ISSN: 2349-5197
Impact Factor: 3.765

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

THE EFFECT OF OPHIOCEPHALUS STRIATUS EXTRACT ON IL-6 SERUM LEVELS IN PATIENTS WITH CANCER CACHEXIA

Hasbi Murdhani[*1], Dairion Gatot[2] & Henny Syahrini[2]

[*1]Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

[2]Division of Haematology and Oncology , Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

DOI: 10.5281/zenodo.3633103

Keywords: Ophiocephalus striatus, Interleukin-6, Cancer cachexia.

Abstract

Background: One of the most common manifestations of advanced cancer is the development of metabolic symptoms, known as cachexia. Cancer cachexia is a multifactorial syndrome characterized by continued loss of skeletal muscle mass (with or without fat loss) that cannot be completely repaired with conventional nutritional support and causes progressive functional disorders. Several studies have found an increase in IL-6 in advanced cancer. Increased IL-6 also increases the risk of developing cancer itself and also triggers cancer cachexia. Previous research on the administration of ophiocephalus striatus extract may decrease IL-6 levels.

Objective: The objective of this study is to determine the effect of ophiocephalus striatus extract on IL-6 serum levels in patients with cancer cachexia.

Methods: This study was held from January until August 2019 in Medan, Indonesia with pre-post test one group design. From all patients with cancer, thirty patients with cancer cachexia were included. IL-6 levels of research subjects were measured before and after the administration of Ophiocephalus striatus extract for 14 days.

Results: There was a very significant relationship between IL-6 before and after 14 days of Ophiocephalus Striatus extract administration ($p = 0.001$).

Conclusion: Serum IL-6 values decreased significantly after the administration of Ophiocephalus striatus extract in patients with cancer cachexia. There was an increased serum albumin levels of patients with cancer cachexia after administration of Ophiocephalus striatus extract 5000 mg twice daily for two weeks.

Introduction

The word of cachexia comes from Latin word, "kakos" which means "bad" and "hexis" which means condition (Argiles, et.al., 2014). Cachexia is a multifactorial and multiorgan syndrome which is one of the main causes of morbidity and mortality in end-stage chronic conditions such as AIDS, chronic obstructive pulmonary disease (COPD), congestive heart failure, multiple sclerosis, tuberculosis, and cancer (Sadeghi, et.al., 2018). Although the pathogenesis of cachexia is very complex and not fully understood, inflammation is a general concept raised by several studies of cancer cachexia (Miller, Laird dan Skipworth, 2019). The main causes of cancer cachexia are changes in various proinflammatory, proectectic and endocrine factors in response to tumors, as well as host-tumor interactions. This causes inflammatory / metabolic changes including systemic inflammation, acute phase response, proteolysis, lipolysis, lipid mobilization, decreased protein synthesis, lipogenesis, and appetite (Del Fabbro, Kenneth and Florian, 2016).

There are several factors that are considered to be the key to the etiology of cancer cachexia, namely tumor factors and the response of patients with tumors. Tumor factors through tumor cells, are produced by proinflammatory factors and procachexia factors. Whereas the response factors of patients with tumors include activation of systemic responsive, metabolic, immune and neuroendocrine responses. In addition, a number of other factors can influence the disease. Cancer therapy factors, such as surgery, radiotherapy, and chemotherapy can have adverse effects on a patient's nutritional intake as a consequence of the development of systemic inflammation and side effects, including nausea, vomiting, mucositis, changes in taste, lethargy and depression. In addition, patients can fast for long periods before certain examinations or major surgeries. Tumor characteristic factors such as tumor location can directly affect food intake, for example upper gastrointestinal tumors can cause obstruction and some cancers can cause discomfort including full stomach and constipation. In

addition, this type of tumor also plays an important role, where cancer cachexia is seen more frequently in patients with advanced lung, pancreas, prostate, stomach and colon cancer. Patient-specific factors, includes genetic factors, body mass index and hypogonadism. Genetic factors in cancer patients with the same type of tumor might cause variability in who will develop cancer cachexia, and may be related to host genotype (Del Fabbro, Kenneth and Florian, 2016).

IL-6 is a soluble mediator with pleiotropic effects on inflammation, immune response, and hematopoiesis (Tanaka, Narazaki dan Kishimoto, 2014). IL-6 consists of 184-212 amino acids, including 28-mino-acid signal peptides, and the gene has been mapped to chromosome 7p21. The size of the core protein is ~ 20 kDa, while the size for glycosylation is 21-26 kDa. IL-6 is synthesized in the early stages of inflammation, and followed by rapid induction of various acute phase proteins such as C-reactive protein (CRP), serum amloid (SAA), fibrinogen, haptoglobin, and A1 -antichymotrypsin. On the other hand, IL-6 reduces the production of fibronectin, albumin, and transferrin. Several studies have found an increase in IL-6 in advanced cancer. Increasing IL-6 also increases the risk of developing cancer itself and also triggers cancer cachexia so IL-6 is used as a prognostic marker. IL-6 has a paradoxical effect on the role of inflammation. IL-6 has an anti-inflammatory effect that plays a role in wound healing and regeneration of mitotic tissue such as skin and liver. However IL-6 is also a pro-inflammatory which is involved in muscle wasting, tumorigenesis, and hypermetabolism. This occurs based on acute or chronic exposure (Scheller, Garbers and Rose John, 2013).

Ophiocephalus striatus has a higher protein levels compared to the other sources of protein. Besides of complex proteins, omega-3 fatty acids, amino acids: glycine, histidine, cysteine, glutamine, and tryptophan, vitamins A, D3, and E, magnesium minerals, it has 64.61% of albumin. Almost all of these compositions have an anti-inflammatory role (Dwijayanti, Djati, and Rifai, 2015).

Albumin is the most abundant plasma protein, binding and transporting many insoluble substances in the blood, playing a major role in forming the plasma colloid osmotic pressure. The molecular weight of albumin is 69 kD which in humans is formed by 584 amino acids. Normal plasma albumin concentrations range from 3.5-5 g / dl in adults, and are produced daily in the liver 130-200 mg / kg / day or around 12-25 grams per day (Nugroho, Sugiarto dan Purwoko, 2016).

Albumin has been determined to have an anti-inflammatory effect. Mulyana,et.al. (2017) found that there was an increase in serum albumin in post-operations patients which were given potential nutrition source of albumin. Research on the administration of ophiocephalus striatus extract in 90 elderly hypoalbumin patients given 2 x 1 sachet (freezy dryer method) for 2 weeks has proven to increase albumin levels after administration ($p = 0.003$) (Mulyana, et.al., 2017). Dwijayanti, Djati, and Rifai (2015) found a significant decrease in IL-6 levels in doing their study on mice which were administered with ophiocephalus striatus extract. Kemik, et.al. (2012) also found a higher IL-6 levels in patients with cancer cachexia. Chen, et.al. (2005) found that the administration of immunonutrient and high-protein liquid diets might lower the IL-6 levels in patients with gastric carcinoma. Wei, et.al. (2014) also found that the administration of fish oil in patients with gastric carcinoma, has increased the albumin levels and lowered the IL-6 levels.

Since there has never been studies of ophiocephalus striatus extract conducted on patients with cancer cachexia, this study was conducted to determine the effect of ophiocephalus striatus extract on IL-6 serum levels in patients with cancer cachexia by measuring the IL-6 serum levels after the administration of ophiocephalus striatus extract for 14 days.

Materials and Methods

Patients Selection

This study was conducted with pre-post test one group design in endoscopy units at tertiary helathcare, Haji Adam Malik General Hospital, Medan, Indonesia, from January to August 2019. Thirty outpatients who had been confirmed cancer histopathologically, aged 18 years and older, and were showing symptoms of cachexia symptoms. Exclusion criteria was patients unwilling to be included to this study, were pregnant, having GFR of

<15, and proteinuria of +3. Informed consent was obtained from each subject. This study had been approved by Institutional Review Board of Universitas Sumatera Utara.

Data was obtained through interviews, physical and laboratory examinations before and after 14 days therapy of Ophiocephalus striatus. The points of interview included demographic data such as gender, age, anthropometry, types of cancer, chemotherapy status. The laboratory parameters were got through measuring complete blood count, liver function test, renal function test, albumin, D-dimer, fibrinogen, CRP and IL-6 levels. IL-6 serum levels were measured through the using of certain reagent with high sensitivity and specificity.

Statistical Analysis

Statistical analysis was performed using SPSS version 22 (SPSS Inc., Chicago) through univariate, bivariate (Chi-square and Fisher's exact tests) and mean difference tests (t-test or Wilcoxon test) after test of normality. Analysis was done at 95% confidence interval and p value of <0.05 was considered significant.

Results and Discussion

Table 1: Sample Characteristic

Karakteristik	n=30	%
Gender		
Male	20	66.7
Female	10	33.3
Age (year)[a]	52 ± 17[a]	
Anthropometry		
Body Weight (kg)[a]	45.4 ± 5.8[a]	
Body Height (cm)[a]	162.7 ± 6.0[a]	
Body Mass Index(kg/m^2)[a]	17.14 ± 1.66[a]	
Upper Arm Circumference	26.4 (22.3-27.5)	
Types of cancer		
Gastrointestinal	14	46.7
Pulmonary	6	20
Nasopharyngeal	4	13.3
Non-Hodgkin Lymphoma	2	6.7
Else	4	13.3
Chemotherapy Status		
Chemotherapy	25	83.3
Non-Chemotherapy	5	16.7

[a]normally distributed, mean±SD
[b]not normally distributed, median (min-max)

This study was attended by 30 cancer cachexia respondents who met the inclusion and exclusion criteria. Out of 30 people, 20 (66.7%) of the respondents were men with an average age of 52 years. The average body weight was 45.4 kg, height was 162.7 cm and Body Mass Index (BMI) was 17.14 kg/m^2. Most respondents had gastrointestinal cancers (46.7%), followed by lung cancer (20%), nasopharyngeal carcinoma (13.3%), Non-Hodgkin Lymphoma (6.7 %) and other types of cancer (13.3%). Based on the status of chemotherapy, the majority of respondents have received chemotherapy and routine treatment (83.3%) (Table 1).

Table 2: Differences of Laboratory Measurement Before and After Ophiocephalus striatus Therapy for 14 Days

Parameter	Before (n=30)	After (n=30)	p
Hb[a]	9.5±1.5	9.9±1.6	0.177
Ht[a]	28.3±4.6	30.0 ± 5.3	0.127
Leukocyte[b]	10,320 (2,480-29,960)	8760 (2,680-31,890)	0.820
Platelet[b]	307,500 (24,000-757,000)	342,000 (25,000-523,000)	0.406
Ureum[b]	30(6-133)	29(13-133)	0.366
Creatinine[b]	0.77(0.34-3.11)	0.70(0.32-2.61)	0.073
SGOT[b]	27(8-175)	24(10-64)	0.490
SGPT[b]	19(6-83)	22(6-106)	0.147
Albumin[a]	2.47±0.43	2.92±0.56	<0.001*
CRP[b]	1.4 (0.7-2.8)	1.4 (0.7-2.8)	0.347

[a]normally distributed, mean±SD
[b]not normally distributed, median (min-max)
*significant, p<0.05

After using Ophiocephalus striatus extract for 14 days, there was increase in mean value of hemoglobin, hematocrite and Albumin levels and increase in median value of platelet and SGPT, but only Albumin levels that was different significantly before and after the therapy (p = 0.177; p = 0.127; p = 0.001; p = 0.406; p = 0.147). Also, there was decrease in median value of leukocyte, ureum, creatinine, and SGOT, and there was none that was different significantly before and after the intervention (p = 0.820; p = 0.366; p = 0.073; 0.490). Last, there was a similar median value of CRP levels before and after the therapy, which differences was also not significant statistically (p=0.347) (Table 2).

Table 3: Differences of IL-6 Serum Levels Before and After Ophiocephalus striatus Therapy for 14 Days

Parameter	**Before (n=30)**	**After (n=30)**	**p**
IL-6[b]	19.37 (5.26-135)	5.83 (4.3-8.2)	<0.001*

[b]not normally distributed, median (min-max)
*significant, p<0.05

The median value of IL-6 before administration of Ophiocephalus striatus was 19.37 pg / mL and after administration was 5.83 pg / mL. Using statistical analysis, the Wilcoxon test, there was a very significant difference between IL-6 before and after therapy using Ophiocephalus Striatus extract (p = 0.001) (Table 3).

This study showed an increase in serum albumin levels of patients with cancer cachexia after administration of Ophiocephalus striatus extract at a dose of 5000 mg twice per day for two weeks. The mean serum albumin level in subjects before receiving Ophiocephalus striatus was 2.47 gr / dL and after getting Ophiocephalus striatus therapy the mean serum albumin increased to 2.92 gr / dL. Research on cork fish albumin has been widely carried out. Previous studies have shown an increase in serum albumin of 0.5 gr / dL after administration of cork fish extract for two weeks. Similar research results were carried out in post-surgery patients at Wahidin Sudirohusodo General Hospital in Makassar where an increase in serum albumin was 0.7 g / dL in patients given cork fish concentrate capsules for 14 days (Asfar dan Mahendradatta, 2014). Cork fish are a potential

source of albumin. Health practitioners have used cork fish extract as an additional food (extra menu) for patients with indicated hypoalbuminemia, burns, and diet after surgery (Nugroho, 2013). From various case studies and research it is known that extra cork fish can significantly increase albumin levels in cases albuminemia.

In our study, IL-6 values were found to have an average value of 19.37 pg / mL prior to intervention with Ophiocephalus Striatus extract. And after the intervention, there was a significant decrease in IL-6 value to 5.83 pg / mL.. This is in accordance with previous research on the administration of ophiocephalus striatus extract to the reduction of IL-6 conducted at Brawijaya University in Malang in 2015 to mice, which showed a significant decrease in IL-6 levels compared to the control group (Dwijayanti, Djati, and Rifai, 2015). Based on the results of research conducted by Kemik, et.al. (2012), there was higher serum concentrations of CRP, IL-1a, IL-1β, IL-6, IL-8, IL-10, TNF-α, VEGF-A, VEGF-C and leptin in patients with cancer cachexia compared to controls ($p < 0.001$) and there was found, albumin, midkine, adiponectin and ghrelin in patients with cancer cachexia were lower than in controls ($p < 0.001$). Based on the results of the study of Chen, et.al. (2005), the administration of immunonutrient and high-protein liquid diets (arginine, glutamine and n-3 PUFAs) in gastric carcinoma resulted in the increase of prealbumin, IL-2, transferrin, albumin, and decrease of IL-6 and TNF-α levels. These results were also similar to the study of Wei, et.al. (2014), with the administration of fish oil to gastric carcinoma, there was an increase of albumin, transferrin, total protein, prealbumin, CRP, VEGF, IGF-1 levels and decrease of IL-1b, IL-6, and TNF-α levels.

From various studies found evidence that people with cancer cachexia are in a state of systemic inflammation. The best known factor for cachexia mediator is cytokine IL-6. These conditions cause patients with cancer cachexia have a tendency to experience increased levels of IL-6 (Miller, Laird dan Skipworth, 2019). Specifically, IL-6 hyperexpression has been identified as one of the main cytokine responses involved in patients with cancer cachexia. Continuous hyperexpression of IL-6 results in progressive anorexia and weight loss. In addition, IL-6 affects several patients with cancer cachexia abnormalities: increased systemic inflammation, decreased adipose and muscle wasting, insulin resistance, increased thermogenesis, and changes in fat and protein metabolism. Cancer cachexia negatively affects quality of life, response to chemotherapy, and survival (Vaughan, Martin dan Lewandowski, 2013).

Chronic inflammation plays a major role in carcinogenesis, cancer cells can depend on the production of proinflammatory mediators for growth, protection from apoptosis, and promotion of angiogenesis / metastasis. IL-6 inhibits adipocytes and differentiation of skeletal myocytes. A possible explanation is that weight loss occurs for two main reasons: a) decrease in skeletal muscle mass and b) decrease in adipose tissue, IL-6 is reported to play a role in both of these cases (Patel and Patel, 2017). Increased IL-6 levels in cachexia correlate with several parameters cancer cachexia associated with poor outcomes (prognosis) (Narsale dan Carson, 2014).

Conclusions

IL-6 serum levels was decreased significantly after administration of Ophiocephalus striatus extract in patients with cancer cachexia.

There was an increased serum albumin levels of patients with cancer cachexia after administration of Ophiocephalus striatus extract 5000 mg twice daily for two weeks.

There were several limitations in this study. Since this study was about nutritional status, IL-6 itself can be affected by the psychiatric status of the patients. Then, this study alone had not assessed the sample nutritional status and had not measured the food recall and psychiatric status during the administration of Ophiocephalus striatus extract. So, there were still several factors that might be the confounding factors in this study

References

[1] Argiles JM, Fontes-Oliveira CC, Toledo M, López-Soriano FJ, Busquets S. Cachexia: a problem of energetic inefficiency. J Cachexia Sarcopenia Muscle 2014; 5:279–286
[2] Asfar M, Mahendradatta M. Potensi Ikan Gabus (Channa Striata) Sebagai Sumber Makanan Kesehatan (Review). Prosiding Seminar Nasional Teknologi Industri II 2014. ISBN : 978-602-14822-1-6
[3] Chen DW, Fei ZW, Zhang YC, Ou JM, Xu J. Role of enteral immunonutrition in patients with gastric carcinoma undergoing major surgery. Asian J Surg. 2005; 28(2):121-124.doi:10.1016/S1015 9584(09)60275-X.
[4] Del Fabbro, E., Kenneth F., Florian S. Cancer cachexia: mechanisms and progress in treatment. 2016. Amsterdam : Elsevier B. V
[5] Kemik O, Kemik AS, Begenik H, et al. The relationship among acute–phase responce proteins, cytokines, and hormones in various gastrointestinal cancer types patients with cachectic. Hum exp taxicol 2012; 31(2):117-125 doi:10.1177/0960327111417271.
[6] Miller J, Laird BJA, Skipworth RJE. The immunological regulation of cancer cachexia and its therapeutic implications. Cancer Metastasis Treat 2019; 5(68) DOI: 10.20517/2394-4722.2019.001
[7] Mulyana R, Setiati S, Martini RD, Harimurti K, Dwimartutie N. The Effect of Ophiocephalus striatus Extract on the Levels of IGF-1 and Albumin in Elderly Patients with Hypoalbuminemia. Acta Med Indones - Indones J Intern Med 2017; 49(4).
[8] Narsale AA, Carson JA. Role of IL-6 In Cachexia – Therapeutic Implications. Curr Opin Support Palliat Care 2014; 8(4):321–327. doi:10.1097/SPC.0000000000000091
[9] Nugroho AY, Sugiarto, Purwoko. Perbandingan Efektivitas Terapi Albumin Ekstrak Ikan Gabus Murni Dibanding Human Albumin 20% Terhadap Kadar Albumin Dan Ph Darah Pada Pasien Hipoalbuminemia. UNS. 2016.
[10] Nugroho M. Uji Biologis Ekstrak Kasar dan Isolat Albumin Ikan Gabus (Ophiocephalus striatus) terhadap Berat Badan dan Kadar Serum Albumin Tikus Mencit. Jurnal Saintek Perikanan 2013; 9(1) : 49-54
[11] Patel HJ, Patel BM. TNF-a and cancer cachexia: molecular insight and clinical implications. Life Sci 2017; 170(56):63.doi:10.1016/j.lfs.2016.11.033.
[12] Sadeghi M, Keshavarz-Fathi M, Baracos V, Arends J, Mahmoudi M, Rezaei N. Cancer Cachexia: Diagnosis, Assessment, and Treatment, Critical Reviews in Oncology / Hematology 2018; 127: 91-104.
[13] Scheller, J., Garbers, C., Rose-John, S. Interleukin-6: From basic biology to selective blockade ofpro-inflammatory activities. Seminars in Immunology 2013; 11.
[14] Tanaka, T., Narazaki, M., Kishimoto, T. IL-6 in Inflammation, Immunity, and Disease. Cold Spring Harb Perspect Biol. 2014; 6: a016295.
[15] Vaughan VC, Martin P, Lewandowski PA. Cancer cachexia: impact, mechanisms and emerging treatments. J Cachexia Sarcopenia Muscle 2013; 4 : 95–109
[16] Wei Z, Wang W, Chen J, Yang D, Yan R, Cai Q. A prospective, randomized controlled study of ω-3 fish oil fat emulsion-based parenteral nutrition for patients following surgical resection of gastric tumors. Nutr J. 2014; 13(1):1-6.doi:10.1186/1475-2891-13-25.