Original Article

Albumin Utilization Evaluation in a Major Teaching Hospital in Iran: Recommendations for Guideline Development

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ABSTRACT

Objective: Human albumin solution is an expensive colloidal preparation which is commonly used in clinical practice. Due to high cost of albumin, increased rate of the inappropriate use worldwide, and many other reasons, it is imperative to establish a practical protocol to use albumin products and limit its usage. The aim of this study was to identify albumin utilization patterns in a teaching hospital and to demonstrate the importance of the need to reconsider prescribing strategies for albumin administration. **Methods:** This retrospective cross-sectional study was performed between August 2016 and December 2016 at Firoozgar Hospital affiliated to Iran University of Medical Sciences, Tehran, Iran. All albumin prescriptions for adult patients during the study period were enrolled for appropriateness evaluation according to the latest evidence-based studies and guidelines. **Findings:** Among 320 albumin prescriptions, 168 (52.5%) were inappropriate according to the current evidence. The most common irrational causes for the albumin usage were hypoalbuminemia (23.4%), nutritional support (13.7%), neuroprotection in subarachnoid hemorrhage (3%), pretreatment for cancer surgery (2.8%), edema (1.6%), hepatic failure (1.6%), and paracentesis (3%). The total amount of albumin used for 320 patients was 52,050 g, from which 28,470 g was inappropriate resulting in $97,398 wastage. **Conclusion:** These findings, along with aforementioned guidelines, support the requirement for physicians' educational programs and proper strategies for appropriate prescriptions and could also be important in modifying the available guidelines concerning expensive drugs such as albumin.

KEYWORDS: *Albumin, Albumin guideline, drug utilization evaluation*

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Introduction

Drug utilization evaluation (DUE) provides a comprehensive review of patients' prescription and medication administration process. DUE programs participate in helping health-care systems to improve the prescription, administration, and medication use and to certify decision-making and patient outcomes. In addition, considering the importance of clinical effectiveness and control of health system funding, most assessments are performed on medications with high price and consumption.[1]

Human albumin solution (HAS) is a colloidal preparation with high cost and is commonly considered for clinical use. HAS is available in preparations of 5%, 20%, and 25%, with different physiologic characteristics, which should not be administrated interchangeably. The 5% solutions have an osmotic pressure nearly equal to that of normal plasma, and its uses are quite different from 20% and 25% solutions that are hyperosmotic.[2] Until now, precise indications for albumin are not defined; its theoretical and pharmacological benefits concomitant with rare reports of adverse reactions have led to an increased willingness to use this product.

Due to high cost of albumin, increased rate of the inappropriate use worldwide, difficult production process, probability of disease transmission, and availability of other economical alternatives with equivalent efficacy, it is imperative to establish a practical protocol to use albumin products and limit its usage.[2]

The aim of this study was to identify albumin utilization patterns in a teaching hospital to demonstrate the importance of the need to reconsider prescribing strategies for albumin administration.

Methods

This retrospective cross-sectional study was performed between August 2016 and December 2016 at Firoozgar Hospital affiliated to Iran University of Medical Sciences, Tehran, Iran. The study protocol was approved by the Ethics Committee of Iran University of Medical Sciences (IR.IUMS.FMD.REC1396.9211060005), and the privacy of the patients was assured. In this period, adult patients (defined as >12 years old) who received albumin were enrolled in this study.

In the mentioned hospital, all attending physicians ordinarily complete a designed form approved by the Food and Drug Department of Iran University of Medical Sciences, to request albumin from the inpatient pharmacy. This form comprises two parts; the first part contains patient demographic data (age, gender, ward, physician's specialty, the reason for the admission, and the type of surgical intervention) and the second part includes data on reasons for albumin prescription, total amount of albumin used, and duration of treatment. At the end of this form, the inappropriate uses of albumin, the relative contraindications, and the other alternative treatments have been recommended.

For evaluation of the utilization pattern of albumin, a list of albumin recipients and the above-mentioned completed forms were provided to a clinical pharmacist from the data bank of the pharmacy. Laboratory data including albumin level before and after the initiation of albumin, liver function tests, blood urea nitrogen, and creatinine level were extracted from the Hospital Information System.

Since there is no comprehensive international guideline available regarding the rational indications of albumin usage, the appropriateness of albumin prescription was evaluated by means of the latest evidence-based studies and guidelines.[1-21] The appropriate and inappropriate indications are shown in Tables 1[2] and 2,[1,2,5-8,10,12,22,17-19] respectively.

Albumin is only available in 20% solutions in Iran containing 10 g of albumin. The amount of albumin used was explained in grams, estimated as the gram of each vial multiplied by the number of vials. The albumin cost was calculated as grams prescribed multiplied by the cost per gram. The cost of each albumin vial was estimated based on the average price announced by the Ministry of Health of Iran. All costs are expressed in US dollars (1 US$ = 38,000 Rial).

Data were transferred from the mentioned forms to SPSS® 20 Software for statistical analysis. The descriptive assessment was stated as mean values ± standard deviation (SD) or median for numerical variables; number and percentages were expressed for nominal variables.

Results

Data from 320 patients were collected; 188 were male and 132 female. The mean age of patients was 58.67 ± 17.89 years. Intensive Care Units (including surgical, neurosurgical, open heart, medical, and neurovascular) allocated the highest albumin utilization, accounting for 34.1%. Regarding the underlying disease, all types of cancers were the most prevalent reason for albumin usage with 45.3%. Patients' demographic and characteristics are shown in Table 3.

The total amount of albumin used for 320 cases was 52,050 g with a mean of 162.6 ± 137.9 g per patient, ranging from 10 to 910 g. Findings are shown that the mean duration of treatment was 7.54 days (SD = 7.64; median = 5).

Table 1: Guidelines for Albumin use

Indication	Note	Reference
Indications for the use of 20% Albumin		
Paracentesis	Appropriate indications	
	5 g of albumin/L ascetic fluid removed, if paracentesis volumes is >4 L	[2]
SBP	Appropriate indications	
	In combination with antibiotics	[2]
Major surgery (>40% liver resection, extensive intestinal resection)	Occasionally appropriate indication	
	If serum albumin <2 g/dl after restoration the circulatory volume	[2]
	Should not be used in the first 24 h postoperation	
Organ transplantation	Occasionally appropriate indications	
	After liver transplantation to reduce ascites and peripheral edema, to replace the ascitic fluid, lost from the drainage tubes, if albumin <2.5 g/dl with a hematocrit >30%	[2]
Nephrotic syndrome	Occasionally appropriate indication	
	Only in patients with albumin <2 g/dl with hypovolemia and/or pulmonary edema	[2]
Malnutrition syndromes	Occasionally appropriate indication	
	Can be used only if the volume of diarrhea is >2 L/day	[2]
	Serum albumin <2 g/dl has not been improved despite the use of short peptide and elemental formulas	
Cirrhosis of the liver with refractory ascites	Occasionally appropriate indications	
	Generally ineffective except in patients with serum albumin <2 g/dl or resistant to diuretics	[2]
Indication for the use of 5% Albumin		
Therapeutic plasmapheresis	Appropriate indications	
	For exchanges of >20 mL/kg in one session or >20 ml/kg/week in more than one session	[2]
Burns	Occasionally appropriate indication	
	In the case of burns of >30% body surface area	[2]
	Should not be used in the first 24 h	
Hypovolemic shock (hemorrhagic)	Occasionally appropriate indication second choice	
	May be used in the following conditions	[2]
	Resistant to treatment with crystalloids or colloids	
	Contraindication to the use of non-protein colloids	
	Crystalloids and colloid solution should not be considered instead of blood transfusion when oxygen transporting capacity is reduced	

SBP: Spontaneous bacterial peritonitis

The distribution of the albumin administrations, total dosage, appropriate and inappropriate indications, and cost of albumin prescribed for any reasons are presented in Table 4. The most common causes for the albumin usage are as follows: hypoalbuminemia 198 (61.9%), nutritional support 44 (13.8%), plasmapheresis 20 (6.3%), paracentesis 10 (3.1%), neuroprotection in subarachnoid hemorrhage (SAH) 10 (3.1%), pretreatment for cancer surgery 9 (2.8%), edema 5 (1.6%), hepatic failure 5 (1.6%), and nephrotic syndrome 4 (1.3%). Other reasons such as volume expansion after cardiac surgery, extensive intestinal resection, wound healing, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome type 1 (HRS1), ovarian hyperstimulation syndrome, posthemodialysis hypotension, and hypovolemic shock included 15 (4.5%) of the total. Albumin was appropriately prescribed in all cases of HRS. The most frequent inappropriate causes for albumin consumptions were hypoalbuminemia, nutritional support, neuroprotection in SAH, pretreatment for cancer surgery, edema, hepatic failure, and paracentesis, respectively.

Among 320 albumin prescriptions, 168 (52.5%) were not concordant with the current evidence and studies.[1-21] The amount of inappropriate albumin prescribed was 28,470 g (55%). Each vial of albumin costs almost $34.21. The total cost of albumin used was almost $177,000 with $97,400 wastage.

Discussion

Our study shows that more than half of albumin administration was not appropriate regarding the reliable studies and guidelines applied in this observation. Due to high costs of albumin, inappropriate usage of albumin leads to great wastage of treatment funds.

Although there are several guidelines concerning the clinical use of albumin, official evidence-based strategies are not yet accurately defined for its appropriate indications. However, we evaluated the consumption

Table 2: Inappropriate indications for Albumin usage

Indication	Causes	Reference
Hypoalbuminemia (serum albumin level >2.5 g/dl) without clear primary reasons	Inappropriate†	[2]
Malnutrition	Should not be used as protein source	[1,2]
Pancreatitis	Inappropriate†	[2]
Wound healing	Inappropriate†	[2]
Cardiac surgery	May be increase acute kidney injury; needs more RCTs	[2,20]
TBI	Increased mortality risk	[7-11]
Neuroprotection in SAH	Needs more RCTs	[10]
Pretreatment for cancer surgery	Needs more RCTs	[12,13]
Sepsis and septic shock	Resuscitation with crystalloid is preferred; needs more RCTs	[5-8,17]
Hypovolemic (nonhemorrhagic)	Inappropriate†	[2]
PHH	Normal saline should be administrated as the initial fluid for the treatment of PHH	[2, 18]
OHSS	Could be have harmful effect on the pregnancy rate in prevention of OHSS	[19]
ARDS	Therapy with albumin improved oxygenation but did not affect mortality; needs more RCTs	[20]
Cirrhosis of the liver with refractory ascites	Inappropriate† Except in patients with serum albumin <2 g/dl or resistant to diuretics	[2]
Burn	Inappropriate† in the first 24 h	[2]

†Use not indicated. TBI: Traumatic brain injury, SAH: Subarachnoid hemorrhage, PHH: Posthemodialysis Randomized Controlled Trials

Table 3: Patients' demographic characteristics and Albumin utilization in different wards

Patients' characteristics	Mean values
Age, year (minimum-maximum)	58.67±17.89 (13-96)
Sex (%)	
Male	188 (58.8)
Female	132 (41.3)
Admission ward (the numbers of enrolled patients in different wards) (%)	
ICU (including surgical, neurosurgical, open heart, medical, and neurovascular ICU)	109 (34.06)
Surgery	40 (12.5)
GI	43 (13.4%)
Oncology	34 (10.6)
Infectious	21 (6.6)
Palliative care	18 (5.6)
Other (including nephrology, neurology, pulmonary, rheumatology, neurosurgery, CCU, endocrine, ENT)	55 (17.18)
Underlying disease (%)	
Cancer	145 (45.3)
Infection	43 (13.4)
Intracranial events (including CVA, SAH, ICH, and TBI)	32 (10)
GI disease	41 (12.8)
Autoimmune diseases	21 (6.6)
Other (including renal, cardiovascular, accident, pulmonary, toxicology, burning, gynecology, endocrine, multiple trauma)	38 (11.87)
Laboratory values	
Serum albumin (before albumin therapy) (g/dl)	2.73±0.67
Serum albumin (after albumin therapy) (g/dl)	3.27±0.61

ICU: Intensive Care Unit, CCU: Critical Care Unit, ENT: Ear, Nose, Throat, SAH: Subarachnoid hemorrhage, ICH: Intracerebral hemorrhage, TBI: Traumatic brain injury, GI: Gastro-Intestinal

patterns of albumin by reviewing a wide range of the latest existing evidence-based studies and guidelines.[1-16,23,24,17-20]

Hypoalbuminemia and nutritional support were the most common irrational reasons for albumin usage. Based on the current evidence, hypoalbuminemia alone should not be considered as an indication for albumin prescription, and the underlying cause should be recognized and treated. However, some literature and guidelines considered serum albumin level <2.5 g/dl

Table 4: Albumin utilization causes and evaluation of its use

Indications	Prescriptions (%)	Total (g)	Appropriate use (%)	Appropriate (g)	Inappropriate use (%)	Inappropriate (g)	Duration of usage (day)	Total cost $ (inappropriate use cost)
Hypoalbuminemia	198 (61.9)	29520	123 (38.4)	17910	75 (23.4)	11610	6.79±5.21 (1-43)	39718
Nutritional support	44 (13.8)	8080	-	-	44 (13.7)	8080	11.63±14.63 (1-91)	27642
Neuroprotection in SAH	10 (3.1)	750	-	-	10 (3)	750	3.80±1.22 (2-6)	2565
Paracentesis	10 (3.1)	1050	5 (1.6)	640	5 (1.6)	410	5.50±3.17 (2-12)	1402
Pretreatment for cancer surgery	9 (2.8)	3220	-	-	9 (2.8)	3220	11.80±7.59 (2-21)	11015
Edema	5 (1.6)	1050	-	-	5 (1.6)	1050	14.77±9.47 (4-29)	3592
Hepatic failure	5 (1.6)	460	-	-	5 (1.6)	460	4.80±4.71 (1-12)	1573
Volume expansion after cardiac surgery	3 (0.9)	30	-	-	3 (0.9)	30	1	102
Extensive intestinal resection	3 (0.9)	800	-	-	3 (0.9)	800	13.33±11.93 (5-27)	2736
Nephrotic syndrome	4 (1.3)	630	2 (0.6)	290	2 (0.6)	340	7.75±5.61 (3-14)	1163
Wound healing	2 (0.6)	850	-	-	2 (0.6)	850	18±9.89 (11-25)	2907
Plasmapheresis	20 (6.3)	4170	19 (5.9)	4000	1 (0.3)	170	4.05±1.87 (1-8)	581
SBP	2 (0.6)	640	1 (0.3)	300	1 (0.3)	340	13.50±4.94 (10-17)	1163
HRS	2 (0.6)	440	2 (0.6)	440	0	0	6.50±2.12 (5-8)	0
OHSS	1 (0.3)	140	-	-	1 (0.3)	140	5	479
Tolerance of hemodialysis	1 (0.3)	100	-	-	1 (0.3)	100	4	342
Shock and dehydration	1 (0.3)	120	-	-	1 (0.3)	120	6	410
Total	320 (100)	52050	152 (47.5)	23580	168 (52.5)	28470	7.54±7.64	97397

SAH: Subarachnoid Hemorrhage, OHSS: Ovarian hyperstimulation syndrome. HRS: Hepatorenal syndrome

as an indication of treatment.[2,13] In this study, out of 198 patients who received albumin for hypoalbuminemia, 75 (23.4%) patients had serum albumin level >2.5 g/dl. Our results were not similar to other studies in Iran or other countries.[1,2,13,15] The first reason for this diversity of results is differences in the design and endpoints of these studies. In addition, our hospital is a referral center especially for cancer surgery, and a main cause of severe hypoalbuminemia might be a consequence of malnutrition due to cancer-induced higher metabolism, decreased intake, and cancer cachexia.[12]

Despite the wide range of information on the nonuse of albumin as protein coadjuvant in nutritional support, unfortunately, albumin is being widely used in nutritional protocols. Generally, oral, enteral, and/or parenteral nutrition with amino acids and sufficient calories lead to achieve better balance between the rates of albumin synthesis and metabolism in patients with nutritional problems. In addition, iatrogenic rise in the serum albumin levels to above 4 g/dl could increase the overall catabolism rate and results in opposite outcome. Hence, the use of albumin is not suggested as a supplemental protein source for malnourished patients.[1-3,13-16,23,25,24,22,17-21] However, according to some guidelines, albumin could be prescribed in malnourished patients if they have serum albumin level of <2 g/dl or suffer from severe diarrhea (>2 L daily), and other causes of diarrhea have been excluded, diarrhea which has not been improved despite the use of short peptide and elemental formulas.[1,3,13-15] None of the patients in our study met these criteria for albumin prescription. Similar results were reported in some studies in Iran and other countries so that 100% of albumin usage in malnourished patients was irrational.[1,13]

The role of albumin for neuroprotection in patients with SAH is unknown.[6-10] SAH occurs in various clinical contexts including head trauma or nontraumatic (ruptured cerebral aneurysm or arteriovenous malformation). One of the serious complications of SAH is cerebral ischemia secondary to vasospasm that is an important cause for morbidity and mortality.[9,10] Patients with SAH are frequently exposed to hypovolemic state and hemodynamic instability a few days after onset of symptom which could lead to the development of symptomatic vasospasm and poor clinical outcome. The current treatment modalities for delayed ischemia are not well defined. Volume expansion with normal saline or human albumin is used to maintain normovolemia or hypervolemia when focal neurologic changes progress. The results of the albumin in SAH (ALISAH) study, an open-label multicenter pilot study with 47 patients, showed that the use of large doses of 25% albumin as volume expander has been associated with beneficial neuroprotective properties in aneurysmal SAH at the end of 90 days.[10] On the other hand, saline versus albumin fluid evaluation (SAFE) study compared the outcome

of fluid resuscitation with 4% albumin or 0.9% saline on mortality in severe traumatic brain injury (TBI) patients.[6,7] This study included 460 patients with TBI diagnosis that 110 and 97 cases in albumin and saline groups had traumatic SAH, respectively. The results revealed increased mortality at the end of 2 years in patients who resuscitated with albumin compared with saline. The most possible mechanism of increased mortality may be intracranial pressure rising due to 4% albumin administration. Although 4% albumin is administrated in the SAFE study as compared to 25% hyperoncotic solution in the ALISAH study, confirmation of the results of ALISAH study demands a large placebo-controlled randomized clinical trial. Hence, albumin should be administered with caution as neuroprotective agent according to the SAFE study 2-year follow-up. In our study, 10 patients received albumin as a neuroprotective agent in traumatic and aneurysmal SAH that were considered inappropriate indication.

Serum albumin level before operation independently affects the survival in various types of cancers and has some prognostic value.[11,12,16] However, regarding the treatment of preoperative hypoalbuminemia, no published study has been able to explain benefits of albumin infusion on morbidity and mortality.[11,12] This might be due to possible outflow of infused synthetic albumin through the vessel walls or inadequate dose of albumin which has been replaced.[12] However, some studies revealed that improvement in perioperative nutrition has promoted the outcomes in patients requiring nutritional support with gastrointestinal cancer.[11,12] In addition, the preoperative nutritional support in severely malnourished cancer patients who are candidate for surgery may be beneficial.[25] In this study, nine patients with gastrointestinal cancer received albumin for preoperative preparation to achieve a serum albumin level of ≥3.5 g/dl; based on the mentioned literature review, this indication for albumin usage was considered inappropriate.

Absolute recommendation concerning the treatment of edema with albumin is the issue of debate. Normal albumin level causes a balance between hydrostatic and colloid osmotic pressure in the intravascular space. Hypoalbuminemia could lead to edema as albumin level is a key factor in maintaining colloidal oncotic pressure.[1] Although there is correlation between low level of albumin and development of edema, many factors affect this issue. Some researchers have mentioned that the beneficial effects of albumin in removing fluid from the interstitial to intravascular space are temporary; a few minutes after administration of albumin, it leaks back from the capillary into the interstitium and could worsen the edema.[1] Hence, according to some guidelines, due to water retention properties, albumin could be used in the treatment of intractable massive edema accompanied with severe hypoalbuminemia (<2 g/dl).[2,13,14] In our case, all patients with edema had serum albumin level above this cutoff.

Generally, there is lack of consensus on the role of albumin in the treatment of hypoalbuminemia due to liver failure. Albumin can play a dual role in liver failure. On the one hand, albumin-binding properties can lead to binding to the excess amount of plasma bilirubin and may be effective in the treatment of hyperbilirubinemia; on the other hand, albumin could support plasma oncotic pressure. However, therapeutic use of albumin in liver failure is only based on theoretical hypothesis.[22] Some evidence support the administration of albumin in the following settings; cirrhosis of the liver with refractory ascites if serum albumin <2 g/dl, HRS1 along with vasoactive agents, SBP, and after large volume paracentesis, between 2 and 5 L, according to different guidelines.[2,13,14] In this study, removal of ≥4 L of ascitic fluid was considered a rational indication for albumin use; out of ten patients who underwent paracentesis, five patients had volume removal of <4 L; hence, albumin administration was considered irrational. The prescription of albumin in HRS1 in all cases was rational in this study. In five patients with liver failure due to cancer metastasis, albumin was administrated without any above indications and was considered inappropriate.

We approximately observed different patterns of albumin usage in our hospital as compared to other studies. Jahangard-Rafsanjani *et al*.[13] and Kazemi *et al*.[14] reported most frequent inappropriate use of albumin in patients after cardiac surgeries at Shariati and Shaheed Rajaei Hospitals, Tehran, Iran. However, Shafiee *et al*.[1] stated hypoalbuminemia and nutritional support as the most prevalent reasons for irrational albumin usage at Imam Reza Hospital, Tabriz, Iran. Although in our study hypoalbuminemia and nutritional support were the most common causes of irrational albumin usage, we encountered two other indications for albumin administration: neuroprotection in SAH and increased albumin level before cancer surgery, which has not been reported in other albumin utilization studies. Hence, it could be concluded that guidelines need to be updated with the latest scientific researches.

In summary, our study attained a high rate of irrational prescription of albumin based on the current guidelines in which about $97,400 could be saved for our health-care system. Therefore, these data show that there is a need for comprehensive educational program for a physician and to establish the reliable guidelines to reduce overtreatment and cost in this hospital.

The findings of our study indicate that albumin utilization evaluation in different hospitals is crucial due to a wide variety of consumption patterns. This type of research is essential to recognize the pattern of costly drugs in the various centers in different time periods. This issue could particularly be important in two aspects; first, to detect patterns of incorrect prescriptions and prevention of possible adverse event; second, it plays a significant role in the improvement and development of guidelines.

Authors' Contribution

Maryam Farasatinasab: Conception, study design, literature review, final approval of manuscript; Atefeh Amouzegar: Acquisition of data, literature review, data analysis, interpretation of data, drafting the article Saeed Safari:Acquisition of data Behrooz Ghanbari: Data analysis Majid Darkahian: Acquisition of data; Sepideh Emami: Acquisition of data Nashmin Pakdaman: Acquisition of data; Maryam Salili:Acquisition of data.

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Conflicts of interest

There are no conflicts of interest.

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