

Pharmacy contribution to the prescription and rational use of human albumin at a large hospital

Contribuição da farmácia na prescrição e uso racional de albumina humana em um hospital de grande porte

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ABSTRACT

Objective: The purpose of this survey was to reduce the use of human albumin 20% in non-supported indications at Hospital Israelita Albert Einstein. **Methods:** During a 30-day period, in December 2006, a preliminary prospective analysis of medical prescriptions of human albumin 20% and therapeutic indications according to ANVISA RDC 115 guidelines was performed. Based on this analysis, a project was developed. In January 2007, a daily routine to follow up albumin prescriptions by the Hospital pharmacists was established. **Results:** From January to October 2007, 14,799 vials of albumin 20% were used, out of which 4,191 had non-supported indications, resulting in a R\$ 1.36 million loss. In 2008 (from January to October), 13,519 vials of albumin 20% were prescribed, and 1,648 of them had non-supported indications, causing a R\$ 535 thousand loss. The ratio between loss risk and consumed amount was 91.99 between January and October 2007. During the same period in 2008, this ratio was 39.60. Between January and October 2007, the average percentage of albumin prescribed for non-supported indications was 28%, whereas this percentage dropped to 13%, i.e., a decrease by 54%, during the same period of 2008. **Conclusions:** The inclusion of a pharmacist in the process of verifying medicine indications and justification of use was translated into safer processes to patients, ensuring that they received the correct medication for the correct indication, therefore reducing the chance of adverse events and contributing to reduce red-tape procedures and unnecessary expenditures by the institution.

Keywords: Medication use; Albumins; Pharmacoeconomy; Clinical pharmacy

RESUMO

Objetivo: O trabalho teve como objetivo a redução da utilização de albumina humana 20% com indicação não-fundamentada no

Hospital Israelita Albert Einstein. **Métodos:** Durante um período de 30 dias (dezembro, 2006), foi realizada uma análise prospectiva preliminar utilizando-se as prescrições médicas de pacientes com Albumina humana, e avaliaram-se as indicações terapêuticas em relação às diretrizes estabelecidas pela resolução ANVISA RDC 115. A partir dessas informações, foi elaborado um projeto de atuação e foi instituída uma rotina de acompanhamento diário das prescrições pelos farmacêuticos a partir de Janeiro de 2007. **Resultados:** De Janeiro a Outubro de 2007, foram consumidos 14.799 frascos de albumina 20%. Destes, 4.191 com indicação não fundamentada, correspondendo a uma perda de R\$ 1,36 milhões. Em 2008 (de janeiro a outubro), foram prescritos 13.519 frascos de albumina 20%. Destes, 1.648 com indicação não fundamentada, o que responde por uma perda de R\$ 535 mil. A relação entre o risco da perda e quantidade consumida de janeiro a outubro de 2007 foi de 91,99. Já no mesmo período de 2008 foi de 39,60. De janeiro a outubro de 2007, a média do percentual de albumina prescrita com indicação não-fundamentada foi de 28%. No mesmo período em 2008, este percentual caiu para 13%. Uma redução de 54%. **Conclusões:** O envolvimento do Farmacêutico no processo de verificação da indicação e justificativa do uso do medicamento representa processos seguros ao paciente, garantindo que ele receba o medicamento certo para a indicação correta, reduzindo com isto a probabilidade de eventos adversos e contribuindo para diminuir burocracias e gastos desnecessários na instituição.

Descritores: Utilização de medicamento; Albuminas; Farmacoeconomia; Farmácia clínica

INTRODUCTION

Albumin is an endogenous protein present at high concentrations on human plasma. Its molecular

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weight is 68 kDa and it is the compound mainly responsible for the maintenance of intravascular oncotic pressure^(1,2).

It is synthesized in the liver by hepatocytes at a daily mean of 120 to 200 mg/kg of body weight, and the average synthesis time is 20 minutes. Two thirds of body albumin are present in the extravascular compartment, and only one third in the intravascular compartment.

Albumin content in liver cells, where it is synthesized, is 200 to 500 mcg/g of liver tissue^(1,2). However, only one-third of hepatocytes actively synthesize albumin, if an average extrusion time from the endoplasmic reticulum of 20 minutes and constant synthesis is assumed⁽¹⁻³⁾. The normal albumin synthesis rate is approximately 100 to 200 mg/kg/day, which may considerably vary as a function of nutritional status, hormone levels, and colloidal content of the liver interstice³. The liver interstice works as a “restricted” domain, with low protein concentration, and functions as an osmoreceptor, sensitive to smaller changes in protein levels as compared to the plasma pool^(3,4).

The administration of dextran or human immunoglobulin or the stimulation of globulin synthesis in normal serum by hyperimmunization leads to decreased albumin synthesis. However, if the colloidal oncotic pressure increases due to albumin (or plasma) administration, the hyperoncotic status is reversed by increasing catabolism, which suggests the interdependence between synthesis and breakdown. The factors that determine synthesis and breakdown are related to the oncotic pressure exerted by colloidal content in the extravascular compartment rather than plasma, emphasizing the importance of osmoreceptors in the liver interstitial space for the control of homeostasis^(3,4).

The liver usually has no influence on the control of albumin catabolism in healthy individuals^(3,5), but in the presence of specific-organ disease, the liver, kidneys, and intestines may be important sites of albumin breakdown⁽⁶⁾.

Commercially-prepared human albumin does not seem to be excreted by the kidneys, and there are reports indicating that renal excretion of albumin is relatively not important under normal health conditions^(3,7,8).

Renal diseases may affect albumin synthesis and breakdown. In nephrotic syndrome, plasma albumin is preserved from breakdown, and decreases when albumin loss is lower than 100 mg/kg/day. At higher albumin loss rates, albumin synthesis may increase to more than 400 mg/kg/day⁽³⁾.

The effects of plasma volume, serum albumin concentration, and plasma osmolality on kidney function were evaluated in cirrhosis patients. A single

50-g infusion of albumin increased plasma volume and average effective renal plasma flow, but had not effect on glomerular filtration rate. No correlation between plasma volume changes and effective renal plasma flow were detected⁽⁹⁾.

Albumin solutions for therapeutic use are obtained by industrial fractionation of human plasma. The plasma used for fractionation can be collected by apheresis or derive from total blood donation, in which case is surplus plasma from therapeutic use⁽¹⁰⁾.

According to the Federal Drug Administration, about 14 million blood units are annually collected from approximately 8 million voluntary donors to obtain blood components that are directly transfused into more than 3.5 million Americans. These products include albumin to restore plasma volume, clotting factors to treat hemophiliac patients, and immunoglobulins to treat or prevent several diseases. It is estimated that more than 400 thousand patients use human albumin.

Since albumin started to be commercially available, in 1940, its increasing use in clinical practice has been debated, because its utilization has been largely based on pathophysiological reasons and not on clinical trial results, as it should be. However, the role of albumin as compared to cheaper therapeutic alternatives such as other colloids or crystalloid solution has not been properly evaluated.

The lack of clinical evidence of efficacy in absolute or comparative terms has led to considerable dissonance among researchers as to its indications. In the 1970s, the National Institute of Health (USA) decided to foster the development and publishing of an albumin usage guide based on the opinion of expert groups. The dissemination of these guidelines in an educational program in some health care centers reduced the rate of inadequate prescription of albumin solutions^(1,2,11-13).

As the process of albumin production is difficult due to high costs and controversial indications, several centers developed studies and protocols on its proper utilization.

In Brazil, in 2004, the ANVISA (*Agência Nacional de Vigilância Sanitária* – National Health Surveillance Agency) issued Resolution RDC no 115, of May 10, 2004, establishing guidelines for the use of human albumin⁽¹⁰⁾, aiming to provide criteria for the indication of this solution in hospital clinical practice. At *Hospital Israelita Albert Einstein*, attempts to determine adequate medical prescription for albumin were developed before RDC was issued, but with no success.

The RDC classifies three categories for the indication of the use of albumin, as follows⁽¹⁰⁾.

Formal indications are those supported by randomized and controlled studies demonstrating the

efficacy of albumin in the treatment of patients. The fact of being included in the formal category does not mean that there are no therapeutic alternatives for the use of albumin; rather, it indicates that if the medical team caring for the patient decided to use it, this decision is supported by specialized literature.

Debatable indications are those which have achieved no consensus, and the results of studies and meta-analyses are conflicting. Albumin may be used in these circumstances until more conclusive evidences are published in literature.

Finally, non-supported indications are those whose studies show that there is no benefit to the patients when albumin is used⁽¹⁰⁾.

OBJECTIVE

To reduce by 50% non-supported albumin prescriptions in the institution, from January to October, 2007, using the guidelines of Resolution RDC no 115, of May 10, 2004.

METHODS

The Hospital Israelita Albert Einstein is a quaternary care hospital with mixed services. It has undergone expansion, and has approximately 500 beds distributed into 15 clinical and surgical units, an adult ICU and a pediatric ICU. There are 40 pharmacists, out of which 30 work in the clinical pharmacy. Each in-patient unit has one clinical pharmacist.

The annual financial resources used exclusively for the use of albumin at Hospital Israelita Albert Einstein are roughly R\$ 6 million.

A preliminary analysis was carried out for 30 days in December, 2006, evaluating medical prescriptions of human albumin according to the guidelines established by ANVISA Resolution RDC 115, and the results showed 42% of non-supported and 35% of debatable prescriptions.

Based on the information obtained, a project was developed, in which clinical pharmacists daily identified patients with human albumin prescriptions, evaluated the indications according to the information written in their medical records, discussed the indications with the medical and multidisciplinary teams, and classified the prescriptions according to RDC 115 as formal, debatable, or non-supported⁽¹⁰⁾.

After this evaluation, a bulletin with information on RDC n° 115 was sent by the Medical Practice Board to the prescribers. The guidelines were discussed in forums and expert meetings, and a daily routine to follow up prescriptions by the pharmacists was established, starting in January, 2007.

The daily follow-up of human albumin prescriptions by pharmacists was performed by using the information available in patient's registers and reports obtained in the electronic prescription and available inventory management system of the hospital. Based on this information, clinical pharmacists intervened by discussing with the prescriber whenever a prescription with a non-supported indication for the use of albumin was identified.

After this intervention, the follow-up routine was informed, and the pharmacists identified and classified the indication using the guidelines provided by the ANVISA RDC 115.

Data were daily recorded in a spreadsheet, monthly compiled, and reported to the managers using written reports.

These reports were used by the Medical Practice Board as an instrument to evaluate the biannual performance of the medical staff of the hospital ("Feedback Program").

RESULTS

During the first period of analysis after the implementation of the routine, between January and October 2007, 387 patients had albumin prescriptions and 14,799 human albumin 20% flasks were used, out of which 4,191 had non-supported indications, resulting in a potential refunding loss of R\$ 1.36 million (Table 1).

Table 1. Non-supported indication for human albumin

Total per period	Jan/Oct 2007	Jan/Oct 2008
Patients	387	327
Consumption of flasks	14,799	13,519
Flasks/Non-supported indication	4,191	1,648
Loss related to non-supported indication of albumin (R\$)	1.36 million	535 thousand
Risk of loss (R\$/Flasks) (loss R\$/total consumption in the period)	91.99	39.60

In 2008 (between January and October), 327 patients had albumin prescriptions and 13,519 human albumin 20% flasks were used – in that, 1,648 had non-supported indications, resulting in a potential refunding loss of R\$ 535 thousand (Table 1).

The ratio between risk loss and consumed amount was 91.99 for the period of January to October 2007, and 39.60 for the same period in 2008.

Between January and October 2007, the average percentage of prescribed albumin with non-supported indications was 28%, whereas the percentage dropped to 13% during the same period in 2008. From the beginning of the project, in January 2007, until December 2008, a 69% reduction was observed (Figure 1).

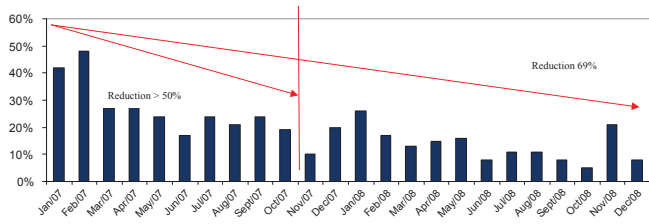


Figure 1. Analysis of the use of albumin with non-supported indication

During this same period, between January 2007 and December 2008, the number of prescriptions with non-supported indications decreased, and the number of prescriptions with supported indications increased (Figure 2).

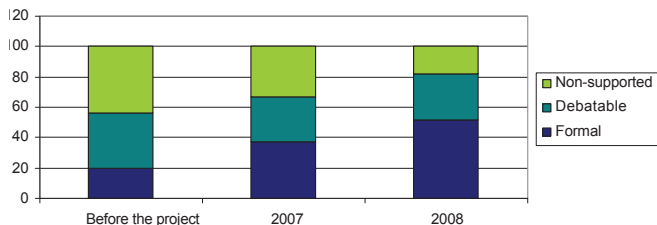


Figure 2. Prescription of albumin in relation to the classification of indications by the RDC n° 115

The monthly analysis of the data collected between January 2007 and December 2008 demonstrates that albumin utilization was mainly concentrated in the adult Intensive Care Unit (21% in 2007 and 25% in 2008), solid-organ transplant unit (28% in 2007 and 31% in 2008), followed by the adult step-down unit (13% in 2007 and 12% in 2008) and the cardiology unit (13% in 2007 and 10% in 2008) (Table 2).

Table 2. Distribution of prescription of albumin at the Hospital Israelita Albert Einstein (HIAE)

Distribution	Before the project (Dec 2006)	2007 (Jan/Dec)	2008 (Jan/Dec)
	n (%)	n (%)	n (%)
Cardiology	3 (12)	55 (13)	37(10)
Adult ICU	7 (28)	91 (21)	95 (25)
Adult step-down unit	-	56 (13)	45 (12)
Geriatrics	4 (16)	20 (5)	19 (5)
Pediatric ICU	-	17 (4)	2 (1)
Pediatrics	-	5 (1)	8 (2)
Oncology	2 (8)	35 (8)	29 (8)
Transplant	6 (24)	124 (28)	119 (31)
Neonatal ICU	-	7 (2)	6 (2)
Maternity ward	-	-	1(0,3)
Gastroenterology	-	20 (5)	20 (5)
Orthopedics	-	6 (1)	1 (0,3)
Neurology	3 (12)	2 (0,5)	3 (1)
Total	25 (100)	438* (100)	385* (100)

ICU: intensive care unit.
 *Reduction by approximately 12% in prescriptions between the two periods
 Number of patients/day 2007: 138.799
 Number of patients/day 2008: 150.045 (increase by 8.1% as compared to 2007)

As to the distribution of non-supported indications during the studied period, albumin was mostly used to correct hypoalbuminemia (Table 3), whereas the main supported indications were the use after evacuating paracentesis in patients with high-volume ascites, and in patients with liver cirrhosis and nephrotic syndrome with life-threatening edema refractory to diuretics (Table 4).

Table 3. Distribution of non-supported indication for albumin at Hospital Israelita Albert Einstein (HIAE)

Non-supported indications	2007 (% of prescriptions)	2008 (% of prescriptions)
Correction of hypoalbuminemia	25	13
Correction of acute large fluid losses, including hemorrhagic shock	1	0
Treatment of patients with hepatic cirrhosis or nephrotic syndrome	1	0
Perioperative period, except in the cases afore mentioned	0	0
Others	6	4
Total	33	17

Table 4. Distribution of formal indications and use of albumin at Hospital Israelita Albert Einstein (HIAE)

	2007 (% of prescriptions)	2008 (% of prescriptions)
Formal indications		
Priming of extracorporeal circulation pumps in cardiac surgeries	0	1
Treatment of patients with voluminous ascites, due to repeated paracentesis	4	6
After draining paracentesis in patients with voluminous ascites	13	10
As a replacement fluid in large therapeutic plasmapheresis (removing over 20 ml/kg of plasma per session)	2	4
Prevention of ovarian hyperstimulation syndrome on the day of ovule collection for in-vitro fertilization	0	0
Patients with hepatic cirrhosis and nephrotic syndrome, with life-threatening edema refractory to diuretics	10	12
Massively burned, after the first 24 hours after injury	1	1
Postoperative care of liver transplant, when serum albumin is lower than 2.5 g%	7	17
Total	37	51
Debatable indications		
In critically-ill patients with hypovolemia, hypoalbuminemia and poor fluid distribution	27	28
Hyperbilirubinemia of neonates due to hemolytic disease of the newborn	-	0
In cirrhotic patients with spontaneous bacterial peritonitis	2	3
Total	29	31

DISCUSSION

The involvement and discussion of authorities and health professionals that led to the publication of Resolution

n° 115 by ANVISA were essential, as they supported the success of the project and the establishment of the procedure of human albumin 20% prescription at hospitals. Despite the short pre-project period (December 2006), the Resolution was used as the basis for the development and implementation of the project and of the routine at the Hospital.

The main non-supported indication and use of albumin were associated to the correction of hypoalbuminemia and, according to the recommendations in literature and of the RDC 115, human albumin 20% is not a good protein source, particularly as compared to parental amino acid solutions and to enteral protein hydrolysate solutions. Moreover, there is no evidence that justifies the use of albumin to correct hypoalbuminemia⁽¹²⁻¹³⁾.

Among the formal indications, the use of albumin after evacuating paracentesis in patients with high-volume ascites, and in patients with liver cirrhosis and nephrotic syndrome with life-threatening edema refractory to diuretics may be associated to patients with severe conditions and justifies the higher use of this medication at the ICUs and Transplant Units.

As to the distribution of non-supported indications during the period of January 2007 to December 2008, it was observed that albumin was mainly used to correct hypoalbuminemia, which is consistent with the findings of other studies on the indications of albumin use⁽¹²⁻¹⁴⁾.

The initial values obtained for non-supported prescription of human albumin in the Hospital were slightly lower than those reported in other studies, which may have also contributed to the successful implementation of the proposed routine⁽¹²⁾.

Another factor that influenced the results of the project was the "Feedback Program", in which the Medical Practice Board, by means of individual performance evaluation and interviews conducted with the physicians, present data in compliance with institutional protocols.

In addition to this program, the multiprofessional work developed by the clinical pharmacists with the medical and multiprofessional team also influenced the obtained results. The clinical pharmacist performs several activities aiming to maximize the effects of therapeutics and to minimize treatment risks and costs⁽¹⁴⁻¹⁷⁾. The work developed shows that the participation of the clinical pharmacist was essential for the success of projects linked to safe and rational use of medicines, promoting the adoption of institutional guidelines by the Hospitals' medical and multidisciplinary teams, thereby increasing patient safety.

A change in the profile of indications for prescription of albumin was observed at the Hospital belonging to Sociedade Beneficente Israelita Brasileira Albert

Einstein, which, in addition to contributing to albumin rational use, had an economic impact.

A reduction in the number of albumin prescriptions was also verified between 2007 and 2008, despite the increased number of patients per day during the same period in that hospital.

The economic impact derived from the rational use of albumin represented savings of R\$ 825 thousand during that period, as well as a reduction of the risk of non-coverage of the costs by health insurance companies. This justifies including or hiring pharmacists who may contribute to this and other processes of safe and rational use of medicines at hospitals. Hiring a pharmacist represents an average annual labor cost, including wages, taxes, and fringes, of R\$ 55 thousand.

CONCLUSIONS

At Hospital Israelita Albert Einstein, the use of human albumin 20% with non-supported indications was reduced by over 50% (from 42 to 19%) between January 2007 and October 2008 (completion of the first analysis), and achieved 69% by the end of 2008, as the project continued.

The action of the clinical pharmacist as to albumin prescriptions had a positive impact in terms of improving prescription accuracy, thus increasing patient safety and contributing to lower unnecessary costs.

REFERENCES

1. Tullis IS, James L. Albumin: 1. Background and use. *JAMA*. 1977;237(4):355-60
2. Tullis IS. Albumin: 2. Guidelines for critical use. *JAMA*. 1977;237(5):460-3.
3. Lewis RT. Albumin: role and discriminative use in surgery. *Can J Surg*. 1980;23(4):322-8.
4. Laurent TC, Ogston AG. The interaction between polysaccharides and other macromolecules: the osmotic pressure of mixtures of serum albumin and hyaluronic acid. *Biochem J*. 1963;89(Pt2):249-53.
5. Cohen S, Gordon AH. Catabolism of plasma albumin by the perfused rat liver. *Biochem J*. 1958;70(4):544-51.
6. Rothschild MA, Oratz M, Schreiber SS. Albumin synthesis (first of two parts). *New Engl J Med*. 1972;286(14):748-57.
7. Katz J, Bonorris G, Sellers AL. Effect of nephrectomy on plasma albumin catabolism in experimental nephrosis. *J Lab Clin Med*. 1964;63:680-8.
8. Mogielnicki RP, Waldmann TA, Strober W. Renal handling of low molecular weight proteins: I. L-chain metabolism in experimental renal disease. *J Clin Invest*. 1971;50(4):901-9.
9. McCloy RM, Baldus WP, Maher FT, Summerskill WJS. Effects of changing plasma volume, serum albumin concentration and plasma osmolality on renal function in cirrhosis. *Gastroenterology*. 1967;53:229-39.
10. Brasil. Ministério da Saúde. Agência Nacional de Vigilância Sanitária. Resolução RDC nº 115, de 10 de maio de 2004. Aprova as Diretrizes para o uso de Albumina. *Diário Oficial da União, Brasília, DF, 11 maio 2004*. [Internet] 2004. [cited 2006 Dec 01] Available from: <<http://e-legis.bvs.br/leisref/public/showAct.php?id=11025>>

11. World Health Organization. Annex 4: WHO recommendations for the production, control and control and regulation of human plasma for fractionation. Presented at the 56th meeting of the WHO Expert Committee on Biological Standardization, Oct 24-28, 2005. [Internet] [cited 2010 May 28]. Available from: www.who.int/biologicals/publications/ECBS%202005%20Annex%204%20Human%20Plasma%20Fractionation.pdf
12. Matos GC, Rozenfeld S. Avaliação do uso de albumina humana em hospital do Rio de Janeiro, Brasil. *Cad Saúde Pública*. 2005;21(4): 1224-33.
13. Vargas E, Miguel V, Portoles A, Avendano C, Ambit MI, Torralba A. Use of Albumin in two Spanish university hospitals. *Eur J Clin Pharmacol*. 1997;52(6):465-70.
14. Aramwit P. Evaluation of serum albumin utilization in inpatient at a private hospital in Bangkok. *Yakugaku Zasshi*. 2004;124(9):631-4.
15. American Society of Health. System Pharmacists. ASHP guidelines on the pharmacists' role in the development of clinical care plans. *Am J Health-System Pharm*. 1997;54(3):314-8.
16. Gomes MJVM, Reis AMM. Ciências farmacêuticas: uma abordagem em Farmácia Hospitalar. São Paulo: Atheneu; 2003.
17. American Society of Health. System Pharmacists. ASPH guidelines on documentation pharmaceutical care in patient medical records: developed through the ASHP council on professional affairs and approved by the ASHP board of director on February 20, 2003. *Am J Health-System Pharm*. 2003;60(7):705-7.