A Randomized Trial of Albumin Infusion to Prevent Intradialytic Hypotension in Hypoalbuminemic Patients

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Abstract

Background: Intradialytic hypotension (IDH) is a frequent complication of intermittent hemodialysis (IHD), occurring from 15 to 50% of ambulatory sessions, and is more frequent among hospitalized patients with hypoalbuminemia [1]. IDH limits adequate fluid removal and increases the risk for vascular access thrombosis, early hemodialysis (HD) termination, and mortality. Albumin infusion before and during therapy has been used for treating IDH with varying results. We evaluated the efficacy of albumin infusion in preventing IDH during IHD in hypoalbuminemic inpatients.

Methods: A randomized, crossover trial was performed in 65 AKI or ESRD patients with hypoalbuminemia (albumin<3g/dl) who required HD during hospitalization. Patients were randomized to receive 100ml of either 0.9%sodium chloride or 25% albumin intravenously at the initiation of each dialysis. These two solutions were alternated for up to 6 sessions. Patients' vital signs and ultrafiltration removal rate were recorded every 15 to 30 minutes during dialysis. IDH was assessed by different definitions reported in the literature. All symptoms associated with a noted hypotensive event as well as interventions during the dialysis were recorded.

Results: 65 patients were submitted to 249 sessions; mean age was 58 (+/-12), 46 (70%) were male with a mean weight of 76 (+/-18) kg. Presence of IDH was lower during albumin sessions based on all definitions. The risk of hypotension was significantly decreased based on the Kidney Disease Outcomes Quality Initiative (KDOQI) definition; (15% with NS vs. 7% with albumin, p=0.002). Lowest intradialytic SBP was significantly worse in patients that received 0.9% sodium chloride in comparison to albumin (NS 83 vs. Albumin 90 mmHg,p = 0.035). Overall ultrafiltration rate was significantly higher in the albumin therapies (NS -8.25 ml/kg/h (-11.18 -5.80) vs. 8.27ml/kg/h (-12.22 - 5.53) with albumin, p =0.011).

Conclusion: In hypoalbuminemic patients who need HD, administration of albumin before dialysis results in fewer episodes of hypotension and improves fluid removal. Albumin infusion may be of benefit to improve safety of HD and achievement of fluid balance in these high-risk patients.

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Introduction

Despite the use of diuretics, fluid overload (> 10% change in body weight from admission) is commonly encountered in hospitalized patients. The amount and duration of fluid overload is a major independent risk factor for adverse outcomes including mortality, reduced renal recovery, and resource utilization2-6. Avoidance of fluid accumulation and early mobilization of fluid are now the main therapeutic goals for these patients and often portend a need for dialysis initiation. Unfortunately, fluid mobilization and removal with intermittent hemodialysis (IHD) are often difficult, particularly in patients with severe AKI/ESRD and multi-organ failure due to the development of intradialytic hypotension (IDH). IDH

complicates 17–70% of acute hemodialysis (HD) sessions in the ICU 7–11, and in as much as 50% in the inpatient setting12. It decreases the efficacy of renal replacement therapy, delays function recovery, and organ failures reversal 13,14. During ultrafiltration, the plasma-refilling rate is dependent on colloid osmotic pressure and consequently, volume expanders, including mannitol, albumin, hypertonic and 0.9% sodium chloride, dextran and hydroxyethyl starch have been used in the management of IDH in chronic outpatient HD with varying results. In hypoalbumenic patients, infusion of albumin would be expected to increase colloid osmotic pressure and thus enhance plasma refilling to improve fluid mobilization and reduce IDH. In this study, we evaluated the efficacy of albumin infusion in preventing intradialytic hypotension during HD in hospitalized patients. We hypothesized that the concurrent use of intravenous albumin during dialysis would result in higher quantities of fluid removal per unit time and would be associated with a reduced incidence of IDH.

Methods

In this prospective randomized controlled trial, we enrolled hospitalized adult patients (> 18 ys) with AKI, AKI on CKD, and ESRD who required fluid removal with dialysis and had a serum albumin level < 3 g/dl at initiation of dialysis. Patients with a renal transplant and those not expected to be on dialysis for more than 24 hrs were excluded. The study was a crossover design where standard care dialysis was supplemented with the addition of a single dose of 25 g albumin (100 ml of Grifols 25%) or 100 ml of 0.9% sodium chloride (normal saline (NS)) given intravenously at the start of IHD. Patients were randomized to start dialysis with albumin or 0.9% sodium chloride and subsequently alternated with the other solution for a maximum of 6 sessions for each patient. Vital signs and ultrafiltration removal rate were recorded every 15 to 30 minutes during dialysis. The dialysis nurse recorded in a standartized case report form, all symptoms associated with hypotension as well as interventions during the dialysis. We utilized 7 different classifications to determine hypotensive episodes (Table 1). Hypotension was defined based on lowest systolic blood pressure, changes in systolic blood pressure, symptoms, and need for intervention during each dialysis session to determine whether the subject experienced any hypotensive episodes during the dialysis session.

Table 1
– Intradialytic hypotension definition and frequency.

Term	Definition	Overall	NS	Albumin	p
Nadir90	Min IHD SBP < 90 mmHg	53 (21.3%)	31 (24.8%)	22 (17.7%)	0.093
Nadir100	Min IHD SBP < 100 mmHg	111 (44.6%)	56 (44.8%)	55 (44.4%)	0.926
Fall20	Pre-HD SBP-min IHD ≥ 20	103 (41.9%)	59 (48.0%)	44 (35.8%)	0.026
Fall30	Pre-HD SBP-min IHD ≥ 30	69 (28.0%)	40 (32.5%)	29 (23.6%)	0.041
Fall20Nadir90	Pre-HD SBP-min IHD ≥ 20 and min IHD SBP < 90	18 (7.3%)	14 (11.4%)	4 (3.3%)	0.016
Fall30Nadir90	Pre-HD SBP-min IHD ≥ 30 and min IHD SBP < 90	12 (4.9%)	9 (7.3%)	3 (2.4%)	0.099
KDOQI	Pre-HD SBP-min IHD ≥ 20 and symptoms of cramping, headache, lightheadedness, vomiting, or chest pain during HD	28 (11.4%)	19 (15.4%)	9 (7.3%)	0.002
HEMO	Fall in SBP resulting in intervention of UF reduction, blood flow reduction, or 0.9% sodium chloride administration	42 (16.9%)	26 (20.8%)	16 (12.9%)	0.072
Hypotension epsisodes	Episodes of Hypotension recorded by the nurse	81 (32.5%)	42 (33.6%)	39 (31.5%)	0.718

Numbers as frequency and percentage.

IHD: intradialytic hypotension; SBP: systolic blood pressure; UF: ultrafiltration; KDOQI: Kidney Disease Outcomes Quality Initiative; HEMO: Hemodialysis Study.

Dialysis Procedures

Standard IHD was prescribed according to the prevailing standard of care according to the nephrology attending physician, with the exception of albumin or 0.9% sodium chloride infusion before the initiation of the procedure. Dialysis prescriptions were individualized for each patient (blood and dialysate flow rates, dialysate composition) to achieve a minimum urea reduction ratio of 65% and achieve target dry weights. Ultrafiltration (UF) rates per hour were determined by the attending nephrologist to achieve desired fluid balance for each session. Standard unit protocols were followed for managing symptoms and hypotension in each session (UF changes, 0.9% sodium chloride boluses, Trendelenburg position, dialysate temperature adjustments).

Outcomes

The study considered co-primary outcomes of efficacy and safety. The efficacy outcome was the achieved fluid removal expressed as ml/kg/hour. The safety outcome included the number and duration of cardiovascular complications, including hypotensive episodes with or without symptoms; symptoms alone without hypotension (nausea, headache, vomiting, altered sensorium, fatigue) and arrhythmias. Secondary outcomes included urea reduction ratios and Kt/V per session, time to correct fluid overload and volume of 0.9% sodium chloride administered during therapy.

Statistical Analysis

Continuous variables and categorical variables were reported as mean (SD) and count (percentage). Generalized estimating equations (GEE) was used to compare the effect of albumin and 0.9% sodium chloride on IHD parameters. We compared the presence of hypotension based on various definitions in Table 1. We used the presence of symptomatic hypotension recorded by nurse as our gold standard for hypotension. Urea reduction ratios (URR) value was calculated based on pre and post blood urea nitrogen value. Kt/V values were recorded from the dialysis machine. GEE was used to compare the effect of the solution on URR and Kt/V. For all of the analysis, an exchangeable working correlation was used for the generalized estimating equation.

Results

Of 65 patients enrolled in the study, 47 (72%) were AKI patients. The baseline demographic characteristics of the participants are shown in Table 2. A total of 249 sessions from 65 patients were recorded, 51 (78%) patients completed at least one session each with albumin and 0.9% sodium chloride, and 24 (36%) completed 6 sessions (3 albumin and 3 0.9% sodium chloride). Mean systolic blood pressure (SBP) and diastolic (DBP) at dialysis initiation were 126 (+/- 25) and 67.38 (+/- 17), respectively. There was no difference in the prescribed or delivered time in sessions with albumin and 0.9% sodium chloride (Table 3). Ultrafiltration rate expressed by ml/kg/hour was significantly higher in albumin sessions ($p = 0.011$).

Table 2
Patient demographics, location and number of sessions on AKI and ESKD patients.

	AKI	*ESKD*	*Overall*
Gender	*n* = 55	*n* = 10	*n* = 65
Female	15 (27.3%)	4 (40.0%)	19 (29.2%)
Male	40 (72.7%)	6 (60.0%)	46 (70.8%)
Age	*n* = 55	*n* = 10	*n* = 65
Weight	58.42 (12.71)	56.30 (8.51)	58.09 (12.13)
Height	*n* = 55	*n* = 10	*n* = 65
Race	75.89 (17.44)	81.60 (24.37)	76.77 (18.56)
African Descent	*n* = 45	*n* = 10	*n* = 55
	171.52 (11.04)	168.90 (9.84)	171.05 (10.79)
	n = 55	*n* = 10	*n* = 65
	4 (7.3%)	1 (10.0%)	5 (7.7%)
Asian	3 (5.5%)	0 (0.0%)	3 (4.6%)
Caucasian	18 (32.7%)	5 (50.0%)	23 (35.4%)
Hispanic	22 (40.0%)	2 (20.0%)	24 (36.9%)
Number of Sessions completed	12 (21.8%)	2 (20.0%)	14 (21.5%)
1			
2	8 (14.5%)	0 (0.0%)	8 (12.3%)
3	7 (12.7%)	2 (20.0%)	9 (13.8%)
4	4 (7.3%)	0 (0.0%)	4 (6.2%)
5	4 (7.3%)	2 (20.0%)	6 (9.2%)
6	20 (36.4%)	4 (40.0%)	24 (36.9%)
Hemodialysis location			
Floor	*n* = 206	*n* = 43	*n* = 249
	177 (85.9%)	38 (88.4%)	215 (86.3%)

AKI: acute kidney injury; ESKD: end stage kidney disease; ICU: intensive care unit.

	AKI	*ESKD*	*Overall*
ICU	29 (14.1%)	5 (11.6%)	34 (13.7%)
Serum albumin at dialysis initiation	*n* = 75	*n* = 23	*n* = 98
	2.68 (0.35)	2.72 (0.30)	2.69 (0.34)
AKI: acute kidney injury; ESKD: end stage kidney disease; ICU: intensive care unit.			

Table 3
Hypotension related parameters among sessions with at least oneepisode of hypotension recorded by nurse.

	Overall	**Albumin**	**Normal Saline**	**p-value**
Initial SBP (mmHg)	107 (21)	105 (18)	109 (23)	0.789
Lowest SBP (mmHg)	87 (14)	90 (15)	83 (12)	0.035
Time to First Episode (min)	57 (65)	53 (65.44)	61 (66)	0.341
Number of Episodes with need for discontinuing UF during the session				
0	47 (58.0%)	27 (69.2%)	20 (47.6%)	< 0.001
1	30 (37.0%)	12 (30.8%)	18 (42.9%)	
2	2 (2.5%)	0 (0.0%)	2 (4.8%)	
3	2 (2.5%)	0 (0.0%)	2 (4.8%)	
Total time with UF discontinued during session (ml)	28 (50)	20 (47)	35 (52)	0.018
Total NS infused during session (ml)	N = 22	N = 9	N = 13	1.00
	177 (75)	166 (86)	184 (68)	
Data are n (%), or mean (SD). SBP: systolic blood pressure; UF: ultrafiltration; NS: normal saline (0.9% sodium chloride). P values are based on GEE analysis.				

Presence of a hypotensive episode during a session of HD varied from 12 (4.9%) to 111 (44%) according to the definition of IDH applied (Table 1). There was varying recognition by the dialysis nurse of hypotensive episodes and subsequent interventions. The Nadir < 100, Fall 20 and Fall 30 definitions based on changes in SBP were encountered 45%, 43% and 28% of the time respectively, however, were recorded 64%, 25% and 24% of the time by the nurse and intervention occurred in 32%, 17%, and 14%. The Hemodialysis Study (HEMO) definition, considering hypotension when an intervention results from an unspecific fall in BP occurred 33% more frequently than the KDOQI definition. Of the sessions with an

absolute intradialytic nadir of SBP < 90 mmHg, 23 (43%) were not followed by any intervention. Symptomatic hypotension, the KDOQI definition, was infrequently encountered and was intervened on 64% and recorded almost always when occurred, in 92% of the cases.

Infusion of albumin at initiation of therapy was significantly associated with less hypotensive episodes defined by SBP decline of 20 mmHg (p = 0.026), 30 mmHg (p = 0.041), the composite definition of decline of 20 mmHg in SBP and minimal SBP of 90 mmHg (p = 0.016), and based on KDOQI definition (p = 0.002).

We used the presence of symptomatic hypotension, recorded by the dialysis nurse, as our gold standard for hypotension. It occurred in 35 patients during 85 dialysis sessions (Table 3). Meantime to the first hypotensive episode was 57 min. Lowest systolic blood pressure was significantly lower in 0.9% sodium chloride sessions; NS 83 vs. albumin 90 mmHg, p < 0.035. Most episodes were not severe enough to require discontinuation of ultrafiltration, however, UF was more frequently discontinued during NS sessions v. albumin and the total duration for which UF was on hold during HD was significantly higher in NS sessions v. albumin (Table 4 or Fig. 1). When 0.9% sodium chloride infusion was necessary to reverse hypotension, the mean volume administered was 177 ml, with no difference between volume given during albumin or 0.9% sodium chloride sessions (Table 4).

Table 4
– Prescribed and delivered fluid removal parameters in 0.9% sodium chloride and albumin sessions.

	Overall	Normal Saline	Albumin	P*
Total Prescribed UF (mL)	-2000 (-2500-1500)	-2000 (-2500 -1500)	-2000(-2500-1500)	0.105
Total Delivered UF (mL)	-2500 (-3000 -1700)	-2500 (-3000 -1700)	-2500 (-3100 -1675)	0.156
Prescribed Time (hour)	3.50 (3.50–3.50)	3.50 (3.50–3.50)	3.50 (3.50–3.50)	0.272
Delivered Time (hour)	3.50 (3.50–3.50)	3.50 (3.50–3.50)	3.50 (3.50–3.50)	0.692
Delta Weight kg (start - stop)	2.00 (1.00–2.50)	2.00 (1.00–2.43)	2.00 (1.00–2.50)	0.222
Prescribed Removal Rate (ml/kg/h)	-7.24 (-9.13 -5.19)	-7.24 (-9.00–5.18)	-7.13 (-9.28–5.24)	0.1
Delivered Removal Rate (ml/kg/h)	-8.26 (-11.32–5.65)	-8.25 (-11.18 -5.80)	-8.27 (-12.22–5.53)	0.011
Data are median (IQR).				
*Generalized estimating equations was used to analyze the effect of albumin on hypotension outcome.				
UF: ultrafiltration.				

There was no significant difference in the efficacy related outcomes within 0.9% sodium chloride and albumin sessions. The urea reduction rate was similar in NS and albumin sessions; NS 69.23 ± 8.36 vs. albumin 69.60 ± 8.58; P = 0.67. Dialysis dose based on Kt/V was also not different; (NS 2.05 ± 8.45 vs. albumin 1.29 ± 0.38; p = 0.34). Total UF and removal rate were lower in patients with IDH episodes (Table 5).

Table 5
– Prescribed and delivered ultrafiltration volumes and rates in sessions with and without hypotension detected by nurse.

	Overall N = 241	With hypotension N = 81	No hypotension N = 162	p-value*
Total Prescribed UF (mL)	-2004 (728)	-1805 (680)	-2102 (732)	0.051
Total Delivered UF (mL)	-2365 (971)	-1947 (844)	-2566 (966)	< 0.001
Prescribed Removal Rate	-7.42 (3.17)	-6.65 (3.07)	-7.81 (3.15)	0.224
Delivered Removal Rate ml/kg/h	-8.85 (4.43)	-7.33 (3.92)	-9.62 (4.49)	0.008
Data are mean (SD). UF: ultrafiltration				
*Generalized estimating equations was used to analyze the effect of albumin on hypotension outcome.				

Discussion

Fluid accumulation is common in hospitalized patients, particularly those in the ICU and is attributed to the need for resuscitation and hemodynamic stabilization. It is now recognized that the duration and degree of fluid overload contribute to the risk of adverse outcomes and correction of fluid overload can reduce this risk. Dialysis is often utilized to remove fluids and restore homeostasis; however, fluid mobilization is often limited by the development of IDH. Several different definitions continue to be used in the literature and clinical practice, preventing the appreciation of the effects of IDH and patient outcomes. Our study confirms the varying frequency of IDH, ranging from 4.9–44% of the dialysis sessions depending on the definition applied and reflects the vast variation in which recognition of hypotension and interventions to correct it occur. Recently, a large epidemiologic study has shown that an absolute nadir of SBP < 90 mmHg was the most potently associated with mortality [15]. In our study, we found that of the sessions with an absolute intradialytic nadir of SBP < 90 mmHg, 30 (56%) were not followed by any intervention.

The pathogenesis of IDH includes a multitude of factors related to the dialysis prescription, process of care, such as sedation, patient comorbidities, and severity of illness. During the therapy of ultrafiltration, plasma volume decreases and oncotic pressure rises [16]. Plasma refilling, which is the shift of fluid from the interstitial and intracellular compartments to the intravascular compartment, is favored by the

resulting rise in oncotic pressure. When the ultrafiltration rate surpasses refilling rate, reduction in pre-load induces a fall in stroke volume that predisposes to hemodynamic instability [17,18,19–22].

While interventions to prevent IDH have been extensively studied in chronic HD, few studies have evaluated the role of albumin infusions and treating hypotension. A previous protocol in patients at inpatient dialysis units and ICU settings the use of NS, mannitol, and albumin were compared in a stepwise approach for intradialytic hypotension treatment. [23]. However, with this protocol, albumin was administered in only 6% of the 2,559 HD treatments as most hypotensive episodes were reversed with NS. The protocol was designed to evaluate cases of established IDH, and final ultrafiltration volume achieved was not an outcome. In a randomized clinical trial, Jardin et al. [24] showed that albumin infusions given at the start of dialysis resulted in greater ultrafiltration and hemodynamic stability for patients with sepsis-induced acute renal failure. A systematic review on IV albumin for IDH in chronic HD patients yielded a single study, which showed that the frequency of IDH was similar between 0.9% sodium chloride and 5% albumin[25,26]. It is important to mention that the studies mentioned above did not evaluate hypoalbuminemic patients separately with mean albumin levels of 3.8 g/dL.

In our study, the patient population consisted of only hypoalbumenic patients and mostly with AKI. We found that albumin infusions reduced IDH events across multiple definitions. Based on the Fall20Nadir90 definition, a patient receiving albumin at the beginning of the dialysis session is 74.2% less likely to experience a hypotensive event. Additionally, in albumin sessions, UF was discontinued less frequently, less NS was required to restore SBP, and the time off UF was almost half of the NS sessions. The reduction in IDH episodes was accompanied by an increase in fluid removal rates to achieve the target weight.

Our study characterizes the variation in recognition of and interventions applied to manage IDH in hospitalized hypoalbuminemic patients undergoing standard of care dialysis. We provide a pragmatic approach for reducing the inherent risk for IDH with albumin infusions administered at the start of dialysis without any changes in the dialysis prescription. In comparison to previously published studies, we show that fluid removal can be enhanced and efficacy parameter met with albumin infusions. These procedures are simple to apply and are applicable for general adaptation. Our study is limited to being a single-center study and a crossover design with albumin levels measured only at the initial dialysis session. Our results could be influenced by changes in albumin levels during the hospitalization course and subsequent dialysis sessions following the albumin replacement. However, our data provide support for further evaluations as has been proposed for a new study evaluating albumin infusions for slow low-efficiency dialysis [27].

Conclusion

In hypoalbuminemic patients who need IHD, administration of albumin before dialysis results in fewer episodes of hypotension and improves fluid removal rates. Albumin infusions may be of benefit to improve the safety and efficacy of HD in these high-risk patients.

Declarations

Ethical Approval and Consent to participate

All patients signed consent to participate in the study according to University of California San Diego Human Research Protections Program

Consent for publication

We hava consent from all parts to publish the results of this study

Availability of data and materials

Main data will be made available

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Authors' contributions

RM designed the study and was a major contributor in writing the manuscript. EM, BK and RM analyzed and interpreted the patient data. EL performed the statistical analysis. All authors read and approved the final manuscript.

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Figures

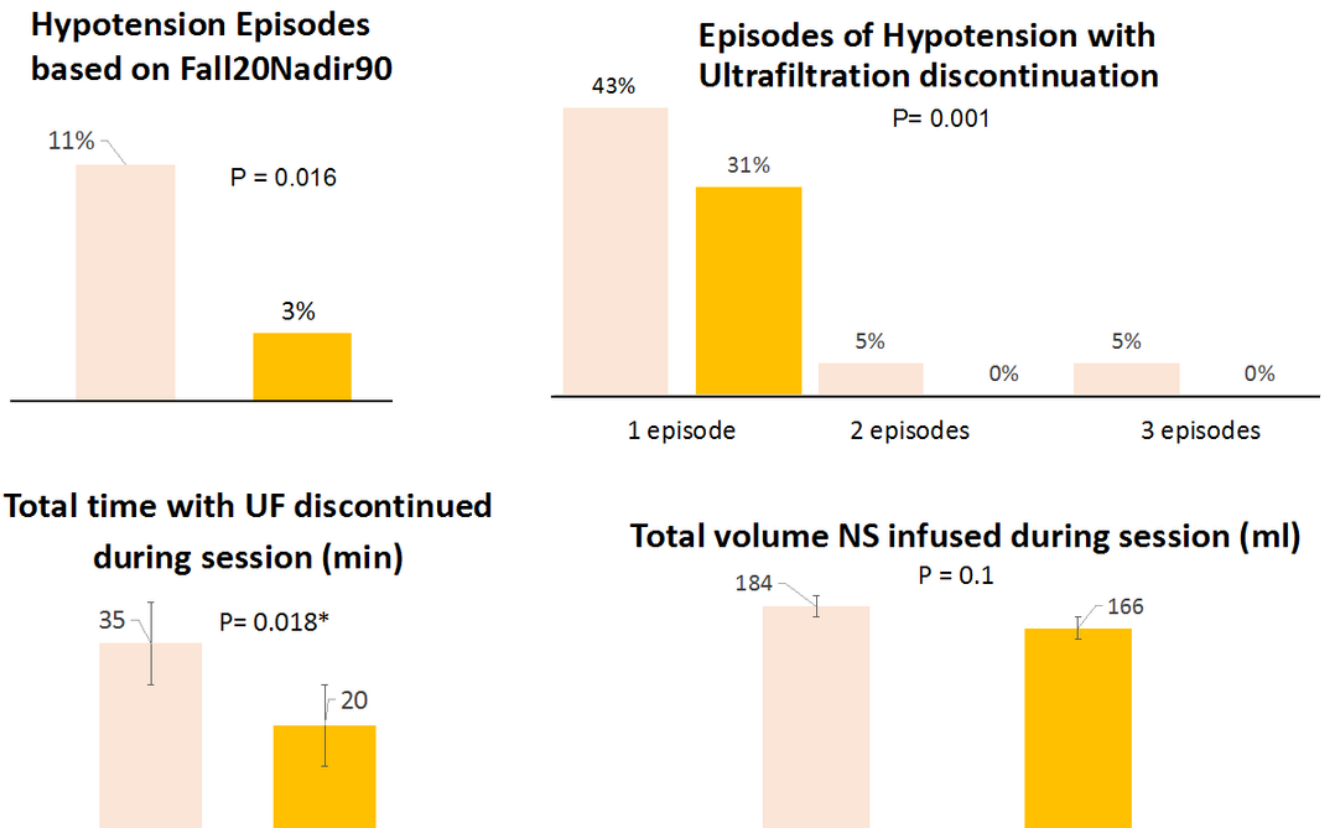

Figure 1

Frequency of complication associated with intradialytic hypotension in albumin and 0.9% sodium chloride sessions. Data are n (%), or mean (SD). SBP: systolic blood pressure; UF: ultrafiltration; NS: normal saline (0.9% sodium chloride). P values are based on GEE analysis.