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Effect of Selenium Supplementation on CRP Levels and Incidence of Delirium in Critically Ill Patients

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ABSTRACT

Background: Selenium (Se), mainly through its incorporation into selenoproteins, plays an important role in inflammation and immunity. Evidence has emerged regarding roles for individual selenoproteins in regulating inflammation and immunity. The aim of this study was to evaluate the response on the inflammatory biomarker C-reactive protein, and its possible impact on the incidence of delirium.
Methods: This prospective, non-randomized, open-label, single-center clinical trial included 100 critically ill patients. Patients in the Selenium group (n = 50) received Se for 5 days (500 µg twice daily infused over 2 hours). Plasma levels of C-reactive protein (CRP), was determined on days 1-5. The incidence of delirium was assessed by the Confusion Assessment Method (CAM) on a daily basis.
Results: CRP decreased in the selenium group from day 1 onwards. The mean of CRP was 11.1 ± 2.20 in the Se group compared to 16.7±1.6 in the control group, the difference was significant (P < 0.0001). 32% of patients in the selenium group and 52% in the control group had delirium (P = 0.07).
Conclusions: Se administration in critically ill patients decreased CRP levels, but did not reduce the incidence of delirium.

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Introduction

Delirium is a common occurrence in critically ill patients and is associated with increased morbidity and mortality (1). Despite increasing awareness, little is known about the underlying mechanisms of delirium (2). Different unraveling pathophysiological pathways are involved in delirium development. The link between inflammation and delirium has been reported (3-6). Delirium is common in systemic inflammatory states, which may contribute to delirium pathogenesis through breakdown of the blood–brain barrier, microglial activation, and neuroinflammation (7). Inflammation and sepsis are known risk factors for Intensive Care Unit (ICU) delirium and therefore these patients are highly susceptible to delirium (8). Several studies have been performed to determine which cytokines are most associated with delirium (9). Ritter and colleagues (10) studied TNFα, soluble TNF receptor (STNFR)-1,

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STNFR2, IL-1β, IL-6, IL-10 and adiponectin in systemic inflamed patients in relation to delirium. In their prospective cohort study, they found significant associations between STNFR1, STNFR2, IL-1β and adiponectin concentrations and the development of delirium. C-reactive protein (C-RP) is known to be elevated, non-specifically in multiple conditions that can precipitate delirium. Ritchie et al., (11) studied 710 patients over 70 years old and found that there was a strong association between elevated CRP and delirium ($t = 5.09$; $p < 0.001$), independent of other potential risk factors for delirium (odds ratio (OR) = 1.32 (95% CI: 1.10–1.58) $p = 0.003$). It is possible that intervention with specific anti-inflammatory agents could reduce the risk of developing delirium.

Selenium (Se) is an important trace element in human biology. It is of great importance in human health and plays a key role in thyroid function, antioxidant defense and immune function. Plasma Se levels are commonly decreased in critically ill patients for several reasons, including decreased Se intake, haemodilution by resuscitation fluids and incompletely replaced the loss of biological fluids that contain large quantities of trace elements (mainly blood loss)(12-14). In addition, Se requirements may increase while a patient has inflammatory conditions, owing to the increase in oxidative stress and production of reactive oxygen species (ROS). Decreased plasma concentrations during the acute phase response have been described in animal and clinical studies (15-17). Plasma selenium is reportedly significantly lower in critically ill adult patients compared with healthy subjects and is associated with oxidative stress, infectious complications, organ dysfunction and higher mortality (12, 15, 18, 19). During conditions of increased oxidative stress and inflammation there is an increased need for intake of selenium. Authors of two recently published meta-analyses reported a trend toward a reduction in the risk of death in patients receiving Se supplementation (19, 20).

The aim of this study was to describe the association between CRP and the incidence and severity of delirium in critically ill adult patients who received Se supplementation.

Patients and Methods

A prospective, nonrandomized controlled study was undertaken in a single center from September 2015 to December 2016. The study population consisted of consecutive patients admitted to the Intensive Care Unit (ICU) of Alzahra hospital (Isfahan, Iran), a tertiary-level university- affiliated hospital. The ethics committee of Isfahan University of Medical Sciences approved the study. Informed consent was obtained from patients or next of kin, or appropriate surrogate before participation in the study.

Eligible patients were 15 to 80 years old and newly admitted to the ICU due to serious medical problems. Patients were admitted via emergency departments to intensive care units or regular acute wards. Patients were excluded from the study if they had an expected stay or life expectancy of less than 48 hours.

The observation period was 1 week, and we considered that it would be difficult during such a short time to discriminate between delirium and cognitive fluctuation in certain diseases, such as severe liver dysfunction or Lewy body disease. Patients with such diseases were therefore excluded in advance.

Because this study was conducted in one single ICU, it was only feasible to use a convenience sampling method, in order to recruit sufficient numbers of patients to the experimental and control groups at the same period of time.

Eligible patients were enrolled, received selenium 500mcg twice daily over 2 hours infusion for 5 days. Plasma levels of C-reactive protein (CRP), was determined on days 1-5. Patients were screened for the presence of delirium by using the tool Confusion Assessment Method for the ICU (CAM-ICU) (21, 22) on a daily basis. There are 4 features in the CAM-ICU tool: acute onset or fluctuating course, inattention, altered level of consciousness, and disorganized thinking. Patients with delirium were categorized into hyperactive, hypoactive, and mixed types of delirium, according to CAM-ICU assessments obtained during delirium episodes. A group of patients with delirium who were not received selenium served as controls.

2 ml blood sample was taken from patients in both groups, and plasma level of CRP was measured by using an enzyme-linked immunosorbent assay (ELISA) kit from Bender MedSystems (Bender MedSystems GmbH, Vienna, Austria). The normal plasma level of CRP was considered up to 10 mg/l.

On ICU entry, demographic data and baseline characteristics of eligible patients, including age, sex, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, type of medical condition and tracheal intubation were collected.

Quantitative data were expressed as mean ± SD or median and interquartile range, as appropriate. Categorical data were expressed as the number and percentage. Comparisons between delirious and nondelirious groups were performed using *t* test or Wilcoxon rank sum test, as appropriate. χ^2 Test was used for categorical data. All statistical analyses were performed using the SPSS software, version 20.0 (SPSS).Two-tailed $P < 0.05$ was considered statistically significant.

Results

During the study period, 50 patients with delirium was assigned to each group (case and control). The demographics and clinical characteristics of the patients

Table 1. Characteristics of included patients in both groups.

Characteristic		Selenium group	Control group	P value
Sex	Male	28(56%)	26(52%)	0.84
	Female	22(44%)	24(48%)	
Age (year)		62.5±14.2	60.7±16.8	0.57
Admission diagnosis	Abdominal surgery	8(16%)	10(20%)	0.19
	Trauma	23(46%)	22(44%)	
	Pulmonary disease	10(20%)	8(16%)	
	Heart disease	1(2%)	3(6%)	
	Neurologic complication	8(16%)	7(14%)	
APACHE II score		19.8±2.2	19.2±2.1	0.13

APACHE: acute physiology and chronic health evaluation, Data are shown as Mean ± SD or n (%).

in both groups are summarized in Table 1. The baseline characteristics were similar in both groups (P>0.05). The mean APACHE II score was 19.8±2.2 in the selenium group and 19.2±2.1 in the control group, which was not statistically different (P=0.13).

Delirium was detected in 16 patients (32%) in the selenium group, and in 26 patients (52%) in the control group. The difference was not statistically significant (P=0.07).

The mean of CRP levels during the study period is presented in Table 2. The average daily CRP levels during the study period was statistically different between both groups (11.1±2.2 versus 16.7±1.6, P<0.0001). In spite of the first day of measurement, the CRP levels were statistically different between both groups in other days of study (P<0.0001).

Discussion

In this non-randomized controlled trial, we found that selenium administration had no effect on the incidence of delirium. Although compared to the control group, selenium administration decreased CRP levels significantly. No consistent association was found between CRP levels and delirium.

The results may be affected by limitations such as limited sample size and monitoring patients for a limited time (5 days) as well as the effect of medications such as steroids, salicylates and non-steroidal anti-inflammatories, which can affect inflammatory factors, are not considered in this study.

Mishra et al.,(23) conducted a prospective single-center study in 40 septic ICU patients who were randomized to high dose Se (Se+ group, N=18 (474, 316, 158 mcg/day), each for 3 consecutive days followed by a standard dose of 31.6 mcg/day of Se given as sodium selenite whereas the control group (Se-, N=22) received only the standard dose of Se. Plasma Se, glutathione peroxidase (GSH-Px), F2 isoprostanes, thyroid function tests (total T4 and total T3), CRP, and red blood cell (RBC) GSH-Px were estimated on day 0, 3, 7, 14. There was a significant negative correlation between plasma Se and SOFA (sepsis related organ failure assessment) (r=-0.36, P=0.03) along with low plasma Se and high CRP at the time of admission. Alhegan et al., (24) supplemented 437 elderly individuals with selenium and coenzyme Q10. In their study, the dietary supplementation with selenium and coenzyme Q_{10} combined reduced the inflammatory response in elderly humans, as judged from measurements of CRP and the soluble part of sP-selectin. Other studies in comparable groups have shown that selenium supplementation decreased NF-κB activation and down-regulated the expression of inflammatory genes (25). Valenta et al., (26) showed that high dose selenium substitution in patients with sepsis reduce markers of inflammation including CRP but did not reduce mortality. Thus, a decreased inflammatory response may result from selenium supplementation.

We didn't observe any association between selenium substitution and incidence of delirium. Although selenium decreased levels of CRP but it has no effect on the incidence of delirium. Zhongheng et al., (27) conducted an observational study of 223 critically ill patients to examine whether CRP on intensive care unit (ICU) entry was associated with subsequent development of delirium. The results showed that patients with delirium showed significantly higher CRP values than those without (120.5 vs. 57.5 mg/L; p=0.0001). An increase in CRP greater than 8.1 mg/L within 24 hours was associated with 4-fold increase in the risk of delirium (odds ratio: 4.47, 95% confidence interval, 1.28-15.6). They concluded that the C-reactive protein measured at ICU entry and its

Table 2. Values of C-reactive protein during the 5 days of the study.

Variable		Selenium group	Control group	P value
CRP	First day	13.8±3.24	14.7±4.68	0.3
	Second day	12.1±1.86	17.1±4.71	<0.0001
	Third day	11.2±1.75	15.5±3.89	<0.0001
	Fourth day	10.6±1.47	18.8±4.45	<0.0001
	Fifth day	7.8±1.82	17.7±4.23	<0.0001
	Average	11.1±2.20	16.76±1.65	<0.0001
Delirium incidence		16(32%)	26(52%)	0.07

CRP: C-reactive protein. Data are shown as Mean ± SD or n (%).

changes within 24 hours are risk indicators of delirium. In the similar study, Macdonald et al., (28) showed that CRP levels independently associated with subsequent development of delirium. Another study conducted by McGrane et al., (29) used delirium-/coma-free days as the study endpoint. They found that higher CRP levels showed trends toward fewer delirium-/coma-free days, but the difference was not statistically significant. This study is limited by its small sample size and low statistical power. Therefore, treatment aiming to ameliorate inflammatory response may help to reduce the risk of delirium. The results of our study indicates that despite the decreasing levels of CRP after Se administration but the incidence of delirium didn't change.

Limitations of the study include the following aspects: (1) this pilot investigation, which evaluated 50 patients, may lack adequate statistical power to detect some clinically important associations. Furthermore, the limited number of patients prevented us from studying potential differences in various subgroups such as surgical versus medical ICU patients. (2) Delirium is a clinical syndrome with complex pathophysiological mechanisms, and a single biomarker may be insufficient to predict the development of delirium. C-reactive protein may be only one part of a pathogenic cascade, and it has to be in association with a vulnerability trait to "cause" a delirious state. Other clinical variables were also independently associated with delirium. Thus, reduction in a single inflammatory marker couldn't decrease the incidence of delirium. (3) A large number of etiological factors associated with delirium will produce inflammation and elevate CRP. C-reactive protein may act as a mediator for the development of delirium. Studies have demonstrated that infection/sepsis, surgery, use of opiates, and propofol will significantly influence CRP levels, which, we didn't consider in our study.

In conclusion, the study showed that Se administration in critically ill patients decreased CRP levels, but did not reduce the incidence of delirium. Further studies exploring the treatment of delirium according to CRP levels are warranted.

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