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Effects of high doses of selenium, as sodium selenite, in septic shock patients a placebo-controlled, randomized, double-blind, multi-center phase II study – Selenium and sepsis

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Abstract

Selenium has a double action. (i) Seleno-compounds, among them sodium selenite have a direct pro-oxidant action leading to acute toxicity but may be also beneficial as drug. (ii) Selenium is an essential anti-oxidant required qfor anti-oxidant seleno-enzymes. Septic shock is a common severe syndrome leading to endothelium damage and multiple organ failure, with increased data suggesting the principle role of oxidative stress. Selenoprotein P, main selenium constituent of the plasma, may decrease dramatically and specifically in septic shock patients and may be involved in the endothelium protection. A prospective, multi-center placebo-controlled, randomized, double-blind study in severe septic shock patients with documented infection has been preformed. Patients received, for 10 days, selenium as sodium selenite (4000 μg on the first day, 1000 μg/day on the 9 following days) or matching placebo using continuous intravenous infusion. Mortality rates did not significantly differ between groups at any time point. Adverse events rates were similar in the two groups. However, high-dose selenium administration has been associated with a tendency to decrease the mortality in septic shock animal and patients, especially when using a bolus administration, whereas studies using a continuous administration failed to find any benefit on mortality. The interest of the successive use of pro-oxidant action of seleno-compounds, followed by anti-oxidant action need to be the further studied in cellular and animal models, preceding new dose–effect phase II. The interest of the selenoprotein-P as a marker of septic shock and for endothelium protection needs also to be studied further.

Keywords: Septic shock; Selenium; Sodium selenite; Oxidant; Anti-oxidant

Introduction

The specificity of selenium is that it has a double action, as a pro-oxidant and as an anti-oxidant [1]. On the one hand, depending on the compound, seleno-compounds have a direct pro-oxidant action. Sodium selenite is among one of the most pro-oxidant seleno-compounds. This action leads to acute toxicity but may be useful as a drug. On the other hand, it is an essential anti-oxidant thanks to the way the selenium atom is incorporated and to the fact that it is required at the active site of on the anti-oxidant seleno-enzymes under the form of the selenocystein amino acid [2]. This action leads to the protection of cell structures against free radicals and oxidative stress. As a consequence of the

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reduction of the intra-cellular peroxide tone it also orients the intra-cellular metabolisms into an anti-inflammatory mode [3].

Septic shock

In developing countries 0.6 million patients suffer each year from septic shock and 1.2 million patients suffer from the less severe form called severe sepsis [4]. Septic shock is characterized by an acute, generalized uncontrolled immuno-inflammatory reaction leading to endothelium damage [5,6]. Although inflammatory mediators such as cytokines are known to be key mediators in the pathogenesis of sepsis, there are increased data suggesting the principle role of oxidative stress in septic shock [7,8]. Moreover, septic shock is associated with low plasma selenium concentration [9]. Such a syndrome may also be observed in non-infectious aggression like polytrauma, or burn where it is called systemic inflammatory response syndrome (SIRS). These syndromes are characterized by reversible multiple organ failure related to endothelium aggression and involving oxidative stress. Mortality of the septic shock syndrome remains high reaching 50% despite supportive care against organ failure provided in intensive care unit (ICU) [4]. In addition, early diagnosis of septic shock is difficult and may lead to delayed initiation of the required intensive therapy.

Currently treatment of septic shock is based on (i) anti-infectious treatments through surgery and/or antibiotics, and (ii) more or less complete supportive care of organ failures like extra-renal therapy, ventilation, catecholamines – for cardio-vascular pressure support, transfusion and nutrition [4]. There are few treatments or therapeutic strategies specifically efficient against the immuno-inflammatory reaction of septic shock. One can cite: early intensive therapy, low dose corticoids, tight glycemic control though intensive insulin therapy and activated protein C [4].

The selenium, selenoprotein-P (Sel-P) and seleno-compounds

Selenium incorporation into seleno-enzymes is known to increase the anti-oxidant cell defenses and to reduce the intra-cellular redox potential. Taking into account of the role of oxidative stress in sepsis [7,8] there is an increased interest in selenium supplementation in septic shock. Moreover, in a situation associated with a low plasma selenium concentration, it is admitted that a daily selenium administration of less than 800 μg in septic shock patients is not dangerous and may even be beneficial as shown in the last two meta-analysis [5,10]. Moreover, Sel-P, the main selenium constituent of the plasma selenium [11] may decrease dramatically and specifically in septic shock patients and related syndromes [12]. This protein may be involved in the endothelium protection in septic shock [12,13].

In healthy individuals, Sel-P is the major selenoprotein in plasma, accounting for 52% of the total plasma selenium. Glutathione peroxidase accounts for another 39%, albumin for 9% and free selenium form for less than 1% of total selenium [11]. In SIRS ICU patients especially in patients with septic shock there is a 40% decrease in plasma selenium concentration, as was confirmed in our study in 1998 [9]. A selenium concentration $<0.7\,\mu mol/L$ was associated in ICU patients with a four time increased mortality and three time increased rate of new organ failure and ventilator associated nosocomial pneumonia [9]. To test the hypothesis of Sel-P fixation at the surface of activated endothelium for protecting purpose, we dosed Sel-P plasma concentration at admission in 21 ICU patients and 7 healthy volunteers. We observed a 70% Sel-P concentration decreased in the 10 patients with septic shock (7 patients) or severe SIRS compared to healthy volunteers, but no significant decrease in the other ICU patients. There was no significant decrease in glutathione peroxidase plasma concentration (non-published data outside abstract, [12]). Moreover, before death, there was a significant Sel-P decrease in septic shock diseased patients compared to non-SIRS diseased patients despite the few patients involved.

Seleno-compounds are also known to be more or less pro-oxidant compounds and thus toxic [14,15]. Acute and chronic intoxication have been evaluated in animal studies and observed in man [15]. Acute lethal intoxications are rare in man [15]. Paradoxically, this pro-oxidant effect of seleno-compound may be very effective in the treatment of septic shock by: (i) reversible inhibition of NF-KB to DNA binding through a peri-genomic action [16], by a transient pro-apoptotic action on pro-inflammatory circulating cells [17]. Moreover, these compounds at high concentration in the blood may have a direct pro-oxidative bactericidal or virucidal action [14].

Our study

We performed a prospective, multi-center, placebo-controlled, randomized, double blind study with an intention-to-treat analysis in 60 severe septic shock patients with documented infection. Patients received, for 10 days, selenium as sodium selenite (4000 μg on the 1st day, 1000 μg/day on the 9 following days) or matching placebo using continuous intravenous infusion. Primary endpoint was time to vasopressor therapy withdrawal. Duration of mechanical ventilation, mortality rates at ICU and hospital discharge, at 7, 14, 28, 180 days and at 1 year after randomization, and adverse

events were recorded. Sixty patients were included (placebo: 29; selenium: 31). Median time to vasopressor therapy withdrawal was 7 days in both groups (95% confidence intervals = [5–8] and [6–9] in placebo and selenium groups, respectively; log-rank: $p = 0.713$). Median duration of mechanical ventilation was 14 and 19 days in placebo and selenium groups, respectively ($p = 0.762$). Mortality rates did not significantly differ between groups at any time point. Adverse events rates were similar in the two groups. Thus a continuous infusion of selenium as sodium selenite (4000 μg on the 1st day, 1000 μg/day on the 9 following days) had no obvious toxicity but did not improve clinical outcome in septic shock patients [18].

Discussion, interest of the bolus

These results need to be analyzed in light of all available data on selenium administration in ICU patients. First of all, it has been observed a probable decrease of secondary infection especially ventilator associated nosocomial pneumonia in ICU patients supplemented with selenium alone as sodium selenite but at doses less than 800 μg/day [19]. Selenium supplementation may be associated in with zinc, cooper supplementation and anti-oxidant vitamins. Such a supplementation may lead to a decreased length of stay in ICU [20].

More interestingly high dose selenium administration has been associated with a tendency to decrease the mortality in septic shock or similar SIRS patients [5,10]. This is especially the case in the SIC study. This randomized double blind multi-center study administered 1000 μg sodium selenite as a bolus followed by 14 daily continuous administration of 1000 μg in 238 ICU septic shock or similar SIRS Patients. It was observed in this study a 10% 28 days mortality decrease from 50% to 39.7% [21]. However, this decrease was not significant in the intention to treat analysis ($p = 0.098$). It is important to note that the first 1000 μg sodium selenite, were administered as a bolus, thus should lead to transient high blood selenite concentration. Bolus administration was also performed in the mono-centre Kuklinsky et al. [22], and Zimmerman et al. [23] studies that observed such a 90%, 35% mortality decrease respectively, in a 17 necrotizes pancreatitis and 40 SIRS with organ failure ICU patients, respectively. One can notice that these two studies had the most weight in the two recent meta-analysis [5,10].

Studies using a continuous administration failed to find any benefit, especially on mortality. This is the case of the mono-centre Mishra et al. [24] or Liedman et al. [25] studies respectively on 40 septic shock or similar patients and 70 pancreatitis patients. Absence of benefit was also observed in the Kazda et al. and Kiessling et al. non-published (outside abstract) studies [27,28].

Effect of bolus administration could be illustrated by our non-published results on 500 LPS rat studies [26] showing a tendency of mortality decrease associated with lower lactate concentration and improvement of quality of life with very high 0.25 mg/kg selenium as of sodium selenite intra-peritoneal administration. However, in this LPS model, there was also an increased Se toxicity increase for doses above 0.35 mg/kg.

Thus to reduce the binding of NF-κB to DNA with selenite in-vivo, or induce apoptosis in activated circulating cells it is perhaps required to perform a bolus administration in order to reach high selenite blood concentrations that could not be attained by continuous administration.

Induction of Sel-P synthesis before endothelium damage may be another explanation for the effect of the bolus administration. Secondly selenium incorporation may increase the immunity defences. Experimental animal studies are required to answer these questions and explore the potential toxic effect of seleno-compound especially selenite in septic shock resuscitated model.

To conclude

This new biochemical approach of septic shock opens a new area focused on redox-potential modulation for therapeutic purposes. The interest of the successive use of pro-oxidant action of seleno-compounds, firstly selenite, followed by anti-oxidant action need to be the further studied in cellular and animal models, preceding new dose–effect phase II. Effect of the bolus administration required particular attention in these studies. But currently doses above 500–800 μg/day of selenium should not be administered in routine practice in ICU patients outside of experimentation. The interest of the Sel-P as a marker of septic shock that may be linked to a major psychopathological mechanism of endothelium protection needs also to be studied further.

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