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The incidences of oxidative-stress occurrence following two metabolic support measures in critically ill patients

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ABSTRACT

Background: A high percentage of patients admitted to the Intensive Care Unit (ICU) have Systemic Inflammatory Response Syndrome (SIRS) criteria. Free radicals play an important role in initiation and development of SIRS. The purpose of this study was to assess and compare the molecular changes of cellular antioxidant power in patients with SIRS who received enteral nutrition (EN) or EN combined with parenteral nutrition (PN).

Methods: Two groups of 10 patients were enrolled in this randomized, controlled clinical trial. Those in the treatment group received EN+PN and the control group received only EN. Venous blood samples were taken just prior to initiation of nutritional support and then 24, 48 and 72 hours following entry into the study for examination of antioxidant parameters including total thiol, total antioxidant capacity and lipid peroxidation.

Results: The two supportive regimens had different affects on total antioxidant capacity (P=0.005). In the EN group the amount of total antioxidant capacity was not significantly different in different days (P>0.05), but in the EN+PN group it was significantly different on third and forth days as compared to the first day. The two other parameters had no significant differences between the two groups.

Conclusion: These results are suggesting that an increase in oxidative stress biomarkers are not necessarily related to the route of pharmaconutrition and may occur independently during metabolic support measures.

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Introduction

A high percentage of patients admitted to the Intensive Care Unit (ICU) have Systemic Inflammatory Response Syndrome (SIRS) criteria. Different acute conditions such as sepsis, respiratory failure, pancreatitis, trauma and burns, or ischemia/reperfusion may cause SIRS(1). The primary trigger of SIRS is microbial toxins or destructive products of tissues which provoke the release of inflammatory cytokines and other inflammatory mediators. Also, during SIRS, many factors may increase production of Reactive Oxygen Species (ROS), i.e. the elevated use of oxygen for respiratory compromised patients, Nitric Oxide(NO) therapy, parenteral nutrition, impaired kidney function, etc (2). Free radicals that are derived from oxygen are major contributing factors in the development of disease in critically ill patients. Oxygen accepts electrons from other substances in the cell and turn to ROS. Normally, ROS are neutralized by an antioxidant defense system that depends on the activity of enzymes (e.g., superoxide dismutase) and other non-enzyme substances (e.g., vitamin E). The imbalance between ROS and this defense system is called oxidative stress. In critically ill patients, ROS become a problem when either a decrease in the elimination or an increase in the production of the radicals occurs (3). Free radical production plays an important role in both direct cellular injury and activation of intracellular signaling cascades within inflammatory cells, resulting in progression of the inflammatory response (1). The human body reacts

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to these events with changes in metabolism and nutrient homeostasis (4). Therefore, in critical illnesses, the body suffers a state of stress resulting in hyper-metabolism and increased energy expenditure (5). Thus, metabolic support is required in these patients to obviate energy demands. The gut plays an important role in the creation and progression of systemic inflammation. Loss of gut barrier function and bacteria and endotoxin translocation are the pathogenesis of SIRS associated with gut origin (6). Lack of enteral nutrients, such as occurs in starvation, or when nutritional support is provided parentrally, is said to result in mucosal atrophy and increased intestinal permeability resulting in bacterial translocation (7).

The new published clinical practice guidelines (8-11) have noted that early enteral nutrition (EN) is the preferred route of nutritional support. In addition, the European Society for Enteral and Parenteral Nutrition (ESPEN) guidelines (8) suggest that patients who cannot achieve the whole energy requirement by using EN should receive additional PN. However the antioxidant properties of such intervention are not clear. No studies have evaluated the oxidative stress potential of pharmaconutrition, so the purpose of this study was to assess and compare the molecular changes in cellular antioxidant power in patients with SIRS who received EN or EN combined with PN.

Patients and methods

This study was a randomized, controlled clinical trial carried out in a 10 bed ICU ward of Sina teaching hospital, approved by an investigational review board for human studies.

Two groups of 10 patients were enrolled in the study. Those in the treatment group received EN+PN and the control group received only EN.

Patients 18 years or older admitted to the ICU for less than 24 hours; having SIRS criteria; an Acute Physiology and Chronic Health Evaluation II (APACHE II) score more than 10; and expected not to be fed via oral route for at least 5 days were included (12, 13). Any patient with a high probability of death within the next 7 days, pregnancy and lactation or having contraindications to EN was excluded.

Venous blood samples were taken just prior to initiation of nutritional support and then 24, 48 and 72 hours following entry into the study. The samples were drawn into glass tubes. The serum was separated by centrifugation at 3600 rpm for 15 min and stored at –80°C for subsequent batch analysis of antioxidant capacity of plasma, total thiol, lipid peroxidation concentrations, and serum levels of copper, selenium and zinc.

Interventions

Enteral nutrition administration

Patients were fed boluses via naso-gastric (NG) tube every 3 hours. The feeding was Fresubin® Original (Fresenius Kabi, Germany) a normo-caloric (1 kCal/mL), fiber free, commercial solution that was composed of protein (15% of energy), fat (30% of energy), and carbohydrate (55% of energy) plus minerals, trace elements, and vitamins. Patients received 50 ml initially, increased with 50 ml increments to a maximum of 300 ml every 3 hours with a rate of 100 ml /h. At the end of each feeding 50 ml tap water was used to rinse the NG tube. Before initiating next feeding residual volume was measured and if it was greater than 300 ml feeding was delayed by 3h and 20 mg of metoclopramide was added.

Enteral plus parenteral nutrition administration

Parenteral support consisted of 500 ml 10% amino acid solution (B Braun, Germany) and 500 ml 50% dextrose solution (Samen, Iran) infused via central venous (CV) line over 24h. EN support was the same as enteral group.

Patients received full supportive therapy as required including: analgesia, supplemental oxygen, intravenous fluids and antibiotics, Deep Venous Thrombosis prophylaxis, stress ulcer prophylaxis, vasopressors, inotropes, and steroids.

We recorded gender, age, date of hospital and ICU admission, reason for admission, weight and height on arrival to the ICU (Day 0). APACHE II was also recorded on day 0. For seven days, routine daily clinical and laboratory tests such as hemodynamic parameters (blood pressure, heart rate, central venous pressure and etc), temperature, arterial blood gas, Glasgow Coma Scale, electrolytes, chemical and hematology tests were evaluated. Length of stay was also recorded.

Laboratory measurement

Determination of the Total Antioxidant Capacity

In the Ferric Reducing Ability of Plasma (FRAP) method, the yellow Fe3+-TPTZ complex was reduced to the blue Fe2+-TPTZ complex by electron-donating substances under acidic conditions. Any electron donating substances with a half reaction of lower redox potential than Fe3+/Fe2+-TPTZ would have drive the reaction and the formation of the blue complex forward (14).

Determination of Sulfhydryl in plasma

Measurement of total free sulfhydryl groups of serum samples were assayed according to the method of Ellman (15).

Determination of lipid peroxidation

Lipid peroxidation was measured as an index of oxidative stress by quantifying thiobarbituric acid reactive substances (TBARS) using Yagi's method (16).

Statistical analysis

All data were analyzed with SPSS 11.5.0 software (SPSS Inc., Chicago). Distribution of data was evaluated by Shapiro-Wilk's test of normality. For non-parametric data, differences between groups were analyzed using the Mann-Whitney test. For normal distributed data, repeated measures analysis of variances and student t-test were done whenever each of them was appropriate. Significance was accepted for *P* values less than 0.05.

Results

The demographic and baseline clinical characteristics were similar for both groups, as shown in Table 1.

The two supportive regimens had different affects on FRAP (P=0.005). In the EN group the amount of FRAP was not significantly different in different days (P>0.05), but in the EN+PN group the amount of FRAP was significantly different on third and forth days from the first day (P<0.05; Figure1).

The two supportive regimens did not have different affects on Thiol concentration (P>0.05). In both the EN and the EN+PN groups Thiol concentration did not significantly change in various days (P>0.05; Figure 2).

The two supportive regimens had different affects on lipid peroxidation (P<0.05). In the EN group, there was a significant difference in lipid peroxidation amount in various days (P<0.05). However, considering adjusted for multiple comparisons, there was not a significant difference between the two groups in each day. In the EN+PN group lipid peroxidation level did not change significantly in various days (P>0.05).

The average length of hospital stay in the EN group was 37.3 and in the EN+PN was 38.3 days and it did not show any significant difference (P>0.05). The average length of ICU stay was 28.9 in the EN group and 26.2 days in the EN+PN group with no significant difference (P>0.05).

Discussion

Conditions such as SIRS and sepsis are characterized by hypermetabolism and an accelerated catabolism state, which cause a rapid expenditure of endogenous stores of protein and energy. Recently the gut has become more important in the investigation of the septic patient. The small intestine and colon make contributions to the preservation of hypermetabolism in sepsis, SIRS and Multiple Organ Dysfunctions (MOD). Changes in gastrointestinal structure develop losses of intestinal barrier function. Increased intestinal permeability is a permissive factor for bacteria and toxins translocation (17). In recent years the role of the gut has been confirmed in initiation and development of critical illnesses. Grisham et.al showed that derivatives of ROS such as superoxide, hydrogen peroxide, and hydroxyl radicals may cause mucosal injury (18). Also Hinshaw and Miller confirmed that oxidants increased the permeability of epithelial cells in the gut (19). The best available tool to preserve gut permeability is the initiation EN as early as possible (20). Despite there being several studies to confirm advantages of EN in contrast to PN (21-23), the adequacy of EN has yet been obscured. Some studies showed patients received lower energy by EN than their demand (24, 25).

In a meta-analysis of 11 studies comparing mortality on EN and PN regimens, Simpson and Doig revealed that Total Parenteral Nutrition (TPN) had significant higher mortality rate (26). Another meta-analysis by Heyland and Samis reported that in critically ill patients there is no increased mortality risk with PN despite increased risk of infections (27). The results of these correlated meta-analyses comparing EN with PN showed no exacerbated clinical outcome and also defended the safety of PN; thus when EN cannot cover energy demands, PN could be added to optimize EN.

In a trial of ICU patients, prevalence of bronchopneumonia was higher in the group receiving EN+PN than EN alone (28), but in a study with larger groups, there were no differences in infection between two groups (29). A meta-analysis of 5 studies which compared mortality in EN and EN+PN regimens revealed that there was no difference between the two groups and addition of supplemental PN to EN regimen has no different effect on complications and length of stay (30). We also demonstrated that the length of staying in ICU and hospital, along with days off mechanical ventilation, were similar between the two groups.

In critically ill patients plasma and intracellular levels of antioxidants and free electron scavengers are reduced. Tsal et al. showed that in patients with SIRS, compared with healthy controls, a significant decrease in plasma

Table 1. Demographic and baseline characteristics of patients.

Variables		EN	EN+PN	*p* value
Age	Mean ± SE	58.4 ± 5.07	54.9 ± 5.16	0.634
APACHE II score	Median(interquartile range)	17 (13-22)	18.5 (14-22)	-
MAP (mm Hg)	Mean ± SE	76.3 ± 3.36	80.1 ± 6.13	0.594
PH	Mean ± SE	7.36 ± 0.027	7.35 ± 0.039	0.757

EN: Enteral Nutrition, PN: Parenteral Nutrition, APACHE: Acute Physiology And Chronic Health Evaluation, MAP: Mean Arterial Pressure, SE: Standard Error.

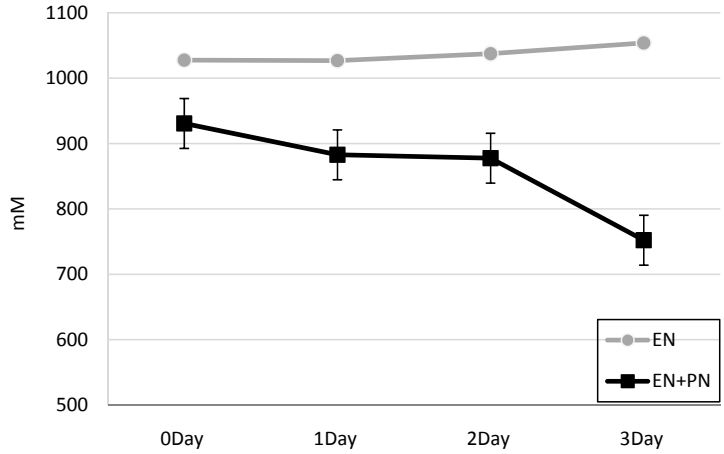

Figure 1. Comparison of FRAP between EN+PN and EN groups. The figure plots show mean FRAP ± SE. Difference between groups was Significant (P<0.05).
EN: Enteral Nutrition, PN: Parenteral Nutrition, FRAP: Ferric Reducing Ability of Plasma.

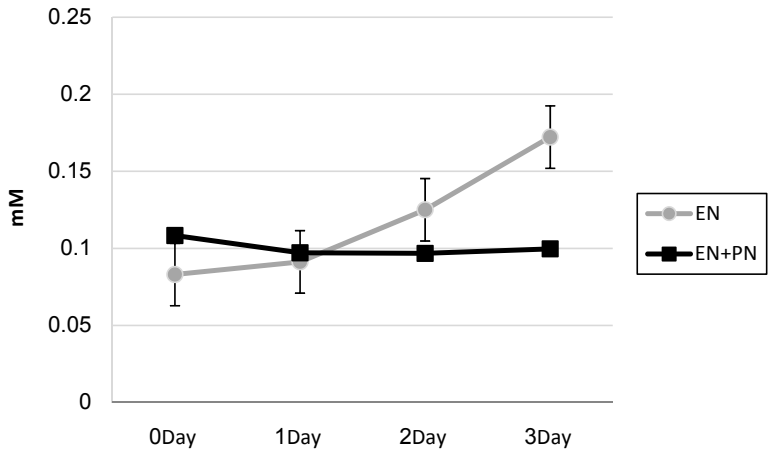

Figure 2. Thiol concentrations between EN+PN and EN groups. The figure plots show mean Thiol concentration ± SE. No Difference was seen between two groups (*P*>0.05).
EN: Enteral Nutrition, PN: Parenteral Nutrition.

Total Antioxidant Capacity (TAC) and increased lipid peroxidation. Patients with SIRS, compared with patients without SIRS, had higher APACHE III scores, lower plasma TAC and thiol concentrations (31).

The early administration of antioxidant supplementation like α-tocopherol and ascorbic acid reduces the rate of organ failure and shortens the length of stay in critically ill surgical patients (32), Micronutrient supplementation in patients with SIRS elevated the plasma Se and α-tocopherol levels. Moreover TAC decreased significantly in early days and activity of plasma GSHPx was greater than before (1). In a previous study we showed that patients with ARDS have an imbalanced oxidant/antioxidant status. N-Acetyl Cycteine (NAC) increased extracellular total antioxidant power, total thiol molecules and the outcome of the patients; therefore supplemental NAC can be useful in these patients (33).

In our study total thiol concentration in both groups had no significant difference, but total antioxidant capacity decreased in the EN+PN group while it didn't change in the EN group. A study of patients with acute pancreatitis showed that over a week of nutritional therapy, patients randomized to PN were diminished in total antioxidant capacity. In contrast, in patients randomized to EN, it was actually increased (34). Plasma concentration of lipid

peroxidation was measured in a study of infants who were admitted to ICU after major surgery. The group of the patients that received EN had lower concentrations of Malondialdehyde (MDA) than the PN group (2). In an animal study, involving 3 groups of rats after surgery, one group served as controls, the other received EN, and third group received placebo feeding for 24 h. The control group was found have increased MDA and decreased superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px). The rats receiving enteral feeding exhibited statistically significantly lower levels of MDA, and higher levels of SOD, GSH-Px, in relation to placebo feeding rats (20). In another study of acute pancreatitis patients, plasma levels of lipid peroxidation in the EN group and the PN group were measured. They found that thiobarbituric acid (TBA) in both groups was increased (35). In our study however there was no significant difference between lipid peroxidation of either group, potentially due to our sample size.

In Conclusion, These results suggest that increases in oxidative-stress bio-markers are not necessarily related to the route of pharmaconutrition and may occur independently during metabolic support measures.

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