Original Article

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The Effect of Exogenous Human Albumin Administration on Acute Kidney Injury Development in Hypoalbuminemic Patients in the Intensive Care Unit

Yoğun Bakım Ünitesindeki Hipoalbüminemik Hastalarda Eksojen Human Albümin Uygulamasının Akut Böbrek Hasarı Gelişimine Etkisi

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ABSTRACT

Objective: Hypoalbuminemia is an independent risk factor for acute kidney injury (AKI) and mortality. The primary aim of our study was to investigate the effect of exogenous human albumin (EHA) administration on hypoalbuminemic patients in the intensive care unit (ICU) regarding the development of AKI. Our secondary aim was to compare the ICU admission duration and mortality rates of these patients.

Methods: After receiving ethics committee approval, the researchers retrospectively screened database for 5,989 patients admitted to the adult ICU from 01.01.2014 to 01.06.2018. The demographic data, serum albumin and creatinine levels, ICU admission duration and mortality rates of patients were recorded. Stage 2-3 AKI was accepted based on the AKI network criteria, while hypoalbuminemia was accepted as serum albumin values below 3.5 g/dL. Patients not given EHA were assigned to group none human albumin (Group NHA), while patients given EHA were assigned to group human albumin (Group HA). The rate of AKI development, duration of stay in ICU and mortality rates were compared between the groups.

Results: The mean age, AKI development rate, mortality rate and ICU admission duration in Group HA were statistically significantly higher than in Group NHA (p=0.0001, p=0.0001, p=0.0001, p=0.0001). There was no difference in terms of the gender distribution in the groups. The mean albumin value in Group HA was statistically significantly lower than Group NHA (p=0.0001).

ÖZ

Amaç: Hipoalbüminemi, akut böbrek hasarı (ABH) ve mortalite için bağımsız bir risk faktörüdür. Çalışmamızın temel amacı, yoğun bakım ünitesinde (YBÜ) izlenen hipoalbüminemik hastalarda eksojen human albümin (EHA) uygulamasının ABH gelişimi üzerine etkisini araştırmaktı. İkincil amaçlarımız ise YBÜ'de kalış süresi ile mortalite oranlarını karşılaştırmaktı.

Yöntemler: Etik kurul onayı alındıktan sonra 01.01.2014-01.06.2018 tarihleri arasında erişkin YBÜ'de izlenen 5.989 hastayı retrospektif olarak inceledik. Hastaların demografik verileri, serum albümin ve kreatinin düzeyleri, YBÜ başvuru süreleri ve mortalite oranları kaydedildi. ABH ağı kriterlerine göre evre 2-3 ABH olarak kabul edilirken, 3,5 g/dL'nin altındaki serum albümin değeri hipoalbüminemi olarak kabul edildi. EHA verilmeyen hastalar Grup NHA, EHA verilen hastalar Grup HA olarak adlandırıldı. ABH gelişimi, YBÜ'de kalış süresi ve mortalite oranları gruplar arasında karşılaştırıldı.

Bulgular: Grup HA'daki ortalama yaş, ABH gelişimi, mortalite oranları ve YBÜ'de kalış süresi Grup NHA'ya göre istatistiksel olarak anlamlı derecede yüksekti (p=0,0001, p=0,0001, p=0,0001, p=0,0001). Gruplar arasında cinsiyet dağılımında herhangi bir fark yoktu. Grup HA'daki ortalama albümin değerleri Grup NHA'dan istatistiksel olarak anlamlı derecede düşüktü (p=0,0001).

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Conclusion: In conclusion, EHA administration in hypoalbuminemic patients prolong stay in ICU in addition to the increase in the development of AKI and mortality.

Keywords: Acute kidney injury, exogenous human albumin, hypoalbuminemia, intensive care units

Sonuç: Sonuç olarak, hipoalbüminemik hastalarda EHA uygulaması ABH ve mortalitenin artmasına ek olarak YBÜ'de kalış süresini uzatmaktadır.

Anahtar Sözcükler: Akut böbrek hasarı, eksojen human albümin, hipoalbüminemi, yoğun bakım üniteleri

Introduction

The global health problem of acute kidney injury (AKI) affects millions of people each year (1). AKI, a syndrome characterised by rapid disruption of renal functions within hours or days, has multifactorial pathogenesis. A variety of changeable (dehydration, intravascular volume loss, hypotension, anaemia, hypoxia and body mass index) or unchangeable (age, gender, invasive interventions, high-risk surgeries, cancer and comorbidities, such as lung, liver or gastrointestinal pathologies) risk factors are reported in the aetiology (2). AKI develops more often in critically ill patients compared to the general population due to increased risk factors. Early diagnosis of risk factors improves prognosis for critically ill patients (3). Serum albumin concentration of less than 3.5 g/dL, defined as hypoalbuminemia, is an independent risk factor for AKI development (3,4). Albumin comprises 60% of plasma proteins and is multifunctional (5). Albumin is the main determinant of colloid osmotic pressure and is an important extracellular non-enzymatic antioxidant that regulates capillary membrane permeability (5,6). Endogenous albumin has a protective effect on the kidney and is proposed to play a role in the integrity of proximal tubule cells and to maintain functions through a variety of signal transduction pathways (3,7). The protective effect in the kidney is thought to be due to scavenging reactive oxygen fragments, preventing oxidative injury via lysophosphatidic protective acid distribution and binding and reducing nephrotoxicity caused by interleukin-2 (3). Administration of exogenous human albumin (EHA) as colloids is not nephrotoxic, unlike some artificial colloids (3). We did not find any studies regarding the effect of administering EHA to patients developing hypoalbuminemia in the intensive care unit (ICU) on the development or prevention of AKI. The primary aim of our study was to investigate the effect of EHA administration on hypoalbuminemic patients in the ICU on the development of AKI. Our secondary aim was to compare the duration of stay in ICU and mortality rates of these patients.

Methods

This study was a single-centre retrospective study and was completed after receiving approval from Hospital Institutional Ethics Committee (date: 02/10/2018, no: 18/235). A total of 5,989 patients who were followed up at our hospital adult ICU between 01.01.2014-01.06.2018 were included in the study after obtaining the ethics committee approval. Only the first admission of patients with multiple admissions in this period was analysed. This study included all patients above the age of 18 who were monitored for more than 48 hours in the ICU, with initial serum creatinine and serum albumin values recorded. Patients who received EHA after developing AKI were excluded from the study. Additionally, patients with a kidney transplant, known AKI on admission to ICU and chronic renal failure diagnoses were excluded from the study.

Clinical characteristics, demographic data and laboratory data were obtained from the institutional electronic medical records system. The AKI was defined according to AKI network (AKIN) criteria, using only serum creatinine levels. The first serum creatinine level measured upon the admission of the patient to ICU or when an increase in serum creatinine began was accepted as basal creatinine. The second serum creatinine value measured within 48 hours was determined to be the highest creatinine value. If the basal creatinine value increased by more than 2 times, AKIN stage 2-3 patients were accepted as having AKI. Serum albumin was measured in the hospital laboratory using an Architect C 16000 (Abbot/USA) device. Serum albumin value lower than 3.5 g/dL was assessed as hypoalbuminemia (8). Patients who were not administered EHA (Human Albumin 20% CSL Behring, Gmbh, Marburg, Germany) were included in Group none human albumin (NHA), while patients administered EHA comprised Group HA. The development of AKI, duration of stay in ICU and mortality rates were compared between the groups.

Statistical Analysis

In this study, statistical analyses were completed by using NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) program.

Descriptive statistical methods (mean, standard deviation) were used in addition to Independent t-test for comparison of two groups and chi-square test for comparison of qualitative data. Logistic regression analysis was used to determine factors affecting mortality and AKI. Results were assessed at a significance level of $p<0.05$.

Results

A total of 5,989 patients were recorded. Of the 1,672 (27.91%) hypoalbuminemic patients, 1,206 who met our criteria were included in the study. Patients were divided into two groups based on whether EHA replacement was administered. There were 625 patients in group NHA (51.82%) and 581 patients in group HA (48.18%). AKI developed in 167 patients in group NHA and 275 patients in group HA (Figure 1).

The mean age in group HA was statistically significantly higher than group NHA ($p=0.0001$). There was no statistically significant difference observed between the groups regarding gender distribution ($p=0.074$). The AKI development and mortality rates

in group HA were statistically significantly higher than group NHA (p=0.0001). The mean albumin value in group HA was statistically significantly lower than group NHA (p=0.0001). The mean duration of stay in group HA was statistically significantly higher than group NHA (p=0.0001) (Table 1).

The mean age, AKI development rate, EHA administration and number of days in ICU were statistically significantly higher in patients with mortality compared to surviving patients (p=0.0001). The albumine value in mortal patients was statistically significantly lower than surviving patients (p=0.0001). There was no statistically significant difference observed in the gender distribution of surviving and mortal patients (p=0.326) (Table 2).

Logistic regression analysis was performed to determine factors affecting mortality among age, AKI presence, number of days in ICU and EHA use. Advanced age (p=0.0001), AKI development (p=0.0001) and EHA administration (p=0.0001) were determined as factors affecting mortality. The number of days in ICU was not determined to affect mortality (Table 3).

Mean age, EHA administration, mortality and days of stay in ICU were statistically significantly higher in patients developing AKI compared to patients not developing AKI (p=0.0001). There was no statistically significant difference observed in terms of gender distribution between patients with and without AKI (p=0.690) (Table 4).

Logistic regression analysis was performed to determine the factors such as age, EHA administration and days of stay in ICU, affecting AKI development. Advanced age (p=0.0001) and EHA administration (p=0.0001) were determined to be factors affecting AKI development (Table 5).

Discussion

According to the results of our study, advanced age and EHA application in hypoalbuminemic patients were determined as important factors effective in the development of AKI. At the same time, EHA application and advanced age were among

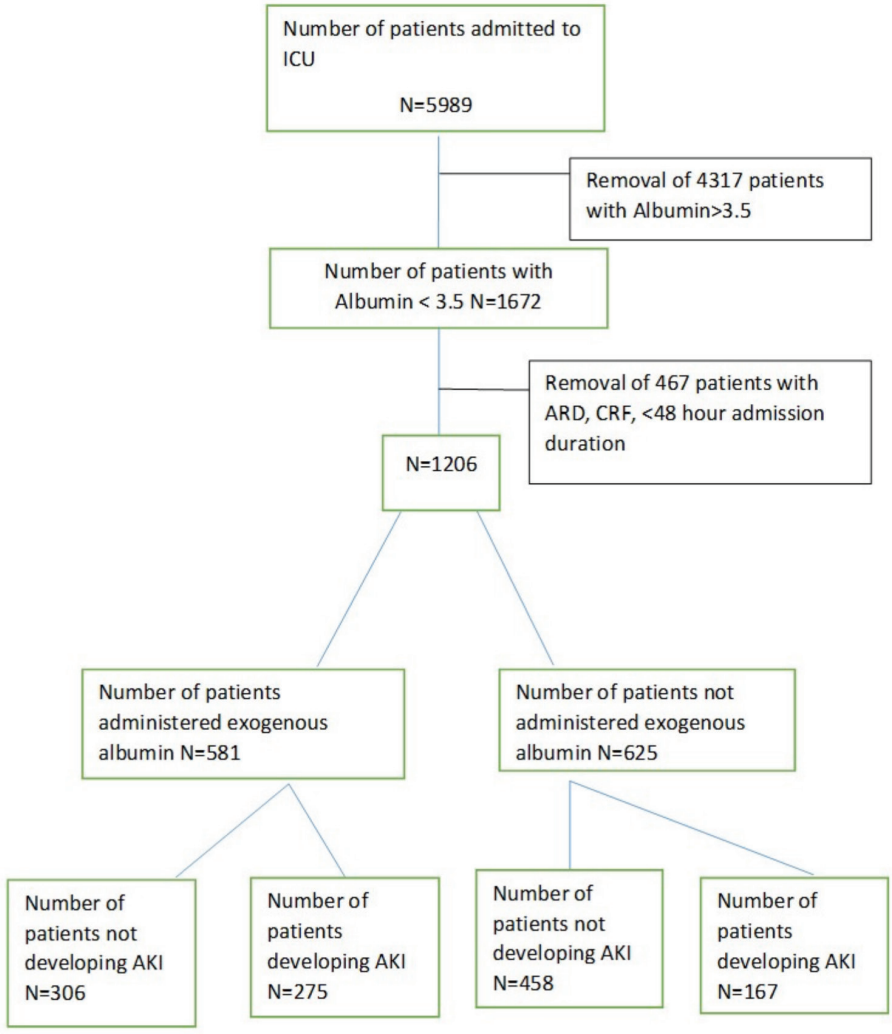

Figure 1. Patient selection algoritm

ICU: Intensive care unit, ARD: Acute renal disease, CRF: Chronic renal failure, AKI: Acute kidney injury

Table 1. Age, gender, AKI development rates, serum albumin values, mortality and number of days admission in the groups

Variables		Group NHA n=625		Group HA n=581		p
Age		59.7±19.95		65.95±17.19		**0.0001***
Gender	**Female**	289	46.24%	239	41.14%	0.074+
	Male	336	53.76%	342	58.86%	
AKI	**No**	458	73.28%	306	52.67%	**0.0001+**
	Yes	167	26.72%	275	47.33%	
Serum albumin value		2.75±0.52		2.36±0.63		**0.0001***
Mortality	**No**	485	77.60%	220	37.87%	**0.0001+**
	Yes	140	22.40%	361	62.13%	
Days of admission		7.54±5.98		14.4±13.43		**0.0001***

*Independent t-test, +Chi-square test
AKI: Acute kidney injury, p<0.05, NHA: None human albumin, HA: Human albumin

Table 2. Mean ages, AKI development rate, exogenous human albumin administration and number of days in ICU of surviving and mortal patients

Variables		Surviving patients n=705		Dead patiens n=501		p
Age		59.6±19.93		67.1±16.47		**0.0001***
Gender	**Female**	317	44.96%	211	42.12%	0.326+
	Male	388	55.04%	290	57.88%	
AKI	**No**	555	78.72%	209	41.72%	**0.0001+**
	Yes	150	21.28%	292	58.28%	
Serum albumin value		2.69±0.55		2.39±0.64		**0.0001***
Exogenous human albumin administration	**No**	485	68.79%	140	27.94%	**0.0001+**
	Yes	220	31.21%	361	72.06%	
Days of admission		10±11.25		12.03±10.08		**0.001***

*Independent t-test, +Chi-square test
AKI: Acute kidney injury, p<0.05, ICU: Intensive care unit

Table 3. Logistic regression analysis to determine the factors affecting mortality

Factors	p	OR	95.0% CI for OR	
			Lower limit	Upper limit
Age	**0.0001***	1.02	1.01	1.02
AKI development	**0.0001***	0.23	0.17	0.30
Days of admission	0.170	0.99	0.98	1.00
Exogenous human albumin administration	**0.0001***	0.20	0.15	0.26

AKI: Acute kidney injury
*p<0.05, CI: Confidence interval, OR: Odss ratio

the factors affecting mortality, along with the duration of hospitalization in ICU. Hypoalbuminemia incidence among patients admitted to ICU is reported as 21% (3). We found this rate to be 27.91%. Hypoalbuminemia alone is an independent risk factor for mortality (5). The literature notes a strong link between developing morbidity and mortality and serum albumin in patients with underlying acute and chronic disease (3). Each 1 g/dL reduction in serum albumin concentration is reported to increase AKI rates by 137% and mortality rates by 147% and lengthen stay in ICU by 28% (4,9). Findik et al. (10) reported that patients with low preoperative serum albumin had higher renal replacement treatment requirements and mortality.

In our study, Group HA with low serum albumin levels had higher mortality and longer stay in ICU, in accordance with the literature.

Serum albumin level is known to decrease with age (11). The mean serum albumin value in Group NHA was 2.75±0.52,

Table 4. Mean ages, gender, exogenous human albumin administration, mortality and number of days in ICU of patients with and without AKI

Variables		AKI (-) n=763		AKI (+) n=167		p
Age		60.34±19.67		66.74±16.79		**0.0001***
Gender	**Female**	338	44.24%	190	43.00%	0.690+
	Male	426	55.76%	252	57.00%	
Exogenous human albumin administration	**No**	458	59.94%	167	37.80%	**0.0001+**
	Yes	306	40.06%	275	62.20%	
Mortality	**No**	555	72.64%	150	33.90%	**0.0001+**
	Yes	209	27.36%	292	66.10%	
Days of admission		10.32±9.55		11.74±12.68		**0.028***

*Independent t-test, +Chi-square test
AKI: Acute kidney injury, p<0.05, ICU: Intensive care unit

while it was 2.36±0.63 in Group HA with a higher mean age. We found that this small mathematical difference increased mortality by a significant rate and lengthened ICU admission at a significant rate. This situation may be explained as advanced age causing hypoalbuminemia and increased comorbidities that increase mortality in critically ill patients (3,5). Additionally, we think it will be beneficial to conduct prospective comparative studies on patients with different albumin values.

The EHA has been used as a therapeutic agent in ICUs for more than 50 years. However, harmful effects were reported in the 1990s, and its use began to be debated (4). The main use of EHA is the field of hepatology. The most controversial results related to EHA replacement treatment were obtained in patients with liver failure and renal function disorder. It was reported that EHA use should be limited to high-risk patients based on obtained data (12). Schortgen et al. (13) reported negative effects of hyperoncotic albumin use on the kidneys in critically ill patients and an increased risk of death. However, Lee et al. (14) reported that 20% EHA replacement treatment before coronary artery bypass surgery in patients with albumin levels lower than 4.0 g/dL increased urine output during surgery and reduced the risk of AKI development. Yu et al. (15) reported EHA administration might contribute to renal amelioration after AKI developed. In the current study, we found that AKI developed at higher rates in group HA. In our logistic regression analysis to determine factors affecting AKI development, we determined administration of EHA in addition to advanced age were risk factors for the development of AKI.

Tablo 5. Logistic regression analysis to determine the factors affecting AKI development

Factors	p	OR	95.0% CI for OR	
			Lower limit	Upper limit
Age	**0.0001***	1.02	1.01	1.03
Exogenous human albumin administration	**0.0001***	0.47	0.35	0.64
Days of admission	0.699	1.00	0.98	1.01

*p<0.05, CI: Confidence interval, OR: Odds ratio, AKI: Acute kidney injury

In elderly kidneys, structural and physiological changes, such as loss of nephron mass, vascular and glomerular tubular degeneration at the microscopic level, reduced glomerular filtration rates and a tendency toward cellular apoptosis may be observed. These physiological changes in renal functions may explain the tendency toward AKI development among elderly patients (16). Male gender is a known risk factor for AKI development (2). However, we found no difference regarding gender among factors affecting AKI development, contrary to the literature. Mortality was higher, and stay in ICU was longer among patients developing AKI.

A variety of studies researching the correlation between EHA administration and mortality have been carried out (17-20). Patel et al. (17) reported that the use of EHA as a part of severe volume resuscitation in sepsis, whether hypoalbuminemia was present or not, might be ineffective in reducing mortality. Additionally, Caironi et al. (18) reported that EHA replacement ameliorated hypoalbuminemia in sepsis but did not improve outcomes. Another study found there was no evidence that EHA administration reduced mortality in critically ill patients compared to cheaper alternatives like saline for patients with hypovolemia in addition to hypoalbuminemia; however, they suggested that EHA might be indicated in a selected critically ill patient population (19). Offringa et al. (20) reported that mortality was higher in critically ill patients given EHA. Our results agree with the literature. Our logistic regression analysis found that advanced age, AKI presence and EHA administration were among factors affecting mortality, while mortality was not affected by the length of stay in ICU.

Some authors have emphasised the need for additional strengthened controlled-randomised studies to further explain the underlying physiological and molecular reasoning (11,20).

Study Limitations

The main points in this study were that, albumin administration did not affect prognosis and might have side effects that would limit its administration and cost benefits. Our study had some limitations, such as being retrospective, including a heterogenous patient group and not being able to research and diagnose accompanying pathologies that might affect the process in

patients. Additionally, another limitation was that we could not identify data related to the dose, frequency and duration of EHA administration.

Conclusion

In conclusion, although we found that EHA administration in hypoalbuminemic patients increased AKI development, mortality and lengthened stay in ICU. The main points in this study were that, albumin administration did not affect prognosis and might have side effects that would limit its administration and cost benefits. We believe that there is a need for prospective randomised controlled studies researching the effects of EHA replacement treatment on AKI.

Ethics

Ethics Committee Approval: This study was a single-centre retrospective study and was completed after receiving approval from Hospital Institutional Ethics Committee (date: 02/10/2018, no: 18/235).

Informed Consent: Retrospective study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: M.T., Design: H.D., M.T., Data Collection or Processing: S.Y., C.G., İ.S., H.U., H.D., M.T., K.K., Analysis or Interpretation: S.Y., C.G., İ.S., H.U., H.D., M.T., K.K., Literature Search: S.Y., H.D., M.T., Writing: S.Y., M.T., K.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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