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Antioxidant supplementation and atrial arrhythmias in critically ill trauma patients

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Abstract

Background—The purpose of this study is to determine if antioxidant supplementation influences the incidence of atrial arrhythmias in trauma intensive care unit (ICU) patients.

Materials and methods—In this retrospective pre-post study, critically ill injured patients aged 18 years, admitted to a single-center trauma ICU for > 48 hours were eligible for inclusion. The control group consists of patients admitted from January 2000 to September 2005, before routine antioxidant supplementation in our ICU. The antioxidant group consists of patients admitted from October 2005 to June 2011 who received an antioxidant protocol for > 48 hours. The primary

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Disclosure

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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outcome is the incidence of atrial arrhythmias in the first 2 weeks of hospitalization or before discharge.

Results—Of the 4699 patients, 1622 patients were in the antioxidant group and 2414 patients were in the control group. Adjusted for age, sex, year, injury severity, past medical history, and medication administration, the unadjusted incidence of atrial arrhythmias was 3.02% in the antioxidant group versus 3.31% in the control group, with no adjusted difference in atrial arrhythmias among those exposed to antioxidants (odds ratio: 1.31 [95% confidence interval: 0.46, 3.75], $P = 0.62$). Although there was no change in overall mortality, the expected adjusted survival of patients in those without antioxidant therapy was lower (odds ratio: 0.65 [95% confidence interval: 0.43, 0.97], $P = 0.04$).

Conclusions—ICU antioxidant supplementation did not decrease the incidence of atrial arrhythmias, nor alter the time from admission to development of arrhythmia. A longer expected survival time was observed in the antioxidant group compared with the control group but without a change in overall mortality between groups.

Keywords

Antioxidants; Atrial arrhythmia; Trauma; Critical care; ICU

Introduction

Atrial fibrillation is the most common arrhythmia affecting the general population and can cause an increase in morbidity and mortality. The incidence of atrial fibrillation has been estimated from 15% to 50% of patients after cardiac surgery,^{1–3} 4%–9% in general intensive care unit (ICU) patients,⁴ and 6% in trauma ICU patients.⁵ In trauma patients, atrial arrhythmias have been independently associated with higher mortality.⁵ Supplementation with high-dose antioxidants including vitamin C, E, and selenium has shown possible improvements in mortality in critically ill trauma patients⁶ but has not been studied in the setting of atrial arrhythmias. In cardiac surgery patients, antioxidants may reduce the rates of atrial fibrillation postoperatively.⁷ One study documented the biochemical evidence of oxidative stress in atrial tissue of patients undergoing a maze procedure for treatment of permanent atrial fibrillation.⁸ It is proposed that the uncontrolled inflammatory state from the decrease in natural circulating antioxidants seen in postsurgical patients may contribute to atrial fibrillation, which may be attenuated with antioxidant supplementation.^{8–10}

Oxidative stress has been recognized as an important factor in the pathophysiology of critical illness. The production of reactive oxygen species can have detrimental effects and contribute to multiorgan dysfunction.^{11,12} While the human body has defense mechanisms against these free radicals, such as superoxide dismutase, glutathione peroxidase (including one of its cofactors, selenium), and vitamins C and E, it has been shown that circulating plasma antioxidants are decreased during critical illness after surgery or trauma.^{13,14} The degree of endogenous antioxidant depletion correlates with the severity of trauma or systemic inflammatory response syndrome.^{15,16}

While the use of antioxidants has been suggested in the prevention of postoperative atrial fibrillation among cardiac surgery patients, there are limited data exploring the effects of antioxidant supplementation on the incidence of atrial arrhythmias in critically ill trauma patients, and there is general equipoise on antioxidant usage. We proposed that high-dose antioxidant supplementation consisting of ascorbic acid, selenium, and vitamin E may have an impact on the development of new atrial arrhythmias in critically ill injured patients by means of reducing oxidative stress.

Methods

Patient population

In this Institutional Review Board–approved, retrospective pre-post study, injured patients admitted to the Trauma ICU at Vanderbilt University Medical Center between January 1, 2000 and June 30, 2011 were eligible for enrollment in our study. Patients aged 18 years and remaining in the ICU for at least 48 hours were included in this study. Patients were excluded if there was a history of cardiac arrhythmias, a baseline serum creatinine of 2.5 mg/dL or greater, or mortality occurred within 48 hours of admission. Subjects receiving high-dose ICU antioxidant supplementation were identified by antioxidant medication charges and excluded if treatment time was under 48 hours.

Protocol

Eligible patients were assigned to one of the two groups based on the implementation of the antioxidant protocol. The control group consisted of patients admitted from January 1, 2000 through September 30, 2005, who did not receive ICU antioxidant supplementation. Any patients who received antioxidants before October 1, 2005 were excluded from the control group. The antioxidant group consisted of patients admitted from October 1, 2005 through June 30, 2011, who received the antioxidant protocol for at least 48 hours. The protocol was included in the admission order set but may have been ordered at any point in the hospitalization. The high-dose antioxidant protocol consisted of ascorbic acid 1000 mg by mouth (PO), per tube (PT), or intravenous (IV) every 8 hours, vitamin E 1000 units PO/PT every 8 hours, and selenium 200 mcg PO/PT/IV daily for a total of 7 days. Data on demographic and physiologic characteristics were collected from the electronic medical record and our trauma registry.

In addition to basic baseline demographic, such as age, sex, admission year, we gathered past medical history data regarding hypertension, myocardial infarction, coronary artery disease, prior cardiac surgery, and congestive heart failure. Injury severity score, predicted survival, abbreviated chest injury scale, and mechanism of trauma were also collected as baseline demographics.

The primary outcome of this study was the incidence of atrial arrhythmias during the first 2 weeks of hospitalization or before discharge, whichever occurred first. The primary outcome was identified through the use of International Classification of Diseases, Ninth Revision (ICD-9) codes, which is depicted in Table 1. A manual chart review was performed on every

patient documented to have an arrhythmia through ICD-9 codes. Secondary outcomes include time from admission to arrhythmia occurrence and in-hospital mortality.

Methodology and statistics

Continuous variables were compared among treatment groups using the Wilcoxon nonparametric test. With regard to categorical variables, they were compared using Pearson's chi-squared test.

To detect a 30% relative difference between groups with an estimated atrial arrhythmia rate of 10%, a sample size of 1422 patients in each group was needed assuming an alpha of 0.05 and a power of 80%. The probability of developing atrial arrhythmia was modeled using multivariate logistic regression, while adjusting for hospitalization year, treatment group, basic characteristics such as age, sex, injury severity score, predicted survival, past medical history (hypertension, myocardial infarction, coronary artery disease, cardiac surgery, and congestive heart failure), and medication administration, specifically the use of beta-blockers, amiodarone, and diltiazem. Adjusted odds ratio was calculated from the multivariate model. Concordance (C-statistic) and Hosmer–Lemeshow test were used to assess the goodness of fit of the model.

Hospital mortality was modeled using a log-normal accelerated failure time model using the same covariates as those in the model for the primary outcome. The goodness of fit for this model was assessed. All of the statistical analysis was conducted using R, version 2.15.0 (<http://www.R-project.org>).

Results

A total of 5679 patients were evaluated for this study, 1643 of whom did not meet eligibility criteria. Of the remaining 4699 patients, 1622 patients met criteria for the antioxidant group and 2414 patients were included in the control group, which met our sample size calculation and power analysis. The most common reason for exclusion was unclear exposure to antioxidants, followed by lack of data in the trauma registry, ICU length of stay <48 hours, history of chronic atrial arrhythmias, and serum creatinine >2.5 mg/dL (Fig. 1).

The patient population, which is shown in Table 2, consisted of critically ill injured patients who were predominately Caucasian and male. The antioxidant group had higher rates of cardiovascular disease, more severe chest trauma, and a less likelihood of survival. We depict the unadjusted incidence rates of arrhythmia in both groups by year, allowing qualitative review of any secular trends (i.e. no improvement of arrhythmias in control group preceding the intervention antioxidant period, Fig. 2).

There was no significant difference in the unadjusted incidence of atrial arrhythmias in the first two weeks of hospitalization or before discharge between the antioxidant and control groups (3.02% versus 3.31%). The odds ratio for the development of atrial arrhythmias in the control group was 1.31 (95% confidence interval: 0.46–3.75, $P = 0.62$), adjusting for covariates. The average time to arrhythmia occurrence was also similar between the two

groups occurring at 4.58 days and 4.56 days in the antioxidant and control groups, respectively ($P = 0.796$).

The hospital mortality rate was similar between the two groups with 178 deaths (10.9%) versus 251 deaths (10.4%) in the antioxidant and control groups, respectively. When these rates were compared using the accelerated failure time model, the adjusted time ratio for the control group was 0.65 (95% confidence interval: 0.43–0.97, $P = 0.04$) indicating a 35% decrease in the expected survival time in the control group compared with the antioxidant group (Fig. 3). Therefore, this was a statistically significant difference in favor of antioxidant supplementation, indicating an increased expected survival time. Also, patients with congestive heart failure, increased age, and those not exposed to beta-blockers were other independent risk factors for hospital mortality.

Protocol compliance was also assessed during this study. Patients in the antioxidant group received the three-drug antioxidant protocol for an average of 5.2 days of a possible seven. The circumstances for stopping the protocol before completion of 7 days include physician discretion based on patient improvement, worsening renal function, or transfer out of the ICU.

Discussion

In this retrospective pre-post study of critically ill patients, high-dose antioxidant supplementation did not significantly decrease the incidence of atrial arrhythmias nor did it impact the time from admission to arrhythmia occurrence. However, the use of antioxidants was associated with a longer expected survival time, without a change in overall in-hospital mortality.

It has been proposed that oxidative stress and free radical formation promote the development of atrial fibrillation. Studies have examined the effect of providing antioxidants in cardiac surgery patients both prophylactically and post-surgery to prevent atrial arrhythmias. Carnes *et al.*¹⁷ found a significant reduction in the rates of atrial fibrillation and atrial flutter when ascorbic acid was given compared with placebo (16% versus 34.9%, respectively). Papoulidis *et al.*¹⁸ found similar results when providing supplemental vitamin C before cardiac surgery and 5 days postoperatively. It was observed that the overall incidence of atrial fibrillation between the vitamin C group and control group was 44.7% and 61%, respectively ($P = 0.041$). Rodrigo *et al.*¹⁹ supported these results in 2013 in a randomized controlled trial that demonstrated a decreased incidence of postoperative atrial fibrillation and decreased levels of biomarkers of inflammation and oxidative stress. The antioxidants used in this study were vitamins C and E, in addition to n-3 polyunsaturated fatty acids. A reduction in the oxidative stress is the likely mechanism for these decreased rates of atrial fibrillation. However, the cardiac surgery population is likely fundamentally different than the critically ill injured patient, as patients after cardiac surgery have typically undergone direct instrumentation of their cardiac tissue and thus are more likely to have localized inflammation and oxidative stress compared with the critically ill injured patients. This potential risk factor for atrial arrhythmias typically does not apply to critically ill

trauma patients and may explain why there was no significant benefit to antioxidant therapy in preventing atrial arrhythmias in our patient population.

The rates of atrial arrhythmias observed in our study were lower than expected and lower than the rates identified in previous studies in ICU patients. Incidence rates of atrial fibrillation have been observed as high as 15% in noncardiac ICU patients²⁰ and 6% in the trauma ICU patients.⁵ One factor that may contribute to the lower rates of atrial arrhythmias in our study is the age of the patient population. Increasing age has consistently been recognized as an important risk factor for the development of atrial fibrillation.¹⁻³ The average age of the patients in our control group was young, around 40 years, typical for an injured population. With rates of atrial arrhythmias lower than expected, it is more difficult to find a statistically significant benefit with high-dose antioxidant supplementation.

When comparing survival times between the two groups, the antioxidant group was shown to have an increased survival time compared with the control group. The adjusted time ratio for the control group showed a 35% decrease in expected survival time compared to patients who received high-dose antioxidant supplementation. This could represent other sequelae from critical illness as a result of decreased circulating antioxidants.²¹ The literature is controversial on whether supplementation with antioxidants improves survival in the critically ill. In 2001, Berger *et al.*²² found that supplementation with antioxidants (including vitamin E) and trace elements has been shown to improve antioxidant capacity through measurement of glutathione peroxidase in critically ill patients. Early supplementation can reduce organ failure and decrease ICU length of stay.^{6,13,23,24} Angstwurm *et al.*²³ showed a decrease in the 28-day mortality among patients with severe sepsis when receiving high-dose selenium. A retrospective study at our institution in 2006 showed a 28% relative risk reduction in mortality among patients receiving antioxidant supplementation.⁶ This benefit was notably seen in the most critically ill trauma patients with an expected survival of less than 50%. On the other hand, several studies have found no benefit to antioxidant supplementation in the critically ill.^{25,26} Most recently, in 2013, Heyland *et al.*²⁷ in the REDucing Deaths due to OXidative Stress (The REDOXS Study) demonstrated an increased mortality in critically ill patients following glutathione supplementation and no effect on mortality with antioxidants supplementation (selenium, zinc, beta carotene, and vitamins E and C). While it is unclear whether supplementing critically ill patients with antioxidants decreases mortality, our results further support a possible positive effect of antioxidant supplementation on mortality.

Although the large sample size is an advantage of this study, there are also several limitations. The first limitation is inherent to the study design of a pre-post cohort, as patients are not randomized into groups, nor are there true comparators. This retrospective study included patients over an 11-year period in which there were many advances in care for the critically ill patient. Glucose control, early goal-directed therapy, and steroids for adrenal insufficiency, to name a few, make it difficult to ascertain the true effect of antioxidant supplementation on mortality. Although, we have no evidence of preintervention improvement of arrhythmias in the control group period, our analysis was limited, and an interrupted time-series may have been a better but more complicated approach.

Also, our control and antioxidant group differed in demographic and medical characteristics. The antioxidant group had higher rates of cardiovascular disease (hypertension, coronary artery disease, and cardiac surgery), more severe chest trauma, and a lower likelihood of survival likely making them at higher risk of developing atrial fibrillation. Our study also did not incorporate other known risk factors for atrial fibrillation such as degree of volume resuscitation (e.g. daily in/out status and weights) or exposure to vasopressors as these items were not available via our data sets and not reliably captured in our electronic medical record during this decade-plus interval. As mentioned earlier, the majority of our patients used in this study (i.e. young trauma patients) were likely at a very low risk of developing atrial fibrillation, and there were significant differences in risk factors across the control and antioxidant groups, which makes it difficult to draw a reliable conclusion from this exploratory work. Furthermore, while age was included in our regression model, this likely is not sufficient to account for the fact that there could be an interaction with age and important cardiovascular risk factors. Another limitation of this study was the use of outcome identification through ICD-9 codes. Patients who may have been coded incorrectly or not coded at all would have been missed in our primary outcome analysis; this misclassification bias is inherent to administrative data sets. Finally, there were a large number of patients in our study who were excluded due to a lack of complete data in our database. Not including these patients in our analysis may have also impacted our results.

Conclusion

High-dose antioxidant supplementation in critically ill patients does not reduce the incidence of atrial arrhythmias nor the time from admission to the development of atrial arrhythmias. Expected hospital survival time appeared to be longer with antioxidant supplementation in our population, without a difference in overall survival; however, this is not easily attributable to antioxidant therapy, given other possible temporal confounders. The antioxidant group was all treated years, in some cases, a decade later. The antioxidant group could have been treated with aggressive protocols (e.g. less crystalloid, more transfusions, earlier transfers offsetting hospital mortality to other facilities) that may have influenced their survival more than or in addition to antioxidant therapy. Further prospective studies accounting for time-varying covariates, known risk factors for atrial arrhythmias, and targeted high-risk populations are indicated to further investigate this issue.

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Fig. 1.

Study eligibility. There were 5679 patients were initially evaluated for eligibility. Of which 1643 patients were excluded: 663 patients had unclear exposure to the antioxidant protocol, 539 had lack of registry data, 282 had an ICU stay less than 48 hours, 109 had a past history of chronic atrial arrhythmias, and 50 had serum creatinine >2.5 mg/dL. Of the initial 5679 patients, 2414 patients were included in the control group, and 1622 patients were included in the antioxidant group.

Fig. 2.

The unadjusted incidence rate of atrial arrhythmias per 100,000 patients between the control group and the antioxidant group over 11 years (2000–2011). The control group is depicted with (black squares) and the antioxidant group with open triangles. Note, in multivariable analysis (see manuscript text), we found no significant difference in the unadjusted or adjusted incidence of atrial arrhythmias in the first 2 weeks of hospitalization (or before discharge) between the antioxidant and control groups.

Fig. 3.

Forest plot for adjusted time ratio of hospital mortality. This figure shows an adjusted time ratio for the control group of 0.65 (95% CI: 0.43–0.97, $P = 0.04$). This indicates a 35% decrease in the expected survival time in the control group compared with the antioxidant group, controlling for other factors in the model. This statistically significant difference suggests an increased survival time in patients with antioxidant supplementation compared with the control group. Also, patients with congestive heart failure, increased age, and those not exposed to beta-blockers were other independent risk factors for hospital mortality. Note, overall mortality was unchanged between groups (see manuscript text). CI = confidence interval.

Table 1

ICD-9 Code list for atrial arrhythmias.

427.0 Paroxysmal supraventricular tachycardia
427.1 Paroxysmal ventricular tachycardia
427.2 Paroxysmal tachycardia, unspecified
427.3 Atrial fibrillation and flutter
427.31 Atrial fibrillation
427.32 Atrial flutter
427.61 Supraventricular premature beats
427.8 Other specified cardiac dysrhythmias
427.89 Other specified cardiac dysrhythmias
427.9 Cardiac dysrhythmias unspecified

Table 2

Baseline characteristics of patients.

Baseline characteristics [†]	Antioxidant group (<i>n</i> = 1622) [‡]	Control group (<i>n</i> = 2414)	<i>P</i> -value
Male, <i>n</i> (%)	1187 (73.2)	1745 (72.3)	0.556
Caucasian, <i>n</i> (%)	1338 (82.4)	1958 (81.1)	0.285
Age, years	41.57 ± 17.79	40.00 ± 18.07	<0.001
Injury severity score	30.15 ± 12.04	30.14 ± 11.96	0.988
Chest abbreviated injury scale	3.61 ± 0.93	3.52 ± 0.89	0.004
Predicted survival [*]	0.54 ± 0.34	0.74 ± 0.29	<0.001
Past medical history			
Hypertension, <i>n</i> (%)	312 (19.2)	308 (12.8)	<0.001
Myocardial infarction, <i>n</i> (%)	30 (1.8)	44 (1.8)	0.954
Coronary artery disease, <i>n</i> (%)	99 (6.1)	90 (3.7)	<0.001
Cardiac surgery, <i>n</i> (%)	74 (4.6)	65 (2.7)	0.002
Congestive heart failure, <i>n</i> (%)	29 (1.8)	23 (1.0)	0.089

^{*} Predicted survival, as measured by Trauma and Injury Severity Score.

[†] The patient population was predominantly male and Caucasian.

[‡] The antioxidant group had higher rates of cardiovascular disease (hypertension, coronary artery disease, and cardiac surgery), more severe chest trauma, and a lower likelihood of survival.