

## The Effect of *Ophiocephalus striatus* Extract on Quantitative Measurement of Biceps Brachii and Rectus Femoris in Patients with Mechanical Ventilation

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### Abstract

#### Background

A freshwater fish *Ophiocephalus striatus* (OS) or known locally to Indonesian as *haruan*, has potentials to retain muscle mass of critically ill patients following its high content of amino acids, fatty acids, minerals, and vitamins. This study was conducted to investigate the effect of OS on quantitative measurements of biceps brachii and rectus femoris in patients with mechanical ventilation.

#### Methods

This was a double-blinded randomized controlled trial at tertiary hospital between July-October 2019. The study included patients aged 18-65 years old with mechanical ventilation whereas patients with chronic kidney disease, paraparesis, or neuromuscular disorders were excluded. Forty-two patients were divided into extract group (n=19) who received 15 g of OS extract daily and control group (n=23) who received none. Quantitative measurements of both muscles were determined by measuring cross sectional area (CSA) using ultrasonography by one radiologist. Data were collected at 1<sup>st</sup> and 7<sup>th</sup> day, while the intervention was administered in-between. Independent sample T-test, Mann-Whitney test, and multivariate study using general linear model (GLM) were used for statistical analysis.

#### Results

The changes of CSA on biceps brachii and rectus femoris muscles from before to after intervention between extract group compared to control group were  $5,30 \pm 2,41 \text{ cm}^2$  to  $6,09 \pm 1,81 \text{ cm}^2$  vs  $5,16 \pm 2,50 \text{ cm}^2$  to  $4,16 \pm 1,94 \text{ cm}^2$  ( $p=0.002$ ) and  $2,80 (1,10 - 5,90) \text{ cm}^2$  to  $3,30 (1,13 - 8,18) \text{ cm}^2$  vs  $3,11 (1,08 - 9,06) \text{ cm}^2$  to  $2,21 (0,65 - 7,27) \text{ cm}^2$  ( $p=0.230$ ), respectively. Multivariate analysis showed significant differences between extract and control group for both muscles with p value of  $<0.001$  and  $0.001$  respectively.

#### Conclusion

Supplementation of *Ophiocephalus striatus* extract was associated with a significant increase of biceps brachii and rectus femoris CSA in patients with mechanical ventilation.

**Keywords:** *Ophiocephalus striatus*, ultrasonography, cross sectional area, biceps brachii muscle, rectus femoris

muscle

## Introduction

The loss of muscle mass and strength is a common problem in critically ill patients. This problem occurs within the first 24 hours since the patient is administered to Intensive Care Unit (ICU) and few hours after the use of mechanical ventilation.<sup>1,2</sup> It is caused by uncontrolled rate of catabolism process which results in protein synthesis and breakdown imbalance leading to the change of muscle mass.<sup>3,4</sup> Body requires adequate intake of protein to balance the catabolism and to stimulate more protein synthesis in order to preserve the muscle mass.<sup>5,6</sup>

A freshwater fish *Ophiocephalus striatus* (OS) or snakehead fish can be a source of high protein oral nutrition. OS, known locally to Indonesian as *haruan*, has high content of amino acids, fatty acids, minerals, and vitamins. It is abundantly available natural resource that has various beneficial features, such as high protein, antioxidant and anti-inflammatory function.<sup>7</sup> Therefore, OS carries potentials to retain muscle mass of critically ill patients following its nutrient contents and benefits. The change of muscle mass can be assessed by measuring quantitative values of the muscles. These values can be assessed by determining cross sectional area using ultrasonography examination.<sup>1,8,9</sup>

This study was conducted to investigate the effect of OS on quantitative measurements of biceps brachii and rectus femoris in patients with mechanical ventilation.

## Methods

This study was conducted in July to October 2019 after obtaining clearance from Ethics Committee of Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo Hospital. This was a double-blinded randomized controlled trial with consecutive sampling method. The study included patients aged 18-65 years old with mechanical ventilation in ICU Cipto Mangunkusumo Hospital whereas patients with chronic kidney disease, paraparesis, or neuromuscular disorders were excluded. Thirty patients were divided into extract group (n=19) and control group (n=23). Baseline characteristic data were collected. The quantitative measurements of biceps brachii and rectus femoris were conducted by performing ultrasonography examination for CSA of biceps brachii and rectus femoris muscles on 1<sup>st</sup> and 7<sup>th</sup> day by one radiologist. Subjects in extract group received 15 g of OS extract (3 sachets) which was divided into 3 administration per day on 2<sup>nd</sup> to 6<sup>th</sup> day. To administer the OS extract, each sachet was diluted with 50 mL of water. The dilution was then given enterally for 15 minutes using nasogastric tube which was priorly applied to patients with mechanical ventilation. Subjects in control group did not receive the extract. Both groups received standard therapy according to the ICU protocol. Their nutritional intake was managed by clinical nutritionists based on the patients requirements. Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences, version 23.0 SPSS Inc,

Chicago, III, USA) software. Before and after treatment comparison was analyzed with independent sample T-test and Mann-Whitney test, as well as the multivariate analysis using general linear model (GLM) while the significance level was decided at p-value <0.05.

**Results**

This study involved 42 subjects divided into 2 groups, extract and control group. Baseline characteristic data for the subjects are presented in table 1. The CSA of biceps brachii and rectus femoris muscles are shown as mean values or median depending on the normality of the data for each course of measurement for both extract and control group.

Table 1. Baseline characteristics data for both groups

Variable (s)	Group Extract (N=19)	Group Control (N=23)
Gender <sup>1</sup>		
Male	12 (63%)	12 (52%)
Female	7 (37%)	11 (48%)
Age (Years) <sup>2</sup>	43.26 ± 13.03	45.61 ± 11.40
Body weight (kg) <sup>2,3</sup>	60,92 ± 13,59	64,60 (37 – 148)
Body height (cm) <sup>2</sup>	160,94 ± 6,05	160,39 ± 8,11
Body Mass Index (BMI) (kg/m <sup>2</sup> ) <sup>2,3</sup>	23,51 ± 4,29	24,5 (15,2 – 60,8)
Total caloric intake (kcal) <sup>2</sup>	6002,06 ± 981,99	6148,55 ± 1924,49
Total protein intake (gram) <sup>2</sup>	318,13 ± 53,48	274,14 ± 79,91
Duration of ventilator		
1-3 days	6 (31%)	6 (26%)
> 4 days	13 (69%)	17 (74%)
Diagnosis <sup>1</sup>		
Surgical	12 (63%)	16 (69%)
Non-surgical	7 (37%)	7 (31%)

<sup>1</sup>Percentages n (%)

<sup>2</sup>Mean ± Standard Deviation.

<sup>3</sup>Median (minimum – maximum)

Figure 1 presents the data of biceps brachii CSA in boxplots for both groups. The CSA measurement was conducted on 1<sup>st</sup> day (Time 1) and 7<sup>th</sup> day (Time 2).

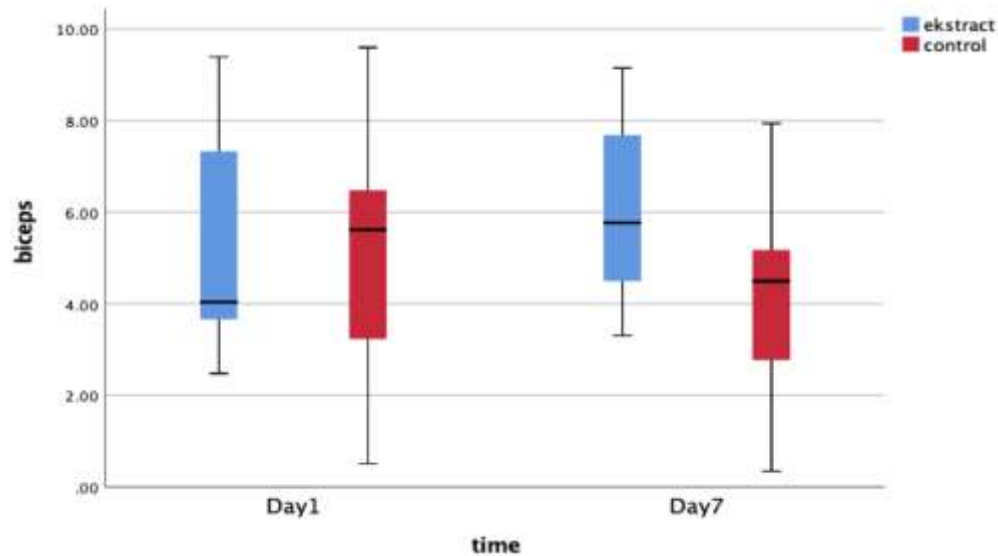


Figure 1. Boxplots for biceps brachii CSA

Figure 2 presents the data of rectus femoris CSA in boxplots for both groups. The CSA measurement was conducted on 1<sup>st</sup> day (Time 1) and 7<sup>th</sup> day (Time 2).

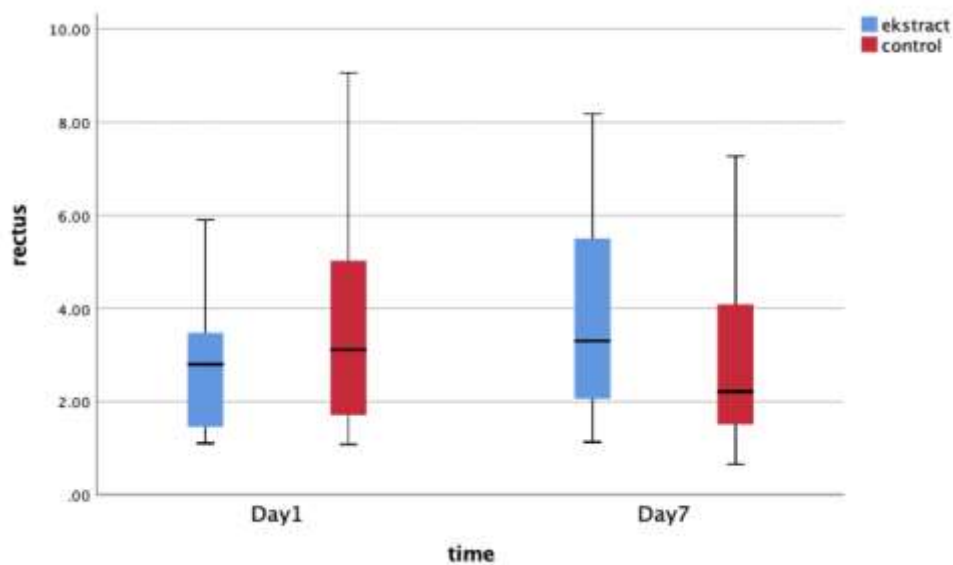


Figure 2. Boxplots for rectus femoris CSA

This study compared mean values for CSA of biceps brachii and rectus femoris muscles. After the analysis, extract group resulted in the increase of CSA for both muscles compared to the control group. The mean and median values for biceps brachii and rectus femoris CSA over two courses of measurements are presented in table 2.

Table 2. CSA mean values for both groups on 1<sup>st</sup> and 7<sup>th</sup> day of measurement

Variable	Extract	Control	P-value
<b>Biceps Brachii CSA (cm<sup>2</sup>)</b>			
Pre-Treatment (1 <sup>st</sup> day) <sup>a</sup>	5.30 ± 2,41	5.16 ± 2.50	0.856 <sup>c</sup>
Post-Treatment (7 <sup>th</sup> day) <sup>a</sup>	6.09 ± 1,81	4.16 ± 1.94	0,002 <sup>c</sup>
<b>Rectus Femoris CSA (cm<sup>2</sup>)</b>			
Pre-Treatment (1 <sup>st</sup> day) <sup>b</sup>	2.80 (1.10 – 5.90)	3.11 (1.08 – 9.06)	0.245 <sup>d</sup>
Post-Treatment (7 <sup>th</sup> day) <sup>b</sup>	3.30 (1.13 – 8.18)	2.21 (0.65 – 7.27)	0.230 <sup>d</sup>

<sup>a</sup>Mean ± Standard Deviation.

<sup>b</sup>Median (minimum – maximum)

<sup>c</sup>Independent Sample T-Test

<sup>d</sup>Mann-Whitney Test

Multivariate analysis was conducted for all variables using general linear model (GLM). The GLM analysis showed significant difference between extract and control group for both CSA of the biceps brachii and rectus femoris. The p values for GLM analysis were <0.001 and 0.001 for biceps brachii and rectus femoris respectively. The summary of the mean value for each courses of measurement can be seen in figure 3 and figure 4.

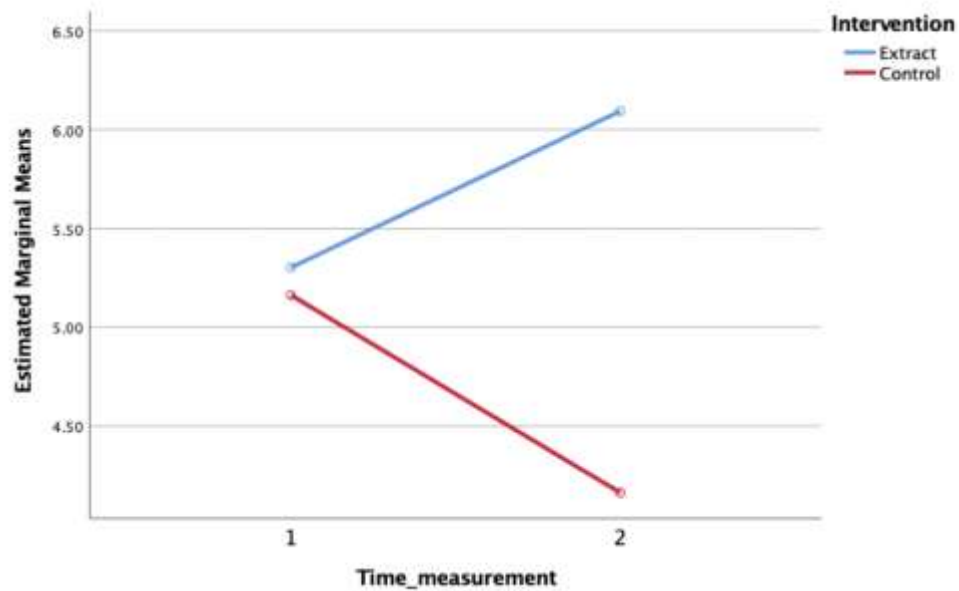


Figure 3. The trend analysis for biceps brachii CSA between two groups

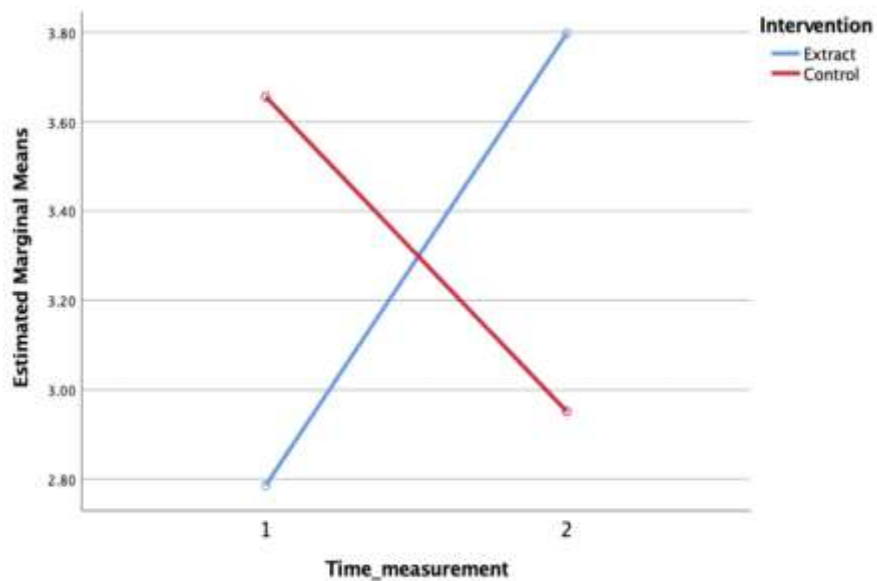


Figure 4. The trend analysis for rectus femoris CSA between two groups

## Discussion

This study was conducted to evaluate the effect of OS extract supplementation as a source of high

protein. To our knowledge, this is a pilot study that explores the effect of OS extract on CSA in critically ill patients with mechanical ventilation. Critically ill condition is defined as a life-threatening condition in which the patient is at risk of one or multiple organ failure. This condition requires intensive care for advanced therapy in ICU. Critically ill patients in ICU varies from conditions like post-surgery patients, patients with metabolic disturbances, sepsis patients, burn injury patients, severe traumatic patients, and others.<sup>10,11</sup> Given the variety of these conditions, this study used mechanical ventilation as the tool homogenize the critically ill patients in ICU. Subjects in both groups were quite comparable since their baseline characteristics were not really different in some measurements. Though the body mass index, calorie intake, and protein intake in each group was quite different, it would not really affect the comparison in this study because calorie and protein intake for each subject was still in their daily requirement based on dietitian's recommendation.

Muscle mass degradation can be affected by various aspects. Conditions like inactivity, aging process, nutritional intake, and certain diseases can directly affect the muscle mass. Therefore, this study used mechanical ventilation as the limitation of mobility. Patients with mechanical ventilation will be "inactive" due to the administration of sedative agents and limited movements. For aging process, this study limited the inclusion criteria to the maximum of 65 years old. This study also excluded certain diseases which could directly affect muscle mass, such as myasthenia gravis, Guillain-Barre syndrome, and paraparesis.<sup>12</sup> The muscle can be assessed both quantitative and qualitatively. Quantitative approach defines muscle mass using parameters, such as anteroposterior diameter, thickness, and cross-sectional area (CSA). Qualitative approach defines muscular structures and presents them in terms of echogenicity.<sup>1,13</sup> Biceps brachii and rectus femoris can be used to represent the upper extremity and lower extremity because these muscles are easier to be examined with ultrasonography than other muscles in similar area.

This study recorded the CSA of both biceps brachii and rectus femoris for extract and control group on 1<sup>st</sup> day (before the treatment) and 7<sup>th</sup> day (after the treatment). First seven days in ICU is an acute phase where 1-3 days refer to an early acute phase and 4-7 days as the late acute phase.<sup>14</sup> This study evaluated the effect of OS on muscles CSA on 1<sup>st</sup> dan 7<sup>th</sup> day to represent the acute phase of critically ill patients. For biceps brachii, the mean values on 1<sup>st</sup> day of measurement for extract and control group were  $5.30 \pm 2.41$  and  $5.16 \pm 2.50$ , respectively. On 7<sup>th</sup> day of measurement the CSA of both groups changed to  $6.09 \pm 1.81$  for extract group and  $4.16 \pm 1.94$  for control group. This showed that there was an increase of CSA in extract group while the control

group decreased. This difference in changes was then analyzed using multivariate analysis for significance and the result was significant ( $p < 0.001$ ). The similar result was shown in rectus femoris CSA measurements. The median values for rectus femoris CSA on 1<sup>st</sup> day of measurement for extract and control group were 2.80 (1.10 – 5.90) and 3.11 (1.08 – 9.06), respectively. The mean values for CSA of rectus femoris were then changed to 3.30 (1.13 – 8.18) for extract group and 2.21 (0.65 – 7.27) for control group, and the multivariate analysis also showed a significant difference between the two groups ( $p = 0.001$ ). To conclude, those results showed an increase of muscles in extract group while the decrease occurred in control group.

The administration of high protein intake in acute phase of critically ill patients remains a controversy among clinicians. Some clinicians are in favor of high protein intake due to the fact that it can increase muscle protein synthesis, can be easily absorbed, and can be safely administered intravenously. Some clinicians are against the idea of high protein delivery on acute phase as it induces the release of glucagon. Release of glucagon can enhance the oxidation of amino acids and can increase ureagenesis.<sup>6</sup> Weijjs *et al*, studied high protein delivery to ICU patients on its effect on 90-day mortality. In this study, it has been reported that the 90-day post-discharge mortality rate was 17% (95% CI: 6-26) lower for each 1 g/kg increase in daily protein delivery (OR = 0.83 (95% CI 0.74-0.94;  $p = 0.002$ )).<sup>15</sup> In concordance to the previous study, Sundström Rehal *et al* reported that the administration of amino acid infusion resulted in improved net protein balance in critically ill patients over time, from  $-1.6 \pm 7.9$   $\mu\text{mol phe/kg/h}$  at 0 h to  $6.0 \pm 8.8$  at 3 h and  $7.5 \pm 5.1$  at 24 h ( $p = 0.0016$ ). This protein balance can enhance more synthesis of protein and preserve the muscle mass.<sup>16</sup> However, the risk-to-benefit of high protein delivery during acute phase for critically ill patients is still largely unknown. There are currently numerous ongoing studies in all over the world to evaluate the effect of high protein delivery. Some aspects have been investigated while others are still unexplored.<sup>6</sup> Despite this controversy, this study was able to show that the supplementation of OS extract in acute phase as a source of high protein is significantly beneficial to the increase of muscle mass, i.e. CSA of biceps brachii and rectus femoris.

This study had some limitations. One of the limitations was related to the measurement made in this study. Though the muscle mass can be measured quantitatively and qualitatively, this study only measured the changes quantitatively. This study focused on CSA of biceps brachii and rectus femoris muscles because those muscles represented the upper and lower extremities. This study did not define the muscle echogenicity as a qualitative measurement approach. Further research in



measuring muscle echogenicity might be important since the OS extract administration was aimed to preserve the muscle mass, thus the myofibrils depletion could be detected as well.

### Conclusion

This study showed that *Ophiocephalus striatus* extract was able to significantly increase CSA of biceps brachii and rectus femoris in critically ill patients with mechanical ventilation, hence can be utilized as nutritional supplementation in ICU.

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