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Research Paper

The Effectiveness of Selenium in Oral Nutritional Therapy for Patients With Subarachnoid Hemorrhage

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ABSTRACT

Background and Aim: Every year, traumatic brain injuries lead to more than one million admissions to emergency rooms and more than 50,000 deaths and millions of disabilities worldwide, among all ages and genders. This study aimed to examine the effects of selenium added to oral nutritional therapy on the mortality rate and length of hospital stay in patients with subarachnoid hemorrhage admitted to the intensive care unit (ICU) for six months.

Methods and Materials/Patients: This clinical trial included 100 patients admitted to the ICU of Loghman Hakim Hospital, Tehran, Iran. These patients were then randomly assigned to intervention or control groups. Standard oral solutions were administered to both groups according to recommended guidelines. Along with the standard nutritional intake, the participants in the intervention group were given 1000 µg of selenium (Selenase-Biosyn, Germany) on the first day of feeding, dissolved in 100 mL of normal saline for 30 minutes, followed by 500µg of selenium daily for 10 days. We screened patients for GCS, and APACHE-II scores, as well as cortisol levels on days 1 and 10.

Results: The APACHE-II mean score on the 10th day was significantly different between the two groups, and this was also true before the intervention. In terms of mortality rates, there was no significant difference between the control group and the intervention group. Neither the control group nor the intervention group spent significantly more time in ICU.

Conclusion: The effects of selenium on other variables were unclear, although mortality rates did not differ significantly between the two groups. Considering the confounding variables through regression analysis, the APACHE-II variable was negatively impacted by selenium, but taking into account the significant effect of age, a definitive conclusion cannot be made.

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Highlights

• There was no statistically significant difference between the control and intervention groups in terms of the death rate.

• There was no significant difference in the time spent in intensive care units between the control and intervention groups.

• Between the control and intervention groups, the Glasgow Coma Scale scores did not differ significantly.

Plain Language Summary

More than one million traumatic brain injuries are treated in emergency rooms every year, more than 50,000 people die, and millions of people are disabled every year, at all ages and from both genders. During six months at Loghman Hakim Hospital, we conducted a study to assess the effects of selenium added to nutritional therapy on mortality rate and length of hospitalization of patients suffering from subarachnoid hemorrhage. The results of this study showed that selenium did not affect mortality or length of stay.

1. Introduction

Traumatic brain injuries cause more than one million admissions to emergency rooms each year and cause more than 50,000 deaths and countless disabilities in people of all ages and genders [1]. Head injuries are caused by both primary and secondary mechanisms. Infections, bleeding, edema, or other pathological conditions can cause the primary form, whereas direct blows to the head can cause the secondary form. There is the potential for complications with both types of injuries, including ischemia, hemorrhaging, or death. As a result of a traumatic brain injury, increased metabolism and greater catabolism of protein are observed. Compared to individuals without a head injury, patients with brain injury consume a significant amount of resting metabolism. The increased metabolic rate and catabolism, as well as impaired immune function, may result in excessive protein degradation, leading to malnutrition in patients with traumatic brain injuries [2].

Malnutrition in intensive care unit (ICU) patients, including patients with head injuries, leads to an increase in the length of hospital stay and in mortality, which can be attributed to increased dependence on mechanical ventilation, high rates of infection, and delayed wound healing [3].

In addition to these pathophysiological changes, some alterations take place at the molecular level, resulting in oxygen-free radical production and oxidative stress reactions. The production of oxygen free radicals is detrimental to the function of brain enzymes and cellular signals. A major part of managing the effects of brain damage on the cells is to control the production of oxygen free radicals. It is achieved by regulating the levels of oxidants and antioxidants within the body. Several studies have examined the role of selenium in promoting this balance [1].

As a vital trace element, selenium plays an important role in antioxidant enzymes, such as glutathione peroxides and thioredoxin reductase [4, 5]. In general, selenium intake should range from 20 to 70 µg per day. Selenium is used to make certain proteins called Selenoproteins whose activity is dependent on selenium. They are found in some human genomes. As opposed to other essential trace elements, like copper, iron, or zinc, selenium is incorporated directly into selenium proteins during polypeptide chain synthesis, rather than after protein synthesis. Numerous studies on metabolism, toxicology, and nutrition have concentrated on the study of selenium in recent years due to its multiple biological functions and its unique ability to combine with proteins [6].

Weber et al. in 1991 for the first time showed that selenium has a special function in the brain. Children with low glutathione peroxidase activity who received selenium supplementation had improved symptoms of seizures. Recent evidence suggests that glutathione-dependent selenium (GSH) is involved in the prevention of cellular damage caused by excessive oxygen free radicals [5]. Selenium, on the other hand, plays a vital role in immunity since it inhibits the secretion of Interleukin

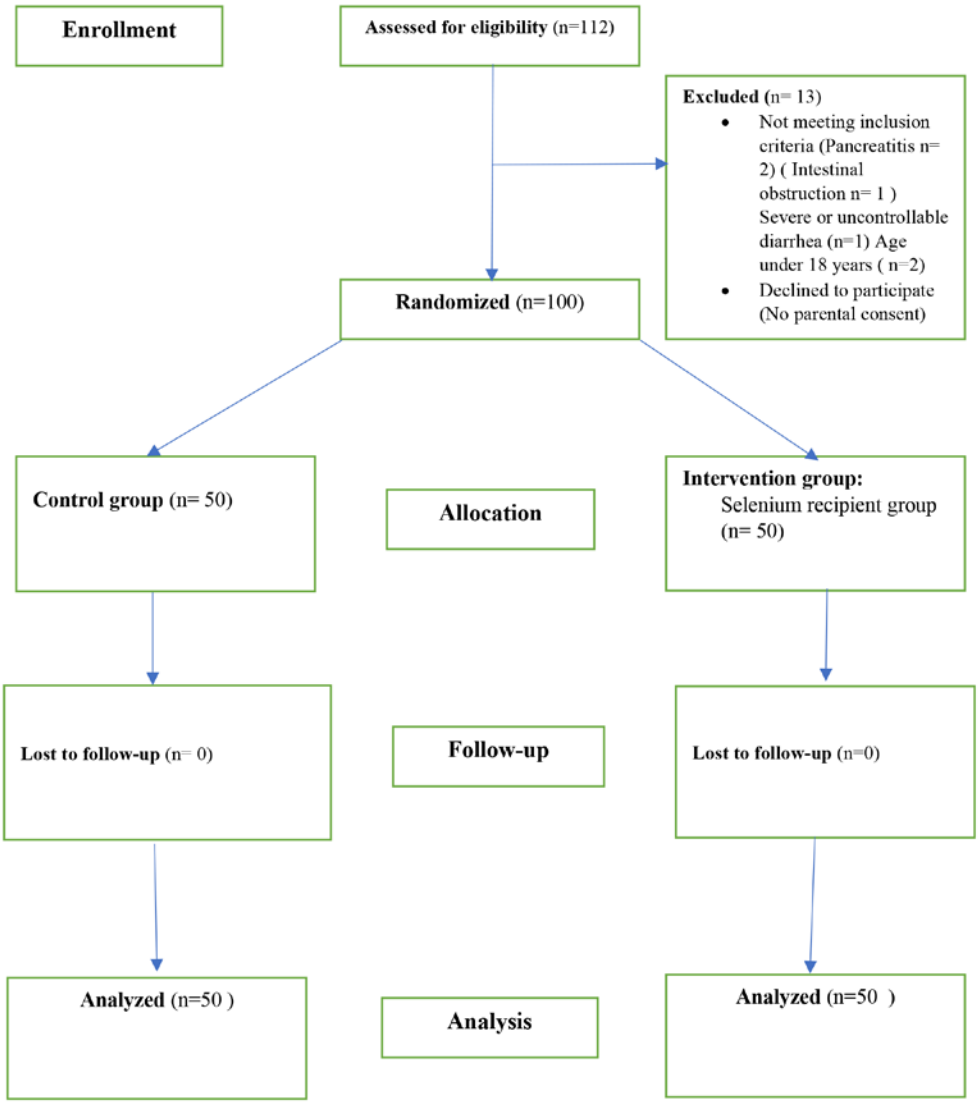

Figure 1. CONSORT diagram; selection, evaluation, and follow-up of the participants

6 and thus accelerates the proliferation and activation of Natural Killer cells (NK cells) and T-lymphocytes [7].

Selenium supplementation enhances the prevention mechanisms against cellular damage caused by imbalances between oxidants and antioxidants. Such imbalances, in turn, cause neurological dysfunction and even sudden death in individuals with brain injuries [8, 9].

This study was undertaken to test the hypothesis that adding selenium to blood can prevent post-traumatic injury and thus improve patient performance. We examined the effect of selenium added to oral nutrition therapy on the mortality outcomes and length of hospital stay of patients with subarachnoid hemorrhage at Loghman Hakim Hospital in Tehran in 2018.

2. Methods and Materials

Type of research

A randomized, controlled trial was conducted between 17 March, 2018 and 06 September, 2018 to examine the effects of supplemental selenium to oral nutritional therapy on mortality and length of hospital stay during hospitalization. We focused on subarachnoid hemorrhage at the Loghman Hakim Hospital in Tehran.

Research sample

As there were no previous studies to compare, and a preliminary study was not possible, we divided the patients into two groups and included 50 patients in each group. Therefore, 100 patients with subarachnoid

hemorrhage admitted to the Loghman Hakim ICU in Tehran who met the inclusion criteria were included in the study as research participants. The participants were randomly assigned to the intervention or control groups. The research was done following the CONSORT guidelines and checklist (Figure 1).

Random allocation software (software that generates random numbers) generated a random sequence prior to the study and provided it to the researcher based on a simple random sampling technique (balanced block randomization).

Inclusion criteria were as follows: subarachnoid hemorrhage in whom oral nutrition was indicated, and hospitalization in the ICU due to trauma or surgery. Exclusion criteria were as follows: leaving the ward less than ten days after being admitted to the ICU due to death, transfer to another ward, or discharge, having intestinal obstruction or ileus, having severe or uncontrollable diarrhea, and having pancreatitis.

Data collection

A checklist was used to collect data, including age (year), gender, cause of hospitalization, number of days spent in the ICU, acute physiology and chronic health evaluation II (APACHE-II) scores, global cognitive score, and blood cortisol level before and ten days after the intervention. A demographic profile of each participant was obtained from their medical records, and the consent form to participate in the study was signed by the patient's legal guardian. The cortisol levels and the scores of APACHE-II were measured at 8 a.m. Standard solutions were administered orally to both groups of patients according to the recommended guidelines. The subjects of the intervention group received 1000 µg of selenium (Selenase-Biosyn co., Germany) once a day dissolved in 100 mL of normal saline for 30 minutes, and 500 µg of selenium dissolved in 100 mL of normal saline from the second to the tenth day. We evaluated several symptoms, including hair loss, white spots on the nails, breathing with a garlic odor, fatigue, and irritability. Using a standard checklist, GCS scores were noted on the first and tenth days. In addition, the researcher performed an assessment of the patient's condition and the APACHE-II scores were recorded in a checklist and a related scoring system. Moreover, a laboratory colleague measured the cortisol level at 8 a.m.

Data analysis

In this study, we analyzed and visualized the collected data using some R statistical packages (R v. 4.1.1). Quantitative data were reported as mean and standard deviation for quantitative data, whereas qualitative data were presented as frequency and percentage. In order to compare qualitative variables, we applied the Chi-square test, and to compare quantitative data, we applied an independent t-test. For all tests, a P of less than 0.05 was considered significant.

3. Results

This section presents the results, starting with a table of quantitative variables, which includes descriptive statistics and t-test results. Variables, including age, APACHE-II score, GCS score, and cortisol levels (on the first and tenth days) and also the changes of these variables between the first and tenth days were also calculated and analyzed. Our goal was to determine the effects of selenium administration on the changes in variables of interest. In this context, 'change' refers to the increase or decrease in these variables between the first and tenth days.

These variables were also visualized using box plots to allow a visual comparison of the two groups (Figure 2). The confounding variables, such as age and gender may play a critical role in this analysis. Therefore, after calculating the changes that occurred in the variables, including age, APACHE-II, GCS, and cortisol level between the first and tenth days, regression analysis and ANOVA were conducted, and their results are presented separately in the following tables. Concerning the qualitative variables, the Chi-square test was used to compare the ratios in the two groups, as well as to display the graphs of the ratios within the two groups (Figure 3).

Based on the results of the present study, the mean age of the intervention group was 45.56 years as opposed to 43.58 years in the control group, and no significant difference between the groups was observed (P=0.483) (Table 1). The frequency of men in the intervention group (56.7%) and the control group (52.9%) was similar and based on the results of the Chi-square test, the gender frequency of patients was not significantly different between the two groups (P=0.428) (Table 2). Among the intervention group, the average length of hospitalization in the ICU was about 6.5 days, which was not significantly different from the average length of hospitalization in the ICU of the control group (P>0.05).

Table 1. Descriptive statistics and t-test results of the quantitative variables (n=50 in each group)

Variables	Group	Min	Max	Mean±SD/ Mean Difference	SE	CI	Statistic	df	P
Age (y)	With Selenium	19	74	45.56±14.809	2.094	4.209	0.704	96.816	0.483
	Without Selenium	18	70	43.58±13.253	1.874	3.766			
Changes in APACHEII	With Selenium	-10	3	-4.46±3.018	0.427	0.858	-7.468	90.105	0.0001
	Without Selenium	-11	4	-0.5±2.225	0.315	0.632			
APACHEII (1st day)	With Selenium	9	22	12.28±3.091	0.437	0.878	-3.428	95.381	0.001
	Without Selenium	6	22	14.6±3.653	0.517	1.038			
APACHEII (10th day)	With Selenium	3	16	7.82±4.079	0.577	1.159	-7.295	96.992	0.0001
	Without Selenium	6	24	14.1±4.519	0.639	1.284			
Changes in Cortisol Levels	With Selenium	-14.3	11.7	-1.606±6.036	0.854	1.715	-0.998	61.119	0.322
	Without Selenium	-9.4	4.3	-0.702±2.139	0.303	0.608			
Cortisol Levels (1st day)	With Selenium	5.5	26.8	15.186±6.148	0.869	1.747	0.934	84.449	0.353
	Without Selenium	7.4	22.4	14.216±4.022	0.569	1.143			
Cortisol Levels (10th day)	With Selenium	6.4	22.3	13.58±4.179	0.591	1.188	0.090	89.227	0.928
	Without Selenium	8	20.4	13.514±3.021	0.427	0.859			
Changes in GCS	With Selenium	-2	4	1.02±1.253	0.177	0.356	1.156	97.559	0.251
	Without Selenium	-3	4	0.72±1.341	0.19	0.381			
GCS (1st day)	With Selenium	7	15	12.4±2.05	0.29	0.583	0.000	89.301	0.999
	Without Selenium	8	14	12.4±1.485	0.21	0.422			
GCS (10th day)	With Selenium	8	15	13.42±1.739	0.246	0.494	0.783	95.070	0.435
	Without Selenium	7	15	13.12±2.076	0.294	0.59			
Hospital stay in the ICU (day)	With Selenium	0	12	6.5±1.502	0.212	0.427	0.960	97.650	0.339
	Without Selenium	0	10	6.08±1.414	0.2	0.402			

Table 2. Descriptive statistics and Chi-squared test results of the quantitative variables

Variables		Group	No.	Proportion (%)	Chi-Squared	df	P
Sex	Male	With Selenium	29	56.7	0.42857	1	0.5127
		Without Selenium	26	52.9			
	Female	With Selenium	21	43.3			
		Without Selenium	24	47.1			
Mortality	Yes	With Selenium	8	0.16	0.083056	1	0.7732
		Without Selenium	6	0.12			
	No	With Selenium	42	0.84			
		Without Selenium	44	0.88			

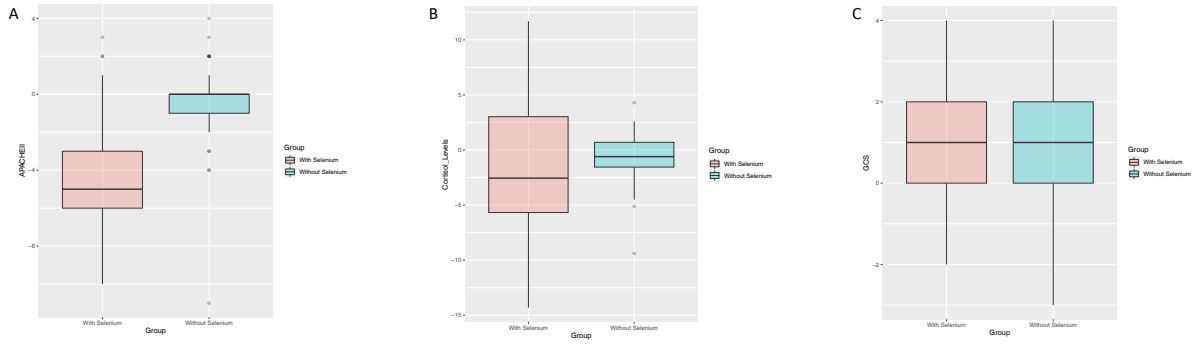

Figure 2. The box plots of (a) APACHE-II scores; (b) Cortisol levels; (c) Glasgow Coma Scale (GCS) scores

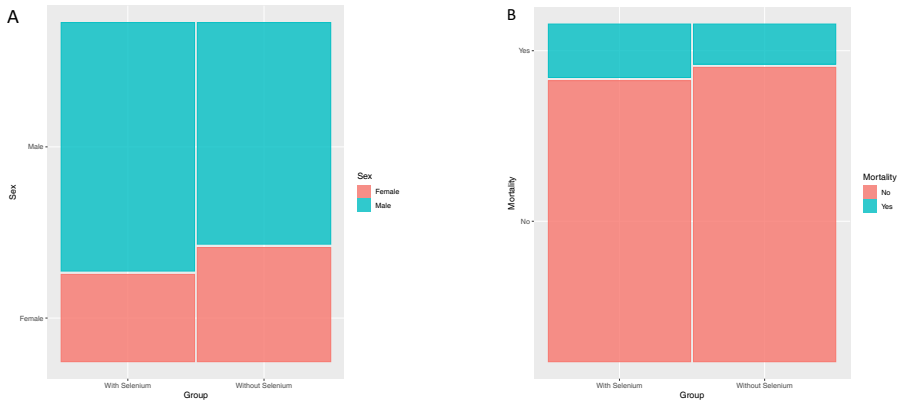

Figure 3. The portion plots of (a) Sex and (b) mortality

Table 3. Regression analysis and ANOVA of changes in APACHE-II scores

Results of Regression Analysis				
Term	**Estimate**	**Std Error**	**Statistic**	**P**
Intercept	-6.40	1.14	-5.59	0.0001
Sex (male)	-0.44	0.59	-0.75	0.45
Age	0.05	0.02	2.59	0.01***
Group (without Selenium)	4.02	0.52	7.79	0.0001***

Analysis of Variance (ANOVA)					
Term	**df**	**Sum Sq**	**Mean Sq**	**F**	**Pr (>F)**
Sex	1.00	33.19	33.19	5.07	0.03
Age	1.00	21.62	21.62	3.30	0.07
Group	1.00	397.54	397.54	60.71	0.00
Residuals	96.00	628.61	6.55		

Table 4. Regression analysis and ANOVA of changes in cortisol levels

Results of Regression Analysis				
Term	**Estimate**	**Std Error**	**Statistic**	**P**
Intercept	2.71	1.99	1.36	0.18
Sex (male)	-1.24	1.02	-1.22	0.23
Age	-0.07	0.03	-2.23	0.03***
Group (without Selenium)	0.66	0.90	0.73	0.47

Analysis of Variance (ANOVA)					
Term	**df**	**Sum Sq**	**Mean Sq**	**F**	**Pr(>F)**
Sex	1.00	9.09	9.09	0.46	0.50
Age	1.00	105.88	105.88	5.34	0.02
Group	1.00	10.61	10.61	0.53	0.47
Residuals	96.00	1904.14	19.83		

As shown in Table 1, the average APACHE-II scores on the first day of hospitalization were significantly lower in the intervention group than in the control group (P=0.001). In addition, the mean APACHE-II scores of patients in the intervention group ten days after selenium treatment were significantly lower than that of patients in the control group (P=0.0001). The difference in APACHE-II scores between the first day of hospitalization and ten days after selenium treatment was significantly lower in the intervention group (P=0.0001).

Table 6. Regression analysis and ANOVA of changes in hospital stay in the ICU

Results of Regression Analysis				
Term	**Estimate**	**Std Error**	**Statistic**	**P**
Intercept	-0.03	0.65	-0.05	0.96
Sex (male)	0.37	0.34	1.09	0.28
Age	0.01	0.01	0.48	0.63
Group (without Selenium)	-0.24	0.30	-0.81	0.42

Analysis of Variance (ANOVA)					
Term	**df**	**Sum Sq**	**Mean Sq**	**F**	**Pr (>F)**
Sex	1.00	2.47	2.47	1.15	0.29
Age	1.00	0.68	0.68	0.32	0.58
Group	1.00	1.42	1.42	0.66	0.42
Residuals	96.00	205.88	2.14		

Table 5. Regression analysis and ANOVA of changes in Glasgow Coma Scale (GCS) scores

Results of Regression Analysis				
Term	**Estimate**	**Std Error**	**Statistic**	**P**
Intercept	1.82	0.54	3.37	0.0001
Sex (male)	0.56	0.28	2.01	0.05***
Age	-0.03	0.01	-2.93	0.0001***
Group (Without Selenium)	-0.31	0.24	-1.27	0.21

Analysis of Variance (ANOVA)					
Term	**df**	**Sum Sq**	**Mean Sq**	**F**	**Pr (>F)**
Sex	1.00	13.92	13.92	9.58	0.00
Age	1.00	11.50	11.50	7.91	0.01
Group	1.00	2.33	2.33	1.60	0.21
Residuals	96.00	139.55	1.45		

In the regression analysis of this variable (Table 3), it is found that although gender did not affect it (P=0.45), age played an effective role as a confounding factor (P=0.01). Consequently, it can be concluded that the changes in APACHE-II scores are not only due to the selenium administration.

According to the results of this study (Table 1), there was no significant difference in the mean cortisol levels on the first day of hospitalization between the intervention and control groups (P=0.353). Furthermore, the mean cortisol levels of the intervention and control groups did not differ significantly ten days after selenium administration (P=0.928). On the other hand, even the changes in this variable did not show a significant difference between the two groups (P=0.321). The results of the regression analysis of this variable (Table 4) suggest that the age factor is also relevant to cortisol levels (P=0.03), and the importance of this confounding variable should not be overlooked. The ANOVA results showed that selenium treatment did not have a significant effect on cortisol levels (P=0.47).

Moreover, there were no significant differences in mean GCS scores between patients in the intervention and control groups on the first day of admission (P=0.999) and also on the tenth day (P=0.435) (Table 1). Furthermore, even the changes in this variable did not indicate a significant difference between the two groups of our study (P=0.251). In Table 5, which shows the results of the regression analysis, selenium treatment did not have a significant effect on this variable (P=0.21), but gender (P=0.05) and age (P=0.0001) significantly affected the mean GCS scores. Also, the ANOVA results (Table 6) revealed that neither age (P=0.29) and gender (P=0.58), nor selenium treatment (P=0.42) had a significant effect on the length of hospital stay in the ICU.

4. Discussion

We conducted an interventional study in 2018 on 100 patients admitted to ICUs to examine the effect that selenium added to oral nutritional therapy can have on mortality and hospitalization in patients with subarachnoid hemorrhage at Loghman Hospital Hakim, Tehran. Regarding the average length of stay in ICU, the average length of stay in the ICU was approximately 6.08 days in the control group and approximately 6.5 days in the intervention group, and this difference was not statistically significant (P>0.05). In a similar study conducted by Moghadam et al. in 2017 aimed at early administration of selenium to patients with brain injury, it was noted that the hospital stay in the ICU in the selenium group averaged 14.51 days and it was 13.71 days in the control group. In the selenium group, the duration of hospitalization was 19.4 days, and in the control group, it was

20.4 days; thus, there was no difference in duration of hospital stay in the ICU and the length of hospital stay on days 1 and 15 [10].

High-dose antioxidants were associated with a reduction in post-traumatic stress disorder in American critically ill trauma patients [7]. Oxidant intake (AO+) was significantly lower than antioxidant intake (AO-) in the antioxidant group [7]. Andrews et al. found that either glutamine or selenium had a positive impact on mortality and infection rates in critically ill patients [11]. Heydari et al. investigated the effect of selenium on the clinical outcome of critically ill patients under mechanical ventilation. They demonstrated that selenium supplementation reduced the duration of hospitalization in ICU and improved the clinical outcome of severely ill patients [12].

This study aimed at determining and comparing the mean score of APACHE-II in the ICU in the two groups of intervention and control and it was the most controversial variable. In addition to the selenium treatment, the ANOVA results showed that the age of the patients also contributed to the difference between the two groups. APACHE-II scores on days 1 and 15 did not differ significantly between the two groups according to the study by Moghadam et al. in 2017. Perhaps the mean difference between the groups observed in our study was due to the same difference seen at the beginning of the study and is not the result of the selenium administration. These questions demand further research and the matching of patients between the control and intervention groups [10].

Angstwurm et al. in 1999 assessed the effect of selenium supplementation on mortality in patients with systemic inflammatory response syndrome and showed that both groups scored significantly lower on the APACHE-II scale. In patients with systemic inflammatory response syndrome, selenium supplementation improved the clinical outcome and reduced the risk of acute renal failure [13]. Angstwurm et al. conducted a study in 2007 aimed at improving the clinical outcome of patients with severe sepsis and septic shock using high doses of selenium. The results showed that the APACHE-II score was significantly reduced in the sulfur group [14].

Another variable that was examined was cortisol, which was crucial to our objective. As part of its functions, cortisol reduces inflammation, lessens immune reactions, affects metabolism, and raises blood sugar levels, and is one of the most important hormones produced in response to stress. There was no significant difference in cortisol secretion between the control and intervention groups in the current study. However, ANOVA results showed that age had a significant effect on cortisol levels, unlike selenium treatment.

In the study by Senol et al., lipid peroxidation and β-IL-1 were reduced by selenium treatment, whereas IL-4 levels, total antioxidant status, and vitamins C and E increased. No significant difference was observed in mortality rates between the intervention and control groups [15]. Moghadam et al. assessed 113 people and found a mortality rate of 15.8% in the selenium group and 19.6% in the control group, with no statistically significant differences between them [10].

Khalili et al. investigated the effect of selenium on stroke patients in Shiraz and concluded that the consumption of selenium did not affect patient survival [16]. Andrews et al. assessed 502 participants and found that selenium administration did not increase survival or a reduction in mortality in critically ill patients [11].

In a clinical trial meta-analysis undertaken by Alhazzani et al., selenium consumption was associated with a lower mortality rate than the placebo in people with sepsis. However, this study involved patients with sepsis rather than individuals with brain injuries [17].

It has been demonstrated that intravenous Selenase (Sodium Selenate Pentahydrate) treatment significantly improves functional neurologic outcomes, according to Khalili et al. Six months after discharge, this effect continues to be evident. The results of the study concluded that Selenase treatment did not improve survival. As shown in this study, the positive effect observed after discharge of the patient and up to six months after stable injury along with the lack of effect observed in other studies may indicate that selenium plays a more important role in improving neuronal potential in the long term than its ability to prevent mortality from primary injury [16]. The GCS score was also examined, which is a measure of the severity of loss of consciousness in people over the age of five. The GCS is frequently used in emergency situations following brain injury [18]. There was no statistically significant difference between the scores of the GCS in the control and intervention groups (P=0.435). There was no similar study reporting GCS scores.

5. Conclusion

A randomized controlled clinical trial was conducted to determine whether selenium added to oral nutritional therapy can reduce mortality and length of hospital stay among patients with subarachnoid hemorrhage. It is not possible to make a definitive conclusion about the effects of selenium on patients. Despite no significant differences between the two groups in mortality rates, the effect of selenium on other variables was unclear, particularly, when we examine gender and age as confounding variables through regression analysis. The APACHE-II score was affected by selenium, but taking into account the significant effect of age, a definitive conclusion cannot be made. Selenium neither has a significant effect on the GSC and duration of hospitalization in ICU nor on the cortisol levels. The cortisol level similar to the GSC score, however, was significantly associated with sex and age. In future studies, it may be necessary to control the effects of gender and age.

Ethical Considerations

Compliance with ethical guidelines

Throughout the entire research process, the following ethical guidelines were applied:

1. Obtaining approval from the ethics committee of Rajaei Heart Hospital (RHC.AC.IR.REC.1396.32).

2. Requesting permission from the research deputy at the Shahid Rajaei Cardiovascular Center

3. Explaining the purpose and nature of the research to the officials of the relevant units and all units under research

4. Providing a letter of introduction to the officials of the units and departments

5. Confidentiality of all information collected in this study

6. Adherence to ethical principles during the collection of library information and at all stages of the research process

7. Informing the patients and families of the patients in the research units about their voluntary participation in the research and the role of the researcher

8. Making the results available to the authorities

9. Preventing patients from incurring additional costs

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Authors' contributions

Conception and design: Seyedeh Zahra Faritous, Mohammadreza Hajiesmaeili; Data collection: Zohre Hashami, Mohammadreza Hajiesmaeili; Data analysis and interpretation: Zohreh Morshedizad, Hooman Bakhshandeh; Drafting of the article: Zohre Hashami, Zohreh Morshedizad; Critically revising the article: Hooman Bakhshandeh; Reviewing the submitted version of the manuscript: Zohreh Morshedizad, Soha Mehrabimahani; Approving the final version of the manuscript: All authors.

Conflict of interest

The authors declared no conflict of interest.

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