Antioxidant therapy in critically ill patients

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Abstract

The increased oxidative stress in critically ill patients could exert pathophysiological role in the pathogenesis of multiple organ failures, as suggested by recent clinical trials of antioxidant therapies. Prophylactic administration of antioxidant vitamins or glutamine, incorporated in the nutritional support or given as separate medications, efficiently attenuates the oxidative stress and in some studies, decreases the incidence of organ failures and ultimately improves the outcome of critically ill patients. Patients at risk of organ failures could benefit from the early adjunction of antioxidant treatment, including vitamins and glutamine.

Introduction

An increase in the oxidative stress is typically present in critically ill patients, as a consequence of the overproduction of reactive oxygen species (ROS) and of the rapid depletion of the endogenous stores of antioxidants [1]. Importantly, oxidative stress has been incriminated in the pathogenesis of the systemic inflammatory response and the dysfunction of organs, via cellular energetic failure and via an interaction with several pathways following lipid peroxidation, and oxidative damage to proteins, DNA and RNA. Therefore, the incorporation of exogenous antioxidants in the treatment of various models of experimental shock, inflammation and ischemia/reperfusion injury [2] and in different categories of critically ill patients have been considered from several years [3]. However, the efficacy of this strategy was confirmed in some studies, while others failed to demonstrate any benefit. Several reasons may be advocated to explain the failures. First, in physiological conditions, an increased oxidative stress is desirable for some cell functions (proliferation, gene expression, apoptosis). The role and importance of the ROS and reactive nitrogen species (RNS) in the regulation of these functions is only partially understood during critical illness. Second, the amount of exogenous anti oxidants required to restore the anti oxidant capacity is not accurately known and could vary according to the clinical situation and could be influenced by several current therapeutic interventions, including the nutritional status. The bio-availability of some anti oxidants administered enterally could also be impaired. Third, the issue of timing of anti oxidant administration is probably a key factor, as the repletion of antioxidant would probably achieve a greater efficacy if given before a massive oxidative injury (major surgery, shock, severe sepsis). Therefore, the anti-oxidant approach can be considered as a preventive as well as a therapeutic modality.

The purpose of the present article is to briefly review the basic mechanisms involved in the production and neutralisation of ROS, to summarize the current knowledge on oxidative stress in critically ill patients, and to present recently published data on the effects of antioxidants administration.

Sources of reactive oxygen species.

Stricto sensu, a free radical or reactive species is an unstable atom with an unpaired electron. ROS include superoxide (O$_2^-$), hydrogen peroxide (H$_2$O$_2$) and the hydroxyl radical (OH$^-$).

In critically ill patients, ROS can be produced from 4 different pathways:

1. The mitochondrial respiratory chain produces O$_2^-$ as a byproduct of the reaction of molecular oxygen with semi-ubiquinone. In case of severe mitochondrial dysfunction, as observed during septic shock [4], this pathway could be up-regulated and massive amounts of O$_2^-$ could be released.
2. The NADPH oxidase enzyme of neutrophils and macrophages is activated in case of cell stimulation and can produce massive amounts of O$_2^-$ as a microbicidal mechanism. This pathway is probably predominant in the overproduction of ROS during severe sepsis.

3. The xanthine oxidase enzyme is an ubiquitous enzyme activated during ischemia, which produced massive amounts of O$_2^-$ during the reperfusion phase. This pathway is probably activated during major cardiac and vascular surgery, and during solid organs transplantations.

4. Some metallic ions (iron, copper) are released in case of cell lysis and can amplify the oxidative stress, as they are co-factors of the conversion of hydrogen peroxide into hydroxyl.

Mechanisms of neutralisation of ROS

If unopposed, the free electron of the ROS will bind to lipids, proteins, DNA, RNA, thereby triggering cell injury and tissue dysfunction. In physiological conditions, the free electron of ROS are scavenged by enzymatic or non-enzymatic anti oxidant defence mechanisms. The mechanisms of inactivation of ROS include successive steps: the dismutation of superoxide into hydrogen peroxide under the influence of SOD and the conversion of hydrogen peroxide into water under the influence of catalase and glutathione peroxidase. Importantly, trace elements (copper/manganese/zinc, iron and selenium) are respectively required for the activity of SOD, catalase and glutathione peroxidase. The major non-enzymatic defence mechanisms include endogenous molecules (glutathione, urate, ubiquinones/ubiquinol, albumin and bilirubin) and vitamins (ascorbic acid, α-tocopherol, β-carotene). Importantly, the reduction of oxidised α-tocopherol, which is necessary for the perpetuation of its antioxidant effect requires the presence of glutathione or ascorbic acid. Therefore, an efficient antioxidant effect would be obtained by the simultaneous administration of vitamins C and E.

In addition to the generation of ROS, oxidative injury can amplified or inhibited by RNS [5,6]. RNS include nitric oxide (NO$^-$), peroxynitrite (ONOO$^-$), nitrosonium (NO$^+$), nitrosyl (NO) and can induce per se nitrosative injuries, or combine to ROS to enhance or attenuate the oxidative injury. At present, the exact physiological role of RNS is only partially understood, and there are very few clinical data on the manipulation of nitrosative injury.

Presence of increased oxidative stress in critically ill patients

Due to the very short half-life of ROS, the proof of increased oxidative stress in patients implies the demonstration of a presence of byproducts of oxidative damage on lipids thiobarbituric-acid reacting substances (TBARS) measured by the malondialdehyde assay (MDA), 4-hydroxynonenal, lipoperoxides), DNA or proteins or a decrease in the stores of endogenous antioxidants (e.g. total radical-trapping antioxidant parameter, TRAP) (for a detailed and comprehensive review see 7).

Numerous studies published until 2001 already demonstrated an increased oxidative stress, mainly in patients with acute respiratory failure, ARDS, sepsis or septic shock. More recent studies confirmed the presence of increased TBARS in patients with systemic inflammatory response syndrome and multiple organ failure (MOF) [8]. The plasma level of TBARS was higher in patients with MOF than in those without MOF, and there was a correlation between the plasma level of TBARS and the Sequential Organ Failure Assessment score. In another recent study performed in 50 critically ill patients [9], there was an increase in MDA and a decrease in the activity of SOD, that were proportional to the disease severity. Consistently, Alonso de Vega et al. [10] recently reported increased levels of MDA and 4-hydroxynonenal in 68 critically ill patients. Similarly, the plasma lipoperoxides concentrations were higher before than after cardiac surgery [11], and were slightly higher in the presence than in the absence of postoperative MOF. TRAP was decreased in patients with SIRS and was progressively restored when patients' status improved or worsened [12]. Interestingly, the increase in TRAP observed in survivors was essentially related to increases in the plasma levels of vitamins C, E and uric acid, whereas in non-survivors, the increase in TRAP was primarily related to an increase in plasma bilirubin.

Clinical data on the effects of antioxidants

Current recommendations

The currently used recommendations for the daily requirements in vitamins and trace elements are known as the Dietary Reference Intakes (DRI) (Table 1) and have been adapted for the enteral and parenteral support [13]. However, higher doses could be necessary to meet the specific requirements of critically ill patients.
Recent clinical trials using higher doses of antioxidants

The most recent clinical studies reported the effects of antioxidants given prophylactically to patients “at risk” of oxidant-related complications, either as a component of nutritional support or as an individual medication. Other recent clinical trials assessed the effects of specific prophylaxis in patients before a scheduled procedure associated with intense oxidative stress.

Besides the antioxidant effect achieved with “conventional” compounds, including vitamins, N-acetylcysteine and trace elements, nutrients or drugs used for other purposes can exert some protective effects against oxidative injury. For instance, glutamine, propofol, ceftazidime, albumin and actually several drugs used during the perioperative period, including calcium-channels inhibitors, anaesthetic agents, muscle relaxants, steroids, inotropes and vasopressors [14-18] exhibit antioxidant effects in vitro or ex vivo. However, whether this antioxidant effect are still present in clinical situations needs to be investigated. In particular, the potential antioxidant effects of propofol could be offset by increased losses of trace elements observed during infusion of this drug [19].

The next paragraph will focus on the recent clinical data related to the effects of conventional and unconventional antioxidant drugs, given as non-specific or specific prophylaxis.

Conventional antioxidant compounds

Non-specific prophylaxis

Antioxidant vitamins

All nutritional support formulas contain antioxidant vitamins, already incorporated in the solution (enteral support) or added prior to infusion (parenteral support). We recently compared the effects of an enteral solution enriched with vitamin A (133 µg/dl including 66.7 µg/dl of β-carotene), vitamin C (13.3 mg/dl) and vitamin E (4.94 mg/dl) with an iso-nitrogenous, iso-caloric control solution in 37 critically ill patients with neurological impairment [20]. This study demonstrated that α-tocopherol (total dose 350 mg over 7 days) and β-carotene (total dose 5000 µg over 7 days) were absorbed, as the plasma and lipoprotein-bound fractions of these vitamins increased in the supplemented, but not in the control group. Importantly, these antioxidants were biologically active, as the resistance of low-density lipoproteins to experimental oxidative stress induced by copper sulphate increased. However, there was no difference neither in plasma TBARS level nor in the resistance of erythrocytes to oxidative stress. Similarly, Nelson et al. [21] demonstrated in 98 patients with ARDS that α-tocopherol and β-carotene incorporated into a nutrition support formula were absorbed, but that the TRAP and the plasma lipid peroxide levels were unchanged, as compared with the control group. Importantly, clinical outcome variables including pulmonary function parameters (PaO2/FiO2 ratio, duration of mechanical ventilation) were found improved in patients receiving this solution [22].

Nathens et al. [23] analyzed the effects of prophylactic administration of vitamin C (1000 mg i.v.) and α-tocopherol (3,000 IU/day enterally) in 301 critically ill trauma patients. The plasma levels of both vitamins were increased. When compared to a matched group of 294 patients not receiving antioxidant supplementation, there was a significant reduction in the risk of developing multiple organ failure (relative risk 0.43, 95% confidence interval 0.19-0.96), and shorter durations of mechanical ventilation and length of stay in the intensive care unit. The incidences of pneumonia and ARDS tended to decrease in the group supplemented with antioxidants. In contrast, in a multi-center recent study on 220 critically ill patients [24] designed to compare the effects of a diet supplemented with antioxidant vitamins and arginine with an isonitrogenous isocaloric control formula on the incidence of nosocomial infections, there was a decrease in the rate of catheter-related infections, but not in the rate of other infections nor mortality.

N-acetylcysteine

Although intensively studied during the last few years (see 25 for review), there are few new data regarding the effects of N-acetylcysteine as a non-specific antioxidant treatment modality in critically ill patients. Heller et al. [26] administered to patients with sepsis, systemic inflammatory response syndrome of multiple trauma N-

### Table 1. Daily requirements of antioxidant vitamins and trace elements (13)

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<th>Enteral</th>
<th>Parenteral</th>
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<tr>
<td>Vitamin A</td>
<td>900 µg</td>
<td>1000 µg</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>90 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>15 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Copper</td>
<td>0.9 mg</td>
<td>0.3-0.5 mg</td>
</tr>
<tr>
<td>Manganese</td>
<td>2.3 mg</td>
<td>60-100 µg</td>
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<tr>
<td>Selenium</td>
<td>55 µg</td>
<td>20-60 µg</td>
</tr>
<tr>
<td>Zinc</td>
<td>11 mg</td>
<td>2.5-5 mg</td>
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acetylcysteine at high (36 g over 3 days) or low (3 x 300 mg/day) doses. The major findings of this study were an increase in the phagocytosis activity of the neutrophils, together with a decrease in the oxidative burst activity in the group randomized to the high dose of N-acetylcysteine. The clinical outcome variables were not recorded in this study.

**Trace elements**

The effects of supplementations with large doses of selenium, zinc, copper and manganese, the four trace elements involved in the enzymatic antioxidant defence mechanisms were the focus of intense clinical research in the last decade (see 27 for review). However, during the last two years, there were few investigations specifically designed to document their effects on oxidative stress in critically ill patients.

**Specific prophylaxis**

In some circumstances, expected oxidant-related damage could be prevented with a large dose of antioxidants prior to the scheduled procedure. For instance, Lassnigg and co-workers tried to prevent with vitamin E alone (4 x 270 mg i.v.) the oxidative damage related to ischemia and reperfusion in patients undergoing cardiopulmonary bypass for cardiac surgery [28]. This strategy was ineffective, as there was no effect of vitamin E on the markers of oxidative stress, nor on clinical outcome variables.

Relevant to critically ill and other categories of patients, the prevention of contrast-induced nephropathy, another ROS-related phenomenon, can be efficiently prevented by N-acetylcysteine (2 x 400 mg the day before and the day of contrast injection) in patients with moderate chronic renal failure, as recently confirmed in a large study [29]. These data are consistent with those reported previously [30].

**Unconventional antioxidant compounds**

Among unconventional antioxidants, glutamine is probably one of the most efficient. The beneficial effects of glutamine on short- and long-term outcome variables in critically ill patients are not completely understood [31]. The antioxidant properties of glutamine could be a key factor, as this amino-acid is a precursor for glutathione and taurine. Indeed, the fall in the intramuscular concentration of reduced glutathione was prevented in surgical patients receiving supplemental glutamine (0.56 g/kg/day parenterally) [32]. Similarly, Boelens et al. [33] recently reported higher concentrations of taurine, an amino acid with antioxidant properties, in trauma patients randomized to receive an enteral nutrition formula containing 15.5 g glutamine/l.

**Conclusions**

The importance of the implication of oxidative stress in the development of multiple organ failures is consistently demonstrated in critically ill patients. Therefore, the administration of antioxidants as a prophylaxis in patients at risk seems to represent an efficient approach, in view of the results of recent clinical trials. Optimal doses and combinations of antioxidants are still to be defined.

**References**


