Evaluation of Human Albumin Use in Bone Marrow Transplantation Patients in a University Hospital in Iran: A Retrospective Study

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Abstract

Introduction: The aim of this study was to evaluate the use of albumin in bone marrow transplanted patients and its possible economic repercussions from its inappropriate use.

Methods and materials: This was a retrospective study in which all patients receiving albumin (from start to end of treatment) at three bone marrow transplantation wards were assessed in two consecutive years. The clinical indications for albumin were evaluated on the basis of guidelines. The concomitant drugs that affected albumin levels were assessed. Characteristic data including age, gender, weight, body surface area(BSA), diagnosis, blood group, type of transplantation were recorded. All lab data which included serum creatinine , alanine aminotransferase , aspartate aminotransferase, alkaline phosphatase, total protein, albumin, hematocrite, calcium before and after albumin use were also recorded . Postconsumption data was in-hospital stay and mortality.

Results: During the study period, 104 patients received albumin at 3 wards (BMT1:36 patients, BMT2:11 patients, BMT3:57 patients). Patients received a meamumber of 24 .52 ± 20.86 vials. The mean treatment duration was 13.96 ± 9.14 days. Drugs decreasing albumin level did not significantly affect the use of albumin. Weight, total protein and calcium have been significantly altered after albumin use .

Conclusion: Drug Use Evaluation is an opportunity for clinical pharmacist to help improve therapy by designing strategies to reduce the medication error and cost or changing prescriber manners.

Keywords: Human Albumin, BMT, SCT

Introduction

Albumin is produced by the liver at a turnover rate of 9 to 12 gram/day; the half-life span is 14 to 21 Days. It is catabolized by the reticuloendothelial system .There is not reservation of albumin in the liver .Under physiological situations, only 20 %to 30 %of hepatocytes produce albumin, but synthesis can be increased on request by 200 % to 300%.

Albumin regulated by nutritional status and hormones like insulin, glucagon, cortisol, and thyroid hormones.

In addition to maintaining colloidal osmotic pressure and binding to other molecules and ions, albumin has a buffering role through binding hydrogen ions; transporting hormones and drugs; and neutralizing poisons such as bilirubin as well as contributing to the redox potential of plasma.(1) The normal range of albumin in adults/older people is 3.5 to 5.0 g/dL .Average levels for newborns are 3.5 to 5.4 g/dL; for infants, 4.4 to 5.4 g/dL; and for children, 4 to 4.9 g/dL.(2)

The most common cause of decreased plasma albumin levels is related to inflammatory processes

such as acute-phase response and chronic inflammatory disorders. Several medications can be leading to a decrease in protein levels .These medications include allopurinol, asparaginase, azathioprine, chlorpropamide, cisplatin, dapsone, dextran, estrogens, ibuprofen, isoniazid, nitrofurantoin, oral contraceptives, phenytoin, high dose prednisone and valproic acid.(3) Solutions of albumin are prepared from the plasma of healthy persons. It can be infused freely of the recipient's blood group. Preparations of 5%, 20 %and 25 % have been registered .The solutions of 5 %human albumin are approximately isoosmotic; the 20 %and 25 %solutions are hyper osmotic.(4)

On the basis of reliable guideline and clinical evidence, albumin can be indicated in the resuscitation in case of major edema with severe hypoalbuminemia in adult and children, graft versus host reaction, ascitic patients post paracentesis, liver transplantation, pre-eclampsia with hypoproteinemia, prevention of kernicterus in the newborn, severe and symptomatic hypoalbuminemia in newborn or infant, hypovolemia of the newborn not corrected by crystalloids or in case of contraindication to the use of artificial colloids, severe burn injury or toxic epidermal necrolysis, therapeutic plasmapheresis, nephrotic syndrome. Table-1 are presented summary of implied guidelines of appropriate and inappropriate use of albumin.

Use of unnecessary expensive drugs such as albumin and its overuse are the most common problems of irrational drug use by prescribers in our hospitals .Human albumin usage in clinical practice due to its high cost, the existence of contaminant transmission (as with any blood derivative) and more economical options of equal efficacy have been debated.(12-14)

On the other hand, Improving drug use would have important financial and public health benefits,(15) although several publications demonstrate high percentage of unjustified use(2, 4, 11- 14, 16) but no evaluations have been done in the BMT department by now. Hence, the reasons for this irrational use, or strategies for improving it, remain uncertain because many factors in addition to of our knowledge could affect appropriate use of drugs.(17)

According to the statistic report by the Food and Drug Organization of Ministry of Health on the Human albumin use, 472089 vials of albumin 20% costing $ 21,600,000 had been used in the first 9 months of 2008. At the same time in Shariati hospital, which is a teaching university hospital, about 10800 vials of albumin 20% were used at cost of $496800. This is a high cost for a medication used in our hospital.

Furthermore the clinical and economic evaluations to determine appropriate therapies, define protocols, and establish recommendations and consensus criteria for albumin use are necessary.

Material and methods

This was a retrospective study in which all patients receiving albumin (from start to end of treatment) in three bone marrow transplantation wards at Hematology- Oncology and Bone Marrow Transplantation Research Center at Shariati Hospital in Tehran, Iran were assessed during 24 months period (2008-2010). This research is based on Drug Utilization Review which can be defined as review of drugs used in population (a state, country, an age group, or subscribers of a health insurance plan) to determine effectiveness, potential dangers, problems with drug interaction, and other issues. Data were collected by clinical pharmacist. The clinical indications for albumin were evaluated on the basis of reliable guideline. The drugs that could decrease albumin level were recorded. Preconsumption assessment included age, gender, weight, body surface area (BSA), diagnosis, blood group, type of transplantation .We also recorded lab data which included serum creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, albumin, total protein, hematocrite, calcium before and after the albumin use. Postconsumption data was in-hospital stay and mortality. Exogenous albumin for therapeutic use is obtained by fractionation of human plasma and is marketed in Iran as 20% (hyperosmotic) and 5% (isosmotic) solutions. The type of albumin used in this study was 20% vials of albumin.

The prescription was considered appropriate if it matched the protocols regarding the reason of administration.(11, 18-20)

The information was gathered and analyzed using basic descriptive techniques with the statistical program, SPSS-PC; version 16. The qualitative variables are presented by their frequency of distribution. The quantitative variables are summarized as mean with standard deviation.

Results

During the study period, 104 patients received vials of albumin %20 at three BMT wards including BMT1: 36 patients (34.6%) and BMT2: 11 patients (10.6%) for adults, BMT3: 57 patients (54%) for pediatrics. The wards comprised approximately 29

beds that 11 of them belonged to pediatric ward. Baseline characteristic of the study patients are shown in table- 2. The patients received a mean number of 24.52 vials (SD: 20.86), ranging from 1 to 116 vials. for a treatment period of 13.96 days (SD: 9.14), ranging from 1 to 53 days.

The diagnosis variations of patients at three wards and percent of error in administration of albumin vials at each diagnosis are recorded in table- 3. The most error in administration of albumin use were reported for patients with AML.

According to clinical evidence, 91% of albumin administrations were inappropriate; only 9% of patients were given albumin as part of the protocol for GVHD and symptomatic hypolbuminemia with serum albumin ≤2.5 and ascitic patients without response to diuretic.

Mostly, albumin was prescribed for hypoalbuminamia (63%), whereas only 7 % of them had serum albumin≤2.5. Table- 4 shows the reasons of albumin prescribed.

Patients with AML had the most common prevalence of hypoalbuminemia (83%). Table- 5 shows the prevalence of hypoalbuminemia in variety of each diagnosis.

Auto graft transplantations had the most common incidence of hypoalbuminemia (95%). Table- 6 shows the prevalence of hypoalbuminemia in sex, age, type of transplantation, diagnosis, and blood group.

Among drugs that could decrease the level of albumin serum, Corticosteroid 74 (54.80%), Phenytoin 39 (28.90%), Oral contraceptive 15 (11.10%), Insulin 6 (4.40%) and Valproic acid 1 (0.80%) were prescribed before or with albumin use in these patients.

Drugs that could decrease albumin level did not significantly affect the use of albumin vials (p-value 0.08).

Albumin usage had a significant correlation with in-hospital stay (Pearson 0.431, p-value 0.000) (Figure- 1).

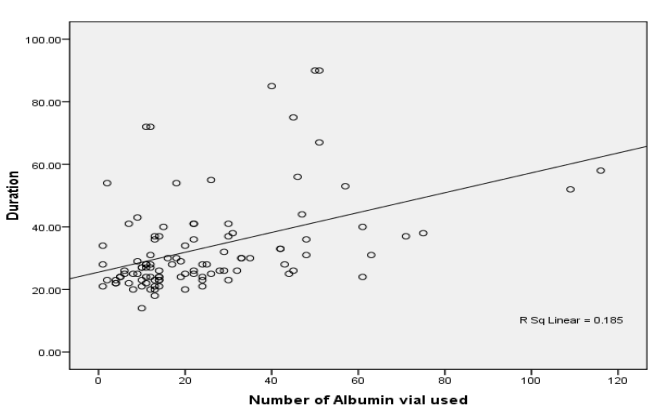

Figure1-correlation between number of albumin vials usage and in-hospital stay

Weight, total protein and calcium had been significantly altered after albumin use. The lab data and changes of clinical parameters after albumin administration are recorded in table- 7.

Discussion

Intravenous fluid therapy should be prescribed based on the appropriate strategy and clinical needs of patients, because medication errors could cause direct patient harm as well as increasing health care costs(21)

In our study in 91% of the patients, albumin prescriptions were considered inappropriate ,that included 47 % of adult patients and 49 % of pediatric patients, and was appropriate in just 9 % of patients.

Despite widespread information and availability of guidelines, it is surprising that the physicians ordered albumin for hypocalcemia. This incorrect indication may be done due to falsely reduced level of calcium in plasma in hypoalbuminemia or in hypocalcemia without hypoalbuminemia, administration of albumin were ordered. However analyses of our data showed that calcium significantly increased after albumin use. Owning to reduced serum albumin concentration, the calcium should be adjusted for the ratio of free versus protein bound calcium according to below formulation:

Corrected total calcium (mg/dl)= total calcium+0.8× [4 -serum albumin (g/dl)]

In agreement with a study done in a private hospital in Bangkok(20) regarding the DUE of albumin, we found a high incidence of unacceptable use of albumin in the treatment of hypoalbuminemia. In fact, low albumin concentrations are a sign, not a cause, of the underlying disease(18, 19) on the basis of guidelines hypoalbuminemia is not enough reason for albumin replacement and infusion of albumin does not improve the outcome.(4, 11, 16) Even though, the guidelines indicate that albumin is useful for treatment of severe hypoalbuminemia.(1, 6, 20)

20 % of the indication for treatment with human albumin was hypoproteinemia. Three cases had total protein ≤3.5 and albumin≤2.5.

A threshold value for albuminemia and proteinemia as indication for treatment is controversy. In one trial, 2g/dl for albumin and 3.5 for protein(14) and in another trial, 1.5g/dl for albumin were considered.(22) Like a study in a university hospital in Belgium, in our hospital albumin was prescribed for hypoprotenemia at albumin level of ≤2.5 g/dl.(23) Our patients had an albumin

Table- 1. Appropriate and inappropriate use of albumin.

Indication	Notes
Paracentesis(4-6)	5 g of albumin/L ascitic fluid removed, after paracentesis of volumes >5 L
Therapeutic plasmapheresis(4, 6-10)	For exchanges of >20 mL/kg in one session or >20 mL/kg week in more than one session
Spontaneous bacterial peritonitis(4)	In association with antibiotics
Heart surgery(4, 6-9)	Last-choice treatment after crystalloids and non-protein colloids.
Major surgery(6)	Albumin should not be used in the immediate post-operative period. Only indication for use :serum albumin < 2 g/dL after normalization of circulatory volume.
Cirrhosis of the liver with generally ineffective, refractory ascites(6)	except in patients with serum albumin < 2 g/dL
Contraindications to the use of non-protein colloids(6)	-pregnancy and breastfeeding -perinatal period and early infancy - acute liver failure -moderate-severe renal failure (particularly when anuria/oligouria) -dialysis treatment in the presence of severe abnormalities of haemostasis and baseline albumin of <2– 2.5 g/dL -intracranial haemorrhage - hypersensitivity
Hemorrhagic shock(4, 6-10)	Only in the case of -lack of response to crystalloids or colloids -contraindication to the use of non-protein colloids.
Hepatorenal syndrome(4, 6-10)	In association with vasoconstricting drugs
Nephrotic syndrome(6-10)	Only in patients with albumin < 2 g/dL with hypovolaemia and/or pulmonary edema.
Organ transplantation(4, 7, 9)	In the post-operative period after liver transplantation to control ascites and peripheral oedema, to replace the loss of ascitic fluid from the drainage tubes, if albumin < 2.5 g/dL with a hematocrit > 30%
Burns(4, 6, 9, 10)	In the case of burns of > 30% body surface area, after the first 24 hours.
Inappropriate indications for the use of Albumin	1. Albuminemia> 2.5 g/dL(4, 7-10) 2. Chronic hypoalbuminemia in the absence of edema and/or acute hypotension(11) 3. Malnutrition(4, 7-10) 4. Non-hemorrhagic shock(4, 7-10) 5. Ascites responsive to diuretics(11) 6. Protein losing enteropathies and malabsorption 7. Acute or chronic pancreatitis(4, 7-10) 8. Hemodialysis(6, 11) 9. Cerebral ischemia(6)

Table- 2: Baseline characteristics of the patients

Sex	No (%)
Male	69 (66.3%)
Female	35 (33.7%)
Type of transplantation	
Allograft	77 (74.0%)
Auto graft	19 (19%)
Cord blood	8 (7.7%)
Blood group	
A+	35 (33.7%)
O+	32 (30.8%)
B+	15 (14.4 %)
O-	8 (7.7%)
A-, AB+, B-, AB-	14(13.4%)
Mean±SD	
Age	17.84±15.45
Weight	40.63±23.72
Height (cm)	135.82±35.89
BSA (m2)	1.20±0.50
Duration (day)	33.24±1.54

Table- 3. Variety of diagnosis and error in albumin use at each diagnosis

Diagnosis	Frequency(%)	Albumin administration errors (%)
Thalassemia	24(23%)	87%
Acute lymphocytic leukemia	17(16%)	88%
Acute myelocytic leukemia	12(11.5%)	100%
Ablastic anemia	9(8%)	88%
Fanconi anemia	6(5%)	100%
Others	34(32%)	91%

Table- 4. The reasons of albumin prescribed

Type of reason	Percent
Hypoalbuminemia	63%
Hypoproteinemia	20%
Hypocalcemia	5%
GVHD and diarrhea	4%
Acsites and edema	3.9%

Table- 5. Variety of diagnosis and percent of hypoalbuminemia

Diagnosis	Percent of hypoalbuminemia
Thalassemia	58%
Acute lymphocytic leukemia	47%
Acute myelocytic leukemia	83%
Aplastic anemia	48%
Fanconi anemia	16%
Others	73%

Table- 6. The most prevalence of hypoalbuminemia in existence of data

Age	Adult>Pediatrics
Sex	Male=Female
Type of transplantation	Auto graft
Diagnosis	AML
Blood group	O+, A+

Table- 7: Resultsof clinical parameters before and after albumin administration.

Lab		Mean ± SD	P-Value
Weight	Before	40 63±23.72	
	After	38 46±21.45	0.000
Hematocrite	Before	27.43±5.04	
	After	32 30±32.11	-
Creatinine	Before	0.75±0.40	-
	After	3.71±2.80	
Albumin	Before	3.36±0.55	-
	After	3.93±0.74	
Total Protein	Before	5.37±0.83	0.000
	After	5.92±1.00	
AST	Before	35 29±30.21	-
	After	50 00±71.71	
ALT	Before	39 61±45.88	0.281
	After	53 42±121.71	
ALP	Before	315.66±206.109	0.363
	After	305.37±197.70	
Calcium	Before	8.57±0.73	0.000
	After	9.11±1.15	

concentrations of >2.5 g/dL and just 5.6 %of them had albumin level of ≤2.5. Furthermore, use of albumin did not get corrected according to guidelines.

Albumin was prescribed completely inappropriate for hypocalcaemia and in ascites when there was no response to diuretics .The most appropriate use of albumin occurred in 4 % of patients with GVHD

when there was hyperbilrubinemia and diarrhea more than two liters and albumin level of at least less than 2.5 g/dl according to guideline.(6, 11, 18)
In general, the use of albumin was more in pediatrics than adults. In our study, most of patients received at least one of the drugs that decreased albumin level in plasma, but there was no correlation between consumption of this medication and number of albumin vials used in comparison with patients on albumin who did not receive any of this kind of drugs.
There were no significant changes in serum creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and hematocite after albumin use but as was expected, total protein was significantly altered after albumin and we had increased in total protein level.
Many factors in addition to of our knowledge could affect appropriate use of drugs, so it seems difficult to define the precise clinical situations in which the use of human albumin could be appropriate.
Our findings need to be in prospective trials because retrospective evaluations are generally
Poorly controlled; therefore, the results of our study must be considered cautiously.

Conclusion

Although DUE of drugs is time consuming but could certainly lead to a better drug treatment and gives an opportunity for clinical pharmacist to help improve therapy by designing strategies to reduce the medication error and cost or changing prescriber manners.

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