The effects of albumin concentration to outcome of acute respiratory distress syndrome (ARDS) patients in intensive care unit RSUP Dr. Sardjito Yogyakarta

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ABSTRACT

Background: Hipoproteinemia mostly happened in critically ill patients, including ARDS, and usually comes to worst clinical appearance. Early ARDS is characterized by a rising of the permeability in the alveolar-capillary barrier, leading to an influx of fluid into the alveoli, and albumin also has a major role to control the osmolatory of plasma.
Aim: The aim of the study was to know about the effect of the albumin concentration to outcome (survivor/non-survivor) of the ARDS patient in the Intensive Care Unit (ICU) RSUP Dr. Sardjito.
Methods: This study used cross-sectional method. The samples of this study were the patients at the ICU RSUP Dr. Sardjito Yogyakarta, from January 2009 until December 2011. The diagnosed of ARDS based on EACC criteria. The inclusion criteria were people with age ≥ 18 years old, fulfill diagnostic criteria of ARDS, and treated in ICU. The demography, laboratory result, and curing process, have been tested statistically in SPSS 17. The variable was analyzed by chi-square and Mann-Whitney test, significantly considered if p < 0,05.
Results: The samples who fulfill these criteria were 61 patients. Mostly women (54,1%) with 49 years-old range and the result were 34 patients (55,7%) died. The biggest cause of ARDS was pneumonia (60,7 %) and the biggest Comorbid was malignant (21,6%). The mortality rate of ARDS was 5,75%. The result of univariat analysis was the increased of transaminase enzyme (p 0,007), COPD Co morbid (p 0, 02) and length of stay in the ICU (p = 0,021) which was significantly given effect to the outcome of the patients. The survivors have higher albumin concentration (2, 6) than in non survivors (2, 4), although not statistically significant (p = 0,621).
Conclusion:The albumin concentration did not have a statistically significant effect to the outcome of the ARDS patient in ICU RSUP Dr. Sardjito Yogyakarta. The main factor was the increase of transaminase enzyme, Co morbid COPD, and length of stay in the ICU.

Keywords: ARDS, albumin concentration, ICU

INTRODUCTION

Nowadays**,** *Acute Respiratory Distress Syndrome* (ARDS) still remains as severe disease with a high mortality rate (around 40-60%). The use of mechanical ventilation and service of treatment in *the Intensive Care Unit* (ICU) possibly may decrease the rate of morbidity and mortality of ARDS patient treated in ICU.[1]

ARDS increased in the condition of direct lung injury (pneumonia, the aspiration of gastric fluid, inhalation of toxically gas, sinking, contusion of the lung, the embolism of the lung) and indirect lung injury (sepsis, trauma, burn injury, acute pancreatitis, cardiopulmonary shunt, drug overdose, and transfusion giving > 50% of the blood volume in 12-24 hours).[1]

Hipoproteinemia is the common condition which happening to the critically ill patients, include acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) cases, and usually correlated with the worst clinical outcome.[2]

Hypoproteinemia accelerates fluid exudation, promotes alveolar edema, and contributes to ventilation-perfusion imbalance.[3] The decrease of serum total protein, especially albumin, is significantly correlated with fluid retention and weight gain, development of ARDS and poor respiratory outcome, prolonged mechanical ventilation, mortality in patients with sepsis. 92% of the patients developing ARDS had low or borderline serum total protein levels (<6 g/DL).[4]

Albumin is a multi-functional protein consists of 585 amino acids, with normal concentration 35-50 g/L in plasma. Albumin has an important physiologic and pharmacologic function i.e.: *metals*, fatty acid, cholesterol, bile pigment, and drug transport. Albumin is also a key element in an osmolarity pressure and fluid distribution in a different compartment.[5]

Albumin is also representing the main antioxidant and predominant in plasma, which is the place where the oxidative stress continuously being exposed. The large amount of antioxidant serum is albumin. The recent study shows that more than 70% free radical

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activity suppressed by albumin serum, which has been shown in a test using *free radical-induced hemolysis test*.[6] So, the giving of albumin for ARDS patients protect them from oxidative stress, and give some beneficial effects in an inflammation regulation process caused by oxidative reduction.[5] There are a lot of clinical studies about albumin role in the outcomes of ARDS patients. But, the study about albumin concentration and the effect of outcomes in ARDS patient treated in ICU RSUP Dr. Sardjito is never been done. This study is expected to be an initial study for the bigger study in the future.

METHODS

The sample was taken as much as the amount of the patients in the ICU RSUP Dr. Sardjito Yogyakarta between January 2009 – December 2011. The diagnose of *Acute Respiratory Distress Syndrome* (ARDS) made in accordance to the diagnostic criteria of European-American Consensus Conference on ARDS: clinical syndrome which was marked with immediate severe dyspnoea (acute onset) with PaO2/FiO2 ≤ 200mmHg, bilateral infiltrates seen on chest radiograph, and pulmonary artery wedge pressure ≤18 mmHg. The inclusion criteria was the patient with the range of age ≥8 years, fulfill the diagnoses of ARDS criteria were acute onset of severe dyspnoea, bilateral infiltrates on chest radiograph and PaO2/FiO2 ≤ 200mmHg from blood gas analysis, whose treated in the ICU and have the complete medical record. The patient was excluded from the sample study if the medical record was not complete. The data consist of demography, laboratory result, follow up and treatment from a patient's medical record.

Statistical Analysis

The data were processed with Statistical Product and Service Solutions (SPSS) 17. The measured variables being analyzed with the Chi-square test for categorical data and Mann-Whitney test for numerical data. P <0, 05 was considered significant with confidence interval (CI) 95%.

RESULT

The sample of the study who fills the criteria were 61 patients, with the large amount of women (54,1%), the biggest range of age was 46-60 years and average age of the subjects was 49 years. 34 patients (55,7%) died and 27 patients (44,3%) survive. The cause of ARDS are pneumonia (60,7%), non-pulmonal infection (10,76%), and trauma 8,2%. The comorbids were malignant (24,6 %), diabetes mellitus (19,7%), COPD (6%), asthma (1,6%), and tuberculosis (1,6%).

Table 1. The Characteristic of Subject Study

The Characteristic of Subject Study N (%)	
Age	49 years (average)
15-30 years	12 (19.7)
31-45 years	9 (14.8)
46-60 years	21 (34.4)
>60 years	19 (31.1)
Men	28 (45.9)
Women	33 (54.1)
Predispotition Factors	
Sepsis, et causa:	28 (45.9)
Pneumonia	17 (60.7)
Non-pulmonal Infection	3 (10.7)
Non sepsis, et causa:	33 (54.1)
Trauma	4 (8.2)
Comorbids	
Diabetes Mellitus	12 (19.7)
Cancer	15 (24.6)
COPD	4 (6.6)
Asthma	1 (1.6)
Pulmonary TB	1 (1.6)

The mortality rate of ARDS patient treated in ICU RS Dr. Sardjito is 55, 75%. This rate shows us that the prognose of the ARDS patient treated in ICU was not good as well. This result was similar to the study of Chan-Yu Lin *et al.* (2009), which shows us about the high number of ARDS mortality rate patients (45-57%). The result of univariat shows us that only liver disorders parameter which represented by the significant increase of transmissions enzyme affect the outcome (survive/non-survive) with p = 0,007. But this thing was being statistically insignificant when the SGPT concentration being grouped into normal and above normal (with the *cut of point* 56). This result was similar to the last study. Wang Deng *et al.* (2012) has done the study to 85 Miliary TB Patient with ARDS, conclude that the independent factor of ARDS was comorbids DM, the increase of transaminase enzyme (AST ALT), D-dimer, hemoglobin and hypoalbumin. The other factor confluence the outcome were COPD with p 0, 02 and length of stay in the ICU with p = 0,021, while the average of albumin concentration in survivor group was higher than non-survivor group (2, 64 vs. 2, 4), although the decrease of albumin concentration was not statistically significant with p = 0,621.

DISCUSSION

In humans, albumin is the most abundant plasma protein, accounting for 55-60% of the measured serum protein. It consists of a single polypeptide chain of 585 amino acids with a molecular weight of 66.500 Da. The serum albumin concentration is

Table 2. The Characteristic of Subject Study Based on Outcome

Characteristic	Survivors 27 (44.3%)	Non-Survivors 34 (55.7%)	P value
Age	53 (42-69)	48 (37.5-60.5)	.220
Men	11 (39)	17 (61)	.471
Women	16 (49)	17 (51)	
Predispotition Factor			
Trauma	3 (60)	2 (40)	.463
Pneumonia	14 (56)	11 (44)	.124
Sepsis	15 (53)	13 (47)	.178
Comorbid			
Diabetes Mellitus	5 (42)	7 (58)	.841
Cancer	5 (33)	10 (67)	.326
COPD	0 (0)	4 (100)	.020
Asthma	1 (100)	0 (0)	.258
Pulmonary TB	1 (100)	0 (0)	.258
Other infection	2 (33.3)	4 (66.7)	.570
Laboratorium			
Leukosit	13.6 (9.5 – 19.9)	15.6 (9 - 17.6)	.835
Absolute Netrofil Count	11.4 (7.23-14.92)	11.1 (7.58-17.54)	.662
Hematocrite	35.1 (26 - 36.9)	34.8 (31 - 39.4)	.379
Trombosite	171 (51.9 - 312)	206 (104 - 320)	.499
Glucose	134 (87 - 164)	133 (122 - 178)	.400
Creatinine	0.9 (0.77 - 1.33)	1.04 (0.63 - 2.12)	.778
Uric Acid	4.5 (3.8 - 7.8)	5.6 (4.6 - 7)	.482
Albumin	**2.64 (2.1 - 2.8)**	**2.4 (1.9 - 2.9)**	**.621**
SGOT	44 (25 - 70)	68 (37 - 96.7)	.064
SGPT	27 (19.1 - 38)	48 (28.3 - 94.8)	.007
SGPT > 56	8 (40)	12 (60)	.640
pH	7.389 (7.28 - 7.45)	7.40 (7.36 - 7.45)	.391
PO2/FiO2	171.0 (113 - 188)	139.0 (92.5 - 171.5)	.059
pCO2	34.2 (29.8 - 46.2)	34.1 (25.6 - 55.7)	.858
Vasopressor	2 (33.3)	4 (66.7)	.573
Others			
Length of stay in the ICU	5 (4 - 15)	3.2 (2 - 10)	.021

The data is being showed in number (%), or median (persentil 25-75)

determined by its rates of synthesis and degradation and its distribution between the intravascular and extra vascular compartments. The total body albumin pool measures about 3.5-5.0 gram/kg body weight (42% in the plasma compartment). Some of this is tissue-bound and is therefore unavailable to the circulation. Each day, 120-145 grams of albumin are lost into the extra vascular space. Most of this is recovered back into the circulation by lymphatic drainage.[9]

Critical illness alters the distribution of albumin between the intravascular and extra vascular compartments. There are also changes in the rates of synthesis and degradation of the protein. The serum albumin concentration will decrease, often dramatically, from early in the course of a critical illness. It will not increase again until the recovery phase of the illness.

The implication of this, given the important functions albumin has on health, is that using exogenous albumin to increase the intravascular albumin concentration during critical illness is beneficial. But studies have failed to show any benefit of albumin over other colloidal therapies in adults.[9]

The altered distribution in critical illness is related to an increase in capillary leakage. This occurs in sepsis and after major surgical stress. It involves dysfunction of the endothelial barrier, resulting in capillary leakage and loss of protein, inflammatory cells and large volumes of fluid into the interstitial space. The rate of albumin synthesis may be significantly altered in the critically ill, that cause hypoproteinemia.[9]

In healthy subjects, albumin contributes up to 80% of the normal colloid oncotic pressure (COP) of

about 25 mmHg. Critically ill patients have a lowered serum COP. A sequential series of 200 critically ill patients had a mean COP of 19, 1 mmHg. A lowered serum COP is associated with increased morbidity and mortality in critically ill patients.[9]

The albumin content in lung interstitial tissue contains about 70% of the albumin in plasma. Under normal conditions, the pulmonary lymphatic system clears albumin and fluid rapidly from the interstitial tissues. When blood becomes hypoosmotic as a result of hypoproteinemia, a transient increase in lung lymphatic flow decreases the amount of albumin in the lung interstitial tissue, quickly counterbalancing the change. This shift promotes reequilibration of the osmotic gradient.

Conversely, an increase in serum COP increases the osmotic gradient in the serum so that cell free fluid drifts from the interstitial tissues into the intravascular space, promoting a drier lung in patients in shock. If signs of shock are not addressed and fluid dynamics restored, misdistribution of extracellular fluid accompanied by plasma volume deficiency can predispose the patient to pulmonary edema and acute respiratory distress syndrome (ARDS).

ARDS is a condition that develops as a result of lung inflammation. Leaking capillaries and pulmonary edema severely injure the lung, leading to respiratory failure. Lymphoid function can become overwhelmed by increased transcapillary escape or fluid flux from edema.[10]

Research by Jia *et al.* (2.583 ARDS patients), shows that the lower albumin were significantly associated with the development of ARDS in univariat analyze. The other major risk factors included sepsis, low pH, elevated lactate transfusion of packed red cells, transfusion of plasma, high net fluid balance and low respiratory compliance.[11]

The last research, which analyzed about the predictive factors of mortality in ARDS patients, showed the varying results. The research of Bhadade *et al* shows us that the predictive factors of mortality ARDS patients are APACHE score, the using of mechanical ventilators, hypoalbuminemia and acidosis. [1] While Chan-Yu Lin *et al.* shows that age, score APACHE III, liver disorders, renal function disorders, cancer metastage, bilirubin serum, and also glucose independently affecting the mortality numbers of ARDS patients.[7] The research of Monchi *et al.*, shows that the predictive factor of mortality ARDS patients are age, COPD, chronic renal failure and liver failure (cirrhosis).[12]

Reduction in serum total protein (STP) has been shown, in a recent retrospective analysis of data from a sepsis patient population with a high frequency of ARDS, to be highly predictive of positive fluid balance, weight gain, the development of ARDS, prolonged mechanical ventilation, and mortality. A prospective RCT was designed and conducted to evaluate combination therapy with furosemide and albumin over a 5-day period in 37 ARDS patients. Both mean serum albumin and mean serum total protein increased promptly and substantially in furosemide + albumin recipients.

The furosemide + albumin group also achieved a mean weight loss of 10 kg by the end of the treatment phase, and their weight loss exceeded that of placebo patients throughout. Hemodynamics improved in the treatment group during the 5-day protocol. Oxygenation, as assessed by the ratio between the fraction of inspired oxygen and the partial pressure of oxygen in arterial blood (PaO_2/FiO_2), was significantly higher within 24 h after commencement of treatment in the furosemide + albumin than the placebo group. Although mortality did not differ between groups, the RCT showed a trend toward reduced duration of mechanical ventilation and length of stay in the intensive care unit in patients receiving furosemide + albumin.[3]

In our study, length of stay in ICU significantly correlates with outcome in ARDS patients (p = 0.021). The median of length of stay is 3.2 days in non survivors group and 5 days in survivors groups. This result is similar to the research of Williams, *et al.* that the effects of critical illness acuteness happen in less than 10 days.[13]

CONCLUSION

The weakness of this study is the least amount of sample. The data are from medical record and using the cross-sectional method, so bias factor could be happening in this study. Otherwise, there are no data about albumin being given to the patients, so we could not give a value about the difference between the patient with or without albumin.

It needs further study with the biggest amount of samples and better method of writing down the album in giving to patients who treated with albumin. So that, we can clearly know that the giving of albumin concentration in outcome ARDS patients can be considered as a therapy of ARDS patients.

REFERENCES

1. Bhadade, R.R., de Saouza, R.A., Harde, M.J., Khot, A. 2011. Clinical characteristic and outcome of patients with acute lung injury and acute respiratory distress syndrome in Topiwala National Medical College Journals Vol 57:286-290. Mumbai.
2. Bourdon, E. and Blache, D. (2001) The importance of proteins in defense against oxidation. Antioxid. Redox Signal. 3, 293–311.

3. Deng, W., Yu, M., Ma, H., Hu L.A., Chen, G., Wang, Y., Deng, J., Li,C.Y., Tong, J., Wang, D.X. 2012. Predictors and outcome of patients with acute respiratory distress syndrome caused by miliary tuberculosis: a retrospective study in Chongqing, China. BMC Infectious Diseases 2012, 12:121.

4. Jia,X., Malhotra,A., Saeed,M., Mark,R.G., Talmor, D.2008. Risk Faktors for ARDS in Patients Receiving Mechanical Ventilation for > 48 h*. Chest Journal.133 : 853-61.

5. Khan, A, Milbrandt, E.B., Venkataraman, R. 2007. Albumin and furosemide for acute lung injury. Journal club critique. Critical Care 2007, 11: 314 (DOI 10.1186/cc).

6. Lin, Chan-Yu., Kao, Kuo-Chin., Tian, Ya-Chung., Jenq, Chang-Chyi., Chang. Ming-Yang. 2009. The RIFLE Score Increases the Accuracy of Outcome Prediction in Patients with Acute Respiratory Distress Syndrome Undergoing Open Lung Biopsy in Respiration 77:398-406.

7. Mangialardi RJ, Martin, G.S., Bernard, G., Wheeler AP, Arthur, P., Christman, B.W., *et al*. 2000. Hypoproteinemia predicts acute respiratory distress syndrome development, weight gain, and death in patients with sepsis. *Crit Care Med*. Vol 28. Pp 3137-45.

8. Martin, G.S. 2000. Fluid balance and colloid osmotic pressure in acute respiratory failure: emerging clinical evidence. *Critical Care* 2000, 4(Suppl 2):S21-S25.

9. Martin GS, Mangialardi RJ, Wheeler AP, Dupont WD, Morris JA, Bernard GR. 2002. Albumin and furosemide therapy in hypoproteinemic patients with acute lung injury. Crit Care Med, 30:2175-2182.

10. Monchi, M., Bellenfant, F., Cariou, A., Joly, L., Thebert, D., Laurent, I., Dhainaut, J., Brunet, F. 1998. A Multivariate analysis-Early predictive factors of survival in the acute respiratory distress syndrome in Am J Respir Crit Care Med 158:1076-1061.

11. Nicholson, J.P., Wolmarans, M.R., Park, G.R. 2010. The Role of albumin in Critical Illness. British journal of Anaesthesia b5 (4) : 599-610.

12. Roche, M., Rondeau, P., Singh, n.R., Tarnus, E., Bourdon, E. 2008. Minireview : The antioxidant properties of serum albumin. FEBS Letters 582 : 1783–178.

13. Williams, T.A., Dobb, G.J., Finn, J.C. Knuiman, M. 2010. Effect of length of stay in intensive care unit on hospital and long-term mortality of critically ill adult patients, British Journal of Anaesthesia 104 (4): 459–64

14. Wingfield, W.E.: Fluid and electrolyte therapy, in Wingfield WE, Raffe MR (eds): The Veterinary ICU Book. Jackson, WY, Teton New Media. 2002. pp 166–188.