

Prospective Cohort Study of Serum Selenium in Surgical ICU Patients

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Background: Many clinical trials have assessed the benefits of inorganic seleno compounds in critically ill patients. However, serum selenium of populations throughout the world is very. We sought to determine the change in serum selenium level of surgical critically ill patients in Thailand.

Objective: To determine the serum selenium level of surgical Intensive Care Unit (ICU) patient and to compare the change in serum selenium level on day 3 and day 5 of ICU stay.

Material and Method: We collected 5 ml clot blood on day 1, day 3, and day 5 from patients admitted to surgical ICU between November 2012 and January 2013. Blood sample was centrifuged, and serum was collected. Serum selenium level was determined by using the Inductive Couple Plasma with Mass Spectrometry (ICP-MS) system. Basic information of patients including age, gender, diagnosis, underlying illness, indication of ICU admission, SOFA score, number of days for ventilator use, nutritional support, number of days of ICU stay, and death after day 5 of ICU stay was recorded.

Results: All 47 patients (100%) who admitted to surgical ICU had serum selenium level lower than average level of healthy Thai (106.95 $\mu\text{d/L}$) on day 1 and day 3 of ICU stay while 44 out of 47 patients (93.6%) had serum selenium level lower than average level of healthy Thai on day 5. Average serum selenium levels were below normal physiological range (70 to 150 $\mu\text{d/L}$) on all study day. Average serum selenium level on day 5 of ICU stay was 67.9 $\mu\text{g/L}$, which was increased significantly from day 1 level (61.8 $\mu\text{d/L}$) and day 3 level (63.5 $\mu\text{d/L}$). No significant factor associated with the reduction in serum selenium level has been found.

Conclusion: Almost all patients who admitted surgical ICU had serum selenium level below average level of healthy population and over 50% of the sample were below normal range on all day of the study.

Keywords: Serum, Selenium, Surgical, ICU, Thailand, Inductively coupled plasma with mass spectrometry (ICP-MS)

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Selenium (Se) is an essential trace element for the human body. It increases immunity, takes part in antioxidant, protects aggravated free radical damage and inflammation, and maintains a healthy metabolism. The selenium rich diet is bread and cereals, meat, fish, egg, and milk⁽¹⁾. The food chain of selenium starts from plants, which take it up from the soil. Soil selenium concentration varies by geographical location. Average serum selenium level for healthy Thai population is 106.95 $\mu\text{d/L}$ ⁽²⁾ and baseline serum selenium level for physiological range is 70 to 150 $\mu\text{d/L}$ ⁽³⁾.

Many clinical trials have assessed the benefits

of inorganic seleno compounds as part of an antioxidant in critically ill patients, but the outcomes are controversial^(4,5). The nutrition guidelines in critical care recommend a combination of antioxidant vitamins and trace elements include selenium for all ICU patients who require parenteral nutrition and enteral nutrition^(6,7).

The primary objective of this study was to compare the serum selenium level on day 1, day 3, and day 5 of ICU stay. The correlation between patient characteristics and serum selenium level was also recorded as a secondary outcome.

Material and Method

Subjects and study design

This was a cross-sectional study. The sample was recruited from patients who admitted in surgical ICU from the Department of surgery, Faculty of Medicine Ramathibodi Hospital, Mahidol University,

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Bangkok, Thailand. The enrolments were done between November 2012 and January 2013. The study protocol was approved by Committee of Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University. All participants are well informed, and they have provided written consent prior to the enrolment.

Sample collection

Non-fasting blood samples were collected via peripheral venous puncture from patients three times, on the first visit day, the third, and the fifth ICU admission day. Five mL of blood from each subject was taken and collected in a clot blood tube. All blood samples were centrifuged to separate serum within three hours after collecting. The serum samples were then stored at -80°C until analyzed. All glassware and plastic wares used in collecting blood samples were treated with HNO₃ overnight to be demineralized before use. This is to prevent contamination of selenium from the environment.

Reagents and standard solution

Nitric acid (HNO₃ 65%), 1-butanol, EDTA, and NH₄OH were purchased from Merck (Darmstadt, Germany). Triton X 100 was obtained from Boehringer Mannheim (IN, USA). Water was deionized prior to use. A 1,000 mg/L selenium stock solution (Merck, Darmstadt, Germany) was used to prepare a working standard solution for calibration. The accuracy of determination was assessed by making comparisons with standard reference materials (Seronorm™) obtained from SERO AS (Billingstad, Norway). All chemicals were of analytical grade purity and all reagents were evaluated for their contribution to Selenium contamination in the blanks. Stock solution and reference materials were stored at 4°C in the dark.

Analysis of serum selenium concentrations

Sample preparation for selenium concentration analysis was modified from that described by Bishop et al⁽⁸⁾ and Labat et al⁽⁹⁾. Briefly, 100 µL of serum was prepared by dilution (1: 50, v/v) in a modifier solution which contained 0.8% 1-butanol, 0.1% EDTA, 0.1% Triton X-100 and 2% NH₄OH. Selenium concentration in serum was analyzed by using the inductively coupled plasma with mass spectrometry (ICP-MS) system. An Agilent 7900 ICP-MS system (Agilent Technologies, Bangkok, Thailand) was used to conduct the experiments. All ICP-MS operating parameters were adjusted to give a maximum signal in the Selenium

concentration studies. The 50-fold diluted sample solutions were introduced directly into the plasma by pneumatic nebulization. Data was calculated using the Agilent ICP-MS Mass Hunter data analysis software version C.01.

Statistical analysis

Continuous data were summarized by mean (SD). Categorical data were summarized as counts and percentages. The differences between serum selenium level on day 1 to day 3, day 1 to day 5, and day 3 to day 5 of ICU stay were tested for statistical significance by using paired t-test. Comparison between low serum selenium level group (less than 70 µd/L) and normal serum selenium level group (70 to 150 µd/L), non-death and death after day 5 of ICU stay used Chi-square test and Fisher's exact test. The *p*-values less than 0.05 were considered statistically significant. All statistical analyses were performed using Stata version 14 (Stata Corp, college station, TX USA).

Results

Seventy-two patients consented to participate in this study. Of these, 25 patients were excluded from this study due to death or transfer to regular ward before day 5 of ICU stay. Final analysis was done from 47 patients. The basic information included gender, age, underlying disease, diagnosis, indication for ICU admission, SOFA score, vasoactive drug used, ventilator free at day 5, nutritional support, total ICU study, death after day 5 ICU stay, and serum selenium level at day 1, day 3, and day 5, as provided in Table 1. Over all serum selenium levels are shown in Fig. 1.

On multivariable analysis with the normal range (70 to 150 µd/L) and below normal range (less than 70 µd/L) of serum selenium level on day 1, day 3, and day 5 as a covariate, no risk factors were significantly associated (Table 2).

Comparison of serum selenium level between day 1 to day 5 and day 3 to day 5 of ICU stay showed that serum selenium level increased significantly on day 5 of ICU stay (Table 3, Fig. 2). Comparison of serum selenium level between non-death and death after day 5 of ICU stay is shown in Table 4 and Fig. 3.

Discussion

All 47 patients (100%) who admitted surgical ICU had serum selenium level lower than average level of healthy Thai on day 1 and day 3 of ICU stay while 44 out of 47 patients (93.6%) had serum selenium level lower than average level of healthy Thai on day 5. Mean

Table 1. Demographic and clinical characteristics of patients (n = 47)

Variables (n = 47)	n (%)
Gender, n (%)	
Male	31 (65.96)
Female	16 (34.04)
Age (years), mean \pm SD	61.26 (19.65)
Underlying disease, n (%)	
Yes	33 (70.21)
No	14 (29.79)
Diagnosis, n (%)	
Trauma	16 (34.04)
Hollow viscus organ perforation or gangrene	10 (21.28)
Vascular disease	7 (14.89)
Malignancy	6 (12.77)
Other	8 (17.02)
Indication ICU admission, n (%)	
Electure post-operative	5 (10.64)
Emergency post-operative	23 (48.94)
Respiratory failure	9 (19.15)
Sepsis	10 (21.28)
SOFA score, mean \pm SD	5.29 (3.33)
Use vasoactive drug, n (%)	
Yes	17 (36.17)
No	30 (63.83)
Ventilator free at D5, n (%)	
Use ventilator at D5	20 (42.55)
Not use ventilator at D5	27 (57.45)
Nutrition support at D3, n (%)	
Yes	28 (59.57)
No	19 (40.43)
Nutrition support at D5, n (%)	
Yes	41 (87.23)
No	6 (12.77)
Total ICU study (day), median (range)	8 (5 to 60)
Death after day 5 of ICU stay, n (%)	
Non-death	38 (80.85)
Death	9 (19.15)
Selenium D1, mean \pm SD	61.78 (14.23)
<70 mg/L, n (%)	35 (74.47)
70 to 150 mg/L, n (%)	12 (25.53)
Selenium D3, mean \pm SD	63.46 (14.55)
<70 mg/L, n (%)	30 (63.83)
70 to 150 mg/L, n (%)	17 (36.17)
Selenium D5, mean \pm SD	67.98 (19.19)
<70 mg/L, n (%)	27 (57.45)
70 to 150 mg/L, n (%)	20 (42.55)

serum selenium level was lower than normal physiological range on all study day. This study confirmed previous finding that there is reduction in



Fig. 1 Overall serum selenium level of patients (n = 47).

the serum selenium level in critically ill patients⁽¹⁰⁻¹²⁾.

This study showed that there is no significant risk factor (such as gender, age, underlying disease, diagnosis, indication ICU admission, SOFA score, use of vasoactive drug, ventilation free on day 5 of ICU stay, and nutrition support on day 3 and day 5 of ICU stay) associated with the reduction in serum selenium level. The most likely explanation for the last finding was that the size of this study was too small and was not sensitive in detecting important risk factors.

Comparison of mean serum selenium level between day 1 to day 5 and day 3 to day 5 of ICU stay showed the serum selenium level increased significantly on day 5 of ICU stay. From REDOXs study, it is found that serum selenium level of antioxidant supplement group (include selenium supplement) increased significantly on day 4 and day 7 of ICU stay compared with no antioxidant supplement group ($p < 0.001$), although median serum selenium level remained increased on day 4 and day 7 of ICU stay in both group⁽¹³⁾. All patients in this study were not receiving selenium supplement. Six of 47 patients (12.77%) were without nutrition support before day 5 of ICU stay and five of these six patients (83.33%) had an increase in serum selenium level on day 5 of ICU stay. The cause of the increase remains unclear.

Severe illness and Systemic Inflammatory Response Syndrome (SIRS) associated with redistribution of trace element from circulation to the tissue involved in protein synthesis and immune cell proliferation could cause a decrease in serum selenium level in ICU stay⁽¹⁴⁾. Redistribution of selenium from tissue to circulation could occur after clinical SIRS has improved.

Comparison of mean serum selenium level between non-death and death after day 5 of ICU stay showed that death group in ICU was associated with significant low serum selenium level on day 3 of ICU

Table 2. Effects of potential risk factor on serum selenium level below normal range (<70 µg/L and 70 to 150 µg/L)

Variables	Selenium D1		p-value	Selenium D3		p-value	Selenium D5		p-value
	<70 mg/L	70 to 150 mg/L		<70 mg/L	70 to 150 mg/L		<70 mg/L	70 to 150 mg/L	
Gender, n (%)									
Male	25 (71.43)	6 (50.00)	0.176	21 (70.00)	10 (58.82)	0.437	18 (66.67)	13 (65.00)	0.905
Female	10 (28.57)	6 (50.00)		9 (30.00)	7 (41.18)		9 (33.33)	7 (35.00)	
Age (years), mean ± SD	62.7 (18.8)	56.8 (21.9)	0.372	64.5 (18.1)	55.6 (21.5)	0.138	65.9 (18.0)	54.9 (20.4)	0.055
Underlying disease, n (%)									
Yes	26 (74.29)	7 (58.33)	0.297	22 (73.33)	11 (64.71)	0.534	20 (74.07)	13 (65.00)	0.501
No	9 (25.71)	5 (41.67)		8 (26.67)	6 (35.29)		7 (25.93)	7 (35.00)	
Diagnosis, n (%)									
Trauma	9 (25.71)	7 (58.33)	0.113	8 (26.67)	8 (47.06)	0.086	9 (33.33)	7 (35.00)	0.465
Hollow viscus organ perforation or gangreen	10 (28.57)	0		9 (30.00)	1 (5.88)		8 (29.63)	2 (10.00)	
Vascular disease	6 (17.14)	1 (8.33)		6 (20.00)	1 (5.88)		4 (14.81)	3 (15.00)	
Malignancy	4 (11.43)	2 (16.67)		4 (13.33)	2 (11.76)		2 (7.41)	4 (20.00)	
Other	6 (17.14)	2 (16.67)		3 (10.00)	5 (29.41)		4 (14.81)	4 (20.00)	
Indication ICU admission, n (%)									
Electure post-operative	4 (11.43)	1 (8.33)	0.600	3 (10.00)	2 (11.76)	0.052	2 (7.41)	3 (15.00)	0.056
Emergency post-op	18 (51.43)	5 (41.67)		19 (63.33)	4 (23.53)		15 (55.56)	8 (40.00)	
Respiratory failure	5 (14.29)	4 (33.33)		3 (10.00)	6 (35.29)		2 (7.41)	7 (35.00)	
Sepsis	8 (22.86)	2 (16.67)		5 (16.67)	5 (29.41)		8 (29.63)	2 (10.00)	
SORA score, mean ± SD	5.03 (3.38)	6.08 (3.17)	0.349	5.5 (3.41)	4.94 (3.25)	0.586	5.78 (3.27)	4.65 (3.37)	0.255
Use vasoactive drug, n (%)									
Yes	12 (34.29)	5 (41.67)	0.646	13 (43.33)	4 (23.53)	0.218	13 (48.15)	4 (20.00)	0.067
No	23 (65.71)	7 (58.33)		17 (56.67)	13 (76.47)		14 (51.85)	16 (80.00)	
Ventilator free at D5, n (%)									
Use ventilator at D5	16 (45.71)	4 (33.33)	0.517	12 (40.00)	8 (47.06)	0.638	10 (37.04)	10 (50.00)	0.374
Not use ventilator at D5	19 (54.29)	8 (66.67)		18 (60.00)	9 (52.94)		17 (62.96)	10 (50.00)	
Nutrition support at D3, n (%)									
Yes	21 (60.00)	7 (58.33)	0.919	18 (60.00)	10 (58.82)	0.937	16 (59.26)	12 (60.00)	0.959
No	14 (40.00)	5 (41.67)		12 (40.00)	7 (41.18)		11 (40.74)	8 (40.00)	
Nutrition support at D5, n (%)									
Yes	30 (85.71)	11 (91.67)	0.999	27 (90.00)	14 (82.35)	0.653	24 (88.89)	17 (85.00)	0.999
No	5 (14.29)	1 (8.33)		3 (10.00)	3 (17.65)		3 (11.11)	3 (15.00)	
Total ICU study (day), median (range)	7 (5 to 60)	9 (5 to 22)	0.546	9 (5 to 60)	8 (5 to 28)	0.876	9 (5 to 60)	7 (5 to 23)	0.232
Death after day 5 of ICU stay, n (%)									
Non-death	28 (80.00)	10 (83.33)	0.999	22 (73.33)	16 (94.12)	0.127	20 (74.07)	18 (90.00)	0.266
Death	7 (20.00)	2 (16.67)		8 (26.67)	1 (5.88)		7 (25.93)	2 (10.00)	
Selenium (µg/L), mean ± SD	55.6 (10.1)	79.7 (7.8)	0.000	54.6 (9.3)	79.0 (6.79)	0.000	55.1 (9.6)	85.4 (14.3)	0.000

stay. Gil hardy et al⁽¹⁴⁾ found the serum selenium level is a relatively good predicting value for ICU mortality and the serum selenium value of 60 µd/L is the cut off for the evaluation and prediction of MODS. This study showed nine of 47 patients (19.15%) died after day 5 of ICU stay and that five of nine death (55.56%) had serum selenium levels were below 60 µd/L on all study days. Thirteen of 47 patients (27.66%) had serum selenium level below 60 µd/L on all study day and five of 13 patients (38.46%) died after day 5 of ICU stay.

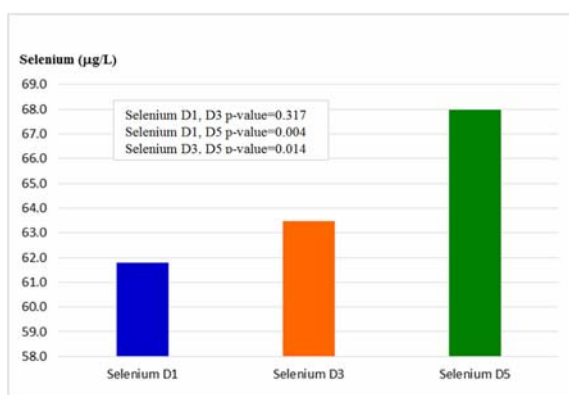


Fig. 2 Mean serum selenium level on days of study.

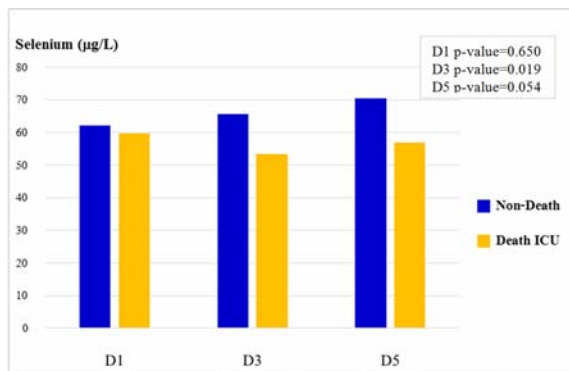


Fig. 3 Mean serum selenium level of non-death and death group after day 5 of ICU stay.

Table 4. Comparison mean serum selenium level between non-death and death after day 5 of ICU stay

Selenium	Non-death	Death ICU	95% CI	p-value
D1, mean (SD)	62.2 (13.1)	59.8 (19.1)	57.61 to 65.96	0.650
D3, mean (SD)	65.8 (13.3)	53.4 (15.9)	59.19 to 67.73	0.019
D5, mean (SD)	70.6 (18.9)	57.0 (17.2)	62.35 to 73.62	0.054

Limitations of this study include small sample size to show statistical significance of risk factors associated with the reduction in serum selenium level. However, this study may be helpful for further investigation on selenium supplement in patients admitted to surgical ICU.

Conclusion

Almost all patients admitted to surgical ICU had a serum selenium level below average level of healthy population and more than 50% was below normal range on all day of study. Mean serum selenium level significantly increased on day 3 and day 5 of ICU stay. Patients who died after day 5 of ICU stay had significant low level of selenium on day3 of ICU stay and tend to be lower on day 5 of ICU stay compare with patients who survived after day 5 of ICU stay.

What is already known on this topic?

Many previous studies found most critically ill patients with SIRS show serum selenium deficiency or distribution. Serum selenium level can be used as a predictor of outcome.

What this study adds?

This is a first study of serum selenium level in Thai surgical ICU population. This study confirmed previous finding of the reduction in serum selenium. The mean serum selenium level in Thai surgical ICU patients was different from other countries.

Table 3. Comparison mean serum selenium level between days of study

Selenium	Mean (±SD)	95% CI	p-value
D1	61.8 (14.2)	-1.66 to 5.01	0.317
D3	63.5 (14.5)	2.06 to 10.33	0.004
D5	67.9 (19.2)	0.95 to 8.08	0.014
D3	63.5 (14.5)		
D5	67.9 (19.2)		

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Potential conflicts of interest

None.

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การศึกษาระดับซีลีเนียมในซีรัมของผู้ป่วยในหอผู้ป่วยหนักทางศัลยกรรม

พงศศิษฎ์ สิงห์ทัศน์, อารีพร สังฆกุล, ปรีดา สัมฤทธิ์ประดิษฐ์, ธาวัน ธรรมพงษา, ชลลดา ครุฑศรี, ภาณุวัฒน์ เลิศสิทธิชัย

ภูมิหลัง: มีการทดลองทางคลินิกหลายการทดลองเพื่อศึกษาถึงประโยชน์ของการให้ซีลีเนียมในผู้ป่วยวิกฤต อย่างไรก็ตามระดับซีลีเนียมในซีรัมของประชากรมีความแตกต่างกันในแต่ละประเทศ ผู้เขียนจึงทำการศึกษากาการเปลี่ยนแปลงของระดับซีลีเนียมในซีรัมของผู้ป่วยวิกฤตทางศัลยกรรมในประเทศไทย

วัตถุประสงค์: เพื่อศึกษาระดับซีลีเนียมในซีรัมของผู้ป่วยที่เข้ามานอนรักษาตัวในหอผู้ป่วยหนักศัลยกรรม และเปรียบเทียบระดับการเปลี่ยนแปลงหลังจากเข้ามานอนรักษาตัวในหอผู้ป่วย

วัสดุและวิธีการ: ขอความยินยอมผู้ป่วยที่เข้ามานอนรักษาตัวในหอผู้ป่วยหนักศัลยกรรมในช่วงระหว่าง เดือนพฤศจิกายน พ.ศ. 2555 ถึง เดือนมกราคม พ.ศ. 2556 ผู้ป่วยจะได้รับการเก็บเลือดปริมาณ 5 มิลลิลิตร ในวันที่หนึ่ง, วันที่สามและวันที่ห้าของการเข้ามานอนในหอผู้ป่วยหนักทางศัลยกรรม และนำเลือดที่ได้ไปวิเคราะห์หาปริมาณซีลีเนียมในซีรัม มีการเก็บข้อมูลพื้นฐานรวมถึง อายุ, เพศ, การวินิจฉัยโรค, โรคร่วมที่พบ, ข้อบ่งชี้ของการเข้าพักรักษาตัวในหอผู้ป่วยหนักศัลยกรรม, คะแนนความรุนแรงของอวัยวะล้มเหลว, จำนวนวันของการใช้เครื่องช่วยหายใจ, การให้สารอาหาร, ระยะเวลาของการเข้าพักรักษาตัวในหอผู้ป่วยหนักศัลยกรรม และการเสียชีวิตภายหลังจากวันที่ห้าของการเข้ามานอนในหอผู้ป่วยหนักทางศัลยกรรม

ผลการศึกษา: พบว่าผู้ป่วยทุกคนที่เข้าร่วมการวิจัย 47 คน (100%) มีระดับซีลีเนียมในซีรัมที่วันแรกและวันที่สาม ต่ำกว่าระดับเฉลี่ยของประชากรไทยทั่วไป (106.95 mg/L) และมีผู้ป่วย 43 คนใน 47 คน (93.6%) มีระดับซีลีเนียมในซีรัมที่วันที่ห้าของการเข้ามานอนในหอผู้ป่วยหนักทางศัลยกรรม ต่ำกว่าระดับเฉลี่ยของประชากรไทยทั่วไป แต่พบว่าระดับเฉลี่ยของซีลีเนียมในซีรัมของผู้ป่วยที่วันที่ห้า (67.9 mg/L) ของการเข้ามานอนในหอผู้ป่วยหนักทางศัลยกรรมมีระดับเพิ่มขึ้นจากวันที่หนึ่ง (61.8 mg/L) และวันที่สาม (63.5 mg/L) อย่างมีนัยสำคัญและไม่พบปัจจัยที่มีนัยสำคัญต่อการเปลี่ยนแปลงของระดับซีลีเนียมในซีรัม

สรุป: ผู้ป่วยเกือบทั้งหมดที่เข้ามานอนในหอผู้ป่วยหนักทางศัลยกรรมพบว่าระดับซีลีเนียมในซีรัมต่ำกว่าค่าเฉลี่ยของประชากรไทยทั่วไปและมากกว่า 50% ต่ำกว่าค่าปกติในทุกวันที่ทำการศึกษา
