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Exogenous human albumin supplementation in total parenteral nutrition of critically ill newborns

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Abstract

Objective: In view of the controversies found in the literature, the present study was conducted to determine the effect of the use of exogenous human albumin on the nutritional status of newborn infants submitted to total parenteral nutrition.

Methods: Thirty critically ill newborn infants weighing less than 2,500 g were divided into two groups: 15 infants receiving total parenteral nutrition without human albumin (C control group) and 15 with human albumin (group A). Total protein, albumin, prealbumin, and retinol-binding protein were determined at the beginning (3-4 days of postnatal age) and at the end of the study (10-11 days of postnatal age). On the seventh day of the study, nitrogen balance (retention) was measured. The following clinical parameters were evaluated: weight, age at the beginning of enteral nutrition, time to reach a full enteral volume, length of stay in the intensive care unit, total hospitalization time, and mortality.

Results: The results showed a significant difference ($p < 0.05$) in serum albumin and total protein levels ($p < 0.05$) between groups at the end of the study. Median albumin levels were 2.95 g/dl in group C (2.71-3.16 g/dl), whereas group A showed median albumin levels of 4.10 g/dl, (3.76-4.66 g/dl). Total protein levels were 4.9 g/dl (4.4-5.2 g/dl) and 5.6 g/dl (5.5-6.3 g/dl), respectively, with no repercussions on any of the remaining parameters evaluated.

Conclusions: On the basis of the results obtained in the present study, no benefits were derived from the use of human albumin in total parenteral nutrition in severely ill newborns; therefore its use cannot be recommended, unless the objective is exclusively to elevate albumin levels.

J Pediatr (Rio J). 2005;81(1):41-6: Albumin, parenteral nutrition, newborn.

Introduction

The combined use of exogenous human albumin with total parenteral nutrition (TPN) for improvement of nutritional status has been reported in the literature for over one decade and is based on the ability of modified TPN to quickly normalize the serum levels of albumin, correcting hypoalbuminemia, maintaining the oncotic pressure and allowing for a better prognosis.[1-4] Low albumin levels often are observed in malnourished adult and pediatric hospitalized patients and in ill and preterm newborns, being associated with several organic dysfunctions (reduction in oncotic pressure, in resistance to infection and in healing ability, peripheral and intestinal edema, decrease in gastrointestinal motility with intolerance to enteral nutrition, pulmonary infiltrate) and adverse clinical outcome.[5,6] The "restorative" properties of albumin in TPN are believed to be related to the amino acid profile and to the caloric content of TPN, resulting in improved protein synthesis or inhibition of albumin degradation. Thus, albumin supplementation in ill, hypoalbuminemic patients with poor nutrition may be useful to improve albumin-related functions. Newborn infants, especially preterm and small ones, have limited body stores of proteins and energy at birth. Moreover, metabolic demands, immature or inadequate enzyme systems, gastrointestinal immaturity, respiratory diseases, poor absorption and/or insufficient amounts of individual nitrogen and amino acid precursors, may restrict the appropriate supply of proteins and calories, reducing hepatic protein

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synthesis. On the other hand, several studies assert that supplementation provides no proven clinical benefit, and that it just elevates serum levels, which does not justify the high cost of such therapy.[7,8] The use of human albumin to improve the general health and nutritional statuses of hospitalized newborns remains unclear. Most times, its use is empirical, as a result of the observed inverse correlation between serum albumin concentration and morbidity and mortality. Considering the controversy over the use of human albumin, and using the available methods for the assessment of nutritional status, the aim of the present article was to evaluate the effect of human albumin in the TPN of severely ill newborns on the serum levels of protein markers such as albumin, total proteins, prealbumin, retinol-binding protein (RBP), on nitrogen retention, parameters related to weight outcome, enteral nutrition, length of stay (in days) in the intensive care unit (ICU) and in the hospital, and morbidity and mortality.

Patients and methods

A case-control study was performed in preterm newborns weighing less than 2,500 g, admitted to the Neonatal Intensive Care Unit (NICU) of *Hospital Universitário de Santa Maria* (HUSM), between November 1997 and November 1998. The patients were not on enteral nutrition as their clinical conditions did not allow so; although they had severe diseases, their clinical and laboratory conditions were stable, that is, the amount of fluids or TPN components for each newborn did not have to be changed during different days within the study period. The exclusion criteria were: acute renal failure, cholestasis, protein loss (fistulas), use of medications that could interfere with water excretion (diuretics, indomethacin) and maternal use of corticosteroids before delivery. Forty newborns were evaluated after being randomly placed in two groups. Thirty newborns met the inclusion criteria at the end of the study, each group consisting of 15 newborns who were receiving standardized TPN, following the routine of the hospital, as described next:

- Control group receiving no albumin (C): received regular standardized TPN;
- Group receiving albumin (A): received standardized TPN combined with 1g/kg/day of human albumin (Zenalb®20-Human Albumin 20%, Bio Products Lab.), given daily at every 12 hours, throughout the study period. After the initial adaptation period, TPN was gradually introduced according to the routine and tolerance of the newborn in the seven-day assessment period (starting on the third or fourth postnatal day and finishing on the 10th or 11th day). TPN solutions were prepared at the pharmacy of HUSM, according to the medical prescription. Amino acid solution (starting with 1 g/kg/day with a gradual increase of 0.5 g/kg/day up to 3 g/kg/day) and lipid solution (1 g/kg/day at the beginning of TPN with an increase 0.5 g/kg/day up to 3 g/kg/day) were, respectively, PEDIAMINO PLM 10%, BBraun and INTRALIPID 10%, Darrow. Data on maternal history, obstetric history, birthweight, gender, gestational age (Capurro's method), appropriateness of weight for gestational age, confirmed clinical diagnoses (on admission, at the beginning and at the end of the study), clinical outcome during the study period, respiratory acuity score (RAS)[9] at the beginning and at the end of the study and observed complications were obtained for each newborn. Each newborn received at least 90% of the prescribed TPN volume. Two ml of blood was collected on the first and seventh days of study. A 24-hour urine sample was collected on the seventh day using a pediatric urine collection bag. Flasks were kept in the refrigerator at -4 ºC for 24 hours. At the end of the nitrogen balance study, volumes were measured, and one sample was frozen at -20 ºC for later analysis and estimation of nitrogen retention. None of the newborns who participated in the study had bowel movement on the day close to or during the balance. A sample of TPN infused on the day of the nitrogen balance study was collected from each newborn. These samples were stored in sterile flasks and kept in the refrigerator at -20 ºC up to the moment of biochemical measurement.

Laboratory measurements

Nitrogen was measured in urine and TPN solutions. Total protein, albumin, prealbumin and RBP were measured in the plasma. The Kjeldahl method was used for the determination of nitrogen . Total protein was determined using the Biuret method, whereas prealbumin and RBP were measured by nephelometry. All measurements were made in duplicate, except for prealbumin and RBP.

Statistical analysis

The individual results of each newborn were recorded in a specific protocol and then stored in a database using Epi-info (version 6.0, July 1996), and later analyzed in Epi-Info and Stata (1998). The nonparametric Kruskal-Wallis test and the chi-square test were used, and a $p < 0.05$ was considered to be significant. The study protocol was approved by the Ethics Committee of *Hospital de Clínicas*, School of Medicine of Ribeirão Preto-USP-SP, and of *Hospital Universitário de Santa Maria* (UFSM-RS). An informed consent was obtained from parents or legal representatives in all cases.

Results

Thirty newborns (n = 30) were included in the study – 15 received albumin and 15 did not (control group). No difference was noted between groups regarding gender, birthweight, gestational age, appropriateness of weight for gestational age, use of oxygen therapy, use of ventilator and RAS (Table 1). The study groups showed a similar disease profile at the beginning of the study, in which there was a predominance of hyaline membrane disease, hypoxic-ischemic encephalopathy, infection and surgical complications, such as esophageal atresia, diaphragmatic hernia, gastroschisis and duodenal atresia, without any significant differences (Table 2). The values, expressed in median and quartiles, regarding the volume and nutrients

given to the newborns in both groups during the study period did not show any statistically significant differences (Table 3).

Serum biochemical markers

There was statistically significant difference between the groups only at the end of study regarding total protein and albumin (Table 4).

Nitrogen balance

The balance at the end of the study did not reveal statistically significant differences between the groups in relation to the amount of nitrogen given, passed in the urine and retained (Table 5).

Table 1 - Characteristics of the clinical status of the populations studied

Variables	Group C Md (Q_1-Q_3)	Groupo A Md (Q_1-Q_3)	p
Sex	15 (100%)	15 (100%)	
Female	6 (40%)	7 (47%)	ns
Male	9 (60%)	8 (53%)	ns
Gestational age (weeks) *	32 (31-33)	33 (31-36)	ns
Adequation	15 (100%)	15 (100%)	
SGA	3 (20%)	4 (27%)	ns
AGA	12 (80%)	11 (73%)	ns
Birth weight (grams) *	1,170 (920-1,840)	1,295 (1,175-2,280)	ns
Initial RAS	45 (22-78)	78 (36-112)	ns
Final RAS	15 (0-39)	09 (0-36)	ns
Use of oxygen therapy (days)	26 (08-33)	20 (10-43)	ns
Use of ventilator (days)	11 (03-18)	09 (05-18)	ns

* Median (Q1-Q3).
ns = non-significant; SGA = small for gestational age; AGA = adequate for gestational age; RAS = respiratory acuity systems.

Start of enteral nutrition, time necessary to reach full enteral volume, length of stay in the ICU, total length of hospital stay and mortality

No difference was observed in these variables between the groups (Table 6).

Weight outcome

No statistically significant differences were found between groups with regard to weight gain during the study period (Table 7). However, in group C only two newborns (13.3%) gained weight, whereas in group A eight newborns (53.3%) gained some weight by the end of the study (Table 7).

Table 2 - Pathologies of newborns from groups C and A in the beginning of the study

Disease	Group C n	Group C %	Group A n	Group A %	p
Hyaline membrane	3	20.0	4	26.7	ns
Neonatal infection	3	20.0	2	13.3	ns
Hyaline membrane + infection	5	33.3	4	26.7	ns
Hypoxic-ischemic encephalopathy + infection	3	20.0	3	20.0	ns
Surgical complications	1	6.7	2	13.3	ns
Total	15	100.0	15	100.0	

ns = non-significant.

Table 3 - Median and quartiles of nutrients given to the newborns from groups C and A during the study

Nutrients	Group C	Group A	p *
Volume (ml/kg/day)	139.0 (125.5-145.10)	139.0 (136.0-144.4)	ns
Glucose (g/kg/day)	12.2 (10.7-13.0)	12.3 (11.9-13.1)	ns
Amino acids (g/kg/day)	1.5 (1.2-1.7)	1.6 (1.2-1.7)	ns
Lipids (g/kg/day)	1.6 (1.3-1.7)	1.4 (1.1-1.7)	ns
Calories (kcal/kg/day)	59.2 (54.1-63.6)	57.5 (53.0-62.6)	ns
Calorie/amino acid relationship (kcal/g)	39.5 (37.4-45.1)	35.9 (36.8-44.2)	ns

* p was not statistically significant neither within groups nor and among groups.

Discussion

Proper nutrition is important for the regulation of albumin synthesis, and serum albumin concentration is still considered to be a good nutritional indicator by many authors, and despite some limitations, it is still used on a routine basis for the assessment of nutritional status in hospitalized patients of all ages.[10] In preterm newborns, albumin and total protein levels are usually lower than in full-term newborns, infants and older children. There is a positive significant correlation between gestational age and the concentration of total protein and albumin,[11] ranging from 20 g/l at 28 weeks of gestation to 30 g/l at term; total protein levels rise

Table 4 - Median and quartiles of albumin values (g/dl), prealbumin (mg/dl), RBP (mg/dl) and total proteins (g/dl) in groups C and A, at the beginning and end of the study

Variables	Group C	Group A *	p
Albumin (g/dl)			
Initial	2.69 (2.48-3.09)	2.54 * (2.36-2.68)	ns
Final	2.95 (2.71-3.16)	4.10 * (3.76-4.66)	< 0.001
Prealbumin (mg/dl)			
Initial	6.20 (5.70-7.20)	6.00 (5.30-6.50)	ns
Final	5.80 (3.80-6.90)	5.60 (4.10-8.00)	ns
RBP (mg/dl)			
Initial	1.30 (0.00-1.70)	1.10 (0.80-1.40)	ns
Final	1.00 (0.90-2.80)	1.10 (0.90-2.00)	ns
Total proteins (g/dl)			
Initial	4.2 (3.7-4.7)	4.1 (3.6-4.7)	ns
Final	4.9 (4.4-5.2)	5.6 (5.5-6.3)	0.001

* There was significant difference within groups ($p < 0.05$) only for the initial and final albumin of group A.
RBP = RNA binding protein; ns = non-significant.

Table 5 - Median and quartiles of the values of infused nitrogen in parenteral nutrition, nitrogen in urine, nitrogen retention and balance at the end of the study (balance day) in groups C and A

Nitrogen	Group C	Group A	p
Infused (mg/kg/day)	289.75 (241.80-362.72)	341.46 (232.96-557.13)	ns
Urine (mg/kg/day)	96.50 (74.75-152.12)	100.08 (57.31-191.47)	ns
Retention (mg/kg/day)	193.25 (167.15-210.60)	241.38 (175.65-365.66)	ns
Balance			
Positive	14 (93.3%)	15 (100%)	ns
Negative	1 (6.7%)	0 (0%)	ns

ns = non-significant.

Table 6 - Median and quartiles of time (days) of variables associated with parenteral and enteral nutrition, length of hospital and ICU stay

Variables	Group C	Group A	p
Postnatal age (days) at the start of parenteral nutrition	3-4	3-4	ns
Postnatal age (days) at the start of enteral nutrition	12 (8-19)	10 (8-18)	ns
Time necessary to reach full enteral nutrition (days)	10 (6-11)	08 (7-10)	ns
Length of stay in the ICU	32 (24-47)	32 (15-55)	ns
Length of hospital stay	35 (33-75)	39 (31-69)	ns

ICU = intensive care unit; ns = non-significant.

Table 7 - Median and quartiles of weight gain (grams) during the study period

Weight (grams)	Group C	Group A	p
Initial	1,170 (920-1,840)	1,295 (1,175-2,280)	ns
Final	1,100 (840-1,730)	1,340 (1,120-2,260)	ns
On discharge	2,085 (1,940-2,780)	2,220 (1,920-2,750)	ns

ns = non-significant.

from 40 g/l at 28 weeks to 60 g/l at birth.[12] With regard to albumin, there was statistically significant difference between groups at the beginning of the study, but a significant difference was observed between the groups ($p < 0.001$) at the end of the study, thus showing that human albumin replacement actually increases the serum levels of total protein and albumin in the short run. The long half-life limits the albumin level for the identification of acute changes in the nutritional status, and low sensitivity and specificity is a poor parameter for the individual assessment of nutritional status of patients, being more appropriate for long-term and epidemiological studies.[13] Prealbumin and RBP levels are more sensitive indicators of appropriate nutrition,[14,15] they seem to correlate best with nitrogen balance during nutritional therapy, demonstrating earlier response to refeeding than albumin, total protein and transferrin,[16,17] and their control is useful to identify early changes in protein and energy intake and to assess the efficacy of nutrition in a short-term period.[18] In the present study, serum levels of prealbumin and RBP are lower than those described in the literature[16] and did not reveal statistically significant difference between or within groups. It is likely that, in the present study, the insufficient protein-energy intake can explain low prealbumin and RBP levels and the maintenance of these nutritional markers at the same level after seven days of TPN. A protein intake less than 2 g/kg/day and an energy intake lower than 100 cal/kg/day result in significantly lower levels of prealbumin and RBP,[19,20] which occurred in our study (Table 3).

The estimation of protein requirements by nitrogen balance assessments is based on the observation that requirements are met when maximum retention is achieved. Protein requirements in newborns obtained from nitrogen balance studies range from 1.6 to 4.2 g/kg/day, depending on the type of protein received by the infant, physical conditions and gestational age.[21,22] In contrast to healthy adults who have a neutral nitrogen balance, newborns need a positive balance so that they can grow and develop properly. Nitrogen requirements result mainly from the amount of metabolized proteins, and are much higher among newborns. In the first months of life, nitrogen retention corresponds to 140-250 mg/kg/day for full-term breastfed newborns and nearly 350 mg/kg/day for formula-fed infants.[23] Protein requirements, however, vary with age: for low-birthweight newborns requirements may correspond to 3.5 g/kg/day (in order to supply around 480 mg/kg/day of nitrogen) and 2 g/kg/day (280 mg/kg/day) for full-term infants.[24,25] Preterm newborns have an immature amino acid metabolism, therefore, the amount to be supplied in order to obtain nitrogen retention similar to that found in utero is not easily reached and depends on the digestibility and use of the protein received.[23] In the present study, patients of both groups received similar amounts of nitrogen, with no statistically significant difference between the groups. Such amounts are compatible with those recommended for newborns, but they may be low for preterm infants. Protein and non-protein sources were similar in both groups. Nitrogen balance was positive in both groups, with retention of 65.8% in group C and of 75.5% in group A of the nitrogen supplied at median levels. This confirms the urge of newborns to retain nitrogen, even receiving a protein-energy intake lower than recommended, as occurred in the present study, which is consistent with the available literature.[26] In our study, in one week, 97.7% of the patients were in an anabolic state, even with a protein-energy intake below that which is recommended and, probably because of that, there were no significant changes in prealbumin, RBP and weight.

Newborns in group A lost less weight, regained birthweight apparently shortly before than did those in the control group, and gained more weight by the end of the study (Table 7). They also started enteral nutrition at an earlier stage and the time necessary to reach full enteral volume was slightly short (2 days before group C), but these differences were not statistically significant. Energy content was similar in both groups, as well as amino acid intake (not computing the protein value of albumin supplementation). Enteral absorption of fluids partially depends on serum oncotic pressure. Low serum albumin levels are correlated with reduced fluid intake and increased intestinal fluid retention.[2] This buildup of fluids reduces intestinal motility and nutrient absorption. Thus, differences in weight gain might be partly explained by positive effects of a higher serum albumin level and of higher oncotic pressure, with improved tolerance of the diet by newborns.[27] Similarly, studies conducted with adult patients also revealed a positive correlation between serum albumin levels and better tolerance of enteral nutrition,[28] which could not be statistically confirmed in the present study. In newborns, the use of albumin in TPN also had some influence on the implementation of enteral nutrition and showed that the treated group regained birthweight more quickly.[3] Differences in weight gain could also be attributed to improved intestinal motility and absorption due to the effect of albumin. In this case, however, improvement in intestinal tolerance should be expected resulting in earlier implementation of enteral nutrition and larger weight gain. In the present study, despite a shorter observation time, differences were not statistically significant between groups regarding weight, age, implementation of enteral nutrition and time necessary to reach full enteral volume. Data available about newborns are scarce and inconclusive when it comes to show the benefits of such practice; and besides, no literature studies have been carried out on albumin supplementation in infants using enteral nutrition. Further studies including a larger number of infants and longer use of albumin are necessary to determine to what extent the early recovery of birthweight in infants is due to some improvement in the tolerance of enteral nutrition or only to an improvement of the underlying disease.

The available literature describes a significant and inversely proportional correlation between albumin levels and length of hospital stay, morbidity and mortality, with evidence that serum albumin level may be a predictive factor for the risk of death,[5,6] thus justifying the administration of albumin. However, many of these studies included groups of very old patients with chronic diseases, in which the disease itself may have caused hypoalbuminemia and death, instead of the nutritional status. Our study used a homogeneous population of critically ill newborns, with comparable initial albumin levels, and no statistically significant difference regarding length of hospital stay and mortality between the groups. Prospective, randomized, controlled and double-blind studies did not find significant differences after albumin supplementation in the total length of hospital stay, in the necessity for mechanical ventilation, in the tolerance of enteral nutrition, morbidity, and in the reduction of mortality, despite a significant increase in serum albumin levels;[4,7,29-31] these data are consistent with those obtained in the present study. In these studies and in the present study as well, there was an increase in serum albumin levels, but this increase did not reveal significant differences in relation to biochemical nutritional status (prealbumin and RBP levels) and did not show any differences as to the analyzed clinical parameters.

The data obtained in this study do not show major benefits from the use of exogenous human albumin in the TPN of critically ill newborns. Therefore, its use is not recommended unless the aim is to exclusively increase serum albumin levels.

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