scores and evidence

of compression fractures (Figure 1E), intracerebral hematomas (Figure 1G), or traumatic subdural hematoma (Figure 1H) upon brain CT imaging.

Changes in cellular macromolecules (e.g., DNA, lipid, nucleic acid, and carbohydrate) caused by ROS that result in cell death are associated with oxidative cell damage. The NADPH-oxidase system, which can be activated by a variety of factors such as pro-inflammatory cytokines and arachidonic acid metabolites, is a major source of ROS in the cell (19,34) and, consequently, plays a role in the pathogenesis of tissue damage caused by trauma (22).

Brain damage can be caused by influx of calcium into the cell following opening of the calcium channels, formation of free radicals due to inactivation of the free radical binders, and brain edema following TBI (17). Secondary damage may occur several hours or days later and includes calcium-dependent cell damage, neurotransmitter release, formation of ROS, gene activation, mitochondrial dysfunction, and inflammatory responses (24). It has been suggested that oxidative stress, caused by an increase in ROS, can play a role in the pathophysiology of TBI (5,34). Paolin et al. found that lipid peroxidation resulting from free radicals may induce post-traumatic neuronal damage in human beings (28). The results of some preclinical and clinical studies, evaluating mitochondria-targeted therapies, such as mitochondria-targeted antioxidants and compounds with pleiotropic effects after TBI, are promising (16,17). In the current study, examination of the total antioxidant/oxidant levels in patients with multiple traumas showed that the TAS levels decreased and TOS levels increased significantly on the third and seventh days after trauma when compared to the first day. This, in turn, potentially induced oxidative stress as secondary damage following trauma can impair the antioxidant/oxidant balance in favor of oxidants.

PON, a calcium-dependent enzyme with an antioxidant effect against lipid peroxidation in cell membranes, is located on HDL in serum (10-12). However, it has been reported that exposure to oxidative stress can reduce PON activity in trauma patients (34). Rael et al. compared the plasma PON activity between 10 healthy individuals and 39 multiple traumas patients and observed significantly lower values in the latter group, suggesting the potential role of PON activity in the evaluation of trauma severity and treatment effectiveness (29). In the current study, patients with multiple traumas exhibited a significant reduction in PON activity on the third and seventh days after trauma when compared to the first day, although no such changes in HDL levels were seen. This decrease in PON activity can be attributed to mitochondrial dysfunction and oxidative stress resulting from an increase in ROS in post-traumatic cells. The findings of this study also suggest that, despite being an antioxidant, HDL is not rapidly affected by trauma and inflammation and cannot, therefore, be considered a marker of acute oxidative stress.

The current study observed significant changes in PON, TAS, and TOS levels within the first 3 days of trauma, although no such changes were observed between days 3 to 7 when the risk of infection and subsequent inflammation increased. This suggests that the levels of PON, TAS, and TOS were specifically altered by the trauma. As CRP is more non-specific with regard to inflammation, it tends to increase progressively after trauma. The current study also found that AST increased immediately after trauma, ALT and GGT increased relatively slowly, and ALP did not significantly change within the first week, suggesting that AST, ALT, and GGT increased simultaneously with CRP upon occurrence of inflammation.

The current study examined the total oxidant-antioxidant levels in the blood serum of patients with head and multiple organ traumas and assessed the correlation between them. The findings showed an increase in total oxidant levels in the first week after trauma. The presence of a positive correlation between CRP, a typical marker of infection, and other oxidant parameters and a negative correlation between CRP and antioxidant parameters suggests that the antioxidant-oxidant balance in the organism was impaired in favor of the oxidant system. Patients also exhibited a decrease in total antioxidant levels and an increase in total oxidant levels on the third and seventh days after trauma when compared to the first day. This can be attributed to the influx of calcium into the cell, impairment of the antioxidant-oxidant balance in favor of the oxidant system, the inability to adequately prevent formation of free radicals or inactivate the formed ones, and the inflammatory response of the organism to oxidative stress. The findings of this study not only support the limited clinical evidence in this area, but also bring a novel perspective to clinical follow-up and treatment of intensive care patients.

Limitation

This study was conducted on a voluntary basis; therefore, patients who did not give consent or who did not want to participate in the study were not included. The study population was limited as the participants had to bear the cost of the study. Moreover, one-week patient follow-up was planned in our study; however, critical patients and that with unstable hemodynamics were not included as they might not be able to complete the study.

CONCLUSION

The findings of this study showed that while some oxidant and antioxidant (e.g., PON, TAS, TOS) levels change significantly from the first day of trauma, others (e.g., HDL) do not. And also, the reaction of the body to trauma can also be determined by means of biochemical parameters.

AUTHORSHIP CONTRIBUTION

Study conception and design: YA, GN, HAD, SKG
Data collection: YA, GN, HAD, SKG
Analysis and interpretation of results: YA, GN, HAD, SKG
Draft manuscript preparation: YA, GN, HAD, SKG
Critical revision of the article: YA, GN, HAD, SKG
All authors (YA, GN, HAD, SKG) reviewed the results and approved the final version of the manuscript.

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