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Original Article

The Effect of *Channa striata* Extract on Serum Albumin and High Sensitive C-Reactive Protein in End-Stage Renal Disease Patients: A Randomized Controlled Trial

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ABSTRACT

Background: Albumin is a marker of nutritioinal inflammation and mortality. Chronic inflammation, as indicated by the concentration of a proinflammatory cytokine, high sensitivity C-reactive protein (hs-CRP) was reported to be high in end-stage renal disease (ESRD) patients. *Channa striata* (CS) contains high protein that can increase albumin levels and has anti-inflammatory effects. This study was conducted to determine the effect of CS extract on serum albumin and hs-CRP on ESRD patients. **Methods:** This study is a randomized, double blind, placebo-controlled study in patients with ESRD on hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD). Subjects were randomized to either a CS or a placebo group and were given a three times daily dosage of 500 mg of CS extract or 500 mg maltodextrin, respectively for 21 days. Serum albumin and hs-CRP were measured at the baseline, and at the end of the study. **Result:** Forty subjects were randomized into the study with 20 in the *Channa striata* group and 20 in the placebo group, with HD and CAPD patient evenly distributed among the group. Significant increase in serum albumin levels (p<0,001) and significant decrease of hs-CRP (p<0,001) were observed in the treatment group compared to control group at the end of the study. At the end of the study, there was no significant difference between serum albumin, hs-CRP, and their gradient between HD and CAPD patients in the intervention group. **Conclusion:** CS extract results in higher serum albumin and lower hs-CRP levels compared to placebo in our population.

Key words: Albumin, Channa striata, End-stage renal disease, hs-CRP, Supplementation.

INTRODUCTION

Chronic kidney disease (CKD) affects 13.4% of the global population in 44 nations.[1] In Indonesia, the prevalence of CKD in adults older than 15 years is 3.8%, with men (4.17%) having a greater prevalence than women.[2] The development of chronic kidney disease to its terminal form, necessitating renal replacement therapy (RRT), also known as end-stage renal disease (ESRD), continues to be a major cause of poor quality of life and early death. In majority of countries, the two most frequent RRT are continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis (HD).[3-5]

Malnutrition is common in patients with CKD, which contributes to increased mortality and morbidity.[6] Malnutrition must be separated from protein energy wasting (PEW), a condition often seen in CKD patients. Malnutrition is induced by low food intake; however, PEW is impacted by various additional variables in addition to poor food intake. Multiple variables, including metabolic disorder, chronic inflammation, hormone imbalances, abnormalities in the gut microbiome, and dialysis treatments, contribute to PEW in CKD.[7,8] One of the nutritional and inflammatory indicators that may predict mortality is serum albumin. In CKD patients, a low serum albumin levels is associated with poorer outcome and cardiovascular complication.[9,10]

A substantial risk of malnutrition inflammation atherosclerosis (MIA) syndrome exists among ESRD patients, and related to malnutrition and inflammation in such patients.[11] In CKD patients, impaired renal function, fluid overload, oxidative or carbonyl stress, and lowered antioxidant levels may increase the proinflammatory cytokines.[12] These proinflammatory cytokines such as IL-1, IL-6, and TNF-α were associated with the severity of CKD,[13] and promote CRP synthesis.[14] CRP may generate oxidative stress, endothelial dysfunction, and vascular calcification, all of which can contribute to atherosclerosis in CKD patients.[15] In individuals with impaired kidney function, elevated hs-CRP, IL-6, and soluble TNF receptors 1 and 2 were substantially linked with coronary heart disease incidence.[16]

Snakehead fish (*Channa striata*) is a very nutritious freshwater fish. *C. striata* (CS) is rich in protein in the form of the body's necessary amino acids and has an anti-inflammatory impact. CS may considerably raise albumin levels in the case of hypoalbuminemia, the wound-healing process, as well as counteract free radicals.[17,18] Currently, there is not enough evidence regarding CS's efficacy among ESRD patients, especially regarding its potential as an anti-inflammation agent. This study will investigate whether the administration of CS can be used to increase can be used to counteract inflammation commonly found in ESRD patients, as measured by hs-CRP, and to increase serum albumin to improve the patient's outcome.

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MATERIAL AND METHODS

Study design

This research was a randomized, double blinded, 2-arm parallel comparative study of CS extract vs placebo. This was conducted at the Department of Kidney and Hypertension, Moewardi General Hospital Surakarta from January 2021-March 2021. The researcher has obtained an ethical clearance from the local ethics commission for basic/clinical research at Moewardi General Hospital, Surakarta.

Patient selection

The population in this study were ESRD patients aged between 18 and 60 years' old who underwent HD and CAPD at Moewardi General Hospital, Surakarta and agreed to being included in this study. Patients with history of malignancies, autoimmune disease, and active infection all were excluded. Patients who had taken any form albumin, herbal supplementation, antioxidant, steroid, immunosuppressive or heparin medication were also excluded. Sample selection was done by consecutive sampling to all eligible ESRD patients. The samples in this study would be divided into 2 groups; treatment group and control group, each had the same proportion of HD and CAPD patient.

Randomization and blinding

The participants were randomized into 2 equal size groups which were the CS and placebo group. Participants were numbered sequentially following time of participation, and the type of RRT received. This separation of numbering according to RRT was performed to ensure an equal proportion of RRT received in both groups. A randomization list was generated using Random Allocation Software and subject numbers were allocated with 1:1 ratio, separately according to the type of RRT received. Blinding of participants and attending physicians were achieved by using identical capsules of placebo and CS extract.

The intervention

The CS extract was obtained from ONOIWA® capsules (PT. Natura Nuswantara Nirmala, Tangerang, Indonesia) and purchased from a retail drug store. Each capsule contained pure 500 mg CS extract powder. The placebo used was 500 mg maltodextrin powder encapsulated in the same capsule color of the CS extract capsule. The placebo was prepared in Pharmacy Department of Moewardi General Hospital, and pre-purchased from a commercial drug store. Both of the groups consumed the extract of the placebo, with a dose of three times a day for 21 days.

Study visit and endpoint

The venous blood samples for hs-CRP and albumin were collected before the administration of intervention, and at day 21. All of the tubes were then sent to the Department of Clinical Pathology at Moewardi General Hospital for the blood analysis to be performed. All social demographic feature of the patients was collected at baseline, including gender, age, type and length of RRT treatment. All of the patients were then monitored at each weekly visit to examine their clinical status and will be drop-outed when clinical deterioration occurred.

Data extraction and statistical analysis

The data were first exported to Microsoft Excel and then imported into Statistical Package for the Social Sciences (version 22) for quantitative statistical analysis software. Baseline social demographic, hs-CRP, and albumin were presented as descriptive statistics in order to describe the subject's frequency, percentage, means, and standard deviations prior to analysis. Normality of numerical data were assessed by using Shapiro Wilk test. Normally distributed data will be presented as mean and its standard deviation, whereas for skewed data will be presented in median and minimal-maximal. At the baseline, gender, age, RRT type and length, as well as hs-CRP and albumin levels, were compared between groups using an independent t-test or a chi-square test, depending on the type of variable. Similar tests were performed to assess the difference in hs-CRP and albumin between the groups at day 21, and between RRT types in each group. Changes of hs-CRP and albumin within groups were assessed using a paired sample t-test for normally distributed data or a Wilcoxon signed rank test for skewed data. The analysis of the difference in hs-CRP and albumin between RRT types within each group was also performed with same test. All of the statistical analysis were two tailed test with p-value of less than 0.05 as statistically significant.

Ethical clearance

Before the commencement of the study, a proposal was submitted to the local ethics committee and a biomedical ethical review was carried out. This study was approved by Health Research Ethics Committee in Moewardi General Hospital with the number: 1.319/XII/HREC/2020. The study protocol also was registered on ClinicalTrials.gov with the ID of NCT05614362.

RESULTS

The present study assessed 50 patients with ESRD in Department of Kidney and Hypertension Moewardi General Hospital for eligibility throughout the recruitment period. Ten patients were excluded due to not fulfilling the inclusion criteria (n=4), and decline to participate in the study (n=6). All of the remaining patients (n=40) were then equally randomized into either C. striatus (n=20) or placebo (n=20) groups, with a 1:1 proportion of HD: CAPD RRT in each group. No drop-out were observed in subsequent visit until study endpoint at day 21. Figure 1 illustrates the flowchart of study participants.

The majority of the patients were males (70%), mean age of 45, with a mean RRT duration of 4 years. Table 1 shows that majority of these individuals were comparable in term of social demographic, and baseline albumin, but not baseline hs-CRP.

Perbedaan eGFR di tiap kelompok ditampilkan

Within group changes of albumin and hs-CRP in each group between RRT type and collectively were covered in table 2 and table 3. Within CS group, there were significant increase in albumin ($p<0.001$) and reduction in hs-CRP ($p=0.006$). Similar changes were observed in CAPD patients, but not in HD patients whereas the hs-CRP reduction was not significant. In control group, hs-CRP was shown to be increased significantly in all, and CAPD patients. Between group comparison of albumin and hs-CRP in day 21 revealed significant higher albumin in HD patients ($p=0.029$), and collectively ($p=0.034$), but no significant difference of hs-CRP was observed between the intervention group (Table 4).

DISCUSSION

In this study, after taking CS extract for 21 days, there was a significant increase of albumin and decreased hs-CRP in intervention group. The increased albumin level was also documented in previous studies using CS extract three times daily for various conditions.[19,20] The increase of albumin was attributed to the high content of amino acids needed in albumin synthesis process in CS extract.[21] The extract was shown to accelerate the wound healing process, have anti-nociceptive, anti-inflammatory, and antioxidant activity by increasing IGF-1 levels which will in turn increase the albumin levels. This contributes in the maintenance of muscle mass, anti-inflammatory, antioxidant and prevents apoptosis.[22]

Limited data was available regarding the CRP improvement after supplementation of CS in previous studies. The inflammatory state

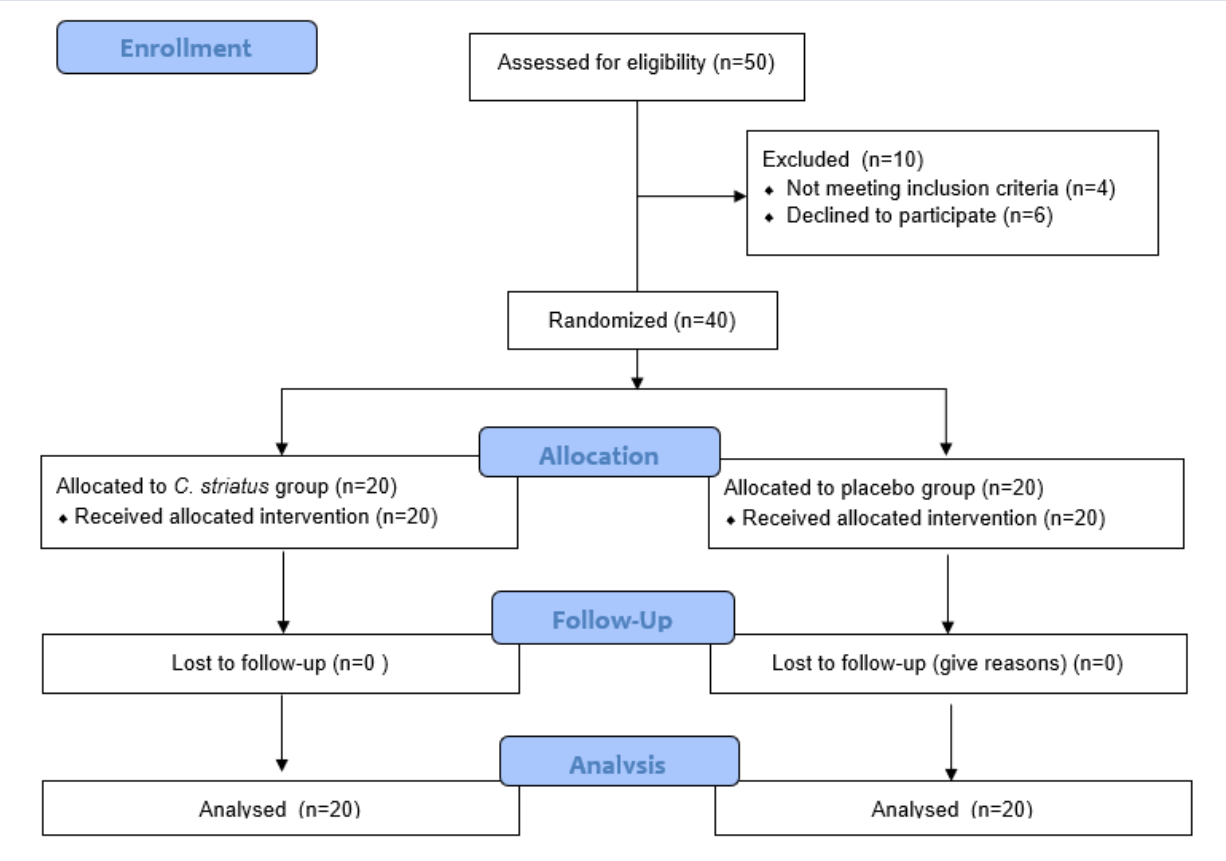

Figure 1: CONSORT flowchart of the study.

Table 1: Social demographic and baseline characteristic of the participants.

Characteristic	Groups [Mean (SD) / Frequency (%)]		p-value
	CS (n=20)	Placebo (n=20)	
Age (years) [a]	45.70 (8.06)	44.80 (6.90)	0.706
Gender[b]			0.634
Male	14 (70%)	14 (70%)	
Female	6 (30%)	6 (30%)	
RRT duration (years) [a]	4.10 (2.10)	4.45 (2.01)	0.594
Albumin (mg/dL) [a]	3.02 (0.23)	3.12 (0.19)	0.150
hs-CRP (mg/dL)[a]	0.87 (0.40)	0.64 (0.27)	0.045[c]

Notes: [a] Analysis used: independent t-test, [b] Analysis used: chi-square, [c] significance p<0.05

Abbreviations: RRT- renal replacement therapy; hs-CRP- high sensitivity C-reactive protein

Table 2: Within group changes of albumin and hs-CRP in CS group between RRT type and collectively.

Variable	Mean ± SD		Mean difference	p-value
	Day 1	Day 21		
HD				
Albumin (mg/dL)	3.07 (0.19)	3.36 (0.24)	0.29 (0.07)	<0.001*
hs-CRP (mg/dL)	0.78 (0.38)	0.77 (0.39)	-0.01 (0.02)	0.158
CAPD				
Albumin (mg/dL)	2.97 (0.27)	3.17 (0.29)	0.20 (0.12)	<0.001*
hs-CRP (mg/dL)	0.97 (0.44)	0.91 (0.43)	-0.06 (0.06)	0.010*
Both				
Albumin (mg/dL)	3.02 (0.23)	3.26 (0.27)	-0.24 (0.11)	<0.001*
hs-CRP (mg/dL)	0.87 (0.41)	0.83 (0.40)	0.04 (0.05)	0.006*

Notes: *significance p<0.05

Abbreviations: HD- hemodialysis; CAPD- continuous ambulatory peritoneal dialysis; hs-CRP- high sensitivity C-reactive protein

Table 3: Within group changes of albumin and hs-CRP in placebo group between RRT type and collectively.

Variable	Mean ± SD		Mean difference	p-value
	Day 1	Day 21		
HD				
Albumin (mg/dL)	3.14 (0.14)	3.13 (0.19)	-0.01 (0.10)	0.758
hs-CRP (mg/dL)	0.64 (0.30)	0.66 (0.31)	0.02 (0.04)	0.151
CAPD				
Albumin (mg/dL)	3.10 (0.24)	3.04 (0.29)	-0.06 (0.14)	0.217
hs-CRP (mg/dL)	0.65 (0.25)	0.69(0.28)	0.04 (0.05)	0.017*
Both				
Albumin (mg/dL)	3.12 (0.20)	3.08 (0.24)	0.03 (0.12)	0.217
hs-CRP (mg/dL)	0.65 (0.27)	0.68 (0.28)	0.03 (0.04)	0.004*

Notes: *significance p<0.05

Abbreviations: HD- hemodialysis; CAPD- continuous ambulatory peritoneal dialysis; hs-CRP- high sensitivity C-reactive protein

Table 4: Between group differences of albumin and hs-CRP on study endpoint between RRT type and collectively.

Variable	Mean ± SD		Mean difference	p-value
	CS group	Placebo group		
HD				
Albumin (mg/dL)	3.36 (0.24)	3.13 (0.19)	0.23 (0.11)	0.029*
hs-CRP (mg/dL)	0.77 (0.39)	0.66 (0.31)	0.11 (0.09)	0.649
CAPD				
Albumin (mg/dL)	3.17 (0.29)	3.04 (0.29)	0.13 (0.14)	0.325
hs-CRP (mg/dL)	0.91 (0.43)	0.69 (0.28)	0.21 (0.05)	0.206
Both				
Albumin (mg/dL)	3.26 (0.27)	3.08 (0.24)	0.18 (0.08)	0.034*
hs-CRP (mg/dL)	0.83 (0.40)	0.68 (0.28)	0.15 (0.11)	0.160

Notes: *significance p<0.05

Abbreviations: HD- hemodialysis; CAPD- continuous ambulatory peritoneal dialysis; hs-CRP- high sensitivity C-reactive protein

commonly found in ESRD, predispose patients to higher level of IL-6 and TNF-alpha, and leads to hypoalbuminemia.[23] Higher plasma TNF-α level leads to higher IL-6 synthesis, and was positively associated plasma CRP level and negatively associated with serum albumin.[14,24] These increment of CRP were associated with increased insulin resistance and obesity.[25,26] These conditions were also observed in individual with lower IGF-1.[27,28] As mentioned before, the CS extract was shown to increase IGF-1 level[22] which in turn will induce anti-inflammatory effect *via* increment of insulin sensitivity,[25,26] and leads to lower CRP.

The higher content of amino acid in CS extract will supply the amino acid necessary for albumin production. The improvement of hypoalbuminemia is associated with better functional status, lower morbidity, and mortality.[29] Furthermore, every 1 mg/dL decrease in albumin is associated with 137%, 89.5%, and 71% increases in mortality, morbidity, and length of stay, respectively.[30] Protein energy wasting (PEW), which is also frequently reported in dialysis patients, is the major contributor to these low albumin serum condition.[31,32] Lower protein intake, and dialysis loss, accompanied with factors usually seen in CKD patients, including metabolic dysfunction, chronic inflammation, hormone imbalances, and changes in the gut microbiota leads to PEW.[7,8]

Increasing albumin levels and overall nutritional status could minimize the likelihood of MIA syndrome in ESRD patients not also by reducing the role of malnutrition in atherosclerosis progression,[11] but also by reducing the role of inflammation. Already higher proinflammatory cytokines in ESRD caused by reduced renal function, fluid overload, oxidative or carbonyl stress, and decreased antioxidant levels[12] were demonstrated by all of our ESRD population with hs-CRP level higher than 0.2 mg/dl, that was considered high risk for cardiovascular events.[33] The low serum albumin levels reflect these persistent inflammatory conditions,[10] and our result of improvement of serum albumin was also reflected by lower hs-CRP by CS administration.

Several limitations of the present study must be noted. First, the clinical trial of the present study was collected from only one medical center for HD and CAPD provider in Indonesia. Our results need a replication of this study in another center with a different population characterization before being generalized. Second, the actual significance of improved albumin and hs-CRP levels should be regarded with caution because the current study did not account for other clinical or laboratory markers.

Despite the limitation, to the extent of our knowledge, this study is the first to document the efficacy of CS extract on albumin dan hs-CRP on ESRD individuals on HD and CAPD. Considering the benefit and safety of the supplementation of CS extract but with limited evidence, we encourage other similar studies to be performed in this field.

CONCLUSION

CS extract supplementation results in higher serum albumin and lower hs-CRP levels on ESRD patient at Moewardi General Hospital, regardless of the dialysis method. Supplementation with CS extract should improve ESRD patients' nutrition status, and overall outcome.

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