



Evaluation of Albumin Administration Pattern in a Teaching University Affiliated Hospital in Iran

Leila Zarepour¹, Mohammad Mehdi Saghafi^{2*}

¹Department of Physiology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.

²Department of Pharmacology and Toxicology, School of Pharmacy and Pharmaceutical Sciences, Iran University of Medical Sciences, Tehran, Iran.

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ABSTRACT

Background: Albumin has long been used as a critical medication in many hospitalized cases, especially for patients in the intensive care unit (ICU) section. Some adverse clinical impacts and economic limitations have made the human albumin an appropriate therapeutic agent for extensive analyses.

Methods: This retrospective follow-up study was performed in Firozabadi hospital as a General Medical Teaching and Research Center with 12 major units and ICU sections. Information of the patients was collected based on the charts, physician and the nursing reports. We evaluated all 153 patients who used albumin in January to June 2016 (first 6-months) before guideline distribution and then during January to June 2018 (second 6-months).

Results: We evaluated current management protocols for hypoalbuminemia, sepsis shock, nephrotic syndrome, hepatorenal syndrome, CVA (Cerebrovascular Accident), cirrhosis, electrolyte disorder, cardiovascular surgery, edema and ARDS (Acute Respiratory Distress Syndrome). During this study, we found that before guideline distribution, 297 numbers (27.1% of total prescribed albumin vials) of albumin vials prescribed for 20 patients (18.6%); while after 18-month interval, guideline adoption the second 6-month administration pattern was not inappropriate; Nevertheless, the number of patients, vials, duration and level of albumin was different in comparison with the first evaluated group and were more accordant with standard instructions.

Conclusion: Some changes in administration strategies would be observed after executing the standard operating procedures and confirms that this approach might remarkably alter the physician's attitude toward more rationalized prescription of critical agents that subsequently reduce the associated implied costs on health systems.

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Introduction

Drug utilization evaluation (DUE) studies, evaluates the appropriateness of a specific prescribed drug indication, its dosing regimen and treatment duration as well as patients monitoring (1). Rational use of drugs has been defined by the WHO as the marketing, distribution, prescription, and

use of drugs in a society with special emphasis on their medical, economical and social consequences. Drug use evaluation is an ongoing, systematic and criteria-based evaluation of drug use that will help ensure that medicines are used rationally (at the individual patient level). Based on the carried out DUE, if treatment is recognized to be

*Corresponding Author: Dr Mohammad Mehdi Saghafi

Address: Department of Pharmacology and Toxicology, School of Pharmacy and Pharmaceutical Sciences, Iran University of Medical Sciences, Tehran, Iran. Tel:+ 982133837356.

E-mail: Saghafi.mm@iums.ac.ir

inappropriate, interventions will be necessary to optimize drug therapy (2). DUE researches are especially critical for high-cost medications and for those with narrow therapeutic index since they would imply greater clinical impact and economic burden on the health care system (3).

Human albumin (HA) is produced about 10–15 grams by hepatocytes under normal physiological conditions every day, with none or very low intracellular storage. Its synthesis is stimulated by hormones, such as insulin, cortisol and growth hormone, while it is inhibited by pro-inflammatory substances, including interleukin-6 and tumor necrosis factor- α . Synthetic albumin is a colloidal, multifunctional therapeutic protein that covers a broad spectrum of approved clinical indications (4). Albumin is one of the most effective renewable plasma (plasma volume expander), that has not been used appropriately (4). Although we are facing a shortage of resource, economic impacts and adverse effects, it could not be easily replaced by crystalloids and other non-protein plasma expanders (4). In the other hand its administration has specific consideration regarding indication, dosage, administration technique and monitoring. Therefore evaluation of the appropriateness of albumin usage pattern is necessary. Due to its osmotic effect, most of the clinical uses of HA (Human Albumin) have been based on its capability as a plasma expander. Fluid resuscitation, which was initially based on the physiological principles of Starling, is a basis in the management of patients admitted to intensive care unit (ICU) with critical illnesses such as shock, sepsis, trauma, acute respiratory distress syndrome, burns or acute clinical situations which are associated with hypovolemia. Other clinical indications of albumin use include various stages of liver problems, extensive burns, cerebral ischemia, spontaneous bacterial peritonitis, cardiac surgery, neonatal hypoalbuminemia, nephrotic syndrome, and organ transplantation (1, 5).

The primary clinical manifestations after albumin infusion generally include: cardiovascular overload (headache, dyspnea, jugular venous congestion) or elevated blood pressure, elevated central venous pressure and pulmonary edema and hypervolemia (6). In these situations the infusion should be stopped immediately and careful monitoring of the patient's hemodynamic parameters such as blood pressure, heart rate, central venous pressure, Wedge pressure in the pulmonary artery, the amount of urine secreted, electrolytes, and hematocrit hemoglobin are necessary (1, 5).

The required albumin dose depends on the patient's weights, the severity of the injury or illness, and further loss of fluids and proteins (1); The criteria that determine the required dose for the suitability of the volume of the fluid in

the bloodstream and not the plasma albumin concentration (7). The guidelines do not recommend albumin as the first-line therapy for indications such as nutritional intervention, hypoalbuminemia, cirrhosis, paracentesis, and Nephrotic Syndrome (NS) (1, 5, 8, 9).

Hypoalbuminemia can result from decreased albumin production and synthesis, different forms of malnutrition, the gastrointestinal track or renal associated disorders and the most commonly, acute or chronic inflammation (5). Serum albumin level is a strong predictive factor in determining the prognosis of disease and the treatment course, since its lower serum levels correlate with an increased morbidity and mortality rate (10).

Previous efforts have been made to establish the appropriate and efficient uses of colloids. In comparison to the accepted indications, the administration of albumin in many cases was wrong (1). In the present study we aimed to evaluate the pattern of albumin prescription and usage and its concordance with rational government treatment guidelines in a referral educational hospital. We also compared the incidence of albumin usage appropriateness before and after the evidence-based guideline administration.

Methods

This was a retrospective, cross-sectional study which has been accomplished in "Firozabadi" hospital affiliated with Iran University of Medical Sciences, Tehran, Iran. This is a referral hospital and medical and research center with total 200 beds in 12 units and ICU sections.

We evaluate patients in two groups of patients before and after albumin guideline implementation; 1st group from January to June 2016 and second group during January to June 2018. We used convenience sampling and include all the 153 patients who used albumin in two aforementioned time intervals.

Patient information was obtained from charts, medical records, nursing documents and inquiring the corresponding physician. We collect age, gender, hypoalbuminemia, edema and diagnosis on admission.

We gathered information about albumin utilization by a standard form of the appropriate prescription of albumin, which was obtained from the validated reference and guideline (11) then it was modified according to attending physician's comments. This form includes information in the following; Indication, number of patients, number of vials, duration of stay (days) and Albumin serum level (g/dl). Physicians measured levels of blood serum albumin, before albumin administration and rechecked 72 hours after first doses. We evaluated the administration of albumin based on rational use, level of <2.5 g /dl albumin (1).

Table 1. Appropriate indications for Albumin use (11)

Indication	Notes	GoR*
Appropriate indications (for which there is a widespread consensus)		
Paracentesis	5 g of albumin/L ascitic fluid removed, after paracentesis of volumes > 5 L.	1C+
Therapeutic plasmapheresis	For exchanges of > 20 mL/kg in one session or > 20 mL/kg/week in more than one session.	2C+
Spontaneous bacterial peritonitis	In association with antibiotics.	1C+
Occasionally appropriate indications (when other criteria are fulfilled)		
Heart surgery	Last-choice treatment after crystalloids and non-protein colloids.	2C+
Major surgery	Albumin should not be used in the immediate post-operative period. The only indication for use: serum albumin <2 g/dL after normalization of circulatory volume.	2C+
Cirrhosis of the liver with refractory ascites	Generally ineffective, except in patients with serum albumin < 2 g/dL.	2C
Contraindications to the use of non-protein colloids	- pregnancy and breastfeeding;	2C
	- perinatal period and early infancy; - acute liver failure; - moderate-severe renal failure (particularly when anuria/oliguria); - dialysis treatment in the presence of severe abnormalities of hemostasis and baseline albumin < 2 – 2.5 g/dL; - intracranial haemorrhage; - hypersensitivity.	
Hemorrhagic shock	Only in the case of: - lack of response to crystalloids or colloids; - contraindication to the use of non-protein colloids	1A
Hepatorenal syndrome	In association with vasoconstricting drugs.	2B
Nephrotic syndrome	Only in patients with albumin < 2 g/dL with hypovolemia and/or pulmonary edema.	2C
Organ transplantation	In the post-operative period after liver transplantation to control ascites and peripheral edema to replace the loss of ascitic fluid from the drainage tubes, if albumin < 2.5 g/dL with a hematocrit > 30%.	1C
Burns	In the case of burns of > 30% body surface area, after the first 24 hours.	2C+
Dose		
The dose needed to obtain a serum albumin ≥ 2.5 g/dL is calculated using the following formula: Dose (g) = [desired albumin concentration (2.5 g/dL) – actual albumin concentration (g/dL)] x plasma volume (0.8 x kg)		

*GoR: Grade of Recommendation

We fed data to statistical analysis software (SPSS 16) and report our descriptive data as mean \pm SD if it was quantitative or as percentage.

Results

During the 1st study period (before guideline implementation), a total of 86 patients were evaluated 63 (73.2%) of these, were male. Their mean age was 67.8 \pm 17years and received 1092 albumin vials in total. Most of the patients were hospitalized in ICUs (83.4%)

with one of following diagnosis; hypoalbuminemia, sepsis, pneumonia, acute respiratory distress syndrome (ARDS), hepatorenal syndrome and cardiovascular failure.

In the other group within second study period (after a one-year and six-month interval), a total of 67 patients with a mean age of 74.3 \pm 15.07 years, received 1006 albumin vials. 39 (58.2%) of patients were male. Most of the patients were hospitalized in ICUs (88.3%) with sepsis, ARDS and Nephrotic syndrome and cardiovascular failure (75.9%) diagnoses.

Table 2. Albumin Pattern Use before Guideline Implimentation.

Indication	Inappropriate		Appropriate		Duration of stay	Albumin level
	Number of Patients (%)	Number of Vials (%)	Number of Patients (%)	Number of Vials (%)		
Hypoalbuminemia, Edema	20(18.6)	297(27.1)	0	0	348±8.5	3 ±0.42
Sepsis	0	0	16(13.9)	145(13.2)	97±2.8	2.3 ±0.53
Acute respiratory distress syndrome	0	0	14(16.27)	170(15.5)	196±7.5	3 ±0.81
Cerebrovascular accidents	0	0	2(2.32)	30(2.74)	90±2.8	2.9 ±0.29
Electrolyte disorder	0	0	5(5.8)	45(4.12)	68±3.6	2.8 ±1.02
Cirrhosis	0	0	3(3.4)	61(5.58)	29±2.8	3.1 ±0.7
Nephrotic syndrome	0	0	4(4.65)	67(6.13)	48±1.8	2.9 ±0.47
Hepatorenal syndrome	0	0	9(10.4)	33(3.02)	57±1.8	3.1 ±0.31
Cardiovascular failure	0	0	11(12.7)	224(20.5)	284 ±12.2	2.7 ±0.26
Hemorrhagic shock	0	0	2(2.32)	20(1.8)	29±5.5	2.5 ±0.31

As seen in Table 2 more than 297 (27.1%) vials of albumin which prescribed for 20 (18.4%) patients have not been administered appropriately based on the reliable guidelines used in this hospital. But in the second group all the albumins were administered appropriately (Table 2). In the first group, 48.6% of all patients had serum albumin

level of 3-3.5 g/dl, 25.4% between 2.5-3 g/dl and 16.2% in 2-2.5 g/dl range. In the second group (Table 3), 13.4% of all patients had serum albumin level within 2.5-3 g/dl range, 86.6% between 2-2.5 g/dl. In Table 3 more details about albumin use and serum levels are available.

Table 3. Albumin Pattern Use after Guideline Implementation.

Indications	Inappropriate ^a		Appropriate		Duration ^b of stay (days)	Albumin serum level (g/dl)
	Number of patients (%)	Number of vials (%)	Number of patients (%)	Number of vials (%)		
Hypoalbuminemia, Edema	0	0	0	0	0	0
Sepsis	0	0	19(28.3)	334(36.8)	543±10.93	2.3±0.21
ARDS	0	0	16(23.8)	265(29.2)	422±13.31	2.4±0.1
CVA	0	0	3(4.47)	67(7.3)	93±13.44	2.3±0.3
Electrolyte Disorder	0	0	3(4.47)	41(4.5)	77±7.71	2.1±0.11
Cirrhosis	0	0	3(4.47)	59(6.5)	60±11.8	2 ±0.22
Nephrotic Syndrome	0	0	7(10.44)	63(6.9)	108±4.04	2.5±0.43
Hepatorenal Syndrome	0	0	4(5.97)	25(2.09)	61±1.69	2.4±0.31
Cardiovascular Failure	0	0	9(13.4)	106(6.5)	194±6.36	2.6±0.31
Hemorrhagic Shock	0	0	3(4.47)	16(0.44)	24±4.1	2.5±≤0.7

ARDS: acute respiratory distress syndrome, CVA: cerebrovascular accident

^aThe percentage of inappropriate use of total prescriptions with each reason ^b Mean ± SD

Discussion

In Different aspects of albumin prescription in the clinical setting have made this human protein eligible for further analyses within a drug utilization evaluation framework which include some meta-analysis derived controversies and also specific economic considerations that debate the extensiveness of albumin indications. In the present study, we have evaluated the administration of albumin based on the rational use protocols that provide the evidence-based assessment of the prescription by the physicians in the health system. Although albumin is expensive, the rate of its use is quite considerable in various disorders. Over the past thirty years, several clinical studies have been conducted, and as a result, the optimized therapeutic guidelines are introduced to improve the administration of albumin treatment; but still about 50-70% of albumin intakes are inappropriate in various health care systems that could have a great impact on health care system and public (12, 13).

Generally, during our first period of data collection, the obtained results indicated a remarkable inappropriate administration that replicated the previous relevant evidences regarding Iranian hospitals (3, 4) and other countries (14, 15). In this study, measuring of the albumin level serum after hypoalbuminemia was inappropriate versions among all the symptoms (8). In our study we evaluated the administration of albumin level of $<2.5\text{g/dl}$ (1); Two serum albumin thresholds have been accepted for the definition of hypoalbuminemia: 2 and 3 g/L (17).

One of the reasons of albumin administration is chronic or acute hypoalbuminemia. Due to the close relationship between amount of albumin and colloid oncotic pressure, declined serum albumin levels ignite the initial edema (8, 16). According to the previous guideline criteria implemented in the hospital, 20 patients in the ICUs received albumin to improve symptoms of hypoalbuminemia. Unfortunately, most of patients had received albumin infusion regardless of serum albumin levels that is a highly recommended measuring parameter in rational use of albumin. Another reason for use of albumin in the ICU was a distributive shock (septic shock) (18). Various body systems are impaired during sepsis shock, which causes different failures and dysfunctions and is significantly correlated with the death rate (19). 13.1% of patients in the first 6-month group that admitted to the intensive care unit received 145 vials of albumin for septic shock. In recent years, a remarkable global rise in unreasonable antibiotic prescriptions, has led to a significant increase in microbial resistance and subsequent crisis of hospital infections; an issue that Iranian hospitals have not been excluded from and was particularly very common in the current studied hospital (20). Some of the patients admitted to the hospital and ICUs sections were reported to have severe bed sores either due to the increased hospitalization period or predisposing factors and diseases for wounds. Exacerbated forms of bed sores require debridement. Therefore, according to the surgeon's order and contrary to the accepted protocol, for patients with albumin levels higher than 3.5, and also with the

level of hemoglobin (10) and international normalization ratio (INR) (1), intravenous albumin was administered. Consequently, administration of albumin for this purpose, in the second period, highlights the importance of the results of the rational use protocol implementation.

Nephrotic syndrome leads to proteinuria, edema, and steroid-resistant states that directly resulted hypovolemia. Lower serum albumin is a significant probable reason for venous thromboembolism (VTE) events in nephrotic syndrome (21). Following the failure of sodium level correction and diuretic medication, albumin would be added to restore euvolemia. Short term combinatory administration of a loop diuretic and albumin has resulted in decreased edema, particularly in patients with acute severe pulmonary or peripheral edema and concurrent hypoalbuminemia (22). Nephrotic syndrome was another cause of the rational use of albumin in our study. According to the rational use items, 67 of the vials of albumin used in ICUs' patients were appropriate before guideline implementation.

Respiratory dysfunction is common in critically ill patients and is perhaps highest in patients with the shock which necessitate fluid resuscitation. With respect to pulmonary edema, it has been shown that administration of albumin to patients with ARDS does not worsen pulmonary edema as long as hydrostatic pressures do not increase and contribute to tissue-directed fluid flux. In the present study, 170 vials are for this indication and then considered rational (11).

After guideline execution, there was not any inappropriate albumin prescribed for patients in the ICU sections or other units. Moreover, based on the guideline items, serum albumin level of the patients was measured two times, immediately before and 72 hours after albumin administration.

Considering the actions taken by albumin rational use, this protocol is suitable and applicable in the hospitals and intensive care units in order to reduce the cost and fractional.

Actually, unusual administration leading to wasted money and resources for patients and the hospital.

In conclusion, guideline implementation has clearly been supported by our current findings and in general we have provided evidence to support the assumption that considerable change in administration strategies would be observed after executing the standard operating procedures and confirms that this approach might remarkably rationalize the prescription of albumin and associated costs. Moreover, pharmacist intervention alongside physician guidance might significantly optimize albumin therapy. This type of DUE can provide information for the physicians to change the pattern of prescriptions, especially for high-cost and critical medications.

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