New standards versus old habits – prescribing albumin in a central hospital

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Abstract

The current study aims to evaluate the adequacy of albumin prescription in a central hospital within the available scientific evidence.

This was a retrospective study from September 2007 to August 2008. 761 demands from 619 patients on human albumin were analyzed. Patients were in average aged 58.1 +/-14.7 years, where 510 were male (77%). Other parameters were also assessed: total proteins, serum albumin, serum creatinine, INR, obtained at the date of request. From a total of 556.831 bottles of albumin requested, only 5033 (0.9%) were actually administered. Patients with liver diseases were the majority (60%), and 36% of the requests were in accordance with the scientific evidence. The main cause for albumin prescription was hypoalbuminaemia (53%). We conclude that grounds for prescribing albumin should be better thought through, and a more restrictive policy for albumin supply from the pharmaceutical department is entirely justified.

Key words: human albumin.

INTRODUCTION

Human albumin has been available for clinical use in the USA since the 1940s.[1] It is traditionally used to replace intravascular volume and increase colloidal pressure in various contexts, and to assist in the transport of nutrients and drugs.[2] It is widely used in several areas of Medicine, but the criteria for its use have never been very clear and have often been based on theoretical arguments rather than on scientific evidence.

The most frequently used formulation in our hospital is 20% desalted human albumin. Because it is an important biological product that is not free of adverse events, scientific production in this area has increased considerably in the past ten years, and prescribers of exogenous albumin are now equipped with scientific instruments for its clinical use.

In 1998, the Cochrane Collaboration published a meta-analysis that showed that the prescription of albumin for volume resuscitation in Intensive Care patients may result in higher mortality.[3] Because albumin is prescribed on a frequent basis, the commotion this publication caused is understandable, but so too is the need to provide this area of knowledge with new and valid decision-making tools. Consecutive reviews by the same group confirmed the initial conclusions.[4] In its last publication, in June 2008, the Cochrane Collaboration carried out a review of the past ten years (1998-2008), performing a new meta-analysis, including 37 trials involving a total of 8716 patients.[5]

The use of albumin is not restricted to the Intensive Care Units (ICU). In various departments, from Medicine to Surgery, it is frequently used. According to the currently available scientific evidence, the indications for the prescription of albumin are:[6] spontaneous bacterial peritonitis (SBP), in patients with a clinical diagnosis of SBP and PMN count in the ascetic fluid higher than 250 cells/mm3, the use of human albumin is recommended (1.5 g/kg within the first six hours after diagnosis, 1 g/kg on day three, evidence level B);[7] tension and refractory ascites, the use of human albumin is recommended when the volume of paracentesis is higher than five litres (it should be administered after the procedure at a dose of 5 to 10 g/litre of removed ascetic fluid, evidence level B);[8,9] hepatorenal syndrome, although there are no well-designed studies that allow a formal conclusion for the use of albumin in patients with hepatorenal syndrome.[10]

Given the above information, the objective of this study was to evaluate the use of human albumin in a

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central hospital, observing the diagnostic groups that are mostly frequently associated with the prescription of albumin, and the reason for prescription, in order to assess the extent to which prescribers are following the new prescription concepts and adhering to the current scientific evidence. We also review the economic situation related to the use of human albumin, calculating its total cost.

MATERIAL

The study included all patients who had been prescribed human albumin over a one-year period, from September 2007 to August 2008. Data was collected based on the requests for albumin to the Pharmacy Service, and from the electronic registration system (SAM) of the hospital. Human albumin is supplied to the departments by means of a special request form, which must include the name of the patient, the reason for the request, the diagnosis, duration and form of intravenous administration.

In the period of time studied, 761 requests forms were filled out, corresponding to 619 patients. A total of 556,831 vials of 50cc albumin 20% were requested. Most of the patients had been hospitalized (n=519, 83.8%).

As an internal rule, the pharmacy dispenses a maximum of thirteen vials for each request form, i.e. if the prescription (frequency x time) surpasses thirteen vials, the prescriber will have to make a new request. This limitation is due to the fact that there are only thirteen fields in each form for the barcodes removed from each vial, which is a compulsory procedure when handling hemoderivatives.

METHODS

The patients included in the study were classified according to their demographics (age and gender), clinical characteristics (diagnosis and reason for prescription) and prescribing areas (the various departments of the hospital). The reasons for prescription and the diagnoses were collected, divided by major organ pathologies and determined prospectively throughout the collection. The following parameters, which were obtained upon clinical prescription, were also evaluated: total protein and serum albumin; international normalized ratio (INR) and total bilirubin; and serum creatinine. Data on diagnosis and reasons for the prescription of albumin were obtained from the request forms analyzed.

For the purposes of analysis, the requests for albumin on the request forms were classified based on the following criteria: requests with indication supported by currently available evidence (spontaneous bacterial peritonitis, paracentesis in patients with tension ascites and refractory ascites, hepatorenal syndrome, specific procedures requiring the use of albumin); requests without evidence support, but also without contraindication; and requests with formal contraindications.

The amount of albumin requested for the treatment, and the amount of albumin actually used, were compared.

The cost of the treatment was calculated by multiplying the number of vials administered by the unit price.

The results were entered into an Excel® spreadsheet and processed with a tool for descriptive statistical methods, presenting variables such as mean, standard deviation and limits. Wherever necessary, a specific statistical program was used (SPSS for Windows Inc., version 18.0). All the study parameters that were not recorded were considered as not completed.

RESULTS

The patients' general demographic and clinical data is shown in *Table 1 and Fig 1*. In relation to gender, a prevalence of males (67%, n=510 patients) is observed compared to females (33%, n=251 patients). In relation to the serum albumin levels on the date of prescription, mean values of which are shown in table 1, the following is observed: in 143 prescriptions, serum albumin levels were lower than 2.0 g/dL; in 400 prescriptions, they were higher than 2 g/dL and lower than 3.5 g/dL; in 59 prescriptions, they were higher than 3.5 g/dL; in 159 prescriptions, the serum albumin levels were not entered in the computer system.

The distribution by pathologies is shown in table 2. Note that of the patients listed as having hepatic disease, 206 are liver transplant patients, since this is a specialty area of the Hospital studied. Attention is drawn to the high number of request forms that did not show the diagnosis, 25.2%, n=192.

Table 3 shows the reasons for the request for albumin. It is observed that 32.8% (n=250 requests) correspond to indications that are supported by currently available scientific evidence. Fourteen prescriptions (1.8%) correspond to specific procedures (purification of albumin in hepatic patients with the Molecu-

lar Adsorbing and Recirculating System technique - MARS). Requests related to hypoalbuminaemia as a supporting diagnosis are clearly observed in 49.4% (n=376) of the request forms.

Table 4 describes the origin of the requests by Hospital Department, with emphasis on the Transplant Unit and the Intensive Care Unit.

A total of 556,831 vials of albumin were requested from the Hospital pharmacy, 6,202 (1.1% of the total requests) were dispensed by the pharmacy, and of these, 5,033 vials were actually administered (0.9% of the total requests). The total cost of albumin administered was 115,763 Euros (considering a unit price of 23 Euros).

DISCUSSION

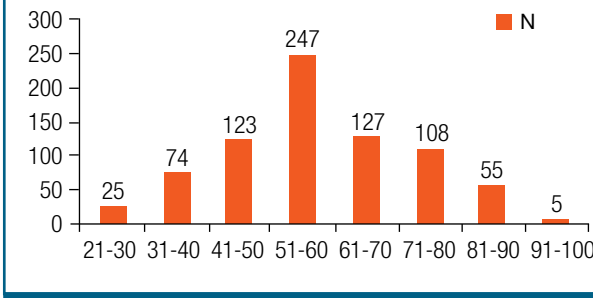
Among the possible study questions posed by this study, we suggest an analysis of the reasons for prescription: requests supported by evidence (with indication); requests without indication, but also without contraindication; and contraindicated requests. The prescribing departments and the discrepancy between the amount of requested albumin to the pharmacy and the amount actually administered to the patients deserve additional comments.

It was observed that of the total requests, 32.8% were actually based on formal indications for the use of albumin. Nevertheless, we observed that the vast majority of the requests were based on reasons not supported by evidence, yet without formal contraindication, for which the use of albumin has not shown any benefits. The most frequent reason for prescription is hypoalbuminaemia (49.4%). It is not clear whether the occurrence of hypoalbuminaemia is a reason that would necessitate the administration of albumin. There is no concrete data in the literature to supports this factor as a reason for the prescription of albumin. Hypoalbuminaemia can have very different causes, and the main determining factor of serum albumin concentration is the rate of its transcapillary transport to the interstitial space.[11] Other reasons can also be mentioned, such as prolonged fasting, consumptive disease, namely neoplasm, infection (HIV infection), and severe infections. Even septic conditions may cause hypoalbuminaemia quite quickly, and in this context, this is considered a negative acute-phase reactant (the more severe the hypoalbuminaemia, the more severe the disease).[1,12-14] In blood volume replacement in case of acute blood loss, probably due to the absence of favorable studies and high costs, the results of the SAFE trial did not show different statistics for mortality when compared to the use of albumin with saline solution.[15] In post-operative patients, it is also usually secondary to albumin redistribution between the intravascular and extravascular spaces, or as a result of protein loss during a surgical procedure.[16] Grundmann and colleagues[17] observed that treatment with albumin of post-operative patients in critical conditions due to hypoalbuminaemia or low colloid osmotic pressure did not alter the evolution, including the need for blood transfusion, duration of mechanical ventilation, duration of stay at the ICU, renal function or mortality. The same was observed by Yuan and colleagues [18] in a trial involving 127 patients who underwent gastrointestinal surgery. In these patients, the administration of albumin did not change the serum albumin levels, compared with a group that did not

TABLE I

General clinical and demographic data

Parameter	Mean, SD and limitations
Age	58,1 +/- 14,7 (20-98)
Males	510 (67%)
Females	251 (33%)
Serum creatinine (mg/dl)	1,77 +/- 1,45 (0,1-13)
INR	1,24 +/- 0,34 (0,5-3,9)
Total bilirubin (mg/dL)	3,64 +/- 6,29 (0,1-48)
Total protein (g/dL)	4,98 +/- 1,23 (2,1-9,2)
Albumin (g/dL)	2,33 +/- 0,75 (0,7-6)



Distribution by age.

FIG. 1

TABLE II

Distribution by major pathologies

Distribution by major pathologies	N
Liver disease	406
Not filled out	192
Others	74
Sepsis	24
Kidney diseases	23
Non-specified post-operative	21
Infectious diseases	10
Irregular heart insufficiency	6
Pancreatitis	5

TABLE III

Distribution according to reason for requesting albumin

Distribution by reason for request	N
Hypoalbubinemia	376
Paracentesis	152
Ascites/ refractory ascites	84
Not filled out	68
Anasarca/edema	28
Specific procedures	14
Others	14
Intradyalisis	12
Non-specified hemodynamic instability	7
Oliguria/anuria	6

receive albumin. Hypoalbuminaemia associated with exudative enteropathy and nephrotic syndrome can be caused not only by intestinal and urinary losses, but also by the increase in capillary permeability and by dilution in an increased interstitial volume. In randomized trials, the use of exogenous albumin in these cases was not beneficial.[19] Many of the oldest concepts establish the prescription of albumin based on its function in the organism rather than on scientific evidence. These includes the tendency to prescribe albumin to treat peripheral edemas, resorting to the assumptions of the Ernest Starling equation formulated in 1896 on the equilibrium between hydrostatic and oncotic forces and the principles of capillary fluid exchange. These principles have been taught for a long time, but doubts are increasing as to whether they work in vivo. It is impossible to establish a direct relation between the serum albumin values and occurrence of edema. Even patients with congenital analbuminaemia do not have significant edemas.[20] This concern, already identified in Starling's principles,[21] is currently the object of renewed interest, leading to the development of new hypothesis, such as the "lymph node paradox", apparently not subject to these forces, or to the concepts of Michel-Weinbaum that propose new models of endothelial filtration.[22] Nevertheless, as can be observed from the results in table 1, the diagnosis of hypoalbuminaemia is vague and unspecific, as the mean serum albumin value of 2.33 +/- 0.75 g/l suggests subjectivity in this parameter. Currently, most authors consider that the use of albumin only to resolve hypoalbuminaemia is inappropriate or, according to Allison and Lobo, a prescription that is "at the very least, naïve".[23]

We observed a few requests for albumin for intradialytic administration and in the treatment of general low blood pressure. Knoll and colleagues compared saline solutions with albumin 4% for the treatment of low blood pressure during dialysis, but no differences were found in the final results, therefore saline solution was recommended as the fluid of choice.[24] By consensus, the haemodynamic effects of albumin are practically non-existent.

It is even more difficult to consider prescriptions due to "irregular heart failure", as this could represent a contraindication rather than an indication. The same concerns may be raised for prescriptions for oliguria or anuria, in which cases the benefit of albumin can raise doubts.

Regarding the origin of the requests, most of them were made by the ICU. Oddly, the most solid scientific evidences were produced in this context. It is important to highlight that the reasons for request and the requesting departments were not cross-referenced, so it is not possible to determine the importance of a particular reason for requests made by the ICU. In the trial SAFE,[15] which involved 6,997 patients admitted to ICUs and served as a great input for the meta-analysis of the Cochrane Collaboration, although the trial was carried out using 4% human albumin, it was observed that the use of albumin in this specific

TABLE IV

Distribution by origin of requests

Distribution by origin of requests	N
Transplant unit	213
Intensive care unit	149
Medicine	147
Others/ unspecified	101
Nephrology	57
Emergency department	46
Surgery	39
Infectiology	7
Cardiology	2

group of patients did not alter the mortality rates, except in cases of head trauma, for which an increase in mortality was observed.[25] Regarding albumin replacement after the first 48 hours of treatment of large burn areas, the trial SOAP [26] demonstrated that, in this group, the use of albumin caused an increase in mortality, as shown in other articles that demonstrated that albumin was less effective than saline solution in re-establishing patients' haemodynamic properties.[16] For acute respiratory insufficiency, albumin infusions did not decrease alveolar secretions, and may even have aggravated diffusion deficits in adult patients with respiratory stress syndrome, when compared to hydroxyethylamide.[27] The reference to the type of albumin should also be taken into consideration. The SAFE trial, and the majority of studies, investigate non-hyperoncotic 4% albumin solutions, whereas we used 10% hyperoncotic solutions. The problem is that this type of solution, such as the 20% hydroxyethylamide solutions, can be particularly nephrotic.[28,29] This topic is clearly beyond the scope of our study, but should be seriously taken into account by prescribers.

Large-volume paracentesis, refractory ascites and prevention of hepatorenal syndrome are perhaps the less controversial indications of albumin prescription. It is not surprising, therefore, that the emergency department is a prescribing department, since it carries out paracentesis before sending patients to the other wards. The role of the Internists in this context seems fundamental, since in the majority of cases, they are in charge of the scientific and technical aspects of the procedures.

It is important to point out a substantial difference regarding the origin of requests. The departments that placed the highest number of requests were the Transplant Unit (TU) and the ICU. While a large number of patients at the TU have liver pathologies, the same does not apply to the ICU. Emphasis on continued training in this context, as in other fields of Medicine, is essential for an up-to-date clinical practice. Regarding the number of hospitalizations, we were a little surprised with the lower frequency of use of albumin in the departments of Medicine. Although the range of pathologies can vary considerably, it is important to observe that the practitioners in these departments appear to use albumin with greater discernment.

A huge difference was observed between albumin administered to the patients and the number of vials requested. Only 0.9% of the requested vials were effectively used. The main cause of this discrepancy was the gap between the estimated length of treatment and the actual length of treatment. There is no record or policy at the Hospital pharmacy for not dispensing an expensive product, or the need for approval by a supervisor.

The easiest way to explain this is by giving a real example: in a certain prescription, two vials of albumin were requested for administration every 8 hours over 7 days, with a total of 42 requested vials. The pharmacy, as a normal procedure, can only dispense thirteen vials, i.e. the other 29 vials to complete the treatment would need an additional prescription, which in the vast majority of cases, does not happen. In some cases, unused vials were even returned to the pharmacy. This would explain the discrepancies between the 556,831 requested vials of albumin and the 6,202 dispensed vials (1.1% of the total requests), and the 5,033 administered vials (0.9% of the total requests). It would also explain the fact that the number of patients is higher than the number of requests. This matter deserves future consideration by prescribers in terms of the need for, and length of treatment.

STUDY LIMITATIONS

This study was possible thanks to the electronic registration system. Without this system, the study would have been virtually impossible. Nevertheless, this methodology has some important aspects since it is not always possible to comply fully with the medical decision. Sometimes, by default, the medical

argumentation is not part of the process.

On the other hand, we observed that in around 25% of the cases (n=192) the requests did not include the diagnosis, which may have created a bias in the results obtained.

The request forms are not always correctly fill out, as they are seen as bureaucratic and non-scientific pieces of paper, therefore the conclusions drawn from their analysis may not be the most accurate. This is due to the retrospective nature of the study.

CONCLUSION

The present study observed that most of the requests for albumin to the pharmacy were not in compliance with the currently available scientific evidence. The departments that requested albumin the most were the ICU and TU.

A marked discrepancy was also found between the amount of albumin prescribed and that actually administered, which justifies restraint in dispensing by the pharmacies.

Continued training in this particular area should be encouraged, in order to match the reasons for prescription of human albumin with the scientific evidence. ■

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