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Early oxidative status in adult patients with isolated traumatic brain injury*

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Aim: To investigate oxidative and antioxidative status, as well as the Glasgow Coma Scale (GCS) and Revised Trauma Score (RTS), reflecting injury severity and neurological outcome during the early posttraumatic period in patients with isolated traumatic brain injury (TBI).

Materials and methods: Fifty-one adult patients with TBI and 45 eligible healthy volunteers as control subjects were enrolled. Plasma total oxidant status (TOS), total antioxidant status (TAS), and the oxidative stress index (OSI) were calculated as biomarkers of early oxidative changes in serum using a novel automated method.

Results: TOS levels and OSI values were significantly higher in nonsurvivors compared with those in survivors. However, there was no significant difference in TAS levels between survivors and nonsurvivors. GCS and RTS showed negative correlations with TOS levels, but neither was significantly related to OSI levels. Furthermore, GCS scores were negatively correlated with TAS levels, whereas RTS scores were not significantly related to TAS levels.

Conclusion: Patients with isolated TBI are exposed to potent oxidative stress. TOS, as an early oxidative stress biomarker, might reflect the severity of cerebral insult in those patients.

Key words: Head injury, clinical outcome, oxidative stress index, total oxidant status, total antioxidant status

Introduction

Traumatic brain injury (TBI) represents a significant cause of death and disability in the young populations of industrialized countries (1). In the neuropsychology research literature, the term "traumatic brain injury" is generally used to refer to nonpenetrating traumatic brain injuries (2). TBI can be classified based on injury severity as assessed by the Glasgow Coma Scale (GCS; mild, moderate, severe), mechanism (closed or penetrating head injury), morphology (skull fractures or intracranial lesions), or other features (e.g., occurring in a specific location or over a widespread area) (3,4). Despite the fact that the GCS grading system is extremely useful in the clinical management and prognosis of TBI, it does not provide specific information regarding the pathophysiological mechanisms that are responsible for neurological deficits (4). The physiological response to brain injury is extremely complex. Oxidative stress, an imbalance between oxidants and antioxidants, plays a critical role in the development of secondary injuries following TBI during the early posttraumatic period (5,6). Experimental studies have demonstrated that destructive oxidative events

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reach their peak within the first 24 h after head-injury trauma and that brain damage occurring due to this impact can be the cause of death or the severity of the trauma in affected subjects (5,7,8). In individuals with critical illnesses such as sepsis, trauma, and burn injury, the occurrence of increased oxidative stress or reduced antioxidative status is related to a poor prognosis (9).

Although TBI is known to result in oxidative stress and this impact influences neurological insult and outcome following TBI in animal studies, clinical reports regarding oxidative stress in TBI are contradictory. Some studies have indicated a significant association between early oxidative changes and neurological outcome (10,11), but others have found no significant correlation (12). Thus, inconsistent results have been reported for all of the commonly measured markers of oxidative stress (i.e. thiobarbituric acid reactive species, glutathione, superoxide dismutase, and glutathione reductase). Accordingly, no reports have investigated the relationship between oxidative status and the severity of injury in patients with TBI during the early posttraumatic period using a more recently developed method of automated measurement.

Therefore, in the present study, we identified early oxidative–antioxidative status using a novel automated measurement method. Serum total oxidant status (TOS), total antioxidant status (TAS), and oxidative stress index (OSI) levels in patients with isolated TBI were assessed and compared with controls. Additionally, we assessed whether early oxidative–antioxidative status might reflect injury severity and outcome of patients. We also evaluated the relationship of oxidative–antioxidative status with the Glasgow Coma Scale (GCS) and Revised Trauma Score (RTS) in these patients and tried to determine whether a correlation exists between the GCS and RTS.

Materials and methods

Subjects

This prospective clinical study included 51 consecutive patients presenting to the Department of Emergency Medicine, Harran University Faculty of Medicine, with symptoms of TBI due to various causes (vehicle accidents, vehicle–pedestrian accidents, falling from heights, and assault). As a control group, we enrolled 45 age- and sex-matched healthy volunteers (mean age: 31.47 ± 8.12 years; 6 females and 39 males). Patients were divided into 3 groups according to their GCS scores: group 1, mild TBI (GCS 14–15); group 2, moderate TBI (GCS 9–13); group 3, severe TBI (GCS 3–8). Patients were provided with basic trauma life support at presentation and advanced trauma life support if required. After vital functions were monitored, written informed consent was obtained from patients directly if they were conscious or from their legal guardians if they were unconscious. Furthermore, the healthy volunteers were informed about the study protocol, and written consent was obtained from all participants. Inclusion criteria were: adult patients (≥18 years) with head trauma as the primary injury and a history of posttraumatic loss of consciousness or amnesia; normal healthy controls with no acute traumatic injuries; and consent provided by all participants. The study protocol was conducted in accordance with the 1989 Declaration of Helsinki and was approved by the Ethics Committee of Harran University, Faculty of Medicine.

Exclusion criteria

To investigate the isolated effects of TBI on oxidative status, subjects (patients with TBI and controls) with conditions that may have potentially affected oxidative markers, such as chronic medical disorders (i.e. congestive heart failure, chronic obstructive lung disease, diabetes mellitus, chronic renal failure, hypertension, or malignancy) and those who had coronary artery disease, peripheral vascular disease, and renal dysfunction; subjects using medications such as sedative–hypnotic drugs or stimulatory substances, smokers, subjects with measurable blood alcohol concentrations or those who had consumed alcohol prior to the study; those following a special diet, subjects who were pregnant or had elevated human chorionic gonadotropin (hCG) levels detected by a quantitative hCG blood test (β-hCG); patients with penetrating injuries such as wounds from firearms or sharp penetrating objects, and those who sustained a fall from a high place with the intention of committing suicide were excluded from the study. None of the subjects was taking drugs known to affect lipid or lipoprotein metabolism. Special care was taken to exclude subjects who were taking anabolic

drugs, diuretics, vitamins, or other antioxidants such as vasoactive and beta-blocking agents.

Blood sample collection

Venous blood samples were obtained from patients within 24 h of trauma onset and from healthy volunteers following an overnight fast, collected into heparinized tubes, and immediately stored on ice at 4 °C. The serum was separated from the cells by centrifugation at 4000 rpm for 5 min. Plasma samples were stored at –80 °C until analysis.

Measurement of total oxidant status

Serum TOS was determined using a novel automated measurement method developed by Erel (13). Oxidants present in the sample oxidize the ferrous ion-*o*-dianisidine complex to ferric ions. The oxidation reaction is enhanced by glycerol, which is abundantly present in the reaction medium. The ferric ions provide a colored complex with xylenol orange in an acidic medium. The color intensity, which can be measured spectrophotometrically, is related to the total amount of oxidant molecules present in the sample. This assay has been calibrated with hydrogen peroxide, and the results are expressed in terms of micromolar hydrogen peroxide equivalent per liter (μmol H_2O_2 equiv/L). The assay has excellent precision values of <2%.

Measurement of total antioxidant status

Total antioxidant status in serum was determined using an automated measurement method (14). In this method, hydroxyl radicals, which are among the most potent of the biological radicals, are produced. In the assay, ferrous ion solution, which is present in Reagent 1, is mixed with hydrogen peroxide, which is present in Reagent 2. The sequentially produced radicals such as brown-colored dianisidinyl radical cations, produced by the hydroxyl radical, are also potent radicals. The oxidation reactions progress among dianisidyl radicals, and further oxidation reactions develop, increasing color formation. Antioxidants in the sample suppress the oxidation reactions and color formation. Using this assay, the antioxidative effect of the sample against the potent free-radical reactions, which are initiated by the produced hydroxyl radicals, was measured. Results are expressed as millimolar (mmol) Trolox equiv/L. The precision of the assay was <3%.

Calculation of the oxidative stress index

The OSI was calculated according to the following formula: OSI (arbitrary units) = TOS (μmol H_2O_2 equiv/L)/TAS (mmol Trolox equiv/L) × 10^{-1}.

Other parameters

Both RTS and GCS scores were calculated by the same healthcare professional for each patient upon arrival at the Department of Emergency Medicine, Harran University Faculty of Medicine. The RTS was calculated from the GCS score, systolic blood pressure, and respiratory rate per minute. Computerized cranial tomography (CCT) scans were performed on each patient by the same investigator after vital signs stabilized.

Statistical analysis

Data analyses were conducted using SPSS 15.0 (SPSS, Inc., Chicago, IL, USA). Intergroup comparisons (controls vs. patients) were performed using the chi-square test and Student t-tests. When comparing numerical data (intragroup comparisons) that were not normally distributed, identified with the Kolmogorov–Smirnov Z test, the Mann–Whitney U test was used if there were 2 groups (survivor vs. nonsurvivor). The Kruskal–Wallis test was used if there were more than 2 groups (mild, moderate, and severe TBI). Spearman's rank correlation coefficient (*rho*) was used to evaluate correlations between oxidative–antioxidative status parameters (TOS, TAS, and OSI) and nonparametric data that were not normally distributed (GCS and RTS scores). $P \leq 0.05$ was considered significant.

Results

Of the 51 patients included, 45 were males and 6 were females. The mean ± standard deviation (SD) age of the patients was 33.55 ± 13.62 years (range: 18–69 years). Patients were classified into 3 groups based on the GCS scores: group 1, n = 28; group 2, n = 31, and group 3, n = 11.

CCT images revealed that 69% of patients had pathological findings, of which a skull fracture was the most common cause (39%). Patient demographic and clinical characteristics are summarized in Table 1. Overall patient mortality was 23.5% (n = 12). The causes of death resulting from TBI were motor

Table 1. Demographic and clinical characteristics of the 51 adult patients presenting with symptoms of traumatic brain injury.

Sex, n (%)	
Male	45 (88)
Female	6 (12)
Age (years), mean ± SD	33.55 ± 13.62
GCS groups, n (%)	
Group 1 – mild	28 (55)
Group 2 – moderate	12 (23)
Group 3 – severe	11 (22)
CCT findings, n (%)	
Normal	16 (31)
Subdural hematoma	2 (4)
Epidural hematoma	4 (8)
Cerebral edema	6 (12)
Cerebral contusion	3 (6)
Skull fracture	20 (39)
Linear	14 (27)
Depression	6 (12)

Data are presented as mean ± SD or n (%) of patients.
GCS, Glasgow coma score: group I, GCS 14–15; group 2, GCS 9–13; group 3, GCS 3–8. CCT, computerized cranial tomography.

vehicle accident (MVA) (n = 2), falling from heights (n = 3), motor vehicle–pedestrian accident (n = 4), and assault (n = 3). Motor vehicle–pedestrian accident was the most common mechanism for TBI, occurring in 17 patients (33%). The TBI mechanisms and TBI-related deaths are shown in Table 2.

No significant differences were observed between patients with TBI and the controls with respect to age or sex (P = 0.385 and P = 0.817, respectively). Plasma TOS and OSI levels were significantly higher (both comparisons, P < 0.001), whereas plasma TAS levels were significantly lower in patients with TBI compared with those in the controls (P = 0.001). The demographic characteristics and oxidative stress parameters among the 51 patients with TBI and the 45 controls are shown in Table 3.

When patients were grouped according to the severity of head trauma by GCS score, statistically

Table 2. Causes of presentation for traumatic brain injury and blunt head trauma-related deaths among 51 adult patients.

Cause of traumatic brain injury, n (%)	
Fall from a high place	3 (6)
Motor vehicle–pedestrian accident	17 (33)
Motor vehicle accident	8 (16)
Assault	23 (45)
Traumatic brain injury-related deaths, n (%)	
Fall from a high place	3 (25)
Motor vehicle–pedestrian accident	4 (33)
Motor vehicle accident	2 (17)
Assault	3 (25)

Data are presented as n (%) of patients.

significant differences were observed among the 3 groups in terms of mean serum TOS and TAS levels (between-group comparisons for all 3 groups, P = 0.006 and P = 0.007, respectively; Table 4). A statistically significant difference was observed between groups 2 and 3 (P = 0.008) with respect to mean serum TOS levels. The mean serum TOS levels were higher in proportion to the severity of head trauma in group 3 compared with group 2 (19.55 ± 5.70 and 14.13 ± 2.21, respectively). TOS was also significantly different between groups 1 and 3 (P < 0.001). The mean serum TOS levels were higher in proportion to the severity of head trauma in group 3 compared with group 1 (19.55 ± 5.70 and 13.44 ± 4.37, respectively). Group 3, which included patients with the most severe head trauma, had the highest TOS levels. A statistically significant difference was observed between groups 1 and 2 in mean serum TAS levels (P = 0.032). The mean serum TAS levels were higher in proportion to the severity of head trauma in group 2 compared with group 1 (1.16 ± 0.12 and 0.95 ± 0.19, respectively). Group 2, which comprised patients with moderate head trauma, had the highest TAS levels.

No significant differences were observed among the 3 groups with respect to OSI values (between-group comparisons for all 3 groups, P = 0.081; Table 4). Mean serum oxidative stress parameter (TAS and TOS) levels and OSI values are presented for the 3 groups classified by GCS score in Table 4.

Table 3. Demographic characteristics and oxidative stress parameters among 51 adult patients with traumatic brain injury and 45 controls.

Characteristic	Traumatic brain injury n = 51	Control n = 45	Statistical significance[a,b]
Age (years)	33.55 ± 13.62	31.47 ± 8.12	P = 0.385
Sex (male/female)	45/6	39/6	P = 0.817
TOS (μmol H_2O_2 equiv/L)	14.92 ± 4.90	8.85 ± 2.46	P < 0.001
TAS (mmol Trolox equiv/L)	1.03 ± 0.19	1.17 ± 0.21	P = 0.001
OSI (arbitrary units)	1.50 ± 0.57	0.79 ± 0.30	P < 0.001

Data are presented as means ± SD or n of patients.
[a]Chi-square test (age, sex), [b]Student's t-test.
TOS, total oxidant status; TAS, total antioxidant status; OSI, oxidative stress index.

Table 4. Comparison of oxidative stress parameters among 51 adult patients classified according to severity of traumatic brain injury by the Glasgow Coma Scale (GCS) score.

Characteristic	Mild (group 1) n = 28	Moderate (group 2) n = 12	Severe (group 3) n = 11	Statistical significance*
TOS (μmol H_2O_2 equiv./L)	13.44 ± 4.37	14.13 ± 2.21	**19.55 ± 5.70**[b,c]	P = 0.006
TAS (mmol Trolox equiv./L)	0.95 ± 0.19	**1.16 ± 0.12**[a]	1.07 ± 0.17	P = 0.007
OSI (arbitrary units)	1.52 ± 0.67	1.23 ± 0.23	1.74 ± 0.49	P = 0.081

Data are presented as means ± SD or n of patients.
Mild, group 1, GCS 14–15; Moderate, group 2, GCS 9–13; Severe, group 3, GCS 3–8; TOS, total oxidant status; TAS, total antioxidant status; OSI, oxidative stress index.
*Kruskal–Wallis test. [a]P < 0.05 compared with group 1. [b]P < 0.01 compared with group 2. [c]P < 0.001 compared with group 1.

Both the GCS and RTS scores were significantly lower in nonsurvivors (both comparisons, P < 0.001; Table 5) than in survivors (n = 39). The evaluation of serum oxidative stress parameters demonstrated no significant differences between survivors and nonsurvivors for TAS levels (P = 0.107), whereas mean TOS levels were significantly higher in nonsurviving compared to surviving patients (P < 0.001; Table 5 and Figure 1). Similarly, although both groups had elevated OSI values, they were significantly higher in nonsurviving compared to surviving patients (P = 0.029; Table 5, Figure 2).

GCS and RTS showed negative correlations with TOS levels, (*rho* = –0.497 and –0.560, respectively; both P < 0.001), but neither was significantly related to OSI levels (*rho* = –0.149 and 0.218, respectively; both P > 0.05). The correlation between GCS and serum TAS level was negative (*rho* = –0.288; P < 0.05), whereas RTS was not significantly correlated with TAS level (rho = –0.197; P > 0.05). The correlations between oxidative stress parameters (TAS, TOS, and OSI levels) and trauma scores (GCS and RTS scores) in patients with traumatic brain injury are shown in Table 6.

Discussion

TBI, also known as intracranial injury, occurs when an external force traumatically injures the brain. The injury may entail any of several types of damage to the skull and brain tissue. Gross structural damage

Table 5. Demographic and clinical characteristics and oxidative stress parameters among 51 adult patients with traumatic brain injury classified as survivors and nonsurvivors.

Characteristic	Survivors n = 39	Nonsurvivors n = 12	Statistical significance[a,b]
RTS[b]	10.89 ± 0.47	7.00 ± 3.50	P < 0.001
GCS[c]	12.27 ± 2.56	6.50 ± 1.75	P < 0.001
TOS (μmol H_2O_2 equiv/L)	13.47 ± 6.41	19.49 ± 7.99	P < 0.001
TAS (mmol Trolox equiv/L)	1.05 ± 0.25	1.16 ± 0.17	P = 0.107
OSI (arbitrary units)	1.24 ± 0.88	1.75 ± 0.69	P = 0.029

Data are presented as median ± interquartile range or n of patients.
[a]Mann–Whitney U-test. [b]Measured on a 0–12 scale. [c]Measured on a 3–15 scale.
TOS, total oxidant status; TAS, total antioxidant status; OSI, oxidative stress index; RTS, Revised Trauma Score; GCS, Glasgow Coma Scale.

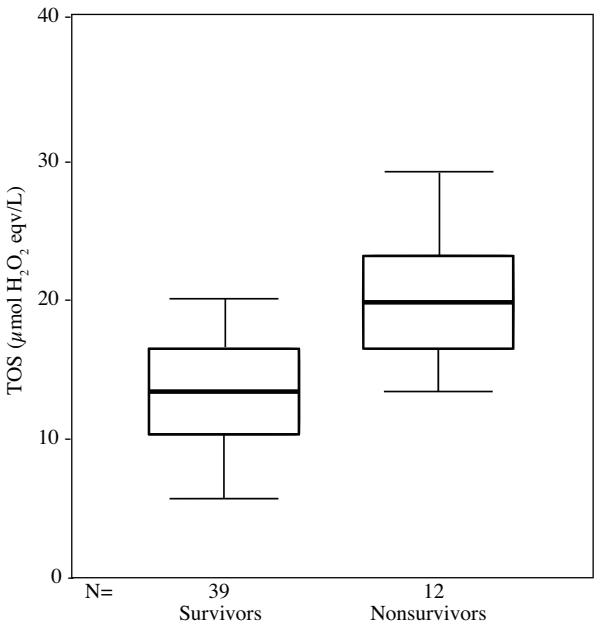

Figure 1. Total oxidant status (TOS) levels in survivors and nonsurvivors.

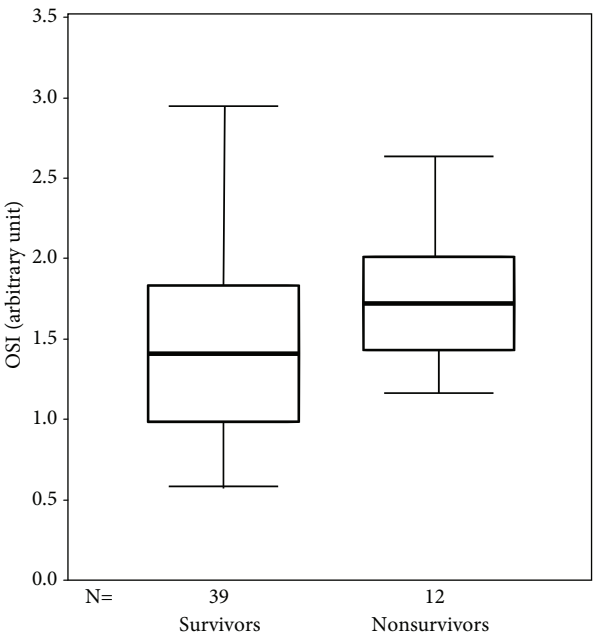

Figure 2. Oxidative stress index (OSI) values in survivors and nonsurvivors.

includes skull fractures, contusions, hemorrhages, and hematomas (2,3). TBI is associated with costly health problems and high mortality in European countries and in the United States, particularly among individuals in younger age groups, and accounts for a disproportionate amount of morbidity in trauma survivors (15,16). Worldwide, several million people, mostly children and young adults, present to emergency departments every year after a head injury. The GCS, the most commonly used trauma scoring system in emergency departments for classifying TBI severity and outcome, grades the individual level of consciousness on a scale of 3–15 based on verbal, motor, and eye-opening reactions to stimuli (17,18). A GCS of 8 or lower is considered representative of a severe brain injury, 9–13 of a moderate head injury, and 14–15 of a mild head injury (18,19). It is estimated that 70%–90% of

Table 6. Correlations between oxidative stress parameters (TAS, TOS, and OSI levels) and trauma scores (GCS and RTS scores) in patients with traumatic brain injury.

		GKS	RTS
TAS	rho	-0.288	-0.197
	P	<0.05	> 0.05
TOS	rho	-0.497	-0.560
	P	< 0.001	< 0.001
OSI	rho	-0.149	-0.218
	P	> 0.05	> 0.05

TOS, total oxidant status; TAS, total antioxidant status; OSI, oxidative stress index; RTS, Revised Trauma Score; GCS, Glasgow Coma Scale.

individuals presenting to emergency departments with TBI can be categorized with mild head injury, 10% with moderate, and 10% with severe (20,21). In the present study, the evaluation of patients in terms of head injury severity by GCS scoring revealed that mild TBI accounted for the largest percentage of the study sample (55%), followed by moderate (23%) and severe (22%) TBI. The RTS, which combines respiratory rate and blood pressure data with GCS score, is also used for evaluating patient outcome with multiple traumas (19). A prospective study conducted by Sogut et al. (22) in 100 patients with blunt head trauma found that a GCS score of ≤8 was an independent predictor of mortality during the early posttraumatic period. Hohl et al. (12) observed a higher adjusted odds ratio for death in patients on admission with a GCS of <5 following severe TBI. Similarly, the mean ± SD of the GCS score in the present study was lower in nonsurviving (6.50 ± 1.75) than in surviving (12.27 ± 2.56) patients. Lower RTS values were also observed in nonsurviving (7.00 ± 3.50) compared with surviving (10.89 ± 0.47) patients. The leading causes of TBI are MVAs, falls from high places, acts of violence, and sports injuries (23,24). MVAs account for the largest number of fatal and severe head injuries (24). In the present study, 25 patients (49%) had TBI as a result of MVAs; of these, motor vehicle–pedestrian accidents (68%; n = 17) had the highest incidence. Of the patients in the study sample who died as a result of blunt head trauma, 7 (50%) deaths resulted from MVAs, and 3 (25%) patients had fallen from a high place.

Oxidative stress can be defined as an increase in oxidants and/or a decrease in antioxidant capacity (5,25). Oxidative stress-induced acute inflammatory responses play an important role in several diseases (9,25). Recent clinical data in numerous medical fields have confirmed an important role for increased oxidative stress in disease mechanisms (9,25–28).

Reactive oxygen species (ROS) play an important role in the pathogenesis of several neurodegenerative processes, including cell death, motor neuron diseases, and axonal injury (29,30). ROS include very transient substances such as hydroxyl radicals, superoxide anions, hydrogen peroxide, and nitric oxide, which lead to lipid peroxidation and oxidation of DNA and proteins. When ROS generation increases to an extent that overcomes the cellular antioxidants, the result is oxidative stress (31). The brain is extremely sensitive to oxidative injury. Previous attempts to assess oxidative stress in patients with varying degrees of TBI have been limited to measurements of single parameters, such as concentrations of individual antioxidant levels (reduced glutathione [GSH] and superoxide dismutase [SOD] activity) or the levels of lipid peroxidation (thiobarbituric acid reactive species [TBARS]) (10,12). Although these parameters may be helpful, they may not provide the clinician with a complete assessment of the degree of oxidative stress occurring in a patient with TBI. Additionally, measuring these parameters is both laborious and time-consuming and is therefore impractical in a clinical setting (32). Moreover, it

has been suggested that oxidants and antioxidant capacity should be measured simultaneously to assess oxidative stress more exactly (27). In the present study, we used a novel automated method that has several major advantages compared with other currently available methods to assess oxidative stress in the study sample. This method is simple and inexpensive and can easily be fully automated. It is also reliable and sensitive and does not interact with commonly occurring serum components such as bilirubin, serum lipids, or anticoagulants. Accurate TOS and TAS measurements can be obtained in as little as 10 min, making this assay eminently suitable for the clinical biochemistry laboratory (13,14,27). In the present study, we found that plasma TOS and OSI levels were significantly higher in patients during the 24-h period following TBI than those in controls, whereas TAS levels were significantly lower. Thus, our data indicated that patients in the study sample were exposed to potent oxidative stress and that the markers reflected oxidative stress; plasma TOS and OSI levels had prognostic value during the early posttraumatic period.

Acute oxidative stress following TBI has been implicated in inducing severe secondary brain damage and influencing the clinical outcome of patients during the early posttraumatic period (11). Published literature is inconclusive as to whether plasma TBARS level, as an oxidative stress biomarker, is related to poor prognosis in patients with severe TBI (10–12). Several studies have reported that early oxidative changes in erythrocytes are valuable serum indicators for establishing the severity of neuronal damage and outcome in patients with various degrees of head trauma (11,12).

Nayak et al. (11) conducted a study involving 50 patients who had sustained various degrees of head trauma. They assessed early oxidative changes in erythrocytes by estimating an indicator of lipid peroxidative damage (TBARS) and antioxidants (GSH levels and SOD activity) in the first 24 h following head trauma and reported a significant correlation among mean serum TBARS levels, severity of neurological insult, and patient outcome in TBI. A study conducted by Nayak et al. (10) evaluated oxidative changes using erythrocyte indicators among 50 patients with varying severities of TBI within 24 h of trauma onset and 30 age- and sex-matched controls and demonstrated that the severity of oxidative stress varies relatively with the severity of head injury in patients with TBI during the early posttraumatic period. However, plasma TBARS levels increased significantly during the first 70 h of the posttraumatic period in 79 consecutive patients with severe TBI but could not be confirmed as an independent predictor of posttraumatic survival in patients with TBI (12). Oxidative stress parameters should be measured with other standard clinical variables before assigning a prime role for these parameters in the prognosis of TBI (11). Consistent with the literature (10–12), the highest serum TOS levels in the present study were observed in proportion to the severity of head trauma in group 3, which consisted of those with severe TBI. Furthermore, mean serum TOS levels in nonsurviving patients were significantly higher than those in surviving patients, which is not consistent with the literature (12).

Mean serum OSI values were elevated in all 3 groups in the present study, although between-group comparisons did not reveal significant differences between groups in OSI values. In accordance with the increased serum TOS levels in nonsurviving compared with surviving patients, the mean OSI value also increased significantly in nonsurviving patients, indicating the presence of enhanced oxidative damage following TBI. The mean ± SD value of the TOS level in nonsurviving patients was 19.49 ± 7.99, whereas in surviving patients it was 13.47 ± 6.41. Higher TOS levels were also observed in patients with more severe blunt head trauma: calculated mean ± SD values were 19.55 ± 5.70, 14.13 ± 2.21, and 13.44 ± 4.37 for groups 3, 2, and 1, respectively. Finally, a negative correlation was demonstrated between serum TOS levels and trauma scores (RTS and GCS scores) in the study sample.

TBI leads to massive production of ROS, with resultant oxidative stress (33). Cellular defenses, such as the GSH system and antioxidant enzymes, protect tissue from the damaging effect of free oxygen radicals. In particular, GSH constitutes an important mechanism against oxidative stress (5,34). Despite the high rate of oxidative metabolism and production of ROS, the brain has a relatively weak antioxidant defense system (31,32). It has been reported that

there is a significant decrease in low-molecular-weight antioxidants in brain tissue after severe TBI in rats (35). Several studies have demonstrated that lipid peroxidation increases concomitantly as GSH levels decrease due to severe TBI, indicating oxidative damage (5,10,11). In the present study, a trend toward higher TAS serum levels was observed in proportion to the severity of head trauma in group 2 patients, who had moderate TBI, compared with group 1 patients, who had mild TBI. Accordingly, serum TAS levels correlated with the severity of injury and decreased faster in patients with higher GCS scores. However, a decrease in serum TAS levels in group 3, which comprised patients with the most severe TBI, compared with group 2 patients supports the notion that severe brain injury induced by trauma is associated with excess oxidative stress and reduces the activity of the antioxidant defense system (33,34). In addition, the mean serum TAS levels were not significantly different in nonsurviving compared with surviving patients, and a significant correlation was not established between serum TAS levels and RTS. It can be considered that the decrease in TAS levels observed in the group 3 patients in the present study could be due to ineffective antioxidant action in the brain in response to severe head trauma.

Our study was unique in that it measured oxidant and antioxidant capacity simultaneously in adult patients with TBI to evaluate oxidative stress using a recently developed automated assay and correlated this capacity with trauma scores, which had the most prognostic value in those patients. We also assessed whether oxidative stress might reflect injury severity and the outcome of the patients. One limitation of the present study was that late-period control TAS, TOS, and OSI values, which may influence long-term neurological outcomes, were not investigated after hospitalization of the patients. This issue should be considered in further studies.

In conclusion, patients with isolated TBI are exposed to potent oxidative stress, which varies with injury severity. Serum total oxidant status levels were significantly related with injury severity during the early posttraumatic period, as assessed by the initial trauma scores (RTS and GCS scores) in patients following TBI. The highest TOS level was noted in patients with severe blunt head trauma. Likewise, nonsurviving patients had a significantly higher mean serum TOS level than surviving patients, and TOS was significantly correlated with trauma scores in the overall study population.

On the basis of our data, we suggest that serum total oxidant status levels might be regarded as a simple, early oxidative-stress serum biomarker and an objective alternative to the GCS and RTS, which are rather subjective trauma scoring systems for determining the prognosis of patients with TBI. More detailed studies are, however, needed to clarify this issue.

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