

Effect of Striped Snakehead fish (*ophiocephalusstriatus*) extract supplement pills compared to human albumin infusion on Albumin Serum, Lipid Profile, Malondialdehyde and IL-8 serum level on Nephrotic Syndrome

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ABSTRACT

Aim. To determine the effect of striped snakehead fish extract supplement pills compared to human albumin infusion on albumin serum, lipid profile, malondialdehyde (MDA), interleukin-8 (IL-8), and body weight in NS.

Method: Randomized controlled trial of children with NS aged 2 -14 years old was conducted in RSUP Dr. Kariadi hospital and other hospitals around Semarang from April 2012 to February 2013. Subjects were divided in group I (received the supplement pills 75 mg/8 hours for 21 days and human albumin infusion 0.5 g/kgBW) and group II (received human albumin infusion only). Protein, lipid profile, MDA, IL-8, diet intake, and body weight were analyzed.

Result: Eighteen patients in group I and 17 in group II were compared. Increased in albumin serum level were $2,2\pm 0,64$ g/dl vs $0,9\pm 0,96$ g/dl ($p=0,001$), mean decreased in total cholesterol were $199,3\pm 101,82$ mg/dl vs $83,1\pm 83,94$ mg/dl ($p=0,002$), decreased in LDL were $159\pm 79,11$ mg/dl vs $88,9\pm 88,66$ mg/dl ($p=0,02$), mean of weight loss were $1,4\pm 0,61$ kg vs $0,7\pm 0,6$ kg ($p=0,003$) respectively. Decreased in MDA level in group I was 2.4 ± 1.12 . No difference of IL-8 serum in both groups.

Conclusion: In pediatric NS, supplementation with striped snakehead fish extract pills effectively increase albumin serum, decrease total cholesterol, LDL, MDA serum, and edema through weight loss, but not decrease IL-8 serum.

Keywords: Snakehead fish extract supplement pills, human albumin infusion, nephrotic syndrome

INTRODUCTION

Massive proteinuria as the result of glomerular filtration dysfunction causes hypoalbuminemia with complications such as edema, hypovolemia, dislipidemia and hypercoagulability that increase morbidity and mortality in children with nephrotic syndrome (NS)^{1,2,3}.

Lymphocyte T cells play a major role in the immunopathogenesis of NS^{4,5,6}. A study by Printza et al. has shown significant increase of B cells CD23+ and CD19+, T cells CD3+/CD69+/IL4, IL-13 and IL-8 in active phase of children with steroid sensitive NS.⁵ Most relapse events in NS are triggered by prior upper respiratory infection that express IL-8 in peripheral blood mononuclear cells. An in vitro study by Garin has shown significant decreased sulfate on MBG in culture which given IL-8 compared with control⁷.

Reactive oxygen species also plays an important role in the pathogenesis of NS. Free radicals will destroy cell membranes via lipid peroxidation and increase glomerular permeability. Reactive oxygen species (ROS) will form Malondialdehyde (MDA) as a marker for oxidative stress, which is increased in NS^{8,9}.

Albumin plays a predominant role as antioxidant in plasma by binding the free radicals and ligand, and to maintain intravascular oncotic pressure. Negative charge of the albumin also maintains about 40% of osmotic pressure by maintaining the positive charge salute to stay intravascular^{2,3,10}.

Hypoalbuminemia triggers a compensation reaction by increasing the synthesis of cholesterol, triglycerides and lipoprotein in the liver. Hyperlipidemia with increase of total cholesterol, low density lipoprotein (LDL), very low density lipoprotein (VLDL) and triglycerides is found in the active phase of NS which could turn to normal after remission^{3,11,12}. About of 87% patients will have total cholesterol of >200 mg/dl and 25% of patients have >400 mg/dl.¹³ This total cholesterol serum level will remain high compared to other lipids (triglycerides, LDL, VLDL) in patients with NS on remission¹⁴.

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Recommended daily allowances for protein intake for patient with NS with normal renal function is 1.5-2g/kgBW/day. Adequate intake was needed to increase the synthesis of protein in the liver^{2,3,15}. Prealbumin is a preferred marker to evaluate the effects of diet interventions for its short half life (2 days) rather than albumin (21 days). Level of prealbumin will increase above baseline in 24 hours after protein supplementation, and will reach normal limit within 8 days¹⁶.

The albumin synthesis rate in patients with NS is higher than in healthy children¹⁷. A study by Cantaldo has shown decrease in albumin synthesis rate in patients given vegetable protein as their main source of protein in the diet.¹⁸ Animal protein has higher biological value and has the same essential amino acid compositions as human protein^{16,19}.

Striped snakehead fish (*Ophiocephalus striatus*) has a content of animal protein 25,5% higher than other kinds of fishes, and an albumin level of 6,224/100 g^{20,21}. The amino acids contained in this fish are best absorbed in jejunum area.²²⁻²⁴ Branched chain amino acids (BCAA) consist of leucine, valin and isoleucine contained in this fish strengthen the immunity, where as leucine with glutamine play a role in decreasing IL-8 level²⁵⁻²⁷

Prior studies of striped snakehead fish extract supplementation in patients with NS were performed by Kusumawardhani²¹ by giving striped snakehead fish powder up to 25% of daily protein intake, and a study by Djajakusli²⁸ by giving striped snakehead fish extract supplementation pills for 10 days. Both studies resulted in increase of serum albumin level. A study by Soemarmo giving enteral striped snakehead fish extract in patient with hypoalbuminemia and enterocutaneous fistula for 16 days showed remarkable increase of albumin.²⁹ Meiji studied amino acid function and has shown that glutamine, leucine, and proline will decrease the production of IL-8.³⁰

Human albumin is a colloid and acts as volume expander that will increase intravascular oncotic pressure that will maintain intravascular volume. Study by Sjostrom showed an increasing albumin serum level near normal range in 24 hours after infusion of human albumin³¹. This finding is similar with study conducted by Zelal Bircan in Minimal Change of Disease-Nephrotic Syndrome (MCD-NS) with severe edema that be given infusion of 20% human albumin with a dose of 0,5 g/kgBW for 1 hour and intravenous injection of furosemide (2 mg/kgBW)³².

Silalahi performed a study in MCD-NS and non MCD-NS patients that were diagnosed from renal biopsy, that showed an increased in serum albumin level after administration of 1 dose infusion afahuan

albumin³³. A study by Haws has significant reduction in edema and weight loss after administration of 3 doses infusions of human albumin and 3 times intravenous injections of furosemide in 3 days in a row³⁴. Margareth has found that infusion of human albumin significantly improved proteinuria in patients with recurrent focal segmental glomerulosclerosis (FSGS)³⁵.

Studies showed benefits of striped snakehead fish extract supplementation and infusion of human albumin as alternative therapy for hypoalbuminemia in NS. But there were no study evaluates the effect of infusion of human albumin combined with striped snakehead fish extract supplement pills compared to human albumin infusion only in children with NS.

The aim of this study was to determine the effect of striped snakehead fish extract supplement pills compared to human albumin infusion on the level of albumin serum, total cholesterol serum and weight of children with nephrotic syndrome.

METHOD

Randomized controlled trial pre and posttest design on children with nephrotic syndrome was performed in RSUP Dr. Kariadi hospital and other hospitals around Semarang in period of April 2012 until February 2013. Patients age 2 -14 years old with normal glomerular filtration rate (GFR), albumin serum level 1 – 2.5 g/dL, and able to take oral diet were included in this study. The exclusion criteria include patients with chronic illness (TB, cardiac disease, malignancies, liver dysfunction which may result in hypoalbuminemia), and severe conditions or complications (shock, peritonitis, septicemia, severe hypertension, hypertensive crisis, hypertensive encephalopathy, and anasarca oedema).

Subjects were divided in two groups (in group I patients received the striped snakehead fish extract supplement pills and human albumin infusion and in group II patients received human albumin infusion only). Striped snakehead fish extract supplement pills given three times a day, 75 mg dose in each pill for 21 days and human albumin infusion dose was 0,5g/kg body weight at the beginning of this study. All subjects received standard therapy of prednisone. Variable of anthropometric, ideal body weight, nutritional status, complete blood count, peripheral blood smear, protein profile (total protein, albumin, prealbumin, globulin), lipid profile (cholesterol, HDL, LDL, VLDL, triglyceride), MDA, IL-8, ureum, craetinine, glomerular filtration rate, and food recalls were measured before and after treatment in both groups.

RESULT

A total of 35 subjects were involved in this study. Group I with 18 subjects received human albumin infusion and striped snakehead fish extract supplement pills, while 17 subjects in group II received human albumin infusion only (Table 1).

Higher mean of protein profile level and body weight were found in group II compared to group I, while the mean of total cholesterol serum level was higher in group I compared to group II. Statistical analysis showed no significant result between these parameters ($p > 0.05$).

After treatment, higher mean of LDL serum level was found in group II compared to group I. Mean level of albumin and total protein were higher in group I compared to group II. These findings showed significant result in statistic analysis ($p < 0.05$) for these parameters.

Group I showed more increased in albumin serum level before and after treatment compared to group II, about $2,2 \pm 0,64$ g/dl and $0,9 \pm 0,96$ g/dl respectively ($p = 0,001$). A mean decreased in total

cholesterol and LDL serum level were lower in group I compared to group II, with $199,3 \pm 101,82$ mg/dl and $83,1 \pm 83,94$ mg/dl decreased for cholesterol level ($p = 0,002$), and $159 \pm 79,11$ mg/dl and $88,9 \pm 88,66$ mg/dl decreased for LDL level ($p = 0,02$) respectively.

Clinically weight loss were found in both groups, the mean of weight loss were $1,4 \pm 0,61$ kg in group I compared to $0,7 \pm 0,6$ kg in group II, and was statistically significant ($p = 0,003$).

Significant decreased in MDA level was found in group received striped snakehead fish extract supplement and infusion of human albumin. This may result from the decreased of LDL level, and was correlated with the function of albumin as antioxidant. This decreased in MDA level might contribute in the remission of 80% patients in this study, since high MDA level plays role in etiopathogenesis of glomerular permeability alterations in nephrotic syndrome. No significant difference of IL-8 serum level in both groups.

Table 1. Subjects characteristics

Characteristics		Group I	Group II	P#
		n (%)		
Age (month) (f,%)	24-48	8 (50,0)	8 (50,0)	0,50
	49-84	6 (66,7)	3 (33,3)	
	85-168	4 (40,0)	6 (60,0)	
Sex (f,%)	Male	11 (42,3)	15 (57,7)	0,12
	Female	7 (77,8)	2 (22,2)	
Social Economic	Low	14 (46,7)	16 (53,3)	0,34
	Middle	4 (80,0)	1 (20,0)	
	High	0 (0,0)	0 (0,0)	
Classification of nephrotic syndrome	Initial attack	1 (33,3)	2 (66,7)	0,65
	Infrequent relapses	11 (57,9)	8 (42,1)	
	Frequent relapses	6 (46,2)	7 (53,8)	
Responds to steroid therapy	Sensitive steroid nephrotic syndrome	17 (58,6)	12 (41,4)	0,09
	Resistant steroid nephritic syndrome	1 (16,7)	5 (83,3)	
Maternal education	Jr High School	5 (50,0)	5 (50,0)	0,37
	Sr High School	9 (45,0)	11 (55,0)	
	College	4 (80,0)	1 (20,0)	
Mother's occupation	Working	8 (57,1)	6 (42,9)	0,58
	Housewife	10 (47,6)	11 (52,4)	

#Chi square analysis

Table 2: Analysis for clinical and laboratory parameters before treatment

Subjects Characteristics	Group I (Mean±SD)	Group II (Mean±SD)	P
Body weight	19,3 ± 7,94	19,5 ± 6,96	0,92 ^s
Albumin serum level (mg/dl)	1,6 ± 0,45	1,8 ± 0,47	0,20*
Globulin serum level (mg/dl)	2,5 ± 0,75	2,6 ± 0,66	0,78 ^s
Total protein serum level (mg/dl)	4,0 ± 0,98	4,3 ± 0,77	0,37*
Total cholesterol serum level (mg/dl)	459,3 ± 85,17	428,4 ± 89,50	0,30*
Degree of proteinuria			
Negative	0	0	0,23 [^]
> 100	0	1	
> 300	15	10	
> 500	3	6	
Presence of infections			
No infection	11	11	0,83 [^]
Infection	7	6	
Calorie intake (kcal/kgbw/day)	1434,4 ± 488,49	1517,7 ± 434,43	0,36 ^s
Protein intake (gr/kgbw/day)	27,1 ± 10,43	27,9 ± 13,93	0,89 ^s

MDA	7,7 ± 4,05	7,6 ± 4,83	0,67 [§]
IL-8	166,2 ± 495,84	170,0 ± 428,54	0,46 [§]
Prealbumin	39,5 ± 15,54	41,7 ± 14,51	0,75 [§]
HDL	44,9 ± 26,69	50,71 ± 23,70	0,27 [§]
LDL	303,7 ± 91,71	304,6 ± 58,69	0,97 [*]
VLDL	56,3 ± 31,26	52,3 ± 24,58	0,73 [*]
Triglyceride	335,7 ± 122,31	389,7 ± 229,37	0,68 [§]

[^]Chi square

^{*}Independent t test

[§]Mann-whitney test

Table 3: Analysis for clinical and laboratory parameters after treatment

Subjects Characteristics	Group I (Mean±SD)	Group II (Mean±SD)	P
Body weight	18,0 ± 7,64	18,8 ± 7,15	0,67 [§]
Albumin serum level (mg/dl)	3,7 ± 0,74	2,7 ± 0,74	0,001 [§]
Globulin serum level (mg/dl)	2,8 ± 0,55	3,1 ± 0,81	0,26 [*]
Total protein serum level (mg/dl)	6,5 ± 0,79	5,8 ± 1,16	0,04 [§]
Total cholesterol serum level (mg/dl)	259,9 ± 81,13	345,3 ± 102,57	0,01 [*]
Degree of proteinuria			
Negative	16	13	0,31 [^]
> 100	1	0	
> 300	1	2	
> 500	0	2	
Presence of infections			
No infection	18	15	0,23 [^]
Infection	0	2	
Calorie intake (kcal/kgbw/day)	1496,1 ± 469,71	1629,4 ± 414,98	0,16 [§]
Protein intake (gr/kgbw/day)	32,3 ± 11,97	32,1 ± 10,69	0,95 [§]
MDA	5,3 ± 2,93	6,2 ± 3,17	0,48 [§]
IL-8	183,3 ± 514,84	35,0 ± 50,59	0,97 [§]
Prealbumin	33,5 ± 15,73	35,5 ± 12,74	0,51 [§]
HDL	72,8 ± 26,70	59,1 ± 27,17	0,11 [§]
LDL	144,4 ± 52,01	223,8 ± 78,38	0,002 [§]
VLDL	35,1 ± 17,68	35,9 ± 16,58	0,60 [§]
Triglyceride	156,6 ± 85,01	210,5 ± 89,65	0,033 [§]

^{*}Independent t- test

[§]Mann-whitney test

[^]Chi square

Table 4: Analysis of variable changes before and after treatment in both groups

Variable	Group	Before Treatment	After Treatment	P value
		Mean±SD	Mean±SD	
Albumin (g/dl)	Group I	1,6 ± 0,45	3,7 ± 0,74	0,000 [#]
	Group II	1,8 ± 0,47	2,7 ± 0,74	0,002 [#]
Globulin	Group I	2,5 ± 0,75	2,8 ± 0,55	0,16 [#]
	Group II	2,6 ± 0,66	3,1 ± 0,81	0,005 [§]
Total Protein	Group I	4,0 ± 0,98	6,5 ± 0,79	0,000 [§]
	Group II	4,3 ± 0,77	5,8 ± 1,16	0,000 [#]
Total cholesterol (mg/dl)	Group I	459,3 ± 85,17	259,9 ± 81,13	0,000 [#]
	Group II	428,4 ± 89,50	345,3 ± 102,57	0,000 [#]
Body weight (Kg)	Group I	19,3 ± 7,94	18,0 ± 7,64	0,000 [§]
	Group II	19,5 ± 6,96	18,8 ± 7,15	0,001 [§]
MDA	Group I	7,7 ± 4,05	5,3 ± 2,93	0,007 [§]
	Group II	7,6 ± 4,83	6,2 ± 3,17	0,44 [§]
IL-8	Group I	166,2 ± 495,84	183,3 ± 514,84	0,983 [§]
	Group II	170,0 ± 428,54	35,0 ± 50,59	0,15 [§]
Prealbumin	Group I	39,5 ± 15,54	33,5 ± 15,73	0,25 [§]
	Group II	41,7 ± 14,51	35,5 ± 12,74	0,14 [§]
HDL	Group I	44,9 ± 26,69	72,8 ± 26,70	0,004 [§]
	Group II	50,71 ± 23,70	59,1 ± 27,17	0,028 [#]
LDL	Group I	303,7 ± 91,71	144,4 ± 52,01	0,000 [§]
	Group II	304,6 ± 58,69	223,8 ± 78,38	0,002 [#]
VLDL	Group I	56,3 ± 31,26	35,1 ± 17,68	0,016 [§]
	Group II	52,3 ± 24,58	35,9 ± 16,58	0,019 [#]
Triglyceride	Group I	335,7 ± 122,31	156,6 ± 85,01	0,000 [§]
	Group II	389,7 ± 229,37	210,5 ± 89,65	0,005 [§]

[#]Paired-t test

Wilcoxon signed ranks test

DISCUSSION

Subjects in this study were aged 2 – 14 years old (24 – 16 months old) with mean age of 69 months old. Previous studies showed mean age of 9 years and 6 years old^{21,28}. Different types of nephrotic syndromes developed in different range of age. Minimal changes disease of nephrotic syndrome (MCD-NS) mostly happened in children age <5 years old. With increasing age, Focal Segmental Glomerulosclerosis (FSGS) happened in children at age of 6 years old, while Membranous glomerulopathies (MPGN) at age of >14 years old^{3,11,36}. This wide range of age in this study may affect the outcomes because of different immunity, absorption, and diet intake of those different range of age. No significant difference on age distribution of both groups. More male subjects involved than female (2,5 : 1) in this study. Nephrotic syndrome effects males more than female (2:1)². Previous study by Damanik showed distribution of 3:1 for male to female subjects.³⁷

About 61% male subjects (age 4 – 14 years old) achieved remission after standard prednisone therapy in this study. A prospective cohort study by Hiraoka M of male subjects with onset of age > 4 y.o showed significant response to prednisolone therapy and correlated with lower relaps³⁸.

Striped snakehead fish (*Ophiocephalus striatus*) is one of animal protein with higher essential amino acid contains and better digestibility than vegetable protein. Absorption of amino acid in portal vein will supply amino acid to the liver and will contribute the synthesis of albumin. Protein contains on diet also influence the synthesis of albumin. This fish can be one of alternative source of protein available in community.

Supplementation of striped snakehead fish extract for 21 days in this study increased the albumin serum level (2,2±0,64 g/dl). Lower increase in albumin level (2,1±1,47 g/dl) was found in previous study by Kusumawardhani by giving supplementation of striped snakehead fish powder about 25% of total daily protein intake for 21 days²¹. This different outcomes may result by higher acceptability in consuming striped snakehead fish extract pills, and the administration of human albumin at the start of treatment. Another study of striped snakehead fish extract supplement for 10 days by Djajakusli showed lower increase in albumin serum level (0,63±0,36 g/dl).²⁸ This may be caused by shorter duration of supplementation compared to median days of remission (11 days) in children receiving 8 weeks of prednisone therapy. Thus, on the albumin measurement in day 10, there was still ongoing albumin loss from the kidney. The

administration of human albumin at the start of treatment may also contribute higher result in our study.

A total of 29(82.85%) subjects in both groups reach remission in the end of the 4th week and were assessed as sensitive steroid nephrotic syndrome. About 80% remission were achieved in 7-14 days after treatment, and increase up to 94% after 4 weeks of treatment^{2,11}. The increasing albumin level in group with supplementation of striped snakehead fish extract and infusion of human albumin were higher after remission, because these substances increase the synthesis of albumin in the liver without protein loss from the kidney. Albumin serum level will not always increase with the increasing synthesis of albumin in the liver if the capillary glomerular abnormality remains³³.

Lipid profile abnormality related to nephrotic syndrome is hypercholesterolemia. Study by Zielleruelo mentioned that LDL, VLDL and triglycerides will remain high even after remission.¹⁴ The decreasing level in total cholesterol and LDL level in this study were similar with previous study by Djajakusli²⁸.

Edema that caused by hypoalbuminemia in nephrotic syndrome gives manifestation of acute weight gain without manifestation of increasing appetite^{2,11}. The increasing of albumin will reduce edema and showed clinical weight loss. Weight loss were found in control group that received infusion of human albumin from 19,5±6,96 kg to 18,8±7,15 kg. Another study by Silalahi showed decreasing weight gain in children with MCD-NS diagnosed from renal biopsy receiving infusion of human albumin only³³. Our study did not perform any renal biopsy procedure on subjects. About 94% of patients with sensitive steroid showed MCD on their renal biopsy^{2,11,12}.

Significant decrease in MDA level was found in group received striped snakehead fish extract supplement and infusion of human albumin. This may result from the decrease of LDL level, and was correlated with the function of albumin as antioxidant. This decrease in MDA level might contribute in the remission of 80% patients in this study, since high MDA level plays a role in etiopathogenesis of glomerular permeability alterations in nephrotic syndrome. No significant difference of IL-8 serum level in both groups.

CONCLUSION

Striped snakehead fish extract supplement pill is an effective therapy for hypoalbuminemia in children with nephrotic syndrome. Clinical and laboratory parameters improvements in terms of decrease

edema through weight loss, increase albumin serum and decrease total cholesterol, LDL, and MDA serum level were higher in subjects received both striped snakehead fish extract supplement pills and human albumin infusion compared to patients received human albumin infusion only, but no decrease of serum IL-8.

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