Analysis of oxidative stress-related markers in critically ill polytrauma patients: An observational prospective single-center study

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ABSTRACT

Critically ill polytrauma patients have increased production of free radicals (FRs) and consequent alterations in biochemical pathways, as well as disruption of cellular integrity, due to increased lipid peroxidation. The aim of this study was to investigate several biomarkers associated with increased oxidative stress in critically ill polytrauma patients, and to evaluate the effect of antioxidant treatment on the clinical outcome in these patients. A total of 67 polytrauma patients from an intensive care unit met the selection criteria. Antiox group included 35/67 patients who received antioxidant therapy, while 32/67 patients without antioxidant treatment were considered as control group. Antioxidant therapy consisted of simultaneous administration of Vitamin C (sodium ascorbate) and N-acetylcysteine, through continuous intravenous infusion. Clinical and paraclinical evaluation of the patients was performed daily until discharge or death. At admission, laboratory parameters did not differ significantly between two groups. At discharge/upon death, statistically significant differences in favor of Antiox group were observed in the following parameters: thrombocytes, activated partial thromboplastin time, prothrombin time, total bilirubin, total cholesterol, high-density lipoproteins, low-density lipoproteins, erythrocyte sedimentation rate, interleukin 6 (all $p = 0.0001$), total protein ($p = 0.0005$), serum albumin ($p = 0.0004$), lactate dehydrogenase ($p = 0.0006$), and C-reactive protein ($p = 0.0014$). Starting from day 5, the APACHE II score was significantly decreased in Antiox versus control group ($p < 0.05$). Finally, the sepsis incidence and mortality rate were significantly lower in Antiox group ($p < 0.05$). Decreasing the level of oxidative stress by antioxidant substances significantly correlated with a better prognosis and outcome in our patients. Further studies should elucidate more clearly the mechanism of action of antioxidants in critically ill polytrauma patients.

KEY WORDS: Polytrauma patients; trauma; vitamin C; N-acetylcysteine; antioxidants; oxidative stress
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INTRODUCTION

The management of critically ill polytrauma patients is complex and often pose a challenge to the intensive care team. Multiple traumas, prolonged mechanical ventilation (PMV), sepsis, pathophysiological disturbances, and posttraumatic changes in biochemical pathways, significantly reduce the survival rate in these patients [1]. Recently, molecular damage and its effect on the clinical outcome in critically ill polytrauma patients has been discussed on a larger scale. One of the most important biochemical processes that can result in a damage of cells and tissues is the production of reactive oxygen species (ROS) and disruption of redox homeostasis [2-4]. Increased concentrations of free radicals (FRs) and decreased antioxidant capacity lead to oxidative stress (OS) [5]. Critically ill polytrauma patients have a drastically increased production of FRs which affects different biochemical pathways as well as mitochondrial function. Moreover, this process results in lipid peroxidation and the disruption of the phospholipid membrane bilayer and cellular integrity [6]. In this state, an uncontrolled inflammatory response is triggered and infections are increased, leading to multiple organ dysfunction syndrome (MODS). In addition, trauma-related complications during surgery can significantly reduce the patient survival rate. Those that considerably affect the clinical prognosis of

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patients include: craniocerebral trauma, spinal cord trauma, thoracic trauma, abdominal trauma, and trauma to the extremities [6-8].

The role of antioxidant therapy in reversing or minimizing the damage caused by impaired redox control has been emphasized [9-11]. However, contradictory results were also reported, probably due to the lack of guidelines on dosage and combination therapy. In this prospective study, we investigated several biomarkers associated with oxidative stress, in critically ill polytrauma patients. In addition, we evaluated the effect of antioxidant treatment on the clinical outcome in these patients.

MATERIALS AND METHODS

Patients

This prospective study was performed at the Intensive Care Unit „Casa Austria" (ICU-CA), of the Emergency County Hospital „Pius Brinzeu" in Timisoara. All patients admitted to the ICU-CA between January 2014 and December 2015 were consecutively included in the study. The inclusion criteria were an Injury Severity Score (ISS) > 16 and age > 18 years. The study was approved by the Clinical Ethics Committee of our hospital and registered at ClinicalTrials.gov with number NCT03095430.

Data collection and processing

The demographic and clinical data of the patients had been securely stored in the hospital database. The personal identification data were not included.

At the time of admission, the following data were obtained: age, sex, ISS, Acute Physiology and Chronic Health Evaluation II (APACHE II), Glasgow Coma Scale (GCS), systolic blood pressure (SBP), heart rate (HR), temperature (T), partial oxygen arterial pressure (PaO_2)/fraction of inspired oxygen (FiO_2) ratio, lactate (Lac) level, and the time between the trauma event and admission to the ICU-CA.

The following parameters were recorded on a daily basis, at admission, during the first 10 days of admission, and at discharge or until death: thrombocytes (TBCs), international normalized ratio (INR), activated partial thromboplastin time (APTT), prothrombin time (PT), lactate dehydrogenase (LDH), aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin (TBIL), total protein (TP), serum albumin (S-Alb), total cholesterol (TC), high-density lipoproteins (HDL), low-density lipoproteins (LDL), triglycerides (TGs), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen (FBN), and interleukin 6 (IL-6). The clinical progress of patients was monitored using the APACHE II score.

Antioxidant therapy

Antioxidant therapy included continuous intravenous infusions of Vitamin C (sodium ascorbate) 3000 mg/24 hours and N-acetylcysteine 1200 mg/24 hours. The therapy was administered continuously during the stay of patients at the ICU-CA. The protocol for administering the antioxidant substances was approved by the Ethics Committee of the hospital. In patients requiring surgical intervention, the antioxidant therapy was continued even during the procedure, with the same concentrations of active substances.

Statistical analysis

Statistical analysis was performed using GraphPad Prism version 6.00 for Mac OS X (GraphPad Software, Inc., San Diego, CA, USA). Qualitative variables were presented as frequencies and percentages and quantitative variables as mean ± standard deviation (SD). The average values were compared by unpaired t-test and percentages by Chi-squared test. Statistical significance was defined as $p < 0.05$.

RESULTS

Patient characteristics

Between 1 January 2014 and 31 December 2014, 71 patients were admitted to the ICU-CA out of which 32 met the inclusion criteria and were considered as the control group. Between 1 January 2015 and 31 December 2015, 65 patients were admitted to the ICU-CA, 35/65 patients met the selection criteria and were included in the group of patients that received antioxidant therapy [Antiox group] (Figure 1). In Antiox group, 26 patients (74.3%) were male, and the mean age (SD) was 45.62 ± 16.88 years. At admission, the mean APACHE II was 11.74 ± 7.11 in Antiox group compared to 12.09 ± 15.94 in control group ($p = 0.9066$). The mean ISS in Antiox group was 26.43 ± 10.25, compared to 24.78 ± 10.35 in control group ($p = 0.5147$). The GCS in Antiox group was 12 ± 4 and it was 13 ± 1 in control group ($p = 0.1740$). In Antiox group, a significant number of patients (18 [51.43%]) suffered a traffic accident, 5 (14.28%) were admitted due to various types of aggression, and 12 (34.29%) suffered other types of trauma. Twenty-four patients (68.57%) from Antiox group presented with a head injury, 30 (85.71%) had a thoracic trauma, 10 (28.57%) had an abdominal trauma, and 24 (68.57%) had pelvic and limb trauma. The main characteristics of the patients in both groups are presented in Table 1. No significant difference was observed in the described demographic and clinical data between the two groups.

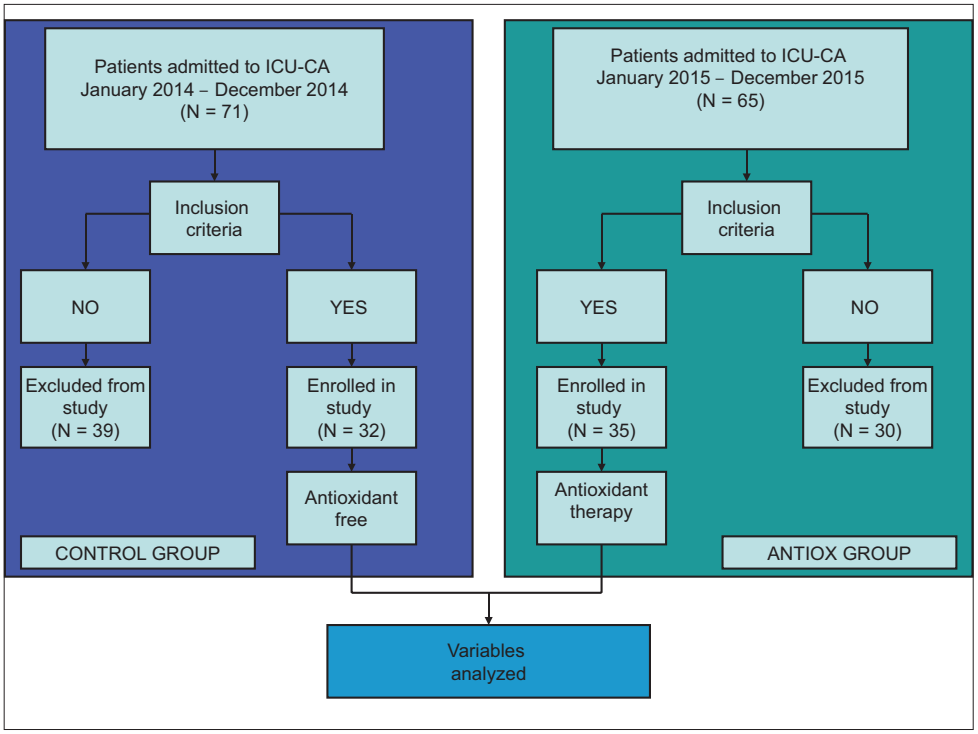

FIGURE 1. Patent selection. Between 1 January 2014 and 31 December 2014, 71 critically ill polytrauma patients were admitted to the Intensive Care Unit „Casa Austria" (ICU-CA) out of which 32 met the inclusion criteria and were considered as the control group. Between 1 January 2015 and 31 December 2015, 65 critically ill polytrauma patients were admitted to the ICU-CA, 35/65 patients met the selection criteria and were included in the group of patients that received antioxidant therapy (Antiox group). The inclusion criteria were an Injury Severity Score (ISS) > 16 and age > 18 years.

TABLE 1. Clinical and demographic characteristics at admission of critically ill polytrauma patients who received antioxidant therapy (Antiox group) and of those without therapy (control group)

Characteristic	Antiox group (n=35)	Control group (n=32)	*p*
Age (years), mean (SD)	45.62 (16.88)	42.67 (16.72)	> 0.05
Gender (male), % (n)	74.28 (26)	75 (24)	0.4755
APACHE II, mean (SD)	11.74 (7.11)	12.09 (15.94)	0.9066
ISS, mean (SD)	26.43 (10.25)	24.78 (10.35)	0.5147
GCS, mean (SD)	12 (4)	13 (1)	0.1740
SBP (mmHg), mean (SD)	96 (20)	98 (16)	0.6548
HR (bpm), mean (SD)	80 (30)	91 (20)	0.0851
T (degrees Celsius), mean (SD)	36.7 (0.91)	36.5 (1.91)	0.5810
PaO_2/FiO_2, mean (SD)	145.55 (5.56)	88.33 (13.2)	0.3657
Lac (mmol/mL), mean (SD)	4.89 (1.99)	5.1 (2.5)	0.7037

APACHE II: Acute Physiology and Chronic Health Evaluation II; ISS: Injury Severity Score; GCS: Glasgow Coma Scale; SBP: Systolic blood pressure; HR: Heart rate; T: Temperature; PaO_2/FiO_2: Partial oxygen arterial pressure/fraction of inspired oxygen; Lac: Lactate

Laboratory tests

At admission, the results of laboratory tests did not differ significantly between the two groups. The patients in Antiox group had the following mean values: for coagulation status, TBCs: 201.22 ± 91.4 × 10^3/μL, INR: 1.88 ± 3.01, APTT: 72.38 ± 21.68 seconds, and PT: 19.20 ± 15.89 seconds; LDH: 72.98 ± 581.42 U/L; AST: 99.69 ± 139.63 U/L, ALT: 123.73 ± 150.07 U/L; TBIL: 11.45 ± 8.72 μmol/L; for protein status, TP: 49.2 ± 9 g/L and S-Alb: 18.3 ± 6.1 g/L; for lipid status, TC: 3.31 ± 1.24 mmol/L, HDL: 0.92 ± 0.32 mmol/L, LDL: 1.31 ± 0.49 mmol/L, and TGs: 1.13 ± 1.06 mmol/L; for inflammation status, CRP: 1011.9 ± 647.14 nmol/L, ESR: 28.14 ± 21.54 mm/h, FBN: 2.64 ± 1.92 g/L, and IL-6: 37.21 ± 2.55 pg/mL.

Statistically significant differences were observed between the two groups in laboratory results at discharge/upon death, as follows: TBCs (p = 0.0001), APTT (p = 0.0001), PT (p = 0.0001), TBIL (p = 0.0001), TP (p = 0.0005), S-Alb (p = 0.0004), TC (p = 0.0001), HDL (p = 0.0001), LDL (p = 0.0001), LDH (p = 0.0006), CRP (p = 0.0014), ESR (p = 0.0001), and IL-6 (p = 0.0001). On the contrary, no statistically significant differences were noted for INR (p = 0.115), AST (p = 0.1581), ALT (p = 0.054), TGs (p = 0.0664), and FBN (p = 0.0951) between Antiox and control group. Figure 2 shows the distribution of markers of oxidative stress evaluated during the hospitalization time in the two groups.

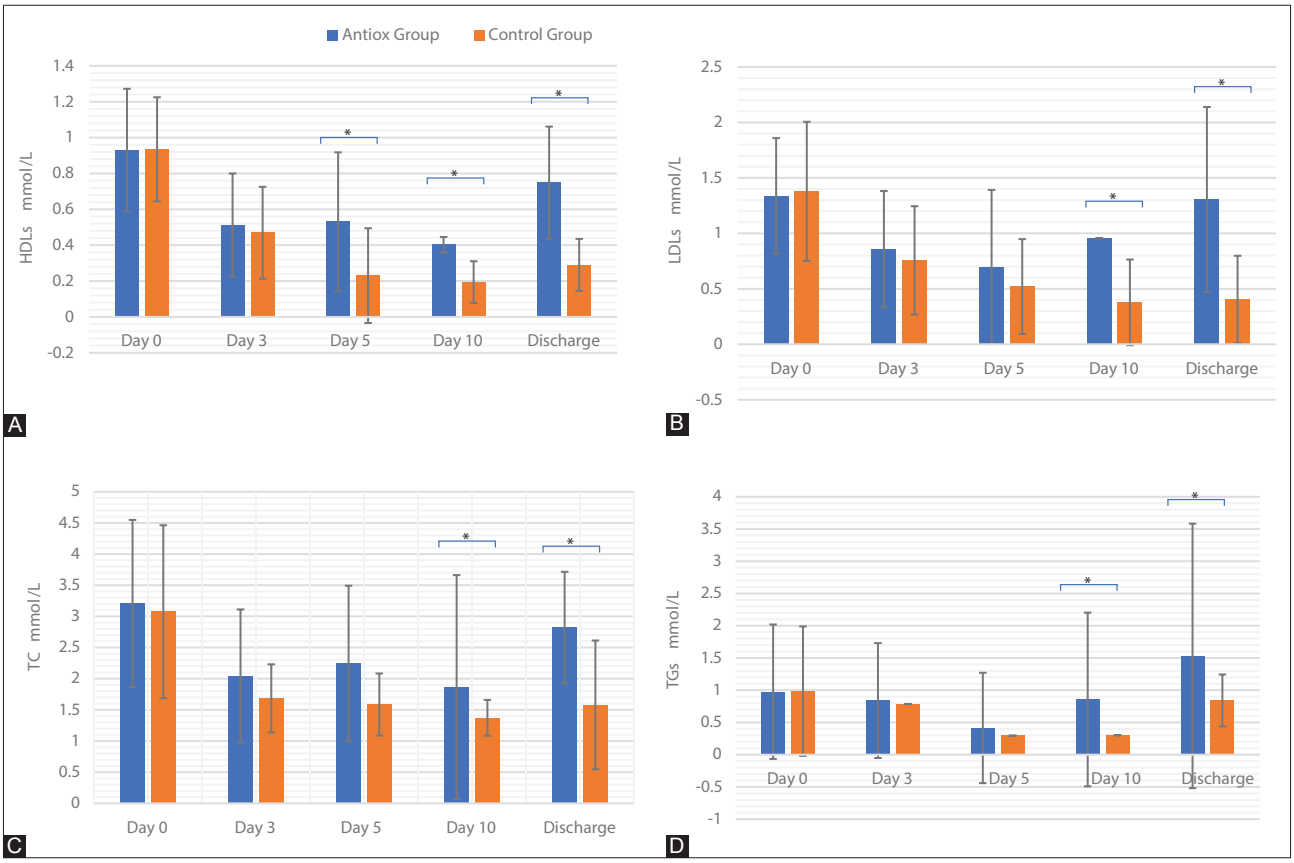

FIGURE 2. Markers of lipid peroxidation in critically ill polytrauma patients who received antioxidant therapy (Antiox group) and in those without therapy (control group). A: High-density lipoproteins (HDLs); B: Low-density lipoproteins (LDLs); C: Total cholesterol (TC); D: Triglycerides (TGs). A rapid increase in lipid levels in Antiox group was observed starting from day 5 for HDL and from day 10 for LDL, TC, and TGs.

Patient outcomes

At admission, the mean APACHE II score was 11.74 ± 7.11 in Antiox group, and it was 12.09 ± 15.94 in control group ($p = 0.9066$). Three days after the admission, the mean APACHE II in Antiox group was 10.46 ± 1.12 and 11.95 ± 0.9 in control group ($p = 0.6043$), at the 5th day it was 8 ± 0.99 in Antiox group and 10.5 ± 2.1 in control group ($p = 0.0111$), at the 10th day it was 7.66 ± 1.21 in Antiox group and 9.35 ± 0.87 in control group ($p = 0.0100$), while at discharge/until death the APACHE II score was 3.21 ± 3.5 in Antiox group and 6.05 ± 0.71 in control group [$p = 0.0001$] (Figure 3). Thirteen subjects from Antiox group (37.14%) developed sepsis, in comparison to 28 (88.75%) from control group ($p < 0.05$). In Antiox group, 8 patients developed MODS (22.85%), which was significantly fewer than in control group (21 patients, 64.62%). The percentage of patients requiring mechanical ventilation more than 96 hours was 54.18% in Antiox group and 53.21% in control group ($p > 0.05$). The average duration of ICU-CA stay in Antiox group was 14.4 ± 16.2 days, in comparison to 18.25 ± 32.55 days in control group ($p = 0.5358$). Furthermore, no statistically significant difference was shown in the hospitalization time between the two groups, which was on average 26.03 ± 20.47 days for Antiox patients and 38.68 ± 40.17 days for controls.

Five patients from Antiox group died during the study period (14.28%), while 11 deaths were registered in control group (33.6%), indicating a statistically significant difference in the mortality rate between the two groups [$p < 0.05$] (Table 2).

DISCUSSION

In critically ill polytrauma patients, impaired redox control significantly affects the clinical status and progress of the patients. One of the main biochemical pathways related to OS is lipid peroxidation [12].

A number of studies indicated that the changes in the coagulation status are associated with the intensity of OS. For example, Shacter et al. [13] showed that plasma fibrinogen was more prone to oxidative modification compared to other plasma proteins, such as albumin, immunoglobulins, and transferrin. [13]. Pawlak et al. [14] investigated whether OS is involved in the activation of extrinsic coagulation pathway in patients on maintenance hemodialysis therapy. The markers of OS (plasma total lipid peroxides, serum autoantibodies against oxidized LDL, and plasma copper/zinc superoxide dismutase) were related to plasma levels of tissue factor (TF) and its inhibitor factor Xa-dependent tissue factor pathway inhibitor (TFPI) in

TABLE 2. Patient outcomes in critically ill polytrauma patients who received antioxidant therapy (Antiox group) and in those without therapy (control group)

Outcome	Antiox group (n=35)	Control group (n=32)	*p*
Sepsis, % (n)	37.14 (13)	88.75 (28)	<0.005
MODS, % (n)	22.85 (8)	65.62 (21)	<0.005
Mechanical ventilation>96 hours, % (n)	54.28 (19)	53.21 (17)	>0.005
Duration of stay at ICU (days), mean (SD)	14.4 (16.02)	18.25 (32.55)	0.5358
Duration of stay in hospital (days), mean (SD)	26.03 (20.47)	38.68 (40.17)	0.1048
Mortality, % (n)	14.28 (5)	33.6 (11)	<0.05

MODS: Multiple organ dysfunction syndrome; ICU: Intensive Care Unit

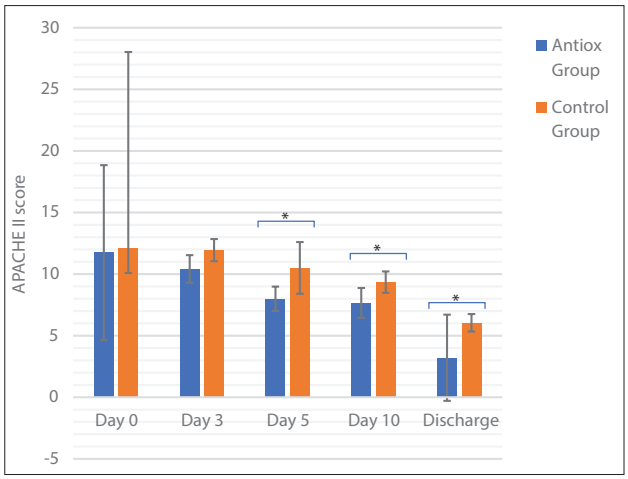

FIGURE 3. Changes in Acute Physiology and Chronic Health Evaluation II (APACHE II) score in critically ill polytrauma patients who received antioxidant therapy (Antiox group) and in those without therapy (control group), from admission until discharge. A statistically significant difference in the APACHE II score was observed between the two groups, starting from day 5 ($p < 0.05$). In Antiox Group, the APACHE II score values dropped significantly and more rapidly compared to controls.

those patients [14]. In our study, the coagulation status in both groups of patients was altered. At admission, there were no significant differences between the two groups in the mean TBCs, INR, APTT and PT. However, at discharge, statistically significant differences were identified in the mean TBCs, APTT, and PT (all $p = 0.0001$), in favor of Antiox group. This indicates that the administration of substances with high antioxidant potential led to faster recovery of coagulation factors, decreasing the complication rates specific to critically ill polytrauma patients.

Several studies analyzed TBIL as a biomarker of a pro-oxidative status. Dani et al. [15] investigated the relationship between TBIL expression, antioxidant system and OS in preterm infants. They observed that a decrease in plasma BIL was correlated with an increase in plasma antioxidant capacity and decrease in oxidative stress [15]. In our control group, the mean TBIL on day 3 upon the admission was 11.45 ± 10.08 µmol/L, on day 5 it was 7.01 ± 5.30 µmol/L, and at discharge 5.13 ± 2.56 µmol/L, compared to the corresponding values in Antiox group, 12.65 ± 10.26 µmol/L on day 3, 9.92 ± 3.59 µmol/L on day 5, and 7.01 ± 3.42 µmol/L at discharge ($p < 0.05$). The higher levels of TBIL observed in Antiox group indicate that the antioxidant treatment possibly decreased the level of FRs in that group, consequently decreasing the consumption of BIL.

Another important marker of OS is protein oxidation, where the role of cysteine thiols in thiol-based redox switches has been emphasized [16]. Rael et al. [17] performed serial measurements of plasma oxidation-reduction potential (ORP) in 39 multi-trauma patients, from the admission until discharge of patients. They showed a rapid increase in ORP during the first days of hospitalization followed by a decrease in ORP to normal levels, until discharge. On the ORP maxima day, plasma paraoxonase-arylesterase (PON-AE) activity and total plasma protein levels were significantly lower compared to admission samples of the same patients [17]. In this study, we observed a significant decrease in protein levels 3 days after trauma, in both groups ($p < 0.05$). After the antioxidant treatment in Antiox group, the level of these proteins significantly increased starting from day 10, compared to the untreated control group in which the protein levels remained low. Moreover, a statistically significant difference in TP ($p = 0.0005$) and S-Alb level ($p = 0.0004$) was observed at discharge in favor of Antiox group.

FR attack on circulating lipids and membrane lipoproteins leads to their aberrant levels in the cells. Gesquière et al. [18] studied the effects of FRs on cholesterol metabolism of smooth muscle cells. They observed an accumulation of cholesterol in the cells exposed to FRs, probably as the result of an increase in cholesterol biosynthesis and esterification, decrease in cell cholesteryl ester hydrolysis, and reduced cholesterol efflux [18]. We observed a rapid increase in lipid levels in Antiox group, starting from day 5 for HDL and from day 10 for LDL, TC, and TGs.

Increased inflammatory response can be observed in patients with trauma [19]. We measured IL-6 levels at admission, during the next 10 days upon the admission, and at discharge/until death in both groups. No significant differences were observed between the two groups on day 3. However, starting from day 5, a significant decrease in IL-6 levels was observed in Antiox group ($p < 0.05$). Moreover, IL-6 concentration was significantly lower in Antiox group at discharge compared to control group ($p < 0.05$). In addition, a

statistically significant decrease of other inflammation markers, such as CRP ($p < 0.05$) and ESR ($p < 0.05$), in Antiox vs. control group indicated the overall improvement of inflammatory as well as oxidative status in patients treated with antioxidant therapy.

Reddell et al. [20] reviewed several antioxidant nutrients (i.e., glutamine, arginine, selenium, zinc, Vitamin C, N-acetylcystine, and fatty acids) important in maintaining oxidant-antioxidant balance in critically ill patients. They indicated that adequate dosing of antioxidants, administration route and timing, duration of therapy, and role of single versus combination therapy still need to be clarified [20]. In our group treated with antioxidant therapy, the occurrence of sepsis was significantly lower compared to the untreated controls (37.14% vs. 88.75%, $p < 0.05$). Furthermore, a significant decrease in the incidence of MODS was observed in Antiox compared to control group ($p < 0.05$).

In most cases, critically ill polytrauma patient require mechanical ventilation. However, prolonged mechanical ventilation increases inflammatory response, as well as the incidence of sepsis in these patients. We observed no significant differences in the number of patients requiring mechanical ventilation for more than 96 hours between the two groups. One explanation for this could be the high number of patients with severe thoracic trauma, as well as an increased percentage of pulmonary infections [21-27].

The duration of ICU stay was similar in both of our groups ($p = 0.1048$). However starting from day 5, the APACHE II score was significantly decreased in Antiox vs. control group ($p < 0.05$), indicating the overall beneficial effect of antioxidant therapy. Finally the mortality rate was significantly lower in Antiox group.

CONCLUSION

In critically ill polytrauma patients, numerous cellular processes are affected, such as lipid function, protein synthesis and inflammatory response, mostly due to increased levels of OS. Decreasing the OS level by antioxidant substances significantly correlated with a better prognosis and outcome in our patients, including the improvement of coagulation, lipid, protein, and inflammatory status. To elucidate more clearly the mechanism of action of antioxidants in critically ill polytrauma patients, further research is required.

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DECLARATION OF INTERESTS

The authors declare no conflict of interests.

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