

Articolo Originale - Original Article

Exogenous albumin administration to hypoalbuminemic patients in the ICU setting: A retrospective analysis

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ABSTRACT: Introduction. This study aimed to retrospectively investigate the consequences of administering albumin as an adjunctive therapy with <2.3 g/dL as a cut-off point, only to patients with serum albumin levels <2.3 g/dL.

Materials and methods. We retrospectively studied the patients admitted to our intensive care unit (ICU) from 2000 to 2001 (153/348 patients in 2000, and 178/402 patients in 2001). In 2000, we used to administer 12.5-25 g/day of albumin to all patients whose serum albumin concentrations were <3 g/dL; from the beginning of 2001 we started to administer 37.5 g/day of albumin, in one single daily administration, only to those patients with serum albumin levels <2.3 g/dL.

Results. During the time in the ICU, blood albumin levels were significantly higher in the 2000 group (3.17 ± 0.44 vs. 2.72 ± 0.44 g/dL, $p < 0.001$) and although the total use of albumin solution was lower in the 2001 group (2911 vs. 1589), in 2001 we observed a reduction in the mortality rate, almost 4% ($p = ns$).

Conclusions. In our opinion, albumin supplementation should be restricted to those patients with serum albumin levels <2.3 g/dL. (RINPE 2005; 23: 36-42)

KEY WORDS: Albumin, Artificial nutrition, ICU, Mortality

PAROLE CHIAVE: Albumina, Nutrizione artificiale, ICU, Mortalità

INTRODUCTION

Currently, there are no precise guidelines for the use of albumin as an adjunctive therapy in hypoalbuminemic critically ill patients receiving parenteral or enteral nutrition (EN) support. In the critically ill patient, hypoalbuminemia is a biologic marker of recent metabolic stress (1-4), it has been used as a malnutrition index and it has been correlated with a poorer clinical outcome (5-7). The routine supplemental administration of albumin solutions can cause a reduction in plasma ionized calcium levels with subsequent myocardial depression (8-11), a reduction in immunoglobulin concentrations with a reduction in the immune response (12-14), an increase in hepatic albumin levels with an inhibiting effect on liver production (15-17), a hypercolloidal state that can precipitate acute renal failure (18-20), and a blood volume expansion that can precipitate congestive heart failure with pulmonary edema. Albumin solutions are very

expensive and represent a large percentage of the hospital's pharmacy expense.

However, in situations of severe hypoalbuminemia with hyponcotic edema, it is necessary to administer exogenous albumin. Therefore, we started to search for the albumin level at which it is necessary to administer albumin as an adjunctive therapy. Based on recent studies (21-24), we chose 2.3 g/dL as a cut-off point. This study aimed to investigate retrospectively the consequences and safety of this therapeutic choice.

MATERIALS AND METHODS

We studied the patients admitted to our intensive care unit (ICU) from 2000 to 2001, except for those who were discharged in <3 days, this was to realize a greater similarity between the two groups. We included in the study, 153/348 patients in 2000 and 178/402 patients in

2001. In 2000 in our ICU, we used to administer 12.5-25 g/day of albumin to all patients whose albumin concentration was below the normal range, <3 g/dL. From the beginning of 2001, there was a substantial change in our therapeutic approach, we started to administer 37.5 g/day of albumin, in one single daily administration, only to those patients whose albumin levels were <2.3 g/dL.

Patients received nutrition support, total parenteral nutrition (TPN) or EN, according to standard medical practice. Energy and protein targets were 30 Kcal/kg/day and 1.5 g/kg/day, respectively. The energy and protein doses were adjusted in relation to eventual renal or hepatic diseases in an attempt to obtain normal serum electrolytes and positive nitrogen balance. For each of our patients, we recorded demographic data including age, sex and weight; other data included major diagnosis (general surgical, medical and multiple trauma; our hospital did not have an emergency room at the time, trauma patients were admitted after being first treated in another ICU; none of our patients was thermally injured), type of nutritional support, respiratory support requirement, length of stay and outcome. To compare the two groups and verify the similarity between the 2000 patients and the 2001 patients, a simplified acute physiology score (SAPS II) was calculated on admission records and the patients were divided in subgroups based on their SAPS score. In addition, the comparison was extended to underlying pathologies that could affect the

results. Serum albumin concentrations were measured daily and the albumin solutions and plasma units administered were recorded. Only 25% albumin solutions are used in our ICU.

Values are expressed as mean \pm standard deviation. A value $p < 0.05$ was accepted as statistically significant. Proportions were compared using the Chi-squared test and continuous variables were compared using the unpaired Student's t-test.

RESULTS

Table I reports the data of the patients studied in 2000 and 2001; the data resulted in being homogeneous for the two groups. In 2001, there were 25 extra patients admitted to our ICU than patients admitted in 2000; there were no significant differences regarding age, sex, major diagnosis and respiratory support requirement.

Total length of stay in the ICU for the 2001 patients was longer than for the 2000 patients (399 days extra), probably because the number of patients in 2001 was higher, but if we observed the mean length of stay in the ICU for each patient we could not find any difference (Tab. I).

Serum albumin levels were different in the two groups, the 2001 patients had significantly lower serum albumin levels than the 2000 patients (3.17 ± 0.44 2000 vs. 2.72 ± 0.44 g/dL 2001, $p < 0.001$).

TABLE I - DEMOGRAPHIC, BIOCHEMICAL AND CLINICAL DATA OF THE STUDY PATIENTS

Year	2000	2001	p
Patients (n)	153	178	
SAPS	13.15 \pm 4.55	12.74 \pm 4.52	ns
Age	62.41 \pm 16.72	58.11 \pm 18.68	ns
Sex (male-female)	93M - 60F	101M - 77F	ns
Mortality	58.16%	54.49%	ns
Diagnosis	103M - 40C - 10T	124M - 45C - 9T	ns
Creatinine >2 mg/dL (n)	74	81	
Bilirubin >5 mg/dL (n)	19	29	
Alkaline phosphatase >275 mg/dL (n)	37	49	
Leucocytes >15000/mm ³ (n)	112	132	
Total length of stay in ICU (days)	2215	2614	
Length of stay in ICU for patient (days)	14.47 \pm 11.4	14.62 \pm 14.02	ns
Serum albumin (g/dL)	3.17 \pm 0.44	2.72 \pm 0.44	<0.001
Serum albumin 1st day (g/dL)	3.14 \pm 0.66	2.93 \pm 0.78	<0.009
Serum albumin last day (g/dL)	3.08 \pm 0.66	2.63 \pm 0.58	<0.001
Total albumin consumption (bottles)	2911	1589	
Mean albumin consumption/patient (bottles)	19 \pm 18.8	8.9 \pm 6.3	<0.001
Plasma consumption (units)	586	598	
IOT (n)	120	126	

Values are expressed as mean \pm SD; M: medical; S: surgical; T: trauma; IOT: endotracheal intubation.

Interestingly, in 2001, despite a longer length of stay in the ICU (2614/2215 days), and a higher number of patients (178/153) had lower serum albumin levels than the 2000 patients, we observed a significant reduction in the mortality rate, almost 4% (58.16 vs. 54.49%, Tab. I).

On admission to the ICU, the 2000 patients had a mean serum albumin level of 3.14 vs. 2.93 g/dL for the 2001 patients, this was statistically significant ($p < 0.009$) (Tab. I).

During all the time spent in the ICU until the last day (Tabs. I-IV), blood albumin levels were significantly higher in the 2000 group, nevertheless, the total use of albumin solutions was lower in the 2001 group (2911 vs. 1589) with a mean use of albumin bottles for patients of 19 ± 18.8 vs. 8.9 ± 6.3 , $p < 0.001$ (Tabs. I-V).

The mean SAPS score and the frequency of underlying pathologies was similar and there were no statistically significant differences between the two groups. Even dividing the groups into subgroups based on their SAPS scores, the 2000 patients and the 2001 patients remained comparable (Tabs. II-IV).

In 2001 we observed a reduction in TPN use (82 vs. 58 with an increase in EN use (15 vs. 21) and TPN plus EN (56 vs. 99) (Tab. VI).

DISCUSSION

Albumin has many well recognized unique features: it binds, and therefore inactivates a large number of toxic products and by its binding property regulates plasma and interstitial fluid concentrations of endogenous and exogenously administered substances and drugs; it has a heparin-like activity enhancing factor Ca inhibition by antithrombin III (25-27); it maintains the microvascular permeability to protein; it reduces bacterial adhesion on exogenous plastic surfaces (vascular catheters and grafts) and it prevents lipid peroxidation scavenging free radicals (28-30).

The plasmatic half-life of exogenous albumin is approximately 16 h, similar to that of the endogenous protein. The 25% human albumin solution is a strong plasma expander (31-34); its oncotic potential increases colloid osmotic pressure and promotes an interstitial to intravascular passage of fluids (however, followed by an interstitial spreading of the exogenous compound).

Hypoalbuminemia is a widely accepted biologic marker of recent metabolic stress and is linked to high morbidity and mortality rates in critically ill adult patients. However, routine administration of exogenous human albumin during parenteral nutritional support in hypoalbuminemic patients does not always offer an ad-

TABLE II - DEMOGRAPHIC, BIOCHEMICAL AND CLINICAL DATA OF THE SAPS 0-9 GROUP

Year	SAPS 0-9		p
	2000	2001	
Patients (n)	28	44	
Age	56.17 ± 19.73	46.75 ± 22.06	ns
Sex (male-female)	20M - 8F	27M - 17F	ns
Mortality (n)	10 (35.7%)	13 (29.5%)	ns
Diagnosis	20M - 4T - 4C	29M - 6T - 9C	ns
Creatinine >2 mg/dL (n)	11	8	
Bilirubin >5 mg/dL (n)	5	1	
Alkaline phosphatase >275 mg/dL (n)	5	16	
Leucocytes >15000/mm ³ (n)	20	27	
Total length of stay in ICU (days)	17.71 ± 15.23	16.38 ± 14.40	ns
Serum albumin (g/dL)	3.37 ± 0.49	2.88 ± 0.55	<0.001
Serum albumin 1st day (g/dL)	3.37 ± 0.57	3.09 ± 0.86	ns
Serum albumin last day (g/dL)	3.34 ± 0.68	2.90 ± 0.65	0.008
Total albumin consumption (bottles)	542	228	
Mean albumin consumption/patient (bottles)	19.35 ± 19.12	5.18 ± 6.73	0.001
Plasma consumption (units)	96	58	
IOT (n)	13	21	

Values are expressed as mean ± SD; M: medical; S: surgical; T: trauma; n: patients number; IOT: endotracheal intubation

TABLE III - DEMOGRAPHIC, BIOCHEMICAL AND CLINICAL DATE OF THE SAPS 10-19 GROUP

Year	SAPS 10-19		p
	2000	2001	
Patients (n)	112	123	
Age	63.25 ± 16.19	62.11 ± 15.56	ns
Sex (male-female)	66M - 46F	68M - 55F	ns
Mortality (n)	68 (60.7%)	76 (61.7%)	ns
Diagnosis	72M - 35C - 5T	87M - 33C - 3T	ns
Creatinine >2 mg/dL (n)	53	65	
Bilirubin >5 mg/dL (n)	11	25	
Alkaline phosphatase >275 mg/dL (n)	28	28	
Leucocytes >15000/mm ³ (n)		84	95
Total length of stay in ICU (days)	13.84 ± 10.38	14.44 ± 14.29	ns
Serum albumin (g/dL)	3.13 ± 0.43	2.67 ± 0.39	<0.001
Serum albumin 1st day (g/dL)	3.08 ± 0.69	2.89 ± 0.73	=0.042
Serum albumin last day (g/dL)	3.07 ± 0.63	2.52 ± 0.54	<0.001
Total albumin consumption (bottles)	2146	1284	
Mean albumin consumption/patient (bottles)	19.16 ± 18.16	10.43 ± 12.03	<0.001
Plasma consumption (units)	408	494	
IOT (n)	94	95	

Values are expressed as mean ± SD; M: medical; S: surgical; T: trauma; IOT: endotracheal intubation.

TABLE IV - DEMOGRAPHIC, BIOCHEMICAL AND CLINICAL DATE OF THE SAPS >20 GROUP

Year	SAPS>20		p
	2000	2001	
Patients (n)	13	11	
Age	68.61 ± 8.13	58.81 ± 17.21	ns
Sex (male-female)	7M - 6F	6M - 5F	ns
Mortality	11 (84.6%)	8 (72.7%)	ns
Diagnosis	11M - 1C - 1T	8M - 3C	ns
Creatinine >2 mg/dL (n)	10	8	
Bilirubin >5 mg/dL (n)	3	2	
Alkaline phosphatase >275 mg/dL (n)	4	5	
Leucocytes >15000/mm ³ (n)	8	10	
Total length of stay in ICU (days)	12.92 ± 9.91	9.63 ± 5.24	ns
Serum albumin (g/dL)	3.07 ± 0.31	2.75 ± 0.36	=0.029
Serum albumin 1st day (g/dL)	3.11 ± 0.39	2.69 ± 0.86	ns
Serum albumin last day (g/dL)	2.70 ± 0.55	2.74 ± 0.36	ns
Total albumin consumption (bottles)	223	77	
Mean albumin consumption/ patient (bottles)	17.15 ± 23.59	7 ± 6.98	ns
Plasma consumption (units)	51	40	
IOT (n)	13	10	

Values are expressed as mean ± SD; M: medical; S: surgical; T: trauma; IOT: endotracheal intubation.

vantageous outcome (35-37).

The analysis of the data that we collected strengthened the similarity between the 2000 patients and the 2001 patients; the two groups remained comparable even when divided into subgroups referring to their SAPS score. As there were no other variables in therapy and medical assistance, we can affirm that the albumin

saving produced in 2001 has not negatively affected our patients. In spite of administering less albumin flacons in 2001 (1589 bottles in 2001 vs. 2911 flacons in 2000, Tab. I) and the significantly lower albuminemia rate in 2001 than in 2000, the mortality and the length of stay in the ICU did not change (total length of stay in the ICU: 2215 vs. 2614 days; length of stay in the ICU for

TABLE V - SERUM ALBUMIN LEVELS IN THE STUDY GROUPS

	2000	2001
Albuminemia 1st day		
<2.3 g/dL (n)	17	43
2.4-3.1 g/dL (n)	65	68
>3.1 g/dL (n)	71	67
Average albuminemia		
<2.3 g/dL (n)	6	29
>2.3 g/dL (n)	147	149

TABLE VI - TYPE OF FEEDING

	2000	2001
Parenteral feeding (n)	82	58
Enteral feeding (n)	15	21
Mixed feeding (n)	56	99

each patient: 14.47 ± 11.4 vs. 14.62 ± 14.02 days, $p=ns$) (Tab. I). In 2001, classifying the patients based on the type of nutritional support used (Tab. VI) and comparing SAPS scores, albumin supplementation and mortality rates for the 2 years, we found a lower mortality rate, although not significant, in the group of patients administered less albumin compared with the homologous group in 2000, this in part is due to fewer patients in the 2000 group, and in part due to a higher SAPS score in the 2000 group, which reveals the worst clinical conditions in this group on admission.

In 2001 in our ICU, we used EN more frequently as nutritional support than TPN, when compared with the 2000 group. Usually, EN is administered in patients unaffected by gastrointestinal disorders; therefore, they are considered less seriously ill than those patients who receive TPN. In our study, the similarity between the SAPS scores of the two groups demonstrated that the choice of one or another type of nutritional support was due not to different clinical conditions, but to a cultural evolution in our ICU regarding the nutritional approach.

When patients were stratified according to mean serum albumin levels on admission (Tab. V), we observed that in 2000 only 17 patients had albumin serum levels <2.3 g/dL, while in 2001 43 patients had albumin serum levels <2.3 g/dL, this stresses once more that the 2001 group had lower albumin levels on admission than the 2000 group, but did not have a higher mortality rate.

Serum albumin concentrations have often been used

prognostically in hospitalized patients to predict hospital or surgical mortality, but it remains unclear if patient prognosis will improve by artificially increasing serum albumin concentrations. In our study, the reduction in serum albumin levels was not associated with increased mortality; it was reduced by nearly 4%. In a study by Golub et al (6), albumin levels on admission were related to the morbidity and mortality rates, and the attempt to increase albumin levels by administering the exogenous protein was not followed by significant benefits. This could be because often in critically ill patients, the major defect that leads to hypoalbuminemia is excessive catabolism rather than diminished synthesis, and as the albumin space is filled by intravenous infusions the catabolic rate increases further with no therapeutic advantage. The study of Rubin et al (20) demonstrated no benefit from administering intravenous albumin to hospitalized hypoalbuminemic patients, despite the increase in serum albumin concentrations. Another study (21) administered albumin only to a concentration of 2.5 g/dL in the therapeutic group, but no benefit was seen with the albumin supplementation, despite documented increases in serum albumin concentrations over the control group. There is only one study, Brown et al (3), which demonstrates a higher complication rate in patients who were given TPN without albumin supplementation than in patients to whom albumin was given with TPN, the greatest difference was in the number of patients who developed sepsis, intra-abdominal abscesses, urinary tract infections and pneumonia, but the results of this study are questionable.

In conclusion, the data obtained in this study indicate that routine exogenous albumin administration, in addition to being very expensive, does not offer significant benefits to patient outcome and should be abandoned in the critically ill; albumin supplementation should be restricted to those patients with serum albumin levels <2.3 g/dL. However, further studies are warranted to confirm this assumption.

RIASSUNTO

Introduzione. Lo scopo del nostro studio è stato quello di valutare retrospettivamente, le conseguenze della somministrazione di albumina esogena solo in pazienti con livelli di albuminemia sierica < 2.3 g/dL.

Materiali e metodi. Abbiamo retrospettivamente studiato tutti i pazienti ammessi alla nostra Terapia Intensiva dal 2000 al 2001 (153/348 nel 2000 e 178/402 nel 2001). Fino al 2000 usavamo somministrare routinariamente 12.5-25 g di albumina esogena a tutti i pazienti con valori di albuminemia sierica < 3 g/dL; dal-

l'inizio del 2001 abbiamo iniziato a somministrare 37.5 g di albumina, in singola somministrazione giornaliera, solo nei pazienti con valori di albuminemia sierica < 2.3 g/dL.

Risultati. Durante tutto il tempo di ricovero in terapia intensiva, i livelli di albumina sierica sono stati significativamente più alti nel 2000 rispetto al 2001 (3.17 ± 0.44 g/dL vs 2.72 ± 0.44 g/dL, $p < 0.001$), e nonostante il consumo di flaconi di albumina sia stato più basso nel 2001 (2911 vs 1589), abbiamo osservato una piccola riduzione della mortalità del 4% ($p = n.s.$).

Conclusioni. È opinione degli autori che la somministrazione di albumina esogena dovrebbe essere limitata solo a quei pazienti con valori di albuminemia sierica < 2.3 g/dL.

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Ricevuto il 21/2/2005

Accettato dopo Revisione il 28/2/2005