Commentary

Is there a place for *N*-acetylcysteine in the treatment of septic shock?

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Abstract

Excessive inflammatory responses and impaired oxygen utilization because of microcirculatory failure are implicated in septic shock. Recent studies have pointed out some beneficial effects in the treatment of septic shock of several vasodilators that exert anti-inflammatory properties. In particular, the antioxidant *N*-acetylcysteine has been demonstrated to enhance cardiac performance, and to improve hepatosplanchnic perfusion and liver function in patients with established septic shock. These clinical observations may lead us to examine further the role of antioxidant agents in developing novel therapies for septic shock.

Keywords blood flow, cytokine, oxygen extraction, oxygen free radicals

Introduction

In the present issue of *Critical Care*, Hein and colleagues report that administration of *N*-acetylcysteine (NAC), a precursor in glutathione synthesis, increased liver perfusion, decreased hepatic lactate production and thus improved liver function in patients with septic shock [1]. The authors suggest that NAC therapy may be beneficial in selected septic patients secondary to peritonitis but not following pneumonia. This study also introduces the use of proton magnetic resonance imaging and spectroscopy, which may provide clinicians with a noninvasive and reliable assessment of liver perfusion and liver function. These findings may have important implications for the management of patients with septic shock.

Pathophysiology of septic shock

Septic shock is characterized by a hyperdynamic state with high cardiac output and low peripheral vascular resistance associated with impaired uptake of oxygen. Dysoxia has been demonstrated in septic shock, as reflected by an increase in regional and systemic lactate production and a high concentration of gastric carbon dioxide [2].

During septic shock oxygenated blood can be directly bypassed from arterial vasculatures to venous ends through a 'shunt' that results from a loss of vascular tone and thus capillary collapse. This underlying mechanism results in impaired tissue oxygen extraction capabilities that lead to cellular dysoxia [3–6]. The hepatosplanchnic region is particularly susceptible to this microcirculatory failure, and the gut has been considered the 'motor' of septic shock [2].

Septic shock is also associated with excessive inflammatory responses including enhanced inflammatory cytokine production [7] and the release of oxygen free radicals [8]. The relevance of the inflammatory responses to clinical outcome is evident from several studies demonstrating that concentrations of inflammatory mediators such as tumor necrosis factor alpha (TNF-α), IL-6 and lipid peroxidation [9] in plasma were higher on admission to hospital and remained elevated in septic patients who subsequently died compared with survivors [10].

Fluid resuscitation and the use of vasoconstricting agents can improve hemodynamics and therefore oxygen delivery,

IL = interleukin; NAC = *N*-acetylcysteine; TNF-α = tumor necrosis factor alpha.

but may not necessarily enhance, or in certain circumstances may even further reduce, regional blood flow and oxygen extraction [6]. A variety of immunological inflammatory mechanisms, triggered in septic patients, can contribute to microcirculatory dysfunction, including alterations in coagulation, mitochondrial dysfunction [11], generation of oxygen free radicals and synthesis of interleukins [7,8].

Effects of anti-inflammatory vasodilators in septic shock

A number of studies have investigated the effects of vasodilators that combine with anti-inflammatory properties in septic conditions to test the hypothesis that such therapies would be able to improve microcirculation and thus oxygen extraction, while at the same time attenuating inflammatory responses.

Prostacyclin, a prostaglandin synthesized in endothelial cells, is a potent vasodilator and an inhibitor of platelet and leukocyte activation. In septic pigs, pretreatment with iloprost, an analog of prostacyclin, increased the cardiac output, increased splanchnic blood flow and increased gastric pH. In patients with sepsis, prostacyclin increased both oxygen delivery and oxygen consumption, probably via recruitment of shunted microcirculatory units that lead to improve tissue metabolism and function [12]. However, induced hypotension and reduced renal perfusion during prostacyclin infusion may limit prostacyclin's clinical application.

Pentoxifylline, a derivate of methylxanthine, inhibits the phosphodiesterase activity, thereby enhancing the intracellular content of cAMP that exerts both vasodilation and anti-inflammatory effects. Pentoxifylline has been reported to inhibit platelet and leukocyte activation and lactate production, and to improve hemodynamics in a variety of animal and human sepsis. Through inhibition of phosphodiesterase activity, pentoxifylline decreased production of TNF-α and IL-6 and reduced the mortality rate in premature infants with sepsis [13].

NAC in animal experimental and human sepsis

NAC increases nitric oxide synthesis and cGMP. Several studies have demonstrated that NAC improves the left ventricular stroke work index through three mechanisms: a decrease in afterload by nitric oxide synthesis; an increase in cardiomyocyte contractility; and an attenuation of cardiac depressing factors such as TNF-α. Moreover, NAC inhibits platelet aggregation and decreases the synthesis of IL-8, an important chemokine for leukocyte infiltration. These anti-inflammatory effects of NAC are probably related to its oxygen free radical scavenging properties [14].

NAC is one of the most extensively studied antioxidant agents in sepsis research. In a dog model of fluid-resuscitated endotoxic shock, Zhang and colleagues demonstrated that the administration of NAC improved whole body oxygen extraction capabilities associated with an enhanced regional blood flow in mesenteric, renal and femoral vasculatures [15]. In a similar septic shock model, NAC attenuates TNF-α production and reduces blood lactate levels [16].

In patients with septic shock, Spies and colleagues previously demonstrated that NAC treatment improved hepatosplanchnic blood flow associated with an enhanced cardiac index [17]. In the present study, the same group of investigators reports that NAC therapy increases liver blood flow and hepatic function assessed by a technique of gadolinium-enhanced magnetic resonance imaging. Using the proton magnetic resonance spectroscopy system, these investigators showed that NAC infusion was able to decrease the liver lactate signal intensity by as much as 89% [1]. It is intriguing that these beneficial effects of NAC were seen in patients with septic shock that resulted from peritonitis but not from pneumonia.

The protective effect of NAC in septic shock demonstrated by Hein and colleagues [1] is in agreement with those reported by others. Spapen and colleagues showed that a short-term infusion of NAC decreased IL-8 production and shortened the intensive care unit stay in septic patients who survived [18]. Paterson and colleagues have recently, demonstrated that the administration of NAC decreased nuclear factor-κB activation associated with decreases in IL-8 in septic patients [19].

In a previous multicenter clinical trial in patients with acute respiratory distress syndrome, Bernard and colleagues reported that treatment with NAC repleted erythrocyte glutathione. There was no difference in mortality between the placebo and NAC groups. The number of days of acute lung injury was decreased, however, and there was also a significant increase in the cardiac index in the NAC-treated group [20].

Conclusions

This is an exciting time for intensivists involved in the care of patients with sepsis, particularly after the positive trial showing that activated protein C can improve survival in patients with septic shock [21]. Although the sample size was small in the extended case report [1], Hein and colleagues have made a significant contribution to our understanding of the important role of antioxidant agents such as NAC in developing novel therapies for septic shock. A large trial is needed to confirm the present report, where the selection of the target patient population is crucial for a successful management of septic patients.

Competing interests

None declared.

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