The Effect of *Ophiocephalus striatus* Extract on the Levels of IGF-1 and Albumin in Elderly Patients with Hypoalbuminemia

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ABSTRAK

Pendahuluan: *Ophiocephalus striatus berpotensi meningkatkan kadar IGF-1 dan albumin karena mengandung asam amino, asam lemak, vitamin, dan mineral. Belum ada penelitian menggunakan ekstrak Ophiocephalus striatus khusus pada pasien usia lanjut dengan hipoalbuminemia. Penelitian ini ditujukan untuk mengetahui pengaruh pemberian ekstrak Ophiocephalus striatus terhadap kadar IGF-1 dan albumin pasien usia lanjut dengan hipoalbuminemia.* ***Metode:*** *uji klinis acak tersamar ganda dilakukan pada pasien rawat inap yang telah melewati kondisi akut dan dibolehkan pulang, berusia ≥ 60 tahun dengan skor Mini Nutritional Assessment ≤23,5 dan kadar albumin <3,5 g/dL. Dilakukan randomisasi untuk mendapatkan ekstrak Ophiocephalus striatus 10 gram sehari atau plasebo selama 14 hari. Kadar IGF-1 dan albumin diperiksa sebelum dan sesudah perlakuan. Pengaruh pemberian ekstrak OS dianalisis menggunakan uji t tidak berpasangan atau uji Mann-Whitney.* ***Hasil:*** *randomisasi dilakukan terhadap 109 subjek, sebanyak 90 subjek menyelesaikan penelitian hingga 14 hari (masing-masing kelompok 45 orang). Median usia 69 (64;75) tahun dengan perbandingan laki-laki dan perempuan 2 : 3. Didapatkan perubahan kadar IGF-1 dan albumin sesudah perlakuan pada kelompok ekstrak OS vs placebo berturut-turut 14,7 (0,30;31,5) ng/mL vs 1,0 (-6;13,15) ng/mL (p=0,002) dan 0,5 (0,15;0,70) g/dL vs 0,10 (0,0;0,50) g/dL (p=0,003).* ***Kesimpulan:*** *ekstrak Ophiocephalus striatus dapat meningkatkan kadar IGF-1 dan albumin pasien usia lanjut dengan hipoalbuminemia.*

Kata kunci: *Ophiocephalus striatus, IGF-1, albumin, usia lanjut.*

ABSTRACT

Background: *a freshwater fish Ophiocephalus striatus or known locally to Indonesian as* haruan,*can potentially increases IGF-1 and albumin levels in elderly patients with hypoalbuminemia due to the contents of amino acids, fatty acids, vitamins, and minerals. This study was conducted to investigate the effect of Ophiocephalus striatus extract on the level of IGF-1 and albumin in elderly patients with hypoalbuminemia.* ***Methods:*** *the study is a double-blind randomized controlled trial involving malnourished elderly inpatients (≥60 years old) recovering from acute condition before hospital discharge, with Mini Nutritional Assessment score ≤23.5 and albumin level <3.5 g/dL. A total of 109 subjects were randomly divided into two groups: one group received 10 g Ophiocephalus striatus extract per day for 14 days and another group received placebo. Albumin and IGF-1 levels were obtained before and after intervention.* ***Results:*** *ninety subjects completed the study (extract group=45 subjects; placebo group =45 subjects) for 14 days. The median of age were 69 (64;75)*

years and the male to female ratio were 2 : 3. The changes of IGF-1 and albumin levels from before to after intervention between extract group compared to placebo group were 14.7 (0.30;31.5) ng/mL vs 1.0 (-6;13.15) ng/mL (p=0.002) and 0.5 (0.15;0.70) g/dL vs 0.10 (0.0;0.50) g/dL (p=0.003), respectively. There were significant differences in the improvement of IGF-1 and albumin levels between extract and placebo group. ***Conclusion:*** *supplementation of Ophiocephalus striatus extract was associated with a significant increase in IGF-1 and albumin levels in elderly patients with hypoalbuminemia.*

Keywords: *Ophiocephalus striatus, IGF-1, albumin, elderly.*

INTRODUCTION

Hypoalbuminemia is a problem commonly found in elderly, especially hospitalized elderly patients. It is a condition of abnormally low blood albumin level, which is a major improtant protein in human body. The effect of hypoalbuminemia can be as obvious as a generalized edema. However, its consequence can also be as subtle to the eye as altering the pharmacodynamics of highly protein bound rugs, which gives rise to higher free drug concentration and complicates patient management. In fact, it is known that hypoalbuminemia is associated with important outcomes such as poor functional status, longer duration of hospitalization, as well as higher morbidity and mortality.[1] In elderly, the presence of hypoalbuminemia is a prognostic indicator for complications and mortality. It is associated with worse recovery following acute illness.

Hypoalbuminemia may result from existence of liver disease or kidney disease in patients. However, besides those disease, serum albumin levels can also be influenced by other conditions such as malnutrition and inflammation.[2] Malnutrition is another major problem among hospitalized elderly, as 20-65% of hospitalized elderly suffers from malnutrition.[3] Hospitalized elderly are at risk of malnutrition due to several reason such as dietary restriction and catabolic condition related to their diseases.[4] Albumin is indeed often regarded as a biomarker for malnutrition and serum albumin levels is usually examined as a part of diagnostic test for malnutrition, although other possible causes must never be disregarded.

Another biochemical marker of malnutrition in elderly is insulin-like growth factor-1 (IGF-1). IGF-1 is an anabolic hormone that plays an active role in the maintenance of muscle mass and strength, protection of oxidative stress and prevention of apoptosis.[5] Besides being associated positively with energy and protein intake, it is also negatively associated with oxidative stress and inflammatory markers. It is an ideal cross-road of hormonal milieu, inflammation and nutritional status.

The treatment of hypoalbuminemia is imperative in managing elderly patients comprehensively. There are several alternatives in managing hypoalbuminemia, one of them is giving high protein nutrition orally as well as parenteral albumin administration. *Ophiocephalus stratius* (OS) or snakehead fish can be a source of high protein oral nutrition. OS, known locally as *haruan*, is a carnivorous freshwater fish indigenous to Indonesia and other tropical-subtropical countries which contains high level of amino acids, fatty acids, minerals, and vitamins, hence its various benefits such as source of high protein intake, antioxidant and anti-inflammatory function.[6,7] OS is believed to promote wound healing, besides alleviating post-operative pain and discomfort.[8] OS extract contains high amino acids content, thus may serve as a source of protein in the synthesis of albumin and may influence IGF-1 positively. In fact, protein supplementation is also found to increase IGF-1 protein in several studies.[9-12] The effect of adjunctive supplementation of OS extract on malnourished hospitalized elderly patients has never been studied. This double-blind, randomized, placebo-controlled study was conducted to assess the effect of OS supplementation on IGF-1 and albumin level in malnourished elderly patients.

METHODS

The study is a double-blind, randomized, controlled trial, which compare the effect of *Ophiocephalus striatus* extract versus placebo.

The study was conducted in malnourished elderly inpatients (aged ≥60 years old) with bypoalbuminemia, nearing their discharged from Cipto mangunkusumo National Hospital, dr. M. Djamil Hospital and dr. Reksodiwiryo Hospital. Patients were recruited and followed up from 17th October 2016 to 20th January 2017.

Study Population

Inclusion criteria were elderly patients aged 60 years old or above, whose mini nutrition assessment score was ≤ 23.5 and albumin serum levels was <3.5 g/dL. The exclusion criteria were those with chronic liver failure, chronic kidney disease with GFR <30 ml/min without hemodialysis, nephrotic syndrome, malignancy, depression, history of hypersensitivity to *Ophiocephalus striatus*, as well as parenteral albumin during hospitalization, patients in acute condition, and those who decline to participate.

Data Collection Procedure

Freeze dried OS extract and placebo were prepared and made available in sachets. Extract group was given 10 g (2 sachets) Ophiocephalus striatus extract per day, while control group was given 10 g maltodextrin (2 sachets) per day for for 14 days. Subjects were randomized according to random table using blocks of six. An external party randomly assigned the group intervention (extract versus control), and kept it sealed until the study was completed. Neither subjects nor the researcher was aware of the allocation. Written informed consent was obtained from the subjects, and/or their next of kin before the study proceeded. The study protocol was approved by the local Ethical Committee.

Outcome Measures

IGF-1 and albumin serum levels were examined at baseline and after 14 days of intervention. Serum IGF-1 was measured by Elisa method and albumin was measured by bromocresol-green method.

Statistical Analysis

Statistical analysis was performed using SPSS 21. Continuous variables values were expressed by means and standard deviations (SD) or alternatively medians and interquartile range in case of non-normal distribution. For normally distributed data, statistical comparisons between the groups were made using the student's independent samples t-test and alternativelyby Mann-Whitney U test for variables with non-normal distribution.

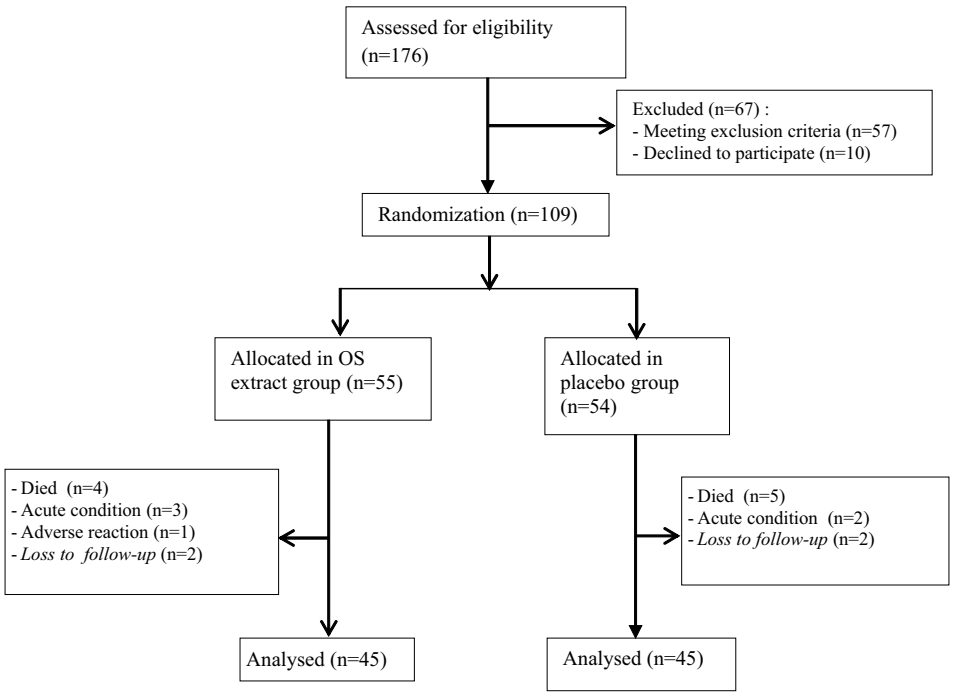

Figure 1. Flow chart of the study

Ethics Statement

Study protocol was performed in accordance with ICH-GCP standard procedure and approved by the Ethics Committee of the Faculty of Medicine, University of Indonesia (Number: 896/UN2.F1/ETIK/2016) on October 17th, 2016. Written informed consent was obtained from each subject and this trial was registered in clinicaltrials.gov (Registration number: NCT03065595).

RESULTS

One hundred and seventy-six elderly patients were screened for the study, of which 57 met the exclusion criteria, and 10 declined to participate. Finally, 109 subjects were randomly allocated to OS extract group (n=55) and placebo group as control (n=54). A total of ninety subjects with 45 subjects in each groups completed the study. (**Figure 1**) Baseline characteristics of the subjects are shown in **Table 1**. The compliance to intervention was 88,9% in both groups.

Most of the subjects were women (56.9%), aged 69 (64;77) years old. The functional status Barthel were mostly mild to moderately dependent (65 subjects) according to index of activity of daily living, while some were independent (7 subjects), and severe to totally dependent (37 subjects). Majority of subjects were malnourished (92.7%), and the rest of them

Table 1. Baseline characteristics of the subjects

Variables	OS Extract(n=55)	Placebo (n=54)
Age, y	68 (64;75)	70 (64;79)
Women/men, n/n	28/27	19/35
Mini Nutritional assessment	13 (9;16)	13 (9;14)
Commorbidities, n		
- Hypertension	25	25
- Diabetes mellitus	21	16
- Cerebrovascular disease	11	9
- Congestive heart failure	3	5
- Chronic kidney disease	4	5
Activities of daily living	14 (6;18)	12 (8;17)
Dietary intakes		
- Energy, kcal/d	1012.31 (377.03)	1021.33 (368.14)
- Protein, g/d	32.72 (13.72)	32.36 (13.48)
- Fat, g/d	25.34 (10.92)	23.86 (13.46)

Table 2. Insulin-like growth factor-1 and albumin levels at baseline and 14 days

Variables	Baseline values		After 14 days		P value
	OS Extract	Placebo	OS Extract	Placebo	
IGF-1 (ng/mL)	47.80 (41.05;60.60)	44.20 (35.20;65.35)	60.40 (47.30;80.15)	45.90 (34.15;72.55)	0.010
Albumin (g/dL)	3.11 (0,53)	3.09 (0,65)	3.59 (0,59)	3.25 (0,71)	0.016

Mean (SD) for normal distribution and median (interquartile range) for non-normal distribution.
OS=*Ophiocephalus striatus*, IGF-1=insulin-like growth factor 1.

Table 3. Changes from baseline in IGF-1 and albumin

Variables	OS Extract	Placebo	p value
IGF-1 (ng/mL)	14.70 (0.30;31.5)	1.00 (-6;13.15)	0.002
Albumin (g/dL)	0.50 (0.15;0.70)	0.10 (0.0;0.50)	0.003

Mann-Whitney U test; OS=*Ophiocephalus striatus*; IGF-1=insulin-like growth factor 1

were at risk of malnutrition (7.3%). Baseline intakes of energy, protein, and fat of both groups were comparable.

Table 2 presents the significant differences in IGF-1 and albumin levels between extract and placebo groups after 14-days intervention (p=0.010 and p=0.016, respectively).

The changes of IGF-1 and albumin levels from baseline value after intervention were shown in **Table 3**. There was a significant increase of those parameters in OS extract group.

DISCUSSION

Ophiocephalus extract was associated with the increase of IGF-1 and albumin levels in malnourished elderly patients. This current study found a significant increase in IGF-1 levels which was similar to the findings of several other studies by Bjorkman[9] Zhu,[10] Schurch,[11] and Chevalley[12] using milk-based protein.

OS contains amino acids, fatty acids, minerals, and vitamins, hence its various benefits include antioxidant and antiinflammatory, in addition to its role as protein source.[7] Paliliewu et al[6] study revealed the antiinflammatory effect of this extract. IGF-1 levels are inversely related to inflammatory markers and oxidative stress and positively regulated by specific nutrients such as selenium, zinc, magnesium, along with energy and protein.[5] Higher levels of IGF-1 reduced the inflammation in those patients, which may explain its correlation to the increase of albumin levels. Inflammation is one factor that influences albumin levels. The study proved that albumin synthesis from nutrition intake was not influenced by aging.[13]

The high albumin content of OS extract may serve as a good source of amino acid which is required for albumin synthesis. The improvement of albumin levels to the normal levels (≥3.5 g/dL) after 14 days of OS extract consumption will lead to better outcomes. Hypoalbuminemia is associated with poor functional status, higher morbidity, longer length of stay, and mortality.[1] Decreased albumin levels by 1 g/dL is associated with the increase of risk of mortality, morbidity, and length of stay by 137%, 89.5% and 71% respectively.[14]

The median of IGF-1 levels in this trial was lower than those reported in Bjorkamn[9] and Zhu[10] studies which was 106.3 (39.1) ng/mL and 11.9 mmol/L (±90.84 ng/mL), respectively. This finding was even lower than the reported findings of the centenarian in Japan, which was 64.4 (28.4) ng/mL.[15] The low levels of IGF-1 in this study may be due to the subjects' characteristics. While Zhu et al[10] assessed the IGF-1 levels of healthy women (70-80 y.o.), this current study investigated hospitalized subjects. There is a possibility that the levels of IGF-1 is still influenced by inflammation from the acute condition.[16]

Moreover, mean calorie and protein intakes in this trial (1017 kcal and 0.5 gram protein/kg body weight/day) were lower than subjects in Zhu's study.[8] The mean of calorie intake in that study was 7056 (SD 1552) kj and the protein was 76 (SD 18) gram per day.[10] It is actually recommended for malnourished patients to consume 1.2-1.5 gram protein/kg body weight/day.[17]

Bjorkman et al[9] reported the increase of IGF-1 levels by 19.5% after supplementation with 20 g whey protein per day for 6 months to subjects in nursing home. Zhu et al[10] study which investigated 2-years whey protein supplementation on healthy women aged 70-80 years old found that the increase of IGF-1 levels at first and second years were 7.3% and 8.0%, respectively.[10] Both previous studies observed smaller increase of IGF-1 levels compared to our study, which discovered 30.8% increase in IGF-1 levels. This may be owed to the fact that Bjorkman[9] and Zhu[10] investigated subjects who were not in acute condition whereas our subjects were inpatients in recovery from acute condition before hospital discharge. The lower levels of IGF-1 at baseline in our study compared to the findings of previous studies might be attributed to the inflammation in acute condition which may still influenced it.[16] Another reason is the high quality protein in OS and the contents of minerals, vitamins, and fatty acids.

IGF-1 is influenced by several factors, such as nutrition intake, inflammation, and oxidative stress. Paliliewu et al[6] reported an anti-inflammatory effect of this extract. Retnaningsih found a decrease of oxidative stress and increase

of antioxidant levels after OS supplementation in acute stroke patients.[14]

To the extent of our knowledge, this is the first randomized clinical trial using OS extract in malnourished elderly patients. Moreover, the procedure of this trial follows the guidance of good clinical practice (GCP) and the outcomes were objective variables (IGF-1 and albumin).

LIMITATION OF THE STUDY

Firstly, there was a 17% drop-out from total subjects. However it did not reduce the significance of this study, since the characteristics of drop out subjects were not different from those included in the analysis. Besides, we use intention-to-treat to analyze all subjects. The drop-out subjects were classified as subjects with por outcomes. Secondly, the outcomes which were measured in this study did not include any clinical outcomes.

CONCLUSION

Ophiocephalus striatussupplements given to elderly patients with malnutrition improved IGF-I and albumin levels.

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