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Original Article

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TO EVALUATE THE EFFICACY OF INTRAVENOUS SELENIUM ADMINISTRATION IN CRITICALLY ILL PATIENTS

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Abstract:

Background:
Sepsis and systemic inflammatory response syndrome continue to be leading causes of death in critically ill patients. These conditions are characterized by elevated oxidative stress and diminished levels of antioxidants. Selenium (Se), a micronutrient, plays crucial roles in antioxidation, inflammation suppression, and immune function, making it pivotal in combating oxidative stress and supporting overall health in such patients. This study aims to assess the impact of intravenous selenium supplementation on sequential organ failure assessment score (SOFA) and to investigate selenium's potential as a biomarker in critically ill patients.

Patients and Methods: Fifty-five critically ill patients received intravenous Se at a dosage of 600 micrograms daily for three consecutive days. Clinical parameters including SOFA score, ICU and hospital stays, and duration of mechanical ventilation and biochemical parameters such as C-reactive protein (CRP), Interleukin-6 (IL 6), Se levels, and total leukocyte count (TLC) were assessed before Se administration and on the fifth day post-administration for analysis.

Results: After administering Se injections, there was a significant increase in serum Se concentrations from 195.45±64.03 to 295.45±87.81 "p <0.001". Additionally, a notable decrease in SOFA score was observed, dropping from 7.21 to 6.41 "p = 0.004". Furthermore, CRP levels showed a statistically significant decrease following Se administration.

Conclusions: Our study findings demonstrate significant improvements in SOFA score and CRP levels among the patients. Se supplementation significantly boosts plasma Se levels, thereby enhancing tissue Antioxidant Capacity inThese Patients

Keywords: Antioxidant, Critically Ill Patients, Selenium, Sepsis, SOFA Score.

Introduction:

Selenium (SE) is a vital micronutrient that plays a crucial role in numerous physiological functions within the body. Numerous studies have highlighted reduced Se levels in critically ill patients[1]. Critical illness is characterized by intense inflammation, cellular immune dysfunction, oxidative stress, and various

forms of mitochondrial dysfunction[2]. Se, a micronutrient, serves essential roles in antioxidant, anti-inflammatory, and immunological functions[3]. It is crucially incorporated into selenoenzymes, protecting against oxidative stress. During inflammatory conditions, Se levels decline due to enzyme destruction and redistribution, as well as increased consumption. Critically ill patients with prolonged stay in the Intensive Care unit (ICU) often experience multiple organ failure and face an elevated risk of poor prognosis. The precise mechanisms underlying the development of multiple organ failure remain unclear, but there is a suggestion that increased production of reactive oxygen species and impaired antioxidative capacity due to depletion of glutathione and Se may play a role[4]. Glutathione peroxidase, a selenoenzyme, exists in eight isoforms with varying substrate specificities. Gpx-3 constitutes 20.0–40.0% of total plasma Se, with a normal value of 0.72 ± 0.16 U/ml reported for Uruguayan subjects. Se plays a crucial role as a cofactor for several enzymes associated with the redox system, immune system, and thyroid hormone axis. In severe sepsis, characterized by inflammation and elevated levels of circulating cytokines, reactive oxygen species (ROS), and heightened phagocytic activity of polymorphonuclear neutrophils (PMN) due to delayed apoptosis and prolonged NF-κb activation, intravenous selenite demonstrates a biphasic effect. Initially acting as a pro-oxidant, it later serves as an antioxidant upon incorporation into selenoenzymes. High concentrations of selenite can inhibit the DNA-binding activity of NF-κb in vitro by reacting with its thiol groups. Selenium's antioxidant and anti-inflammatory properties are essential in the context of systemic inflammatory response syndrome (SIRS)[3].

Se functions as a cofactor for enzymes involved in the redox system, immune system, and thyroid hormone regulation. Selenoprotein P (sepp), which serves as a carrier protein for Se, is proposed to protect the endothelium during severe insults such as burns, trauma, and sepsis[4]. Saturation of sepp in plasma has been used to establish reference values for Se intake in adults. In Se deficient regions like China, sepp saturation is achieved with a daily Se intake of 49 µg. Based on reference body weights used in the D-A-CH guidelines, estimated Se intake values are 70 µg/day for men and 60 µg/day for women. Estimates for children and adolescents are extrapolated from adult values adjusted for body weight[5].The primary aim of this study was to evaluate the impact of intravenous Se supplementation on SOFA scores, with

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selenium's role as a biomarker in critically ill patients serving as a secondary objective.

Ptients and Methods

Fifty-five adult patients requiring ICU admission for more than 24 hours were enrolled after providing informed written consent. Exclusion criteria included age below 18 years, ICU stay less than 24 hours, malignancy, and pregnancy. Upon admission to the ICU, all eligible critically ill patients had their serum Se levels assessed. Intravenous Se was administered to optimize levels in response to ongoing oxidative stress, consisting of 600 micrograms diluted in 100 ml of normal saline over 10 minutes daily for three consecutive days. Serum Se levels were re-evaluated on the fifth day of ICU admission.

Clinical parameters such as the reason for ICU admission, need for mechanical ventilation and the mode of ventilation were recorded. Vital signs including heart rate (HR), blood pressure (BP), oxygen saturation (SpO2), fraction of inspired oxygen (FiO2), and blood gas analysis were monitored. SOFA scores were calculated based on assessments of respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems with scores ranging from 0 to 4 indicating the severity of organ dysfunction.

Additionally, patients were evaluated for the effects of serum Se levels on SOFA scores, liver function tests (LFT), renal function tests (RFT), C-reactive protein (CRP), interleukin-6 (IL-6), total leukocyte count (TLC), differential leukocyte count (DLC), protein levels, and serum albumin levels. Serum Se levels were determined by assessing the activity of glutathione peroxidase, which relies on Se for its normal function.

Data were analyzed using the statistical package for social sciences (SPSS) 24.0 (SPSS Inc., Chicago, IL). Qualitative variables were compared using Chi-Square test /Fisher’s exact test. An unpaired t-test was applied to see the mean difference between the groups. p-value less than 0.05 was considered as significant at 95.0% confidence level.

Results

Age: our study involved 55 patients, the age range spanned from 19 to 88 years, with a mean age of 44.64 years. More than half of the participants were older than 41 years.

Gender: Regarding gender distribution, the majority of the participants (87.3%) were male, while females constituted only 12.72% of the study group.

SOFA score: We observed a statistically significant reduction in SOFA score following selenium administration, decreasing from 7.21 before treatment to 6.41 afterward "p = 0.004". (Figure 1)

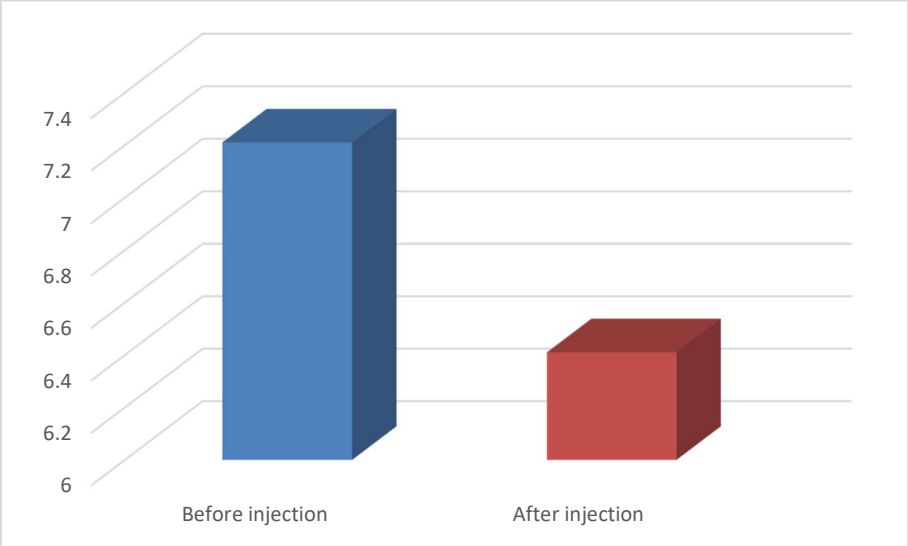

Figure1. Change in SOFA score from Day 1 to Day 5 after administration of selenium

Biochemical Parameters: We conducted a comparison of hematological and biochemical parameters from day 1 to day 5, both before and after Se administration. Following Se administration, we observed increases in TLC, serum creatinine, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and blood urea levels. Conversely, there were decreases in total bilirubin, alkaline phosphatase (ALP), serum protein, and serum albumin levels after Se administration. However, these changes were not statistically significant except for serum protein levels, which showed a statistically significant decrease from before Se administration to after "p < 0.05". (Table I)

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Table I: Biochemical Parameters

	MEAN (S.D.)		
	Before injection	After injection	
TLC	14167.27 (5906.43)	14352.72 (11653.27)	0.911
S. Creatinine	1.21 (0.72)	1.3 (1.11)	0.313
Blood urea	57.03 (37.23)	66.96 (53.28)	0.053 *
Total bilirubin	0.9 (0.56)	0.87 (0.41)	
SGOT	56.08 (36.61)	58.34 (47.35)	0.683
SGPT	42.36 (27.73)	43.07 (28.63)	0.828
ALP	109.49 (66.07)	108.8 (58.3)	0.934
Serum protein	5.88 (0.85)	5.64 (0.81)	0.011 *
Serum albumin	2.84 (0.58)	2.77 (0.48)	0.268

S.D.= Standard Deviation

CRP levels: Before Se administration on Day 1, CRP levels were found to be positive in 96.4% of cases. After Se administration on Day 5, this proportion decreased significantly to 63.6% "$p < 0.05$". (Table II)

Table II: CRP Levels

CRP Levels	Number of cases (%)		p- value
	Before injection	After injection	
Positive	53 (96.36%)	35 (63.63%)	<0.001 *
Negative	2 (3.63%)	20 (36.36%)	

IL-6: There was an observed increase in IL-6 levels from before Se administration to after administration, but this change was not found to be statistically significant "$p = 0.733$". (Table III)

Table III: IL-6

	MEAN (S.D.)		p- value
IL 6	Before injection	After injection	
	54.76 (21.07)	55.58 (26.13)	0.733

S.D.=Standard Deviation

Mechanical ventilation: More than half of the patients (50.9%) required mechanical ventilation for less than one week. Eighteen cases necessitated mechanical ventilation for more than one week but less than two weeks. The

mean duration of mechanical ventilation in the study cohort was 9 (TableV)

Table IV: Duration of mechanical ventilation

Duration of mechanical ventilation	Number of cases (%)
1-7 days	28 (50.9)
8-14 days	18 (32.72)
15-21 days	5 (9.09)
More than 22 days	4 (7.27)
Mean duration of mechanical ventilation in days (S.D.)	9.4 (7.49)

S.D.=Standard Deviation

Hospital and ICU stay: It was noted that over half of the cases were discharged within less than 10 days from admission. The average duration of hospitalization for the study group was 13.22 days. (Table V)

Table V: Length of hospital stay

Length of hospital stay	Number of cases
4 – 10 days	29 (52.72%)
11 – 20 days	17 (30.9%)
21 – 30 days	6 (10.9%)
More than 30 days	3 (5.45%)
Mean length of hospital stay in days (S.D.)	13.22 (10.24)

S.D.=Standard Deviation

Discussion

Sepsis manifests as a systemic inflammatory response triggered by infection, posing a significant mortality risk among critically ill patients, primarily due to multiple organ dysfunctions. Proinflammatory mediators and reactive oxygen species (ROS) are implicated in activating polymorphonuclear leukocytes and other reticuloendothelial cells. Concurrently, there is a reduction in antioxidants as part of the biological response to ROS presence[6]. Low levels of Se in the bloodstream have been observed in critical illness, correlating with unfavourable clinical outcomes and

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increased mortality rates. Se is crucial in managing inflammation and oxidative stress. Given that excessive production of inflammatory cytokines and heightened oxidative stress are prominent features of critical illnesses, supplementing Se has shown potential benefits for these patients[7].

Our study focused on 55 ICU admitted patients requiring mechanical ventilation. It was a prospective, single-arm study where selenium supplementation was administered to all patients, and various parameters were monitored before and after treatment. We compared our findings with those of other studies across different parameters.

SOFA Score: In our study, we observed a significant decrease in SOFA score from 7.21 to 6.41 following Se administration "p = 0.004". Contrasting findings were reported by Forceville et al., who noted a reduction in SOFA scores in both placebo and selenite groups, with significant decreases observed only in the selenium group by day 7 and day 14 compared to day 0 "p = 0.08" on day 7 and "p = 0.09" on day 14 for placebo[8]. Mishra et al. found no significant differences between selenium and placebo groups on either day 7 "p = 0.59" or day 14 "p = 0.40"[9]. Manzanares et al. concluded that the SOFA score significantly decreased in the selenium group compared to the placebo group by day 10 (1.3 ± 1.2 versus 4.6 ± 2.0, "p = 0.0001"[3]. Similarly, Chelkeba et al. reported a significant reduction in SOFA score on day 10 in the selenium group compared to the placebo group[10].

Serum selenium levels: In our study, the mean serum Se level before injection was 195.45 (S.D. = 64.03), which increased to 295.45 (S.D. = 87.81) after injection. This difference was statistically significant "p < 0.001". In a study conducted by Angstwurm, the mean serum selenium concentrations in the Se and placebo groups were 0.48 ± 0.23 µmol/L and 0.46 ± 0.16 µmol/L, respectively, and were similar between both groups upon admission[11].

In a study conducted by Quintana HL, researchers examined Se levels in both plasma and erythrocytes, alongside measuring gpx and Superoxide Dismutase (SOD) activity, as well as Total Antioxidant Capacity (TAC). The results indicated significantly lower levels of selenium in both erythrocytes and plasma upon ICU admission compared to a healthy reference group "p < 0.001". These levels declined further after one week "p < 0.001". Minor fluctuations in plasma Se levels were linked to more pronounced changes in the SOFA score "p < 0.05". Critically ill patients exhibited reduced gpx activity compared to controls "p < 0.05", which inversely

correlated with baseline severity scores "p < 0.05"and normalized after one week "p < 0.05". SOD activity demonstrated a direct correlation with TAC "p = 0.03", and both parameters were positively associated with albumin levels "p < 0.05" after seven days in the ICU. In conclusion, the study identified deficient selenium status upon icu admission, which deteriorated further over time regardless of the patient's clinical progression and antioxidant parameters. Initiating adequate selenium supplementation upon admission may help maintain and improve Se - related outcomes, potentially aiding in the recovery of critically ill patients during prolonged ICU stays[12].

In our study, we did not find a statistically significant change in IL-6 values following selenium administration "p = 0.733". IL-6, an inflammatory cytokine, typically rises in plasma during ICU hospitalization among patients with severe sepsis. Elevated IL-6 levels have been linked to the severity of organ dysfunction, mortality, and clinical outcomes in critical illness. Previous research has shown that decreased selenium levels are associated with higher IL-6 levels in sepsis. Additionally, a negative correlation between plasma selenium concentration and serum IL-6 has been observed in critically ill patients. However, the impact of selenium supplementation on IL-6 concentrations remains a topic of debate[7].

In a study done by Mahmoodpoor A et al, forty patients with ARDS were randomized into two groups: the SEL+ group being administered sodium selenite and the SEL– group receiving normal saline for 10 days. Blood samples were taken on day-0, day-7, and day-14 for assessment of IL-1 beta, IL-6, C-reactive protein, gpx-3, and selenium. Sodium selenite replenished selenium levels in the SEL+ group. Selenium concentrations were linearly correlated to serum concentrations of gpx3 "P < 0.001". Serum concentrations of both IL 1-beta "p < 0.001' and IL-6 "p < 0.001" were inversely correlated to the serum concentrations of selenium. They concluded that Selenium restored the antioxidant capacity of the lungs, moderated the inflammatory responses, and improved the respiratory mechanics. Despite these changes, did not effect on the overall survival, the duration of mechanical ventilation, and ICU stay.[13]

Chelkeba et al did not report the influence of supplementation with Se on IL-6 levels in patients with sepsis admitted to ICU. [10]

CRP: In our study, we observed a statistically significant decrease in CRP levels after administering Se. Before Se administration, CRP was positive in 96.4%

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of cases, whereas on day 5 after Se administration, it was positive in 63.6% of cases. Angstwurm et al. reported no significant difference in CRP levels between the Se and placebo groups[11]. Conversely, Valenta et al. Found that both the se and placebo groups showed peak CRP values on day 2, but significantly lower values were observed in the selenium group.[14]

Adverse events: No adverse events were observed in our study.

Limitation - A limitation of our study was the absence of a control group to compare the efficacy of selenium in critically ill patients. There is a clear need for a large, multicenter, prospective randomized controlled trial to thoroughly assess the impact of selenium supplementation on clinical outcomes in this patient population.

Conclusion: Our research has revealed notable enhancements in SOFA score and CRP levels after administering selenium supplements, leading to faster resolution of organ dysfunction among critically ill patients. Selenium supplementation significantly boosts plasma selenium levels, thereby enhancing tissue antioxidant capacity in this patient group. Ensuring adequate selenium support from the onset of admission may help maintain and improve selenium-related outcomes and promote the recovery of critically ill patients over extended ICU stays.

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Work concept and design 1,2
Data collection and analysis 1,2,3,4,5
Responsibility for statistical analysis 1
Writing the article 1,2
Critical review, 1, 2,5
Final approval of the article 1,2,3,4,5
Each author believes that the manuscript represents honest work and certifies that the article is original, is not under consideration by any other journal, and has not been previously published.
Availability of Data and Material: The corresponding author is prompt to supply datasets generated during and/or analyzed during the current study on wise request.

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