ORIGINAL ARTICLE

Is Albumin-based Resuscitation in Severe Sepsis and Septic Shock Justifiable? An Evidence from a Cost-effectiveness Evaluation

Bereket Tigabu[1,2,3], Majid Davari[1,2]*, Abbas Kebriaeezadeh[1,2], Mojtaba Mojtahedzadeh[4,5], Kourosh Sadeghi[4], Zahra Jahangard-Rafsanjani[4]

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Affiliation and Correspondence:
[1]Department of Pharmacoeconomics and Pharmaceutical Administration, Faculty of Pharmacy, International Campus, TUMS, Tehran, Iran
[2]The Institute of Pharmaceutical Science, Faculty of Pharmacy, TUMS, Tehran, Iran
[3]School of Pharmacy, Haramaya University
[4]Department of Clinical Pharmacy, Faculty of Pharmacy, TUMS, Tehran, Iran
[5]Sina Hospital, Division of Critical Care Medicine, TUMS, Tehran, Iran
*Email: m-davari@tums.ac.ir

ABSTRACT

BACKGROUND*: Fluid and antimicrobial therapy are the essential parts of sepsis management. The type of fluid to resuscitate with is an unsettled issue in the treatment of severe sepsis and septic shock. The objective of this study was to evaluate the cost-effectiveness of albumin-based resuscitation over crystalloids.*
METHODS: *A cost-effectiveness analysis was conducted by extracting data from a database of Sina Hospital, Islamic Republic of Iran. A decision tree was constructed by using Tree Age Pro 2011. The patients were grouped based on the types of fluids used for resuscitation into crystalloid alone or crystalloid + albumin groups at the initial decision node. The patients were followed from the onset of severe sepsis and septic shock upto 28 days. The healthcare payers' perspective was considered in constructing the model. The cost was measured in US dollars and the effectiveness was measured by life years gained.*
RESULTS: *The addition of albumin during resuscitation of patients with severe sepsis and septic shock has an effectiveness gain of 0.09 life years and cost increment of 495.00 USD. The estimated ICER for this analysis was 5500.00 USD per life year gained. The probability that albumin is cost-effective at one GDP per capita is 49.5%.*
CONCLUSION: *Albumin-based resuscitation is not cost-effective in Iran when a GDP per capita was considered for a life year gain. The cost-effectiveness was insensitive to the cost of standard care. We recomend the caustious use albumin as per the Surviving Sepsis Campaign guideline.*
Keywords: *Albumin, cost-effectiveness, crystalloids, economic evaluation*

INTRODUCTION

Fluid resuscitation is the main part of severe sepsis and septic shock management (1,2). The ultimate goal of resuscitation is to enhance stroke volume and cardiac output (3). The Surviving Sepsis Campaign recommends patients with hypotension or a lactate concentration >4 mmol/L, to receive a 30 ml/kg bolus of fluid within the first 3 hours, with additional fluid based on reassessment

(4). However, considering the short-lived benefit of the hemodynamic fluid bolus, studies also recommended a conservative resuscitation strategy (5,6).

Fluids used for volume replacement and resuscitation are generally classified into two groups: crystalloids and colloids (1,7). Crystalloids are composed of different electrolytes and water; can diffuse through the cell membranes. Nevertheless, colloids cannot diffuse through the cell membrane but create a positive oncotic pressure which leads to retention of fluid in the vascular compartment (8). The advantage of colloids over crystalloids is the volume sparing property (9). Albumin, normal saline and Ringer's lactate are the common fluids used for resuscitation in the Islamic Republic of Iran (10).

Large clinical trials came up with contradicting results on the mortality benefit of albumin over crystalloids. The SAFE study showed a 28-days mortality reduction benefit of albumin compared to normal saline (11). However, this effect was not confirmed for both 28-days mortality and 90-days mortality in ALBIOS study that compared the use of 20% albumin and crystalloid solution versus crystalloid solution alone (12). Although a few studies have been conducted on the cost-effectiveness of albumin-based resuscitation (13,14), the economic evaluation of fluid therapy in sepsis patients is not given important attention. In the US, albumin-based resuscitation had shown a 0.21 life years gain with an incremental cost of 270 US dollars when compared with crystalloids based resuscitation in severe sepsis and septic shock (13).The role of evaluating the effectiveness and cost of therapy is intuitively known by any policy maker and manager. Reasonable cost containment should be a target for each health sector particularly when the acquisition cost of the drug is expensive. Albumin is one of the drugs which can inflate healthcare expenditure if prescribed haphazardly. Therefore, we conducted this economic evaluation to evaluate the cost-effectiveness of albumin compared with crystalloids in IRI.

METHODS

A retrospective database analysis was conducted for patients admitted with severe sepsis and septic shock in Sina Hospital from March 21, 2016 to September 22, 2017. The commonly used crystalloids, colloids, survival of patients under crystalloids, the average volume of fluids for fluid therapy and the cost of standard care for severe sepsis and septic shock patients were identified. This economic evaluation was done on crystalloids used for resuscitation of patients with severe sepsis and septic shock in Iran. The normal saline (0.9% NaCl), Ringer's lactate, and 20% albumin were considered.The odds ratio for mortality was taken from a meta-analysis done on head-to-head comparison clinical trials to allow the calculation of probabilities for 28-days survival with the addition of albumin (15).

Decision analysis model: A decision tree was constructed based on a hypothetical severe sepsis or septic shock patient population by using Tree Age Pro 2011 (Figure 1). The patients were grouped based on the types of fluids used for resuscitation into crystalloid alone or crystalloid + albumin groups at the initial decision node. The patients were followed from the onset of severe sepsis and septic shock upto 28 days. The healthcare payers' perspective was considered in constructing the model. Each treatment arm has a chance node specifying 28-days mortality. Treatment-related adverse drug events were not considered.

Life years gained were calculated by the Declining Exponential Average Life Expectancy (DEALE) (16). A cost equivalent of one GDP per capita of the Islamic Republic of Iran was used arbitrarily as a threshold to decide cost-effectiveness.

Model Inputs

Mortality: The variables used to populate the decision tree and the formulas used in the calculation are shown in Table 1 and Table 2. The odds ratio (OR) derived from the meta-analysis was converted to a probability of mortality with albumin and crystalloids using data for a 28-days mortality rate for patients with severe sepsis, and septic shock obtained from the retrospective

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hospital database analysis using the formula given below.

$$OR = \frac{P(death \mid albumin)/(1 - P(death \mid albumin))}{P(death \mid crystalloids)/(1 - (death \mid crystalloids))}$$

Where OR is the odds ratio

The effectiveness of each treatment was calculated using theformula given below.

$$LET = \frac{1}{\left(\frac{1}{LEA}\right) + \left(MR - \frac{1}{LEA}\right)}$$

Where LET is life expectancy with a given treatment, MR is the mortality rate in a given treatment and LEA is life expectancy for the general population at a given age

Cost input: The standard cost of care for severe sepsis and septic shock was taken from a retrospective database analysis in Sina Hospital. The standard cost of care was expected to include all the costs except the cost of albumin. The cost of albumin was added to this cost to determine the cost of treatment with albumin. The price of albumin was taken from the Iranian Food and Drug Administration (IFDA) market report for 2016. The average volume of albumin required for the treatment was determined from the retrospective database analysis. All the costs were inflated to 2017 costs using the Consumer Price Index (CPI) for health in 2016 and 2017 (17). Since all the costs were calculated for a time period of less than a year, no discount rate was used.

Cost-effectiveness: Cost-effectiveness was evaluated using the incremental cost-effectiveness ratio (ICER). The ICER shows the incremental cost per additional life year gained from one treatment compared with another.

Sensitivity analysis: The robustness of the model was checked by one-way sensitivity analysis, tornado diagram and probabilistic Sensitivity Analyses (SA). The probabilities of survival with the standard care and after the addition of albumin, the cost of standard care and cost of albumin were varied during the analysis.

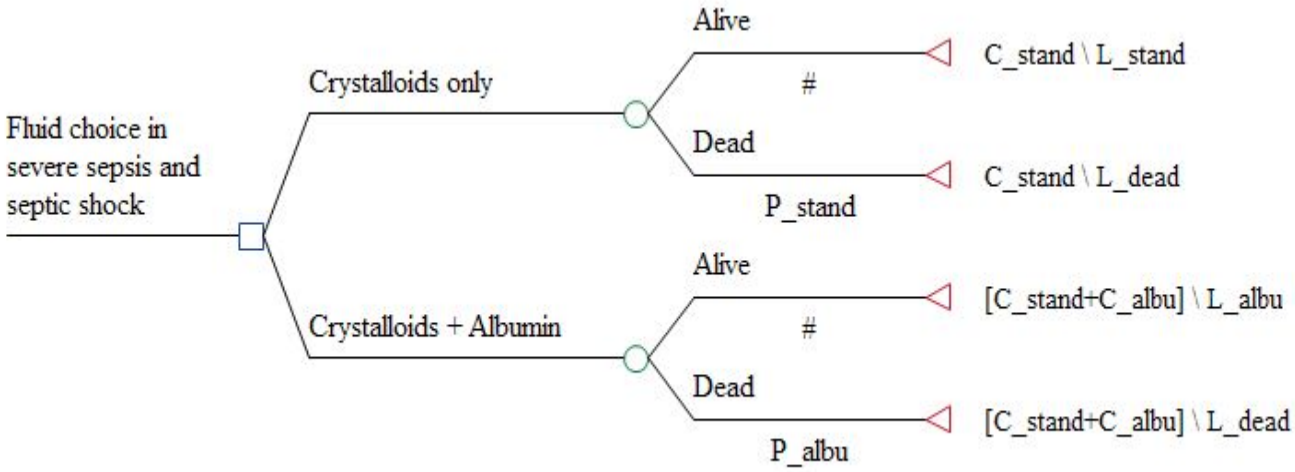

***Figure 1**: Decision tree*

RESULTS

One hundred twenty-four severe sepsis and septic shock patients resuscitated only with crystalloids were identified from the retrospective database analysis. The average age of patients was 61 ± 2 years and the mortality rate was 0.52 ± 0.05. The costs incurred during 2016 were adjusted to 2017 before calculating the average cost. A consumer price index for health from the central bank of Iran for Iranian years 1395 (100) and 1396 (108.9) was used for adjustment (17). The average cost of treatment was US $10,362.7 ±1017.6. A total of 155 severe sepsis and septic shock patients resuscitated with crystalloids and albumin were

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analyzed and the average volume of albumin was 569 ±48ml. The volume was converted to bags of albumin (1 bag=20%,50ml albumin). Therefore, the average bags of albumin was 11.4± 1 bags. The average price of albumin taken from the IFDA market report for 2016 was 1,267,757 Iranian Rials. The average exchange rate for one American dollar during the data collection period was 31,820 IR (17).

Base case analysis: The addition of albumin during resuscitation of patients with severe sepsis and septic shock had an effectiveness gain of 0.09 life years. However, the addition of albumin increased the cost of treatment by 495.00 USD compared with the standard treatment. Accordingly, the estimated ICER for this analysis was 5500.00 USD per life year gained (Table 3). Therefore, considering the GDP per capital of IRI (5219.2 USD) (18), the use of albumin for resuscitation in severe sepsis and septic shock cannot be regarded as cost-effective.

Sensitivity analysis: The one-way sensitivity analysis showed that the cost-effectiveness was insensitive to the cost of standard care. However, it was sensitive for the changes in the cost of albumin, the probability of mortality with crystalloids only, mortality with the addition of albumin, life years gained with albumin, life years gained with crystalloids alone (Table 4).

The cost-effectiveness acceptability curve (Figure 2) showed that, relative to the assigned threshold of US $5219.2 per life year gained, albumin was cost-effective around 49.5% of the iteration.

Table 1: Variables used to populate the decision analysis model

Variable name (abbreviation in the model)	Base case value	Values for one way sensitivity analysis	Probability Distribution	Remark
Cost of albumin (C_albu)	495	412-578	Gamma	Calculated by taking the average price of albumin in IRI and the average volume of albumin used for resuscitation
Cost of standard care (C_stand)	10362.70	8348-12377	Gamma	Taken from a retrospective cohort study
28-days mortality with crystalloids (P_stand)	0.52	0.43-0.61	Beta	Taken from a retrospective cohort study
28-days survival with crystalloids (Pa_stand)	0.48	Not applied	Not applied	1-(P_stand)
28-days mortality with crystalloids + albumin (P_albu)	0.50	0.37-0.52	Beta	Calculated by using OR from meta-analysis and 28-days mortality with crystalloids from the retrospective cohort
28-days survival with crystalloids + albumin (Pa_albu)	0.50	Not applied	Not applied	1-(P_albu)
Life expectance of general population at 61 years (LEA)(19)	14.5	Not applied	Not applied	Calculated by subtracting the average age of severe sepsis or septic shock patients (61 years) from the average life expectancy of Iranians (75.5 years)
Life expectancy with crystalloids (L_stand)	1.9	1.64-2.30	Not applied	Calculated based on DEALE by using life expectance of the general population and the mortality under the given treatment
Life expectancy with crystalloids + albumin (L_albu)	2.0	1.9-2.7	Not applied	Calculated based on DEALE by using life expectance of the general population and the mortality under the given treatment
Life expectancy of expired patients (L_dead)	0	Not applied	Not applied	

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Table 2: Formulae for calculations of pay-offs for cost and effectiveness

Pay-off	Formula
Cost	
Cost of treatment with albumin +crystalloids at survival (path1)	Cost_std + cost_alb
Cost of treatment with albumin +crystalloids at death (path2)	Cost_std + cost_alb
Cost of treatment with crystalloids at survival (path3)	Cost_std
Cost of treatment with crystalloids at death (path4)	Cost_std
Effectiveness	
Life expectancy with albumin+crystalloids	1/[(1/LEA) +(P_albu -1/LEA)]
Life expectancy with crystalloids	1/[(1/LEA) +(P_cryst -1/LEA)]

Table 3: Result summary table

Summary measures		Values
Average cost	Albumin+crystalloid	$10857.7
	Crystalloid only	$10362.7
Life years gained	Albumin+crystalloid	1.0 LYs
	Crystalloid only	0.91LYs
Cost/life years gained	Albumin+crystalloid	10,857.70 dollars/LY
	Crystalloid only	11387.58 dollars/LY
ICER	$ICER = \frac{Cost\ AlCr - CostCr}{Life\ gained\ ALCr - Life\ gained\ Cr}$	5500.00 dollars/LY

Cost ALCr-cost of albumin+crystalloid, CostCr- cost of crystalloid, life gained ALCr-life years gained by albumin+crystalloids, life gained Cr-life years gained from crystalloid

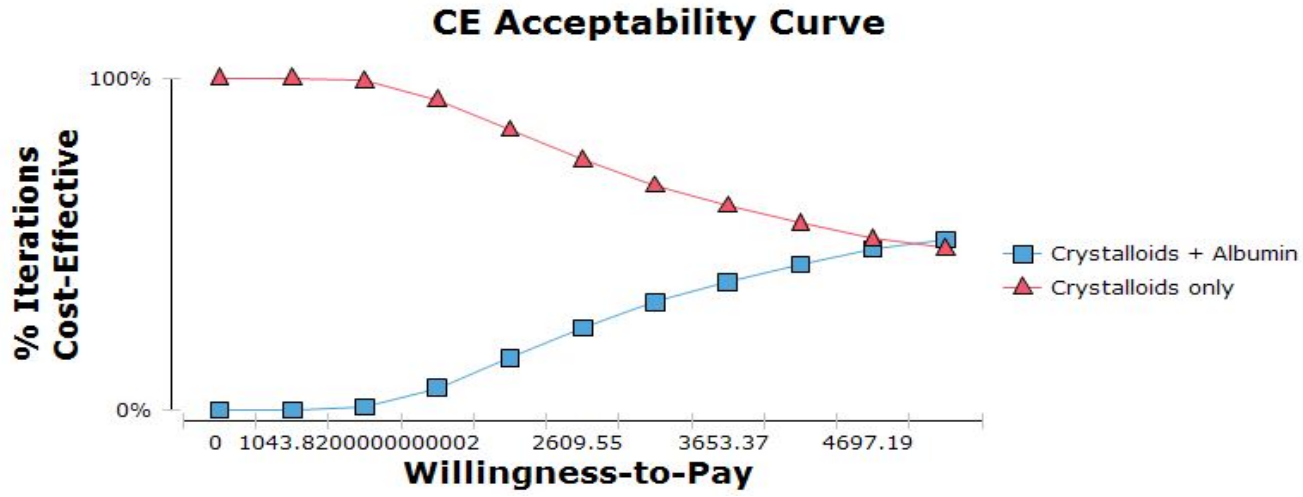

***Figure 2**: Cost-effectiveness acceptability curve*

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Table 4: Results of one-way sensitivity analysis

Variables		ICER (low)	ICER (high)	ICER (low)	ICER (high)
Probability of mortality with the addition albumin	Albumin Crystalloids	1422.41	10312.50	CE Not CE	Not CE CE
Probability mortality with standard care only	Albumin Crystalloids	-5963.86	1911.20	Dominated Dominant	CE Not CE
Cost of albumin	Albumin Crystalloids	4681.81	6568.18	CE Not CE	Not CE CE
Cost of standard care	Albumin Crystalloids	5625.00	5625.00	Not CE CE	Not CE CE
Life expectancy with albumin	Albumin Crystalloids	13026.32	1130.14	Not CE CE	CE Not CE
Life expectancy with crystalloids	Albumin Crystalloids	2326.13	-4759.62	CE Not CE	Dominated Dominant

CE-cost-effective at one GDP per capita for a life year gain

DISCUSSION

The results of our decision analysis indicate that albumin was not cost-effective relative to crystalloids in one GDP per capita for a life year gained. The total cost per life year for albumin ($10,858) was lower than that of crystalloids ($11,388). Sensitivity analysis showed that this result was robust over a range of standard care cost. However, the result was sensitive to the cost of albumin, mortality rates and associated life year gains. A similar study from the US revealed the cost-effectiveness of albumin-based resuscitation in severe sepsis and septic shock (13). The differences in the economic status and healthcare capacities might have contributed to the cost-effectiveness in US.

Our study was based on two fundamental assumptions. First, crystalloids and albumin were deemed to have no significant differences in terms of treatment-related adverse events. The crystalloids can be classified as physiologically balanced and isotonic saline (7). Isotonic saline differs from balanced crystalloids in two aspects (20). First, it does not contain a buffer. Second, it has a higher chloride concentration. These peculiar characteristics lead to the important adverse effect of isotonic saline, hyperchloremic metabolic acidosis and acute kidney injury. However, high-chloride fluids use did not affect mortality (19,21). The second assumption is that albumin and crystalloids preparations show biopharmaceutical equivalence in each product class.

Recent studies on the volume of fluid for resuscitation, generally, discourage large volume resuscitation and positive fluid balance in severe sepsis and septic shock (22-24). A total volume of albumin equivalent to a third of the total volume of crystalloids is enough for a similar level of resuscitation (7). This may give albumin a privilege to reduce fluid overload. Albumin's additional properties like binding to nitric oxide, protection against lipid peroxidation and regulatory effects on inflammation might provide albumin a modulatory effect on sepsis pathogenesis (1). However, the main factor for fluid leakage and end-organ failure in sepsis is the damage on the endothelial glycocalyx (25,26). As a result, fluid therapy does not follow the usual Starling's principle. This makes fluid resuscitation in sepsis complex. A number of studies concluded that albumin has no additional mortality benefit over crystalloids for patients with severe sepsis and septic shock (27-29).

The strengthes this study includes the use of patients from one of the few hospitals that have a well-equipped intensive care unit. This will serve to rule out other factors that might have contributed to the overall mortality. The cost of standard care, the

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price of medications and the exchange rate were taken from the hospital and national databases without any estimation to avoid bias. Both deterministic and probabilistic sensitivity analyses were done. This study has a few limitations. First, the extraction of probabilities from a meta-analysis might introduce some bias. Second, the cut-off point employed for cost-effectiveness was chosen arbitrarily. Third, the practice variation among hospitals might decrease the generalizability the result extracted from a single center for the whole country. Last but not least, the volume of albumin was determined from dispensary database which might not necessarily indicate the volume administered to patients.

We cautiously conclude that the use of albumin for resuscitation of patients with severe sepsis and septic shock is not cost-effective at a GDP per capita for a life year gain in IRI. The cost-effectiveness was insensitive to the cost of standard care. We strongly advise policy-makers and hospital administrators to consider this economic evaluation during the design of resuscitation protocols. However, to clearly show both the effectiveness and cost of albumin-based resuscitation, we recommend a piggyback randomized clinical trial.

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