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High-dose antioxidant administration is associated with a reduction in post-injury complications in critically ill trauma patients

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ABSTRACT

Background: We recently demonstrated a high-dose antioxidant (AO) protocol was associated with reduction in mortality. The purpose of this study was to evaluate the impact of AO on organ dysfunction and infectious complications following injury.
Patients and methods: High-dose AO protocol: ascorbic acid 1000 mg q 8 h, α-tocopherol 1000 IU q 8 h, and selenium 200 mcg qd for 7-day course. Retrospective cohort study evaluating all patients admitted after protocol implementation (AO+), October 1, 2005 to September 30, 2006. Comparison cohort (AO−): all patients admitted in the year prior to implementation, October 1, 2004 to September 30, 2005.
Results: 2272 patients included in the AO+ group, 2022 patients in the AO− group. Demographics and injury severity were similar. Abdominal compartment syndrome (ACS) (2.9% vs. 0.7%, <0.001), surgical site infections (2.7% vs. 1.3%, $p = 0.002$), pulmonary failure (27.6% vs. 17.4%, $p < 0.001$), and ventilator-dependent respiratory failure (10.8% vs. 7.1%, $p < 0.001$) were significantly less in the AO+ group. Multivariate regression showed 53% odds reduction in abdominal wall complications and 38% odds reduction in respiratory failure in the AO+ group.
Conclusions: Implementation of a high-dose AO protocol was associated with a reduction in respiratory failure and ventilator-dependence. In addition, AO were associated with a marked decrease in abdominal wall complications, including ACS and surgical site infections.

Introduction

Severe and sustained oxidative stress from trauma, infection, burn, or other critical illness results in depletion of endogenous antioxidants due to the rapid and massive production of reactive oxygen species (ROS).[12,23] This systemic stress results in wound complications, increased infections, and leads to multiorgan dysfunction (MOD), contributing to increased morbidity and mortality.[15,25,29] In these patients, serum and tissue levels of antioxidants are markedly decreased.[26,28] Numerous investigators have shown that exogenous supplementation of various antioxidants, including ascorbic acid (vitamin C), α-tocopherol (vitamin E), and selenium, results in systemic and local tissue levels returning to baseline.[2,4,9]

In the burn population, supplementation of various antioxidants in both human and animal models has resulted in decreased organ failure.[22,27,28,31] Additionally, copper, selenium, and zinc replacement resulted in shorter hospital stay, reduction of pulmonary infections, as well as lower skin grafting requirements.[9,10] In acute respiratory distress syndrome (ARDS) patients, antioxidants were used along with fish oils to decrease organ failure and ventilator days.[19] In critically ill surgical patients, vitamins C and E reduced the incidence of organ failure and shortened intensive care unit (ICU) length of stay.[26] Recently, we presented a historical cohort study with sufficient patients and power to show vitamin C, vitamin E, and selenium supplementation in acutely injured patients resulted in a reduction in overall mortality.[16]

Many well-designed trials have provided great support for antioxidant supplementation, but these studies have been unsuccessful in demonstrating significant reduction in critical illness morbidities and a decrease in overall mortality. Given the recent findings that antioxidant supplementation is associated with a 28% relative risk reduction in mortality, it is important to

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define potential avenues through which such a reduction could be observed.[16] The purpose of this study was to evaluate the impact of high-dose vitamin C, vitamin E, and selenium supplementation on the incidence of post-injury complications in critically injured patients.

Methods

Study design and setting

The Vanderbilt University Institutional Review Board approved this study. Vanderbilt University Medical Center is a state verified level I trauma centre that evaluates over 3000 acutely injured patients annually; over 700 patients are admitted to the trauma ICU and require mechanical ventilation for greater than 24 h. Patients are cared for by a group of trauma and critical care trained physicians according to evidence based practice management guidelines for sedation, ventilator weaning, hemodynamic monitoring and support, nutrition supplementation, fluid resuscitation, transfusions, infection diagnosis and treatment, glucose control and appropriate prophylaxis.

Selection of participants

We queried the institution's Trauma Registry of the American College of Surgeons (TRACS) for all trauma patients admitted from October 1, 2004 to September 30, 2006, 1 year before AO implementation (AO−) and 1 year after AO implementation (AO+). Statistical analyses were performed on an intention to treat basis; therefore, all patients included after the implementation of the protocol were included in the AO+ group whether or not they actually received the AO.

Following approval by the trauma, critical care, and pharmacy faculty, the antioxidant protocol was implemented October 1, 2005 for all acutely injured patients. The protocol consists of ascorbic acid (Hospira, Lake Forest, IL) 1000 mg intravenously in 100 mL NS every 8 h, alpha-tocopherol (DL-alpha-tocopherol acetate, PCCA, Houston, TX) 1000 IU (1 mL) via naso- or orogastric tube every 8 h, and selenium (selenious acid, American Regent, Shirley, NY) 200 mcg intravenously in 100 mL NS once daily. Ascorbic acid was administered as a bolus over 1 h (0600–1400–2200 time schedule) and selenium as a bolus over 2 h (1000 time schedule), although both were permitted to be changed to an enteral dosage form once enteral access was established. The course of treatment was 7 days or until hospital discharge, whichever came first. All dosing was the same for each patient regardless of illness or weight, ensuring high compliance with the protocol within the practices of the trauma unit. The total per-patient hospital cost of full 7 days AO therapy is $11.00 USD. Patients who were pregnant (admission β-human chorionic gonadotropic) or had a serum creatinine greater than 2.5 mg/dL did not receive antioxidants. The AO protocol was ordered upon admission to the trauma service as a part of the routine admission order set. The compliance with this protocol is well over 90% according to hospital and pharmacy administrative databases.

Demographic and outcome data

We evaluated trauma registry data for age, gender, race, and injury scores including initial Glasgow Coma Scale (GCS), weighted Revised Trauma Score (w-RTS), and Injury Severity Score (ISS). The w-RTS incorporates the initial GCS, systolic blood pressure, and respiratory rate, using coded and weighted values which range from 4 (normal) to 0 (poor) for each of the physiological variables (yielding a high of 7.841 and a low of 0). The Abbreviated Injury Score (AIS) is an anatomic injury scoring system that quantifies injuries in various body regions from a score of 1 (minor injury) to 6 (non-survivable). ISS is calculated by summing the squares of the three highest AIS scores in three different body regions (values range from 1 to 75). Predicted survival based on previously described Trauma Related Injury Severity Score (TRISS) methodology was calculated and evaluated. TRISS is calculated and weighted for the patient's ISS, RTS, age, and mechanism of injury.

The primary outcome of interest was the development of organ failure or dysfunction. Pulmonary failure was defined as a PaO_2/FiO_2 (P/F) ratio less than 300 at any time after the initial 48 h post-injury. Renal failure was defined as a serum creatinine level >2.5 mg/dL at any time after the initial 48 h. Systemic inflammatory response syndrome (SIRS) was defined as two or more of the following variables in the absence of an infectious source at any time after the initial 48 h: (1) core body temperature of more than 38 °C or less than 36 °C, (2) heart rate of more than 90 beats per minute, (3) respiratory rate of more than 20 breaths per minute or a $PaCO_2$ level of less than 32 mmHg, or (4) abnormal white blood cell count (>12,000/μL or <4000/μL or >10% bands). Organ dysfunction occurring in the first 48 h of admission was not considered to be organ failure in keeping with the concept put forth by Ciesla et al.[14] Using this definition, organ dysfunctions occurring within the first 48 h of injury was felt to represent reversible physiologic responses to injury and resuscitation that had the potential for resolution once resuscitation was complete. As such, only organ failure as a clinical processes described above (that occurring after 48 h) was recorded and analysed.

Secondary outcomes evaluated include infectious complications, lengths of stay, and abdominal wall complications. Infectious complications were defined as clinical or culture positive diagnoses of ventilator-associated pneumonia, catheter-related bloodstream infection, abdominal surgical site infection, or intra-abdominal infection, in accordance with the guidelines of the American College of Chest Physicians and the Society of Critical Care Medicine.[1] The rates of ventilator-associated pneumonia were expressed in pneumonias per 1000 ventilator days. As well, the rates of catheter-related blood stream infections were expressed in catheter-related infections per device days. Septic shock was also defined according to standard accepted criteria from a consensus statement of the American College of Chest Physicians and the Society of Critical Care Medicine. Hospital length of stay (in days), ICU length of stay (in days), and ventilator days are expressed in calendar days. Ventilator-dependent respiratory failure was defined as the need for mechanical ventilation greater than 72 h. With respect to abdominal wall and wound complications, the following definitions were used: abdominal compartment syndrome (ACS) was defined as intra-abdominal pressure greater than 25 mmHg, at least one organ system failure not identified prior to abdominal hypertension, and attending surgeon documentation of concern for ACS prior to decompressive celiotomy. Surgical site infection was defined as above. Wound dehiscence was defined as attending documentation of a separation of the layers of a surgical wound. Sacral decubiti were defined as attending documentation of ulceration of the skin and soft tissue. Abdominal wall complications were defined as the occurrence of any of the following: ACS, wound dehiscence, or surgical site infection.

Statistical analysis

Univariate analyses comparing categorical risk factors by AO use were conducted using chi-square test. Normally distributed continuous variables were summarised using mean and standard deviation and were compared using the two-sample *t*-test; non-normally distributed continuous variables were summarised by reporting the median and interquartile range and compared using the Wilcoxon Rank Sum test. Unadjusted relative risks of primary

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and secondary outcomes were performed and calculated for AO exposure. Multivariate logistic regression was used to estimate the association between AO use and the development of respiratory failure and abdominal wall complications, adjusting for age, gender, and injury severity (ISS). A subset analysis was performed to evaluate the impact of AO exposure on ICU patients. All patients with less than 24 h in the ICU were excluded. This exclusion criterion included those who were critically ill and admitted to the ICU but died prior to 24 h post-admission. However, it allowed for a focused assessment of the impact of antioxidants on the sickest of patients who lived long enough to receive the protocol. STATA version 10.0 (STATA Corp., College Station, TX, USA) was used for analysis. Tests for statistical significance were two sided with an alpha of 0.05.

Results

Demographic and clinical characteristics

Patients in the AO+ group were more likely to be male, older, and have a lower calculated probability of survival by means of TRISS (Table 1). There were no statistical differences in race or Injury Severity Scores (ISS) between AO groups.

Clinical course and durations of care

The overall mortality rate in the AO− group was 8.5% compared to 6.1% in the AO+ group ($p < 0.001$). Intensive care median length of stay was significantly shorter ($p < 0.001$) in those patients exposed to high-dose antioxidants compared to those not exposed (2 days, interquartile range of 1 and 4 days vs. 3 days, interquartile range of 1 and 6, respectively). Overall hospital median length of stay was also shorter in the AO+ group compared to the AO− group (3 days, interquartile range of 1 and 6 days vs. 4 days, interquartile range of 2 and 8, respectively). Ventilator free days showed a statistical distribution advantage towards the AO+ group, however the median number of days and interquartile ranges were the same (3 days with interquartile range of 1 and 6 days, $p = 0.02$).

Organ failure

Table 2 demonstrates the univariate analysis of organ failure. Lowest P/F ratios were higher in the AO+ group (225 vs. 184, $p < 0.001$). Respiratory failure rates were significantly lower in the AO+ group when compared to that of the AO− group (27.6% vs. 17.4%, $p < 0.001$). However, acute renal failure and SIRS were not significantly different between the two groups. Simple logistic regression confirmed the relationship between AO exposure and respiratory failure (OR 0.55, $p < 0.001$, 95% CI 0.479–0.641) and ventilator-dependent respiratory failure (OR 0.63, $p < 0.001$, 95% CI 0.509–0.781).

Table 1
Clinical and demographic characteristics by antioxidant (AO) group.

	AO−, $n = 2022$	AO+, $n = 2272$	p-Value
Males, n (%)	1452 (72%)	1832 (81%)	<0.001
White race, n (%)	1587 (78%)	1291 (79%)	0.981
Mean age, years (±SD)	39 ± 18	40 ± 17	0.01
Mean admission GCS (±SD)	13 ± 4	12 ± 5	<0.001
Mean ISS (±SD)	21 ± 12.6	20 ± 12.3	0.088
Mean predicted survival (±SD) by TRISS methodology	0.885 ± 0.222	0.822 ± 0.285	<0.001

ISS: Injury Severity Score; TRISS: Trauma Revised Injury Severity Score.

Table 2
Comparison of organ failures by antioxidant exposure.

	AO−, $n = 2022$	AO+, $n = 2272$	p-Value
Respiratory failure, n (%)	558 (27.6%)	395 (17.4%)	<0.001
Ventilator-dependent respiratory failure, n (%)	218 (10.8%)	160 (7.1%)	<0.001
Mean lowest P/F ratio (±SD)	184 (±153)	225 (±135)	<0.001
Renal failure, n (%)	26 (1.3%)	30 (1.3%)	0.921
SIRS, n (%)	283 (13.8%)	360 (15.0%)	0.070

P/F: PaO_2/FiO_2 ratio; SIRS: systemic inflammatory response syndrome.

Table 3
Infectious complications by AO exposure status.

	AO−, $n = 2022$	AO+, $n = 2272$	p-Value
Ventilator-associated z pneumonia (per 1000 ventilator days)	13.2	11.8	<0.001
Catheter-related blood stream infections (per 1000 device days)	5.2	4.9	0.017
Septic shock, n (%)	10 (0.5%)	14 (0.6%)	0.443
Abdominal surgical site infections, n (%)	55 (2.7%)	30 (1.3%)	0.002
Post-injury infectious complications, n (%)	303 (15.0%)	334 (12.3%)	0.014

Infectious complications

While there were no differences in the development of septic shock, there was a significantly lower incidence of surgical site infections, ventilator-associated pneumonias and catheter-related bloodstream infections (Table 3). These translated into a lower incidence of overall post-injury infectious complications. Simple logistic regression supported these findings with a 20% reduction in the odds of infectious complications in patients exposed to antioxidants (OR 0.80, $p = 0.02$, 95% CI 0.661–0.975).

Abdominal wall complications

As stated above, abdominal wall surgical site infections were lower in the AO+ group as were the incidence of wound dehiscence (Table 4). In addition, the incidence of ACS was markedly reduced in the AO exposed patient population. Overall abdominal wall complications were noted to be less in the AO+ group and these findings were confirmed with simple logistic regression. There was no difference in the incidence of sacral decubiti.

Multivariate regression analyses

A multivariate logistic regression model was constructed to determine the association of AO exposure and development of abdominal wall complications. The findings are illustrated in Table 5. After adjusting for age, male gender, and ISS, exposure to antioxidants was associated with a greater than 50% odds reduction for development of abdominal wall complications. A similar model was constructed for development of respiratory

Table 4
Abdominal wall complications by AO exposure.

	AO−, $n = 2022$	AO+, $n = 2272$	p-Value
Wound dehiscence, n (%)	20 (0.9%)	17 (0.7%)	0.492
Abdominal surgical site infections, n (%)	55 (2.7%)	30 (1.3%)	0.002
Abdominal compartment syndrome, n (%)	58 (2.9%)	16 (0.7%)	<0.001
Abdominal wall complications, n (%)	133 (6.6%)	63 (2.8%)	<0.001

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Table 5
Multivariate logistic regression model predicting development of abdominal wall complications.

	Odds ratio	95% CI	*p*-Value
Received AO	0.47	0.330–0.672	<0.001
Male gender	1.09	0.758–1.566	0.643
Age (years)	0.99	0.981–1.000	0.070
Injury severity score	1.055	1.039–1.062	<0.001

Table 6
Multivariate logistic regression model predicting development of respiratory failure.

	Odds ratio	95% CI	*p*-Value
Received AO	0.62	0.530–0.736	<0.001
Male gender	1.15	0.926–1.380	0.118
Age (years)	1.01	1.010–1.020	<0.001
Injury severity score	1.05	1.050–1.060	<0.001

failure. Table 6 illustrates that AO exposure is associated with an almost 40% odds reduction for developing respiratory failure, adjusting for age, gender, and injury severity. However, when adjusting for similar covariates, AO exposure was not associated with a reduction in infectious complications (OR 0.98, $p = 0.931$, 95% CI 0.616–1.557). As an individual diagnosis, the risk of abdominal surgical site infections was reduced in patients who were exposed to antioxidants (OR 0.61, $p = 0.043$, 95% CI 0.380–0.984).

ICU subset analysis

A subset analysis was then performed on those patients with greater than 24 h spent in the ICU. This excluded 2578 patients, leaving 830 in the AO− group and 885 in the AO+ group. With the exception of gender (73% male in AO− group and 78% male in the AO+ group, $p = 0.005$), there were no significant differences in the demographics of ICU patients who were exposed to AO and those who were not exposed. Both overall hospital length of stay (10.6 days vs. 8.8 days, $p = 0.002$) and ICU length of stay (4.9 days vs. 3.9 days, $p = 0.002$) were reduced in the AO+ group. The incidence of VAP was less in the AO+ group (14.8 pneumonias per ventilator days vs. 15.5 pneumonias per ventilator days, $p = 0.053$), as were surgical site infections (2.6% vs. 5.1%, $p = 0.005$), and catheter-related bloodstream infections (6.3 infections per 1000 device days vs. 6.7 infections per 1000 device days, $p = 0.025$). Evaluation of diagnosis groups, both abdominal wall (5.5% vs. 10.8%, $p < 0.001$) and infectious (19.7% vs. 23.9%, $p = 0.029$) complications were markedly reduced in the AO+ cohort. There were no differences in sepsis, acute renal failure, and SIRS.

Discussion

Surviving initial injuries is of primary focus in the care of trauma patients; however, those who survive but continue to undergo systemic inflammation and stress often succumb to multiorgan failure.[15,25,29] An increased amount of evidence has linked the excess production of reactive oxygen species (ROS) to these systemic complications.[11,21] When they accumulate, ROS injure cell membranes and structural proteins, and induce apoptosis.[21,27] In the normal state, these ROS are neutralised by endogenous antioxidants. In critically ill patients, levels of vitamin C, vitamin E, and selenium are diminished and their depleted levels are associated with worse outcomes.[4,13,18,26,28] Supplementation and repletion of levels has been shown to improve outcomes in various patient populations, including those acutely injured.[2,4,26,28,31] In the present study, we were able to demonstrate a reduction in infections, pulmonary complications, and abdominal wall complications in trauma patients following implementation of a high-dose AO protocol. These improvement in critical illness related morbidities might explain the reduction in overall mortality we previously described.[16] To our knowledge, this is the first study that has been able to potentially link improvements in mortality with improved secondary outcomes in the trauma population.

The pulmonary benefits of antioxidant supplementation have also been well documented. Gadek was able to show that in ARDS patients supplemented with antioxidants enterally, P/F ratios improved and corresponded with decreased ventilator days and organ failure.[19] Others have also reported reductions in ventilator days, pulmonary failure, and ARDS with antioxidant supplementation in the critically ill and injured populations.[4,26] The current study demonstrated a reduction in acute lung injury and ventilator-associated pneumonias during the period of high-dose antioxidant supplementation.

Another population in which AO supplementation has been frequently studied is burn patients. AO supplementation in burn patients with depleted levels of these critical substrates has been shown to replace diminished local tissue levels and reduce both wound and infectious complications.[8,9,22,27,31] In addition, AO supplementation has been shown to decrease burn edema acutely and lower long-term skin graft requirements.[7,9,31] Specifically, vitamin C supplementation impacts dermal fibroblast proliferation and improves wound healing.[3,7,28] These effects could result in improved strength and continuity of healing wounds, reducing breakdown and infection risk.

In evaluating this population for the development of abdominal wall complications, we noted a significant reduction in surgical site infections and cases of abdominal compartment syndrome in those patients exposed to high-dose AO supplementation (Table 4). One possible explanation for these findings is the potential for reducing early fluid resuscitation volumes. Several authors have demonstrated the ability of high-dose ascorbic acid supplementation to reduce fluid resuscitation requirements in burn patients.[17,30] In a prospective randomised trial, Tanaka and colleagues have previously demonstrated that ascorbic acid infusions in the burn population reduces early resuscitation requirements.[30] In trauma patients, large volume, crystalloid based resuscitation strategies have been associated with the development of abdominal compartment syndrome (even in the absence of intra-abdominal injuries and in the already open abdomen) by numerous investigators.[5,6,20,24] While reducing fluid resuscitation volumes through high-dose ascorbic acid infusion is quite plausible, the current study was not randomised like the burn trials and we did not evaluate the volumes of fluid resuscitation and techniques of initial volume management.

Major improvements at our institution in critical care such as glucose control, ventilator-associated pneumonia bundles, goal-directed resuscitation, the use of steroids for adrenal insufficiency, and deep venous thrombosis and stress gastritis prophylaxis preventions were all in place prior to AO protocol implementation. As well, no other significant critical care changes were observed during the AO+ group time period of October 1, 2005 moving forward. Despite these strengths and the large sample size of our study, there are several important limitations. The historical cohort study design itself has inherent limitations. Because patients were not randomised to therapy, the reduction in critical illness related morbidities in the AO group could not be specifically attributed to this treatment. These limitations and others further support the need to carry this work forward into a large, multi-institutional, randomised trial. In the absence of such a study, the true impact of these agents remains unproven.

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Conclusion

Severely injured patients are subject to significant systemic stress resulting in an overwhelming production of ROS and depletion of endogenous antioxidants. These key substrates are thought to be key in preventing additional tissue injury, organ system failure, and the resultant mortality. Following implementation of a high-dose AO protocol in trauma patients, we noted a reduction in respiratory failure, abdominal wall complications, surgical site infections, and overall infectious complications. This association was maintained when analysing only the most severely injured patients requiring ICU care. Given the excellent safety profile and low cost of this intervention, vitamin C, vitamin E and selenium show promise in potentially reducing ICU-related complications in acutely injured patients. However, as this was a single centre, retrospective study, a causal link with AO and post-injury complications cannot be determined at this time. A randomised, multicentre trial is needed to determine the benefit (if any) of such an AO protocol. As well, the ideal dosing and schedules (and potential inclusion of other antioxidant supplements), has yet to be determined and should be evaluated in future studies.

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Conflicts of interest

The authors of this article have no financial or other conflicts of interest.

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