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Review

Oxidative stress in sepsis: Pathophysiological implications justifying antioxidant co-therapy

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ABSTRACT

Sepsis is one of the main causes of death among critically ill patients. Sepsis pathogenesis includes infection by gram-negative and gram-positive bacteria, fungi, or both; exacerbated inflammatory response; hypotension, with potential to cause vasodilatory shock; and lesser delivery of oxygen to tissues due to impairment of oxygen utilization by cells. The participation of reactive species and/or free radicals such as nitric oxide ($NO^{\bullet}$), peroxynitrite ($ONOO^{-}$), superoxide ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($^{\bullet}OH$) has been reported to underlie these effects. Mitochondrial dysfunction is related to loss of inner membrane potential and inhibition of the mitochondrial electron transfer chain and FoF1-adenosine triphosphate-synthase, resulting in cellular energetic failure. In addition, overproduction of $NO^{\bullet}$ due to inducible nitric oxide synthase (iNOS) activity has been associated with harmful effects such as general vasodilatation and hypo-responsiveness to therapeutic vasoconstrictor agents. Considering that iNOS expression is regulated by nuclear factor-κB, which may be activated by ROS, antioxidants could inhibit the overexpression of iNOS in sepsis. In line with this, several antioxidants such as vitamins C and E, polyphenols, melatonin, β-glucan, *N*-acetylcysteine, mitochondrion-targeted antioxidants (MitoQ, MitoE, and peptides associated with dimethyltyrosine), selenium salts, and organoselenium compounds were effective in ameliorating oxidative stress in animal models of sepsis and in a number of clinical trials with septic patients.

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1. Introduction

Sepsis is the combination of pathological infection and physiological changes collectively known as the systemic inflammatory response syndrome (SIRS) [1]. In general, authors include pathological conditions such as septicemia, septicemic shock, bacteremia, disseminated fungal infection, disseminated candida infection, and disseminated fungal endocarditis as part of sepsis [2]. Clinical complications of sepsis vary from SIRS to septic shock when worsened and even to multiple organ dysfunction syndrome. Microbial causes include infection by gram-positive and gram-negative bacteria, fungi, or both. Concomitant factors such as diabetes, transplantation, surgical intervention, chronic obstructive pulmonary disease, congestive heart failure, and renal disease may either increase a person's susceptibility to sepsis or aggravate their clinical score. In USA, it was reported that the incidence of sepsis was higher in the elderly population (60 years and older), men, and non-white people than in women and white populations. Although the incidence of sepsis and total mortality increased from 1979 to 2000, relative mortality decreased in this period because of improvements in treatment strategies [2].

Inflammatory cytokines produced by activated leukocytes, such as tumor necrosis factor (TNF)-α, IL-1α, IL-1β, and IL-6, and chemokines such as IL-8 and KC also contribute to sepsis severity. Early studies indicated the presence of a factor in the blood of septic patients that is responsible for the cardiac depression observed in these patients, which was verified as an increase in the diastolic volume and decrease in the ejection fraction. This depressant factor causes reduction in the shortening of myocytes, resulting in lesser ventricular contraction force [3]. Later, these factors were identified as TNF-α and IL-1β [4], which act through the induction of nitric oxide ($NO^{\bullet}$) synthesis and downstream elevation of cGMP levels to reduce cardiac myocyte contractility [5,6]. Further, it was reported that the expression of several pro-inflammatory factors is regulated by the transcription factor nuclear factor (NF)-κB [7,8].

Among the biochemical parameters related to sepsis, $NO^{\bullet}$ overproduction causes decreased vascular tonus and consequently hypotension, which is a characteristic of this syndrome. Particularly, $NO^{\bullet}$ overload in sepsis seems to result from the activity of inducible NO synthase (iNOS). Therefore, iNOS inhibitors (aminoguanidine and L-canavanine) and anti-inflammatory agents could be promising drugs to ameliorate the outcome of patients suffering from sepsis [9–11]. Moreover, other reactive species that participate in sepsis pathogenesis include superoxide ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^-$), hypochlorous acid (HOCl), and the powerful hydroxyl radical ($^{\bullet}OH$) [12].

Reactive species directly attack endothelial cells, thus promoting the deterioration of the endothelium and enhancing vascular permeability and thereby aggravating hypotension and decreasing the colloid osmotic pressure of the plasma. Moreover, they affect oxygen consumption by cells, which accelerates the process causing multiple organ failure [12]. Furthermore, oxidative activation of cGMP-dependent protein kinase 1 alpha results in blood vessel dilatation and permeability and decreased cardiac output [13]. Therefore, this process shows the potential to decrease organ perfusion and oxygen delivery, causing ischemia to organs.

Under ischemic conditions followed by subsequent reperfusion, the enzyme xanthine oxidase catalyzes the formation of uric acid with the co-production of superoxide. Indirectly, reactive species activate the transcription factor NF-κB and, in turn, increase the expression of iNOS [7,8,14,15].

Regarding protective systems, the levels of antioxidants such as α-tocopherol [16–18], selenium [19–21], vitamin A, β-carotene, lycopene [18], acid ascorbic [22], and reduced glutathione (GSH) [23] may be decreased in sepsis.

Markers of oxidative stress in sepsis include decreased levels of GSH, increased levels of malondialdehyde (MDA), increased protein carbonyl groups, and increased superoxide dismutase (SOD)/catalase (CAT) ratio, causing accumulation of H_2O_2 in cells [24–28]. Although reactive species originate from several sources, it is believed that respiratory burst is the most important generator of oxidants in sepsis [29,30]. Moreover, oxidative stress in the mitochondrion appears to play a role in the reduction of the respiratory capacity of severely affected tissues because of the partial uncoupling of mitochondrial oxidative phosphorylation, leading to low levels of intracellular adenosine triphosphate (ATP) and increased levels of lactate [31–33]. Cellular energetic failure is related to the release of calcium ions from intracellular stores and deflagration of programmed cell death [23,24,34,35].

While apoptosis is a cascade for controlled cell death, which is dependent on ATP levels, even at low levels, necrosis occurs in cells with depleted ATP levels and is an uncontrolled/accidental manner of cell death. Underlying both pathways is the opening of high conductance mitochondrial permeability transition pore (MPTP) that may be induced by oxidative stress, ischemia/reperfusion injury, and Ca^{2+} toxicity. Therefore, cells severely depleted in ATP and acutely affected by these metabolic/chemical stresses undergo necrosis [36,37]. However, it should be emphasized that in practical terms, independent of the concept or the mechanism involved, both cell death pathways contribute to organ failure, which is the worst outcome for patients suffering from sepsis.

Furthermore, it has been suggested that in certain conditions including severe inflammation, such as that observed in sepsis, cells of underperfused/ischemic tissues could initiate a process called "stunning" or "hibernation" that would protect them against uncontrolled release of reactive species by the mitochondrion [38,39]; however, for some organs, it appears to be a nonplausible solution. For example, cardiac muscle requires a constant supply of ATP to guarantee contractile activity. Therefore, downregulating the mitochondrion and/or basal metabolic rate could aggravate cardiac depression and decrease its output [39,40] that in turn would potentiate hypotension and diminish organ perfusion. Thus, protecting the mitochondrial electron transfer chain from oxidative stress may prevent substantial energy deficits and apoptosis, and it seems to be a more promising strategy.

Many studies have demonstrated that combining antioxidant therapy with conventional pharmacological interventions may decrease sepsis severity and/or ameliorate the outcome of septic patients [26,41–43]. Thus, the primary objective of this mini-review is to outline some topics related to the pathophysiology of sepsis that sustain arguments for