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The Efficacy of Albumin Channa Striata Extract Administration in Stabilizing PAI-1 and Platelet Levels in Septic Patients: A Randomized Control Trial Study

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Abstract

BACKGROUND: Recently, sepsis has become a serious problem worldwide. There are many studies trying to find the etiologies of morbidity and mortality of sepsis. One of them is the damage of endothelial glycocalyx layer, which can lead to an increase in plasminogen activator inhibitor-1 (PAI-1) level and a decrease in platelets. This damage can be prevented by administering albumin; unfortunately, it is costly. Therefore, an alternative albumin is required. Channa striata extract albumin has been found to be relatively effective in increasing serum albumin levels. However, studies on its effectiveness are still limited. Hence, we analyzed this channa striata extract albumin in stabilizing PAI-1 and platelet levels of septic patients.

AIM: This study analyzed channa striata extract albumin in stabilizing PAI-1 and platelet levels of septic patients.

METHODS: We conducted a randomized control experimental study in patients with sepsis hospitalized at Dr Moewardi Hospital, Surakarta, Indonesia. The samples were taken by consecutive sampling technique. These patients were allocated into two groups, the albumin extract of channa striata, and human albumin 20% (the control) groups. We examined the PAI-1 and platelet levels on the 1st and 3rd days. We used Mann–Whitney test for statistical analysis with $p < 0.05$ was considered significant.

RESULTS: There were 21 subjects in each group of channa striata (study) and human albumin (control). The increase of PAI-1 level in the study group (0.36 ng/ml) was lower than that of in control group (0.72 ng/ml). More subjects in study group experienced decreased PAI-1 level (n = 5) than those in control group (n = 3), the decrease more profound in control group (p = 0.004) than study group (p = 0.054). The decrease of platelet level was also greater in study group (22 × 103/mcl) than that of in control group (1 × 103.md) despite insignificant difference (p = 0.364 and p = 0.468).

CONCLUSION: The administration of channa striata extract effective in stabilizing PAI-1 level in sepsis patient and also had potential benefit as human albumin in stabilizing platelet levels of septic patients.

Introduction

Today, sepsis has become a major problem in health services, in terms of morbidity and mortality as well as in financial problems. This encourages health practitioners to make strategies to overcome this problem. One of the therapeutic strategies in current sepsis is the use of albumin. This albumin is important in maintaining the endothelial glycocalyx layer which is one of the factors that play a role in morbidity and mortality of septic patients. Unfortunately, this strategy of presenting albumin requires a large amount of money. This facilitates the implementation of the strategy in developing countries as well as in rural areas. For this reason, it is necessary to carry out this albumin administration strategy but at a lower cost, and with the same effectiveness as the existing albumin therapy [1], [2], [3], [4], [5], [6], [7], [8], [9], [10].

Recently, several studies have proposed the use of channa striata extract albumin as an alternative to human albumin as this type of fish apparently has high albumin content and several studies have shown a comparable effectiveness to that of intravenous albumin in terms of increasing albumin levels in critically ill patients. However, further studies are still required its in maintaining the endothelial glycocalyx layer which is related to function in maintaining patient hemostasis. One of functions glycocalyx layer is to maintain the body's blood clotting function so that microthrombus does not occur which will result in decreased perfusion to cells and tissues. Decrease in perfusion caused by microthrombi in septic patients will increase the risk of morbidity, multi-organ disorders, and mortality. The function of the glycocalyx in maintaining blood coagulation is characterized by increased levels of plasminogen activator inhibitor-1 (PAI-1). The role of albumin in preventing the elevation of PAI-1 is through stabilization of the endothelial glycocalyx layer [4], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], [21], [22].

Apart from PAI-1, one of the commonly used markers of impaired hemostasis in septic patients is a decrease in platelet levels or thrombocytopenia. At

present, there is a scoring system using hemoglobin, albumin, leukocytes, and platelets/platelets (HALP) which a one marker of the severity of inflammation occurring that occurs in sepsis. There are several studies showing that show that albumin has the ability as well as an anti-inflammatory effect, whereas its administration to sepsis is expected to reduce severe inflammation which, in turn, can prevent a decrease in platelet levels in septic patients. This is probably due to the ability of albumin to bind to arachidonic acid, which, in turn, is able to prevent platelet aggregation. It should also be assessed the effectiveness of intravenous albumin compared with albumin extract of *Channa striata*. Therefore, we conducted this study to assess the effectiveness of albumin extract of *Channa striata* on its effect on PAI-1 and platelet levels in septic patients [11], [12], [19], [20], [21], [22], [23], [24].

Methods

We performed a double-blind experimental randomized control trial in septic patients treated in Critical Care Installation of Dr Moewardi Hospital Surakarta Indonesia, during 2020. We only included septic patients meeting the Qsofa2 criteria (two of three criteria such as tachypnea, decrease in blood pressure, and decrease in awareness), aged > 18 years old and willing to participate in the study by signing informed consent. These subjects were randomly assigned in two groups, the treatment group receiving channa striata extract albumin 15 g/day orally for 2 days, and control who received 20% human albumin orally for 2 days and control group who received 20 g intravenously on the 1st day. We double blind the subject and the main researcher. We evaluated all subjects for three days. Blood samples were taken from all subjects. We drew 5 ml of venous blood and 3 ml of atrial blood from each subject in both groups before the procedure and after completing the therapy (on the 3rd day), the venous blood was put in a tube containing EDTA, while the arterial bloods were placed in a tube containing citrate. These blood samples were measured for platelet level and PAI-1.

The data obtained were analyzed statistically with statistical programming applications. The data obtained in the form of differences in levels before and after treatment of each dependent variable were compared between the control and treatment groups. Initially, the data were checked for normality using the Kolmogorov–Smirnoff test, if the data were distributed normally, homogeneity test was then carried out using the Lavene test. Paired t-test and unpaired t-test were done in the same group and between groups, respectively, for homogenous normal distribution data. However, if the data were not distributed normally or hetergenous, then Mann–Whitney test was applied. If the external variable was suspected to have an influence (confounding), then a multivariate analysis with linear regression was carried out. The hypothesis would be accepted if $p > 0.05$, meaning there is no significant difference between the effectiveness of albumin extract of *Channa striata* and that of intravenous albumin on the dependent variable.

Table 1: Patient sample distribution

Variable	Mean ± SD
Sex, n (%)	
Male	26 (62)
Female	16 (38)
Age (years)	53.05 ± 11.13
Mean arterial pressure (mmHg)	75 ± 14
SpO^2 (%)	96 ± 2.2
Albumin (mg/dL)	3.37 ± 0.6
Random blood sugar (mg/dL)	209 ± 46
Platelets (×10^3/mcl)	281 ± 112
Bilirubin (mg/dl)	1.07 ± 0.57
PAI-1 (ng/ml)	0.8 ± 1.2
Sepsis due to	
Pneumonia	14
Blood stream infection	25
Others	3

PAI-1: Plasminogen activator inhibitor-1, SD: Standard deviation.

Results

Forty-four patients met our inclusion criteria who were then equally allocated into channa striata extract albumin as a study group and 20% human albumin as the control group. Males were predominant subjects (62%). The mean age of the subjects was 53 years

Table 2: Distribution of samples after being grouped based on treatment

Variable	Mean ± SD		n		p
	Albumin *C. striata*	Human albumin intravena	Albumin *C. striata*	Human albumin intravena	
Sex					
Male			13	13	1*
Female			8	8	
Age (years)	51.57 ± 12.18	54.52 ± 10.05			0.397**
Mean arterial pressure (mmHg)	79.14 ± 16.5	71.24 ± 10.76			0.101***
SpO_2 (%)	95.52 ± 1,86	96.4 ± 2.54			0.075***
Albumin (mg/dL)	3.48 ± 0.52	3.25 ± 0.6			0.133***
Blood glucose in the 1st day (mg/dL)	197 ± 32.4	221.52 ± 54.3			0.032**
Blood glucose in the 3rd day (mg/dL)	207.19 ± 14.1	216.24 ± 37.69			0.309**
Difference in blood glucose at 1st and 3rd day	3.19 ± 49.1	−5.29 ± 48.5			0.358***
Platelets (×10^3/mcl)	297 ± 93	265 ± 127			0.354**
Bilirubin (mg/ml)	1.05 ± 0.37	1.09 ± 0.72			0.813**
PAI-1 (ng/ml)	0.59 ± 0.5	0.98 ± 1.65			0.406***
Sepsis due to					
Pneumonia	7	7			0.830*
Blood stream infection	13	12			
Others	1	2			

*Chi-square, **t-test independent, ***Mann–Whitney. *C. striata*: *Channa striata*, PAI-1: Plasminogen activator inhibitor-1, SD: Standard deviation.

old. The mean arterial pressure was 75 mm Hg with oxygen saturation of 96%. The mean levels of albumin, platelet, and PAI-1 were 3.37 mg/dl, 281 × 103/mcl, and 0.8 ng/ml, respectively (Table 1).

All subjects recruited in the study were randomly assigned into study and control group, in which each group comprised 13 males and eight females. Regarding mean general pressure, oxygen saturation, albumin level, platelet level, bilirubin level, and PAI-1 at baseline were comparable between groups. Only blood glucose level showed a significant difference, whereas it was higher in the control group (221.52 + 54.3) than that of in study group than that of in study group (197 + 32.4) obtaining p value of 0.032. However, on the 3rd day, the blood glucose level of the study subjects increased to 209.19 + 14.1, while, in control group, there was a decline of blood glucose level from 221.52 + 54.3 to 216.24 + 37.69 (Table 2).

Table 3: Distribution of plasminogen activator inhibitor-1 (ng/ml) on the 1st and 3st days

PAI-1 distribution	1st day (ng/ml)	3rd days (ng/ml)
Range	0.007–5.97	0.03–10.135
Median	0.26	0,32
Mean ± SD	0.793 ± 1.22	1.27 ± 1.95

SD: Standard deviation, PAI-1: Plasminogen activator inhibitor-1.

In term of PAI-1 level, we found an increase from 0.793 ng/ml at baseline to 1.27 ng/ml. The majority of subjects experienced elevated PAI-1 level 6n the 3rd day (n = 34), while eight subjects had a decrease in PAI-1 level (Tables 3 and 4).

In comparison to control group, subjects in study group (0.36 ng/ml) had a lower increase of PAI-1 level than those in control group (0.72 ng/ml), though the difference was not significant (p = 0.503) (Table 5).

Table 4: Changes in plasminogen activator inhibitor-1 levels on the 1st and 3rd days

Changes in PAI-1	Sample (n)
Level increase	34
Level decrease	8
Ties	0
P	0.00*

*Wilcoxon signed-rank test. PAI-1: Plasminogen activator inhibitor-1.

We also found that the initial platelet levels on the 1st day of the study were 281 × 10^3/mcl and on the 3rd day it dropped to 270 × 10^3/mcl (Table 6).

Table 5: Administration of albumin extract of *Channa striata* compared with human albumin on the difference in plasminogen activator inhibitor-1 levels between 1st and 3rd day

Intervention	Difference level PAI-1 (ng/ml)	Level decrease (n)	p
Channa striata extract albumin	0.36 ± 0.85	5	0.150*
Human albumin 20%	0.72 ± 2.3	3	0.004*

*Wilcoxon signed-rank test. PAI-1: Plasminogen activator inhibitor-1.

There were 26 subjects who had a lessen platelet level, while the other l6 subjects experienced an elevation (p = 0.645) (Table 7).

Table 6: Distribution of platelet (10^3/mcl) on the first and third days

Platelet distribution	1st day	3rd day
Range	31–511	17–573
Median	266.5	244.5
Mean ± SD	281 ± 112	270.19 ± 131

SD: Standard deviation.

Both at the baseline and at the end of the observation, the platelet level of subjects in the study group was lower that of in control group. The decline was more pronounced in the study group from 249 × 10^3/mcl to 227 × 10^3/mcl than in control group, from 304 × 10^3/mcl to 303 × 10^3/mcl. However, this difference was insignificant statistically (p = 0.187) (Table 8).

Table 7: Changes in platelet levels on the 1st and 3rd day

Platelet changes	Sample (n)
Level increasing	16
Level decreasing	26
P	0.645*

*Wilcoxon signed-rank test.

Discussion

This present study obtained 42 subjects comprising 26 males and 16 females.

Table 8: The relationship between the administration of *Channa striata* extract albumin compared with human albumin on the difference in platelet levels

Intervention	Initial platelet (10^3/mcl)	Final platelet (10^3/mcl)	Level decreasing (n)	p
Channa striata extract albumin	249 ± 116	227 ± 122	12	0.364*
Human albumin 20%	304 ± 101	303 ± 127	13	0.468*

*Paired t-test.

These subjects were then assigned into control (intravenous human albumin) and treatment (channa strata albumin) group. These subjects were distributed to both group evenly (p = 1). The mean age of subjects in control (54.5 years old) and treatment (51.5 years old) groups were comparable (p = 0,397). Only blood glucose level showed a significant difference, whereas it was higher in the control group (221.52 + 54.3) than that of in study group than that of in study group (197 ± 32.4) obtaining p value of 0.032. However, on the 3rd day, the blood glucose level of the study subjects increased to 209.19 ± 14.1, while, in control group, there was a decline of blood glucose level from 221.52 ± 54.3 to 216.24 ± 37.69. It means that blood glucose did not affect the outcome.

This study also revealed no significant differences in both control and treatment groups regarding the levels of albumin, platelet bilirubin, and PAI-1, with p values of 0.133, 0.354, 0.813, and 0.406.

We found that the mean PAI-1 level of our subjects increased from 0.793 ng/ml at baseline to 1.27 ng/ml on day 3 at the end of our observation. Of the 42 subjects, 34 of them experienced an increase in PAI-1 levels on the 3rd day, while eight samples had a decrease in PAI-1 levels (p = 0.00). The PAI-1 levels of our subjects were relatively low when compared to PAI-1 levels of septic patients in general. This indicates that the administration of albumin can suppress the increase in PAI-1 levels in septic patients. Hence, it is expected to reduce the complication rate which occurs

as a result of elevated PAI-1 levels in septic patients. The increase in PAI-1 levels in sepsis is caused by an inflammatory process that occurs in the endothelial glycocalyx layer which causes damage to this layer. This leads to an increase in the systemic release of PAI-1. Inflammation occurring in the endothelial glycocalyx layer can be ameliorated by administration of albumin, besides that albumin is also an important component of the endothelial glycocalyx layer. Thus, administering of albumin can prevent damage to the glycocalyx layer as well as help the regeneration of the layer, and this further leads to inhibition of the release of PAI-1 to the systemic [4], [11], [12], [13], [18].

In this study, the increase of PAI-1 level in subjects, receiving channa striata albumin, was lower ($p = 0.054$) than that of in those getting intravenous human albumin which the increase was more profound ($p = 0.004$). Channa striata albumin also succeeded in lowering PAI-1 level in five subjects, which was more than the intravenous albumin group which only reduced PAI-1 levels in three patients. This finding is in accordance with the previous studies reporting that albumin extract of *Channa striata* has an anti-inflammatory and antioxidant effect which can stabilizing PAI-1 level in sepsis patient because besides containing albumin, Channa striata extract also contains chitosan and glutathione [19], [23], [25], [26], [27], [28], [29], [30], [31], [32], [33].

Sixty percentages of the total subjects experienced a decrease in platelet levels as well as in other septic patients. However, this decline is still in the normal range. It indicated that the administration of albumin in septic patients can suppress the decrease in platelet levels so that it can be expected to reduce the risk of complications such as disseminated intravascular coagulation which is common in septic patients. Thrombocytopenia also frequently occurs in sepsis. Its occurrence is about 50% in sepsis. One of the factors causing thrombocytopenia in sepsis is the occurrence of platelet aggregation resulted from its adhesion and activation by vascular endothelium. This is consistent with our study, whereas the majority of samples experienced a decrease in platelet levels. Adhesion and activation of platelets can be prevented or suppressed by protecting the vascular end hotel from being damaged, one of which is by administering of albumin preparations [14], [16], [20], [22], [26].

Channa striata albumin administered to our subjects prevented a decrease in platelet levels in 9 samples, while intravenous albumin could prevent a decrease in platelet levels in eight samples. In samples that experienced a decrease in platelet levels, the difference the reduction in platelet level was greater in *Channa striata* albumin group (22×10^3/mcl) when compared to the control group (1×10^3/mcl), although the difference was statistically not significant ($p = 0.364$ and $p = 0.468$). This indicates that both channa striata albumin human albumin can suppress the decrease of platelet level. It is thought the mechanism is through the protective pathway of the glycocalyx layer and anti-inflammatory properties [19], [23], [24].

The administration of *Channa striata* extract albumin in our study was much cheaper than intravenous albumin. With a dose for 2 days of at 15 g/day, albumin extract of *Channa striata* only costs 25% of the price of 20% intravenous albumin. It is very cost effective with equal effectiveness in terms of PAI-1 and platelet levels for septic patients, particularly for developing countries.

Study limitation

Albumin from channa striata extract given only by enteral route, but in septic shock patient we usually found gastrointestinal bleeding. Hence, our strategy to handle this study limitation was by collect the sample as early stages of sepsis as possible, by collecting septic patients, not only in Intensive Care Unit (ICU) but also in High Care Unit (HCU).

Conclusion

Channa striata extract albumin has better effectiveness in stabilizing PAI-1 level in sepsis patient than human albumin 20%. Moreover, Channa striata extract has equivalent effectiveness to intravenous albumin in its ability to prevent decrease in platelet levels in septic patients, even though it is much cheaper than intravenous albumin.

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