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RESEARCH ARTICLE

Drug utilization evaluation of albumin in a teaching hospital of Mashhad, Iran: an interventional pre–post design study

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Abstract *Background* Albumin is a protein colloidal solution with limited availability and high cost. It should be used in such approved indications as paracentesis, extensive burn, spontaneous bacterial peritonitis, and nephrotic syndrome. *Objectives* The aim of this study was to evaluate and compare the appropriateness of albumin usage before and after an evidence-based guideline. *Setting* Four wards of Imam Reza Hospital, Mashhad, Iran. *Method* An interventional pre–post design study was performed on 2 groups of patients; in gGroup 1 as a preparation phase group in 6 months from February 2015 to July 2015 and Group 2 as an interventional group from September 2015 to February 2016. A guideline for proper indications of albumin, designed and finalized based on the physicians' comments, was implemented in Group 2. *Main outcome measure* The pattern of albumin consumption. *Results* Fifty patients were evaluated in each group. The implementation of the guideline resulted in reduction of improper albumin use from 62 to 57.5%, which was not statistically significant; however., it reduced inappropriate dose and duration of albumin therapy (55.5–16.7%), the number of consumed albumin vial, and the average cost for each patient (317.78 ± 3.15–149.81 ± 1.91 USD) significantly, as well. *Conclusion* This study illustrated that in this hospital in most cases, albumin was used inappropriately and at an alarming rate. This improved after the introduction of an evidence-based guideline. Moreover, guideline implementation resulted in significant cost reduction.

Keywords Albumin · Cost reduction · Drug use evaluation (DUE) · Inappropriate use · Intervention · Iran · Teaching hospital

Impact on practice

- Development and implementation of a guideline for albumin prescription and consumption is likely to improve its use.
- Reduction of the dose and duration of albumin use will decrease albumin therapy average cost per patient.
- The staff involvement in guideline development helps to achieve optimal effect. Regular monitoring the guideline implementation will facilitate its proper use.

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Introduction

In recent years, irrational drug use has become one of the growing concerns in the health care system. With regard to albumin resources limitation, it is necessary to utilize existing ones appropriately [1]. Drug use evaluation (DUE) is defined as a continuous program for evaluating the accuracy of drugs indications, dosing, rate and duration of administration, interactions, and monitoring of patients during their treatment course [2]. DUE is especially vital for high cost and high volume medications and also those with narrow therapeutic index or potential for developing antimicrobial resistance, as they would have the greatest clinical and economic impact on health care system and may reduce the microbial resistance occurrence [1–5].

Human albumin is an expensive medication derived from blood with limited supply and difficult production process. There are some clinical conditions and/or procedures such as plasmapheresis, paracentesis, extensive burn, spontaneous bacterial peritonitis and nephrotic syndrome that require albumin as the first line option but in lots of cases it is used in indications where cheaper alternatives exist [3, 5–9]. Several DUEs have been performed on this medication in Iran and other countries are indicating that in most cases (ranged 50–70% and even more than 90% in some studies) it is used in unapproved indications which are not well-supported by high quality clinical evidence [1, 3, 4, 10–14].

In Imam Reza Hospital of Mashhad University of Medical Sciences, which is a 918 bed teaching hospital, albumin is in the top ten lists of the most expensive medicines, but no DUE has so far been performed in this center.

Moreover, precise constructed practice guidelines could decrease the unnecessary use of expensive medications [5, 15]. A major concern about the implementation of these guidelines is ensuring that they are actually used based on clinical decision making, which could significantly prevent medication errors, improve appropriateness of prescription, and cause substantial cost reduction [5, 16].

Aim of the study

The aim of this study was to evaluate the appropriateness of albumin usage before and after implementation of an evidence-based prepared guideline in selected wards of a tertiary hospital in Mashhad, Iran.

Ethics approval

The study protocol was approved by the local Ethics Committee of Mashhad University of Medical Sciences (code = 94142).

Methods

Study design

A pre–post designed interventional study was performed at Imam Reza Hospital, Mashhad, Iran from January 2015 to February 2016. This general teaching hospital has 24 wards and 918 beds. In September 2014, a consensus was reached in our center regarding the need to control cost of expensive medicines. So, the DUE center began to work in December 2014 by employing two pharmacists who worked under the supervision of two clinical pharmacists.

Sample size

We selected 50 subjects out of all patients receiving albumin in pre-and post-implementation phases respectively for evaluation. It would have been better to evaluate all patients who received albumin but it was not feasible, since only two pharmacists worked on a part-time basis in DUE center. And besides, the patients' records were only available as hard copy in wards.

We, therefore, defined sample size as 50 cases in each phase based on the estimated number of patients who had received albumin in selected wards.

Preparation phase

This phase was carried out during January 2015. Two pharmacists working in DUE unit checked the frequency of albumin 20% vials requests by all the wards in the hospital, between February 2014 and February 2015 by using hospital information system (HIS) of pharmacy. Four wards with the highest albumin consumption were determined and chosen for albumin use evaluation (Table 2).

Then a standard protocol on albumin indications was designed by some clinical pharmacists based on some updated international consensus guidelines in literature that best matched such local conditions as AHFS, and American Society of Health-System Pharmacists (ASHP) [6, 8–11]. A form for collection of albumin consumption data was also developed by the clinical pharmacists (Supplement 1).

Pre-implementation phase

The medical records of 50 patients who had been prescribed albumin, were reviewed by two pharmacists working in DUE unit of hospital between February 2015 and August 2015. Data including demographic information (e.g. age, gender and weight), paraclinic tests (including albumin level, total protein, hepatic transaminases, hematocrit, platelets, urea, creatinine, Na, K and fasting blood

sugar), medications, vital signs, indication for albumin prescription, the rate of albumin administration, the length and the amount of albumin use and possible alternative treatments were collected in the aforementioned form (supplement 1). During the hospitalization, if the patient received albumin more than one time with different indications, the information about each session was recorded separately. But if the patient received albumin several times with similar indications, the information was recorded only once.

Realization phase

In this phase which took place during August 2015, all the obtained data from the first phase were analyzed based on the evidence-based designed guideline and the results were reported in some written reports sent to faculty members, residents, physicians and nurses who were involved in the administration of albumin in the selected wards. Then, before finalizing the prepared guideline and taking into consideration the local circumstances, it was sent to the heads of the wards to receive comments from them. We received comments on the guideline from all heads of the wards. These comments were reviewed by clinical pharmacists and the necessary changes were performed on prepared protocol. Finally, the guideline was completed and approved in a face to face meeting with hospital administrator, treatment deputy director and the heads of the related wards. Thereafter, a hard copy volume of the final check list of the appropriate indications was sent to the heads and the matrons of hospital wards through automation software to be presented to the wards' staff for application. Moreover, the guideline was presented orally and also as a printed copy on the educational board of the ward. This check list is available in Table 1. To the best of our knowledge, it is the first guideline for prescription of a medication presented to this extent in our hospital.

Post-implementation phase

In this phase which was carried out from September 2015 to February 2016, medical records of 50 patients who had received albumin were reviewed in the same manner as the preparation phase. In this phase, it was expected that physicians had already ordered albumin based on the approved check list.

Outcome analysis

The preliminary purpose of this study was to decrease inappropriate utilization of albumin after the implementation of the clinically-based guideline. Specific outcome criteria such as inappropriate dose, inappropriate duration of therapy, and cost reduction were evaluated and compared for the pre-and post-implementation groups.

For evaluation of the medication dose, prescribed dose more than 5% over or under the recommended dose was considered as inappropriate dose.

Breaking the recommended duration of therapy even for one day was considered as inappropriate duration.

Cases of albumin consumption with none of the indications listed in Table 1, were defined as inappropriate.

Statistical analysis

Data recruited from the standard forms were gathered and then analyzed with SPSS version 20.0 (Systat Software, Inc., Chicago, IL). For descriptive assessment, mean ± standard deviations of continuous variables were provided. For nominal variables, number and percentages were reported. Chi squared test and *t* test were applied for continuous and nominal data, where appropriate. Independent sample t test was employed when it was appropriate, to compare the differences between pre-and post-intervention. P value ≤ 0.05 was considered significant.

Results

Patients' size and characteristics

During this study a total of 100 patients treated with albumin, were studied in 2 groups; before ($n = 50$) and after ($n = 50$) intervention, respectively. Demographic information and laboratory tests, including serum albumin and total protein level, in both groups are given in Table 2. There was no significant difference between patients' demographic and laboratory data in pre-and post-phase.

The highest albumin consumption in pre-intervention phase was found for the burn ward (54%), followed by intensive care unit (ICU) and internal ward. This trend remained unchanged in post-intervention phase (P value = 0.198).

Drug utilization review

Thirty-one cases of inappropriate albumin indication (62%) were identified in the pre-intervention phase. This was reduced to 27 cases (57.5%) in post-intervention phase but the difference was not significant (P value = 0.648). Nutritional supplementation (48.39%) and hypoalbuminemia (19.35%) were the two most frequent reasons for inappropriate albumin use in pre-intervention phase. This trend remained constant in post-intervention phase

Table 1 Approved indications for the use of albumin (implied guideline)

Administration of albumin is appropriate for the following conditions	
Hypovolemia	In hypovolemic shock:
	12.5–25 g albumin 5% (250–500 cc)
	25 g albumin 20% (125 cc)
	25–50 g albumin 25% (100–200 cc)
	If no response, repeat the dose after 15–30 min
	Only in the case of lack of response to crystalloids or colloids; Contraindication to the use of non-protein colloids
Thermal injury	In the case of burns of >30% body surface area
	Target: serum albumin 2–3 g/dl and plasma oncotic pressure 20 mmHg
	Use crystalloids resuscitation in first 24 h, then albumin start with dose of 25 g.
	Continue albumin administration until serum protein achieve to 2.5 g/dl
Nephrotic syndrome	Diuretic therapy is the initial treatment. The short-term use of albumin 20% with diuretic therapy is appropriate for the patients with acute severe peripheral or pulmonary edema who have failed diuretic therapy with serum albumin less than 2 g/dl
Cirrhotic ascites and ascetic patients post paracentesis	Six to eight g of albumin/L ascetic fluid was removed in patients with serum albumin <2 g/dl
Hepatorenal syndrome	If albumin indicates with vasopressors, the starting dose is 1 g/kg in first day (max. 100 g) then 20–40 g/d
	Continue treatment until serum creatinine <1.5 mg/dl
	Discontinue albumin, if its serum level achieves to 4.5 g/dl or pulmonary edema
Spontaneous bacterial peritonitis	If there is more than 250 PMN in ascites fluid or serum creatinine > 1 mg/dl, urea > 30 mg/dl or total bilirubin > 4 mg/dl, 1.5 g/kg albumin in first 6 h and then 1 g/kg in third day is administered
Hypoproteinemia in adults	Administer 50–75 g of albumin 5%
Liver transplantation	Albumin may be used in post-operative period to control ascites and peripheral edema if the following conditions are met: (1) Serum albumin less than 2.5 g/dl; (2) Pulmonary capillary wedge pressure less than 12 mmHg; (3) Hematocrit greater than 30%
Therapeutic plasmapheresis	Albumin is appropriate for the exchanges in the range of >20 ml/kg in one session or the range of >20 ml/kg/week in more than one session

Table 2 Patients' characteristics and laboratory data

Variable	Before intervention (N = 50)	After intervention (N = 50)	*P* value
Age (mean ± SD)	35.1 ± 21.5	41.3 ± 26.2	0.208*
Sex (F/M)	0.78	0.62	0.569**
Weight (mean ± SD) (kg)	56.9 ± 18.93	57.2 ± 19.85	0.750*
Serum albumin (mean ± SD) (g/dl)	2.80 ± 0.63	2.86 ± 0.57	0.752*
Total protein (mean ± SD) (g/dl)	5.08 ± 1.09	5.00 ± 0.87	0.957*
Distribution of albumin utilization in hospital wards (%)			
Burn	54	50	0.198**
ICU	24	12	
Internal	12	22	
Surgery	10	16	

* Independent sample T test

** Chi square

SD standard deviation, *ICU* intensive care unit

(nutritional supplementation 40.74% and hypoalbuminemia 25.92%; $P > 0.05$).

In post-intervention phase among patients whom received albumin for appropriate indications, 13.04% (n = 3) of patients received albumin with inappropriate dose, while it occurred in 10 patients (52.63%) of pre-intervention phase. The intervention was significantly effective in reducing the number of inappropriate doses

($P = 0.015$). The same results were obtained on duration of albumin therapy as it significantly reduced after intervention ($P = 0.015$) (Fig. 1).

The albumin dosage form which was used in this study was vial 50 ml of albumin 20%. The average number of vials which was used inappropriately for each patient was 8.80 ± 8.7 vials before the intervention. After the intervention it significantly decreased (4.15 ± 5.3 vials per patient; $P = 0.002$).

The average cost of inappropriately prescribed albumin for each patient was reduced significantly from 11.44 ± 11.35 million Rials ($\approx 317.78 \pm 3.15$ USD) in pre-intervention group to 5.393 ± 6.878 million Rials ($\approx 149.81 \pm 1.91$ USD) in post-intervention group ($P = 0.002$). It should be noted that the price of albumin 20% vial was about 35 USD in pre-implementation phase based on the hospital procurement price, which is increased in post-implementation group (1560 Rials $\approx$ 43 Cents per vial). Taking this into consideration, the cost saving was in fact more significant between pre-and post-implementation groups.

Drug utilization for individual wards

Inappropriate indications for albumin did not change significantly for any of the wards ($P > 0.05$). However, there were non-significant reductions in the burn and ICU wards which had the highest albumin consumption rate. The most common inappropriate indications by ward in pre-and post-intervention groups are summarized in Table 3.

The number of inappropriately given doses was significantly changed only for the burn ward ($P = 0.05$). Moreover, a decreasing trend was found for the ICU ward. Similarly, inappropriate duration of therapy was significantly reduced in the burn ward ($P = 0.05$), with a decreasing trend found for the ICU ward. No change was found in the other two wards (Table 3). It should be noted that the appropriateness of the dose and duration of albumin therapy were just evaluated in group of patients with appropriate albumin indication.

Discussion

Drug utilization evaluation could be an effective approach to ensure proper prescription and administration of medications [4]. Performing one-time DUE studies without follow-up could however have limited success in improving patient outcomes. The effectiveness of initial actions must be assessed and the action plan be adjusted, if necessary [5].

This study is one of the first interventional DUE of albumin in Iran. Results of this study showed that albumin was prescribed inappropriately in more than fifty percent of cases, in this hospital. In the past few years, some studies on human albumin use have been carried out in a number of countries. The previous studies revealed that 50–70% of prescriptions were inappropriate [1–4, 10–13]. Even in a study performed in Spain, the incompatibility with the university hospital consortium guideline for the use of albumin was reported more than 90% [12]. Hypoalbuminemia and nutritional supplementation are the most

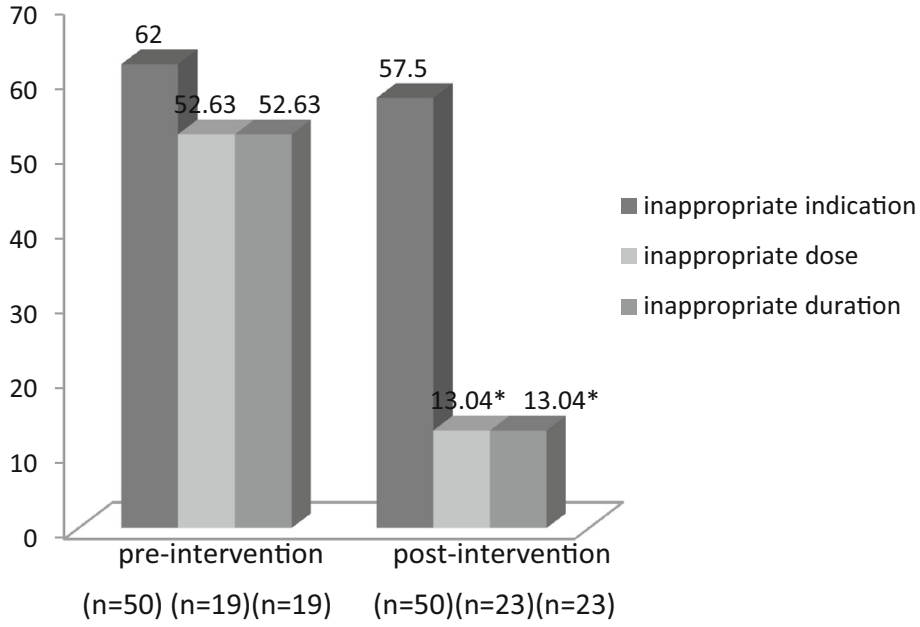

Fig. 1 Frequency of inappropriate indication, dose and duration of albumin therapy in pre-and post-intervention phases

Table 3 Comparison of inappropriate indication, dose and duration of albumin therapy in pre-and post-intervention phases in different wards

Variable	Before intervention N (%)			After intervention N (%)			*P* value[a]
Inappropriate indication							
Burn ward	N = 27			N = 25			0.756
	18 (66.7)	Nutrition	7 (38.89)	15 (62.5)	N nutrition	5 (33.33)	
		Hypoalbuminemia (but burn < 30%)	4 (22.22)		Hypoalbuminemia (but burn < 30%)	5 (33.33)	
		No serum albumin checking	4 (22.22)		No serum albumin checking	4 (26.67)	
		Before crystalloids in first 24 h	3 (16.67)		Accelerating wound healing	1 (6.67)	
ICU ward	N = 12			N = 6			0.9
	6 (50)	Nutrition	4 (66.67)	2 (40)	Nutrition	1(50)	
		Nephrotic syndrome (without sufficient diuretic therapy and albumin check)	1 (16.67)		Nephrotic syndrome (without sufficient diuretic therapy and albumin check)	1(50)	
		Hypoalbuminemia	1(16.67)				
Internal ward	N = 6			N = 11			0.957
	3 (50)	Nephrotic syndrome (Alb > 2)	2 (66.67)	6 (60)	Nutrition	3 (50)	
					Nephrotic syndrome (without sufficient diuretic therapy)	2 (33.33)	
		Cirrhotic ascites (Alb > 2)	1 (33.33)		Cirrhotic Ascites (Alb > 2)	1(16.67)	
Surgery ward	N = 5			N = 8			0.565
	4 (80)	Nutrition	2 (50)	4 (50)	Nutrition	2 (50)	
		hypoalbuminemia	1 (25)		Hypoalbuminemia	2 (50)	
		Edema (without sufficient diuretic therapy and albumin check)	1 (25)				
Inappropriate dose							
Burn ward	6 (66.7)			1 (12.5)			0.05*
ICU ward	3 (60)			1 (33.3)			0.87
Internal ward	1 (33.3)			1 (33.3)			1
Surgery ward	0			0			–
Inappropriate duration							
Burn ward	6 (66.7)			1 (12.5)			0.05*
ICU ward	3 (60)			1 (33.3)			0.87
Internal ward	1 (33.3)			1 (33.3)			1
Surgery ward	0			0			–

[a] Chi Square; Fisher's exact test

* *P* value < 0.05 is considered significant

common conditions where albumin is not indicated but frequently used [3]. The reason for this diversity in reported size of inappropriate albumin use in various studies could be the widespread controversy about correct indications of albumin despite many available guidelines. So, different check lists might have been used in these studies.

In our study, after guideline implementation, inappropriate use was reduced but not significantly (62–57.5%). In another study performed in a tertiary hospital in Shiraz, Iran, a significant reduction in albumin improper use (from 51.2 to 32.7%) was reported [5]. The reason for our finding may be the lack of effective communication with physicians who ordered albumin and the lack of authority to impose on the medical staff to follow this guideline. Everyone affected by the DUE process should understand its importance to the health system, its goals and procedures. Holding educational meetings for the medical staff

may be useful to reduce albumin improper use more efficiently. In a study carried out by Mahmoudi et al. [5] in Shiraz, they used a pre-printed form for albumin prescription that physicians should complete, to be able to receive albumin from the hospital pharmacy. Furthermore, they applied a computer decision support program which was designed in line with the printed order forms. But in our study, in post-implementation phase we just sent the finalized protocol to wards without any changes in the prescription system. However, at the end of the post-implementation phase, after reporting the findings to the hospital administrator and the medical deputy director, we also designed a pre-printed form for albumin prescription. All physicians and residents are now required to use this form (Supplement 2). The effects of this intervention on albumin use are evaluated in another study.

The most common inappropriate indications in both pre- and post-intervention groups were nutritional support and hypoalbuminemia. Unfortunately, as total parenteral nutrition (TPN) ordering and preparation are difficult processes in our hospital, physicians often prefer to order albumin for nutritional purpose instead of TPN. Providing suitable clean room in the hospital for TPN preparation managed by pharmacists and also assignment of TPN formulation responsibility to clinical pharmacists could help to reduce this inappropriate use. Holding regular interactive educational meetings with physicians to receive feedback on guideline use is also necessary to modify this process.

On internal ward, one of the common inappropriate indications for albumin is in nephrotic syndrome or cirrhosis of the liver with refractory ascites without checking serum albumin level or prescribing suitable diuretics. This may be because it takes about two days to get the result from the hospital laboratory. Therefore, physicians prefer to start albumin therapy to avoid losing time. However, in many cases, it is administered instead of proper diuretic therapy with loops diuretic (e.g. giving low dose and giving oral form of medication). Educational meeting in this field could be helpful.

On the other hand, our intervention reduced improper albumin dose, duration of therapy and number of inappropriate albumin vials significantly. One of the main problems of albumin prescription in our hospital was starting albumin with appropriate indication but not discontinuing it at proper time. The physicians did not check albumin level regularly during treatment course, while in many indications albumin should be discontinued after achieving albumin serum level of 2 g/dl. It seems that implementation of this guideline was effective in changing this trend.

Moreover, in post guideline implementation group, cost of the albumin therapy was also significantly reduced for each patient ($P = 0.002$). According to a report from the Iranian Food and Drug Organization of the Health Ministry published in 2008, albumin had the highest cost paid for a single drug used in hospitals [5]. So, it is very important to reduce albumin use and consequently its costs. Similarly, in Mahmoudi et al.'s [5] study, the total monthly number of units of albumin used and the cost were significantly reduced after guideline implementation ($P < 0.0001$).

Considering each ward separately, incorrect dose and duration of albumin therapy were significantly reduced in burn ward, which had the highest albumin consumption, showed decreasing trend in ICU ward but remained unchanged in two other wards. Inappropriate indications also showed a decreasing trend in burn and ICU wards, although not significant. The reason for this finding may be the limited number of patients, evaluated in each ward. If it had been possible to include a greater number of patients by ward in both pre-and post-implementation phases, a decreasing trend might also have been evident in the two other wards. Besides, diversity of patients admitted to surgery and internal wards and similarly, different specialties of physicians working in these wards make the modification more difficult. It should also be mentioned that the increasing/decreasing trend of albumin use in some wards just can be due to natural variation over time.

This study had some limitations due to resource shortage. Firstly, a limited number of patients could be evaluated in pre-and post-intervention groups. So, we could not perform sub-analysis of albumin use for each ward, separately. Secondly, we only delivered a written report of pre-implementation phase findings to the wards. Having interactive oral presentation of findings can improve physicians' adherence to guidelines and would probably have improved the results. Thirdly, use of the prepared protocol for post phase was not mandatory for physicians, so some of them continued their previous practice of albumin prescription.

Conclusion

Development and implementation of an evidence-based guideline for use of albumin can significantly decrease cost and improper use of albumin. Our study showed that implementation of a drug-utilization evaluation programme for albumin can optimize duration of medication administration and significantly reduce number of inappropriate doses. As a result, more than 50% of albumin cost could be saved for each patient. However, it seems necessary to find suitable strategies including preprinted order forms, local experts' opinions as well as audit and feedback to ensure physicians' adherence to these guidelines.

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Conflicts of interest None.

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