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ORIGINAL RESEARCH INTENSIVE CARE

Non-inferiority trial of Channa striata extract on endothelial glycocalyx layer protection in septic patients

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ABSTRACT

Background: Sepsis causes significant damage to the endothelial glycocalyx layer, which albumin can protect against. Unfortunately, human albumin is quite expensive, so cheaper substitutes must be found without sacrificing effectiveness. Albumin extract called snakehead fish extract (SHFE) is one that is commonly used in Indonesia It is also called Channa striata extract. We conducted a non-inferiority study between human albumin and SHFE in protecting the glycocalyx layer through syndecan-1 levels.

Methodology: It was a prospective cohort study of adult patients with early sepsis, treated at ICU of Dr Moewardi Hospital, between May and October 2021. The study group was divided by giving Channa striata extract 15 mg/day for two days and the control group was given 20 grams of human albumin on the other day, and then syndecan-1 levels were compared before treatment and on the third day of the study.

Results: We discovered a statistically significant decrease in syndecan-1 levels in both the study (P = 0.013) and control groups (P = 0.027) from the 44 samples we obtained.

Conclusion: In both groups, there was a significant decrease in syndecan-1 levels, proving that Channa striata extract is not inferior to human albumin in terms of glycocalyx layer protection. And it has a higher economic value because the price is lower.

Key words: Sepsis; Channa striata; Albumin; Syndecan-1; Glycocalyx

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1. INTRODUCTION

According to the Global Burden of Disease, sepsis kills more than 10 million people each year and contributes to 3-10 deaths per 1,000 people in high-income countries.[1] One of the first signs of sepsis is changes in the composition of the glycocalyx as a result of inflammatory factors and oxidative stress.[2,3] Syndecan-1 levels are a commonly used biomarker in assessing glycocalyx layer damage.[4,5] Some studies demonstrated animal models with damage to the glycocalyx, that use

of albumin was sufficient to maintain the glycocalyx.[6,7] This albumin is quite expensive, particularly for the low-resource developing countries, so there is a need for effective and cheaper substitutes, one of which is albumin extracted from Channa striata (snakehead fish), which is already commonly used in Indonesia.[8–12] As a result, studies comparing the non-inferiority of channa striata extract to human albumin in preventing damage to the glycocalyx layer as measured by syndecan-1 levels in sepsis patients are required.

To fulfil this need, we conducted a non-inferiority study between human albumin and snakehead fish extract (SHFE) in protecting the glycocalyx layer through syndecan-1 levels.

2. METHODOLOGY

2.1. Study Setting

We used an analytic observational design with a prospective cohort study method. The aim of the study was non inferiority trial between SHFE and human albumin. We grouped sepsis patients, who met the qSOFA 2 criteria, were 18 y old, and were hospitalized in the intensive care unit (ICU) at our hospital with a sampling period of 2021 into two groups; control group and treatment group, following a three-day evaluation of the patient.

The research sample was obtained using a consecutive sampling technique. Whereas the sample of this study consisted of adult patients who were admitted to our ICU in May-October 2021 with a diagnosis of sepsis and who met the qSOFA 2 criteria. The exclusion criteria were subjects who met the inclusion criteria but were unable to participate in the study. Also patients with severe trauma and a bleeding class of more than 2, and those who had a history of nephrotic syndrome, were excluded.

2.2. Ethical Aspect

Formal approval to conduct research was obtained from the Faculty of Medicine, Sebelas Maret University, Ethical Committee. The study was carried out with the goal of not violating medical practice ethics or conflicting with human research ethics.

2.3. Study Setting

From all patients, a 5 ml sample of venous blood and 3 ml of arterial blood was collected. The venous blood sample was placed in a tube containing EDTA, to measure syndecan-1, creatinine, albumin, urea, sodium, potassium, chloride, and blood sugar; and the arterial blood was poured into a tube containing citrate, to measure PaO2/FiO2 ratio.

Patients were divided into two groups for this study. The study group (SHFE group) was given 15 mg of SHFE orally for two days. We used Onoiwa®, a SHFE that was commonly used in our hospital.

The control group was given 20 mg of human albumin intravenously for 2 days. In this control group we used Albapure® 20, a brand of human albumen 20% .

On the third day, 5 ml of blood was drawn and placed in an EDTA-containing tube from all patients and syndecan-1 levels were measured in blood samples.

2.4. Data Analysis

The Shappiro-Wilk test was used to determine the normality of the results. A paired t-test was performed for the same group and an independent t-test was performed between the two groups for normal and homogeneous results. If the distribution was abnormal and nonhomogeneous, the non-parametric Wilcoxon test for the paired group and the Mann-Whitney test for the two groups were used. STATA version 16.1 was used for the statistical analyses.

Table 1: Demographic characteristics and pre-test blood values

Parameter	Min–Max	Mean ± SD	Normal range
Gender (Male : Female)	26 : 18		
Age (y)	29–72	52.34 ± 11.497	
Initial Syndecan-1 (ng/ml)	2.187–9.760	7.83241 ± 1.630153	20 ng/ml
Creatinine (mg/dL)	0.3–12.0	26 ± 18	0.8–1.3 mg/dL
Urea (mg/dL)	11–229	50.45 ± 37.605	20–40
Sodium (mmol/L)	118–145	131.02 ± 5.394	136–145
Blood sugar (mg/dL)	107–357	211.27 ± 47.965	65-110 mg/dL
PaO_2/FiO_2 (mmHg)	53.1–265.0	113.69 ± 54.5845	400-500
Albumin (g/dL)	1.7–4.7	3.395 ± .5811	3.4 to 5.4
Chloride (mmol/L)	92–112	100.00 ± 3.870	96 to 106
Potassium (mmol/L)	3–6	3.98 ± 0.65	3.5 to 5.2
Lactate (mmol/L)	1.8–8.5	4.361 ± 1.567	0.5 to 2.2

3. RESULTS

The patients' average age was 52 y, and with 60% of the patients were male and 40% female. The patients had an increased blood sugar and a decreased PaO_2/FiO_2 ratio, with moderate grade of acute respiratory distress syndrome (ARDS) (Table 1).

Comparative biochemistry values of patients in two groups before the start of the study are presented in Table 2. There was statistically no

difference in any of the parameters in between the two groups. In our study the dependent variable that we examined was syndecan-1 variable. Where is the distribution of the levels of syndecan-1 results obtained. We found that the initial syndecan-1 level was 7.83 ng/ml and on the third day the level decreased to 6.805 ng/ml. We found that on the third day the majority of samples experienced a decrease in syndecan-1 levels in a total of 36 samples, and there were 8 samples that increase in syndecan-1 levels on the third day (P = 0.001).

Table 2: Comparative biochemical analysis between the groups

Variables	Contol Group (Human albumin)	Study Group (SHFE)	P-value
Initial Syndecan-1 (ng/mL)	7.99 ± 1.46	7.68 ± 1.78	0.503**
Creatinine (mg/dL)	1.71 ± 2.54	0.92 ± 0.38	0.517**
Urea (mg/dL)	57.43 ± 45.19	44.09 ± 28.61	0.192**
Sodium (mmol/L)	131.57 ± 5.51	130.52 ± 5.35	0.810*
Blood sugar (mg/dL)	221.52 ± 54.33	201.91 ± 40.26	0.054**
PaO2/FiO2 (mmHg)	122.98 ± 65.07	105.21 ± 42.61	0.672**
Albumin (g/dL)	3.25 ± 0.61	3.52 ± 0.52	0.072**
Chloride (mmol/L)	100.10 ± 4.53	99.91 ± 3.24	0.531*
Potassium (mmol/L)	3.95 ± 0.59	4 ± 0.71	0.804**
Lactat (mmol/L)	4.36 ± 1.78	4.35 ± 1.38	0.438**

t tes independent; ** mann whitney independent test; * pearson chi square test*

Table 3: Effect of SHFE albumin compared to human albumin on the difference in syndecan-1 levels

Groups	Syndecan-1 on 1st day	Syndecan-1 on 3rd day	p
SHFE Albumin	7.99 ± 1.46	6.99 ± 1.76	**0.027***
Human Albumin 20%	7.68 ± 1.78	6.63 ± 1.68	**0.013***
P	0.503**	0.459**	

**Wilcoxon signed rank test; **Mann Whitney independent test*

After dividing the syndecan-1 levels by study and control groups, we discovered that the study group had a 1.05 ng/ml decrease in syndecan-1 levels. Syndecan-1 levels in the control group fell as well, the difference was 1 ng/ml between 1st and 3rd day. On the 1st day, the level of syndecan-1 wasn't different between two groups (P = 0.503), as well as on the 3rd day (P = 0.459). On the 1st and 3rd days, both groups showed a significant decrease in syndecan-1 levels (P = 0.013 and P = 0.027, respectively), indicating that albumin can protect the glycocalyx layer and the protective effect on the glycocalyx layer was balanced between two groups.

4. DISCUSSION

There is damage to the endothelial glycocalyx layer in sepsis patients, and one of the biomarkers assessed is syndecan-1, whereas sepsis patients with elevated syndecan-1 have a worse prognosis than those who do not have elevated syndecan-1. Because the endothelial glycocalyx layer is composed of albumin, albumin is given to septic patients who have already damaged the endothelial glycocalyx layer. The endothelial glycocalyx layer is a semi-permeable layer for albumin molecules, and the presence of albumin in the layer determines its filter function. The endothelial surface layer is the functional unit of the endothelial glycocalyx layer and the albumin it contains. [13–16]

Although albumin is an important component of the endothelial surface layer and administration of albumin appears to be a reasonable suggestion for maintaining and improving the vascular barrier, experiments in isolated organs have shown that the endothelial surface layer can still function well at albumin concentrations as low as 10 g/L. As a result, failure of vascular barrier function in severe acute illness is caused by damage to the endothelial structures of the glycocalyx caused by hypervolemia, ischemia, or other forms of systemic inflammation, rather than hypoalbuminemia. [6,17–20]

The endothelial glycocalyx layer, on the other hand, can be stabilized by supplementing albumin in the endothelial surface layer. Furthermore, albumin contains sphingosine-1-phosphate, which inhibits Matrix Metallo Protein (MMP) activity on the endothelium. According to several studies, giving albumin for fluid resuscitation in septic patients can reduce mortality. According to some research on experimental animals, giving albumin in sepsis succeeded in reducing edema and maintaining

fluid balance, as well as preventing more severe damage to the glycocalyx. [6,19,21]

Aside from albumin, which has long been known to have anti-inflammatory benefits, SHFE albumin contains other complex proteins, omega-3 fatty acids, amino acids such as glycine, histidine, cysteine, glutamine, and tryptophan, vitamins A, D3, and E, and the mineral magnesium, which also functions as an anti-inflammatory. According to some study, SHFE albumin in vitro was able to inhibit pro-inflammatory cytokines such as TNF-, IL-6, which directly affect the formation of ROS, which is a source of damage to the endothelial glycocalyx layer and a source of organ failure in sepsis patients. [9–12]

The protective effect of albumin on endothelial glycocalyx layer has been shown in our research to reduce lining damage, which is characterized by a decrease in syndecan-1 levels from 7.83 ng/ml to 6.805 ng/ml for 3 days. This research backs up previous findings that albumin administration can protect the endothelial glycocalyx layer. Syndecan-1 levels stabilized in both the treatment and control groups, with both groups significantly lowering syndecan-1 levels ($P = 0.013$ and $P = 0.027$) from the first day levels. It also shows that administration of SHFE albumin is able to stabilize the endothelial glycocalyx layer when compared to 20% human albumin intravenously because previous studies have shown that administration of SHFE albumin is able to increase albumin levels equivalent to human albumin, so with comparable albumin levels, it turns out from our research that the protective effect on the glycocalyx layer is similar.

5. CONCLUSION

In our study, albumin from snakehead fish extract was found to be just as effective as human albumin in protecting the endothelial glycocalyx layer by significantly lowering syndecan-1 levels in septic patients. Even in terms of economic value, albumin derived from Channa striata extract outperforms human albumin because, in addition to being less expensive (1/3 the price of human albumin), the raw material is easy to obtain in developing countries with tropical climates.

6. Data availability

The numerical data generated during this research is available with the authors.

7. Acknowledgement

The authors of this study are grateful to Dr Moewardi Hospital for providing them with the opportunity to work within the clinics and use all of the facilities.

8. Conflict of interest

The authors declare that they have no conflict of interest. The study utilized the hospital resources only, and no external or industry funding was involved.

9. Research ethics

All procedures in studies involving human participants were carried out in accordance with the institutional and/or national research committee's ethical standards (Dr Moewardi Hospital ethical committee number 1.130 on September 29th, 2020), as well as the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

10. Authors' contribution

All authors took part in the concept, conduct od the study, data collection, literature search and manuscript preparation. All authors approve the final proof.

11. REFERENCE

1. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. Lancet. 2020;395(10219):200-211. DOI: 10.1016/S0140-6736(19)32989-7
2. Sullivan RC, Rockstrom MD, Schmidt EP, Hippensteel JA. Endothelial glycocalyx degradation during sepsis: Causes and consequences. Matrix Biol Plus. 2021;12:100094. DOI: 10.1016/j.mbplus.2021.100094
3. Iba T, Levy JH. Derangement of the endothelial glycocalyx in sepsis. J Thromb Haemost. 2019;17(2):283-294. DOI:https://doi.org/10.1111/jth.14371
4. Bertrand J, Bollmann M. Soluble syndecans: biomarkers for diseases and therapeutic options. Br J Pharmacol. 2019;176(1):67-81. DOI: 10.1111/bph.14397
5. Ushiyama A, Kataoka H, Iijima T. Glycocalyx and its involvement in clinical pathophysiologies. J intensive care. 2016;4(1):59. DOI: 10.1186/s40560-016-0182-z
6. Aldecoa C, Llau J V, Nuvials X, Artigas A. Role of albumin in the preservation of endothelial glycocalyx integrity and the microcirculation: a review. Ann Intensive Care. 2020;10(1):85. DOI:10.1186/s13613-020-00697-1
7. Uchimido R, Schmidt EP, Shapiro NI. The glycocalyx: a novel diagnostic and therapeutic target in sepsis. Crit Care. 2019;23(1):16. DOI: 10.1186/s13054-018-2292-6
8. Isamahendra N, Hariani L, Murtiastutik D. Systematical Review Efektivitas Pemberian Kapsul Ekstrak Channa striata Terhadap Kadar Albumin pada Kasus Luka Bakar. J Rekonstruksi dan Estet. 2021;6:65. DOI: 10.20473/jre.v6i2.31835
9. Suhendi A, Puspa F, Pawarti H. AKTIVITAS ANTIOKSIDAN EKSTRAK IKAN GABUS (Channa striata) PADA TIKUS YANG DIINDUKSI DENGAN RIFAMPISIN-ISONIAZID. J Kesehat. 2020;13:69-77. DOI: 10.23917/jk.v13i1.11103
10. Ramadhanti N, Sandhika W, Widodo A. The Effect of Snakehead Fish (Channa striata) Extract on Inflammation Reaction of Skin Wound Tissue in Rattus novergicus Wistar

Strain. Berk Ilmu Kesehat Kulit dan Kelamin. 2021;33:48. DOI:10.20473/bikk.V33.1.2021.48-54

11. Kania D, Oktiani B, Candra C, Adhani R. ANTIOXIDANT ACTIVITY POTENCY OF CHITOSAN FROM HARUAN (CHANNA STRIATA) SCALES. Dentino J Kedokt Gigi. 2020;5:139. DOI: 10.20527/dentino.v5i2.8951
12. Dwijayanti D, Djati M, Rifa'i M. The role of VipAlbumin® as an immunostimulatory agent for controlling homeostasis and proliferation of lymphoid cells. Cent J Immunol. 2016;41:31-38. DOI: 10.5114/ceji.2016.58814
13. Piotti A, Novelli D, Meessen JMTA, et al. Endothelial damage in septic shock patients as evidenced by circulating syndecan-1, sphingosine-1-phosphate and soluble VE-cadherin: a substudy of ALBIOS. Crit Care. 2021;25(1):113. DOI: 10.1186/s13054-021-03545-1
14. Joffre J, Hellman J. Oxidative Stress and Endothelial Dysfunction in Sepsis and Acute Inflammation. Antioxid Redox Signal. 2021;35(15):1291-1307. DOI: 10.1089/ars.2021.0027
15. Ince C, Mayeux PR, Nguyen T, et al. THE ENDOTHELIUM IN SEPSIS. Shock. 2016;45(3):259-270. DOI: 10.1097/SHK.0000000000000473
16. Schött U, Solomon C, Fries D, Bentzer P. The endothelial glycocalyx and its disruption, protection and regeneration: a narrative review. Scand J Trauma Resusc Emerg Med. 2016;24(1):48. DOI: 10.1186/s13049-016-0239-y
17. Vincent JL, Russell JA, Jacob M, et al. Albumin administration in the acutely ill: what is new and where next? Crit Care. 2014;18.
18. Taverna M, Marie AL, Mira JP, Guidet B. Specific antioxidant properties of human serum albumin. Ann Intensive Care. 2013;3(1):1-7. DOI: 10.1186/2110-5820-3-4
19. Vincent JL, De Backer D, Wiedermann CJ. Fluid management in sepsis: The potential beneficial effects of albumin. J Crit Care. 2016;35:161-167. DOI: 10.1016/j.jcrc.2016.04.019
20. Caironi P, Tognoni G, Masson S, et al. Albumin Replacement in Patients with Severe Sepsis or Septic Shock. N Engl J Med. 2014;370(15):1412-1421. DOI: 10.1056/NEJMoa1305727
21. Wiedermann CJ. Phases of fluid management and the roles of human albumin solution in perioperative and critically ill patients. Curr Med Res Opin. 2020;36(12):1961-1973. DOI: 10.1080/03007995.2020.1840970

