

Effect of Intravenous Fluids on Blood Pressure Course during Hemodialysis in Hypotensive-Prone Patients

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Abstract. Hypertonic and hyperoncotic solutions are generally used as acute treatment for symptomatic hypotension during dialysis. Administration of hydroxyethylstarch (HES) was recently shown to be an effective substitution fluid in preserving blood volume (BV) and systolic BP (SBP) in a group of stable dialysis patients during dialysis. In this study, in nine cardiac-compromised dialysis patients with frequent symptomatic hypotensive episodes, the efficacy of three fluids (hypertonic saline [3%], albumin [20%], and HES [10%]) was assessed during three treatment sessions with combined ultrafiltration and hemodialysis, which only differed in the type of fluid administered intravenously. Changes in SBP and relative BV were compared. Fluids were given when SBP was less than 100 mmHg or when the decrease in SBP was more than 25 mmHg *versus* the start of the treatment. The ultrafiltration was continued at the same rate. When comparing SBP at the end of the dialysis session ($t = \text{end}$) with that at the time of infusion

($t = \text{iv}$), SBP decreased with saline, increased with albumin, and increased significantly with HES. The change in SBP in $t = \text{end}$ *versus* $t = \text{iv}$ was significantly greater when using saline compared with HES, and tended to decrease more when using saline compared with albumin ($P = 0.09$). Between albumin and HES there were no significant differences. BV decreased significantly ($t = \text{end}$) *versus* baseline ($t = 0$) during ultrafiltration and hemodialysis in all three treatment sessions. The decrease was significantly higher when using saline compared with albumin and saline compared with HES. Between albumin and HES there were no significant differences. When the values at $t = \text{end}$ were compared with those at $t = \text{iv}$, BV decreased, although not significantly, with saline and albumin, but remained unchanged with HES. It is concluded that HES is an effective fluid in maintaining SBP and preserving BV in hypotensive-prone dialysis patients, comparable to albumin but superior to hypertonic saline.

Despite the growing understanding of the pathophysiologic mechanisms that contribute to hemodynamic instability during hemodialysis (HD), HD-associated hypotension still remains one of the most cumbersome complications in dialysis therapy (1).

Hypotension during dialysis may induce minor but troublesome side effects in the patient, such as nausea, vomiting, and dizziness, but may also lead to more serious complications, such as cardiac or cerebral ischemia. There are dialysis patients who hardly suffer from hypotensive episodes. However, HD-associated hypotension is especially frequent in elderly people and in those patients with a compromised cardiovascular system (2–8). Particularly in the latter group, hypotension may have serious consequences.

The immediate cause of the decrease in BP during HD is intravascular hypovolemia, which is related to the dialysis procedure itself. It has been shown that preventing the reduc-

tion in osmolality during HD could improve hemodynamic stability (9). Limiting the reduction in extracellular osmolality can be done by injecting hypertonic fluids such as hypertonic saline (10). However, because of the side effects of hypertonic saline (thirst, interdialytic weight gain, and hypertension, which could be of great clinical importance in cardiac-compromised patients), this fluid is not without drawbacks. Volume expansion can also be performed by hyperoncotic infusions, such as dextran and mannitol (10). However, because of their side effects, these fluids are of limited clinical importance (11–18). An intravenous infusion of albumin, an expensive and widely used fluid, or other hyperoncotic fluids could enhance further vascular refilling and could improve hemodynamic stability (19). Recent data raise questions about the safety of albumin infusions: It was reported that there was an increased risk of death in patients treated with albumin as a result of hypovolemia (20). Furthermore, data on the effect of both hypertonic saline and albumin on the systolic BP (SBP) course in cardiac-compromised dialysis patients with frequent hypotensive periods are scarce. In a previous study, we compared the efficacy of isotonic saline, hyperoncotic albumin, and hydroxyethylstarch (HES) on blood volume (BV) and BP during HD combined with ultrafiltration (UF) in patients without hypotensive episodes (21). We showed that BV was better preserved when using HES and albumin compared with saline, whereas BP tended to decrease more with saline compared

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with HES and albumin. HES is a relatively inexpensive synthetic colloid, which has, because of its physicochemical qualities, a long-standing volume effect, and in our previous study only 100 ml of HES had a distinct effect on the preservation of BV and, as a result, SBP (21–24). It can be expected, based on the results of our previous study (21), that hyperoncotic HES (10%) is of even more clinical importance in cardiac-compromised dialysis patients who often experience hypotensive episodes. In this study, the efficacy of hypertonic saline (3%), albumin (20%), and HES (10%) on BP course and BV during combined UF and HD in cardiac-compromised dialysis patients was compared.

Materials and Methods

Patients and Dialysis

After obtaining informed consent for participation in the study, which was approved by the ethics committee of the Maastricht University Hospital, nine patients (five women and four men) undergoing chronic, intermittent HD were included. All patients were cardiac-compromised, defined as complaining of symptoms with less than normal activity and symptoms at rest (New York Heart Association classifications III and IV) (25). Moreover, these patients had a mild-to-severe left ventricular dysfunction, defined as an ejection fraction of 40% or less, which was obtained by performing a two-dimensional echocardiogram after dialysis with the patient in the left lateral decubitus position for measurement of left ventricular ejection fraction according to the method of Dodge and Sheehan (26). All patients experienced a hypotensive period more than once a week.

The mean age of the patients was 70.4 yr (range, 56 to 80 yr), and the mean time on HD was 22.1 mo (range, 6 to 36 mo). Heart failure was caused by one or more myocardial infarctions ($n = 8$) and ischemic heart disease ($n = 1$). Renal failure was caused by hypertensive nephrosclerosis ($n = 5$), diabetic nephropathy ($n = 3$), and unknown cause ($n = 1$). The mean ejection fraction of the patients in our study was $29.83 \pm 7.65\%$ (range, 22 to 40%).

The dry weight was estimated by echography of the inferior caval vein (27). The UF rate was prescribed according to the estimated dry weight and interdialytic weight gain, and was constant during the dialysis session. Dialysis was performed using a Gambro AK-100 module (Lund, Sweden) with hemophane membranes (GFS-16; Gambro) or using a Hospal Integra module (Uden, The Netherlands) with polysulfone membranes (F6HPS; Fresenius, Den Bosch, The Netherlands). The blood flow was 250 ml/min and the dialysate flow was 500 ml/min. The dialysate composition was as follows: 2.0 mmol/L potassium, 3.0 mmol/L acetate, 0.5 mmol/L magnesium, and 2.0 g/L (11.2 mmol/L) glucose. The dialysate calcium concentration was 1.75 mmol/L because in previous studies we and others (28–31) showed that this leads to a better hemodynamic stability due to an increase in myocardial contractility, especially in cardiac-compromised patients.

To prevent the effect of large interindividual changes in serum sodium concentrations on changes in BV (32) during dialysis, the dialysate sodium concentration was individualized and set to be equal to the predialytic serum sodium concentration in the first treatment session. The dialysate bicarbonate concentration was individualized and adjusted to achieve a postdialysis serum bicarbonate level between 26 and 30 mmol/L. The dialysate temperature was adjusted to the predialytic body temperature of the patient because it has been shown that higher dialysate temperatures may impair vascular reactivity and BP stability, especially in patients with a low predialytic body temperature (33–35). Dialysate temperature and dialysate composition did not differ between the three treatment sessions.

Study Protocol

The patients were studied on the regular day of their dialysis schedule with a weekly interval during UF and HD. Each patient served as his or her own control and was studied during three HD sessions that differed only in the type of intravenous fluid administered. The study started with the insertion of the needles, after which patients were placed in the supine position for the duration of the dialysis session.

An intravenous infusion of 33 ml of saline (3% sodium chloride; Baxter, Utrecht, The Netherlands), 100 ml of albumin (20% Cealb; Centraal Laboratorium Bloedtransfusie®, Amsterdam, The Netherlands), or 100 ml of HES (10% Haes-steril; Fresenius) was administered at room temperature (22°C) when SBP was less than 100 mmHg or when the decrease in SBP was more than 25 mmHg *versus* the start of UF and HD, in which case UF was continued. The osmolar load of the administered saline (30.9 mosmol) was similar to the osmolar load of HES (30.8 mosmol). UF was continued at the same rate. The order of the intravenous infusions was randomized. Measurements of arterial BP and relative BV were performed just before the start of UF and HD ($t = 0$), when SBP was less than 100 mmHg or when the decrease in SBP was more than 25 mmHg *versus* the start of UF and HD ($t = iv$); after 1 ($t = 1$), 5 ($t = 5$), and 30 ($t = 30$) min after $t = iv$; and at the end of UF and HD ($t = end$).

Methods

Arterial BP (SBP, diastolic BP [DBP], and mean arterial BP) was measured with an automatic BP monitor (Dinamap 1486 SX; Critikon, Norderstedt, Germany) and was recorded every 10 min. Moreover, BP was also measured at $t = iv$, $t = 1$, $t = 5$, $t = 30$, and $t = end$. Changes in relative BV were measured continuously and noninvasively by an optical reflection method that measures the absorption and scattering properties of red blood cells as they pass through the HD circuit (Crit-line; In-Line Diagnostics, Riverdale, UT). The optical sensor was clipped to the in-line blood chamber on the arterial line, and trends of hematocrit and percent BV (*versus* time) were logged over the entire treatment period. In previous studies it has been shown that relative changes in BV can be determined reliably during HD by the serial monitoring of hematocrit (36–38). The baseline value was obtained after 2 min of extracorporeal circulation at a blood flow of 250 ml/min without UF to exclude the influence of saline (recirculation) present in the extracorporeal circuit at the start of dialysis.

Before as well as at the end of dialysis, a blood sample was taken to determine levels of serum sodium (Beckman CX-7; Brea, CA), ionized calcium (ABL 505 radiometer; Copenhagen, Denmark), and blood urea nitrogen (BUN; Beckman CX-7).

Statistical Analyses

Changes within patients in hemodynamic parameters during each session as well as within-patient differences between sessions were analyzed by repeated-measures MANOVA (Statistical Package for the Social Sciences, version 6.1) (39). If the sphericity of the variance-covariance matrix of repeated measures appeared to be violated, degrees of freedom in the univariate MANOVA tests were corrected using the Greenhouse-Geisser epsilon to avoid type I error in testing the F ratio. Reversed Helmert contrasts were used to test between sessions, and in addition, orthogonal polynomial contrasts within time were made, taking $t = 0$ as well as $t = iv$ as baseline values. Predialysis weights, UF rate, time of infusion of the fluids, interdialytic weight gain after the treatment sessions, and predialysis and postdialysis laboratory parameters were analyzed using Friedman analysis of variance and, when appropriate, by Wilcoxon signed rank

Table 1. Blood pressure course^a

Variable	Saline (3%)	Albumin (20%)	HES (10%)
Systolic blood pressure			
$t = 0$	156 (25)	127 (22)	139 (29)
$t = iv$	107 (14)	90 (17)	90 (16)
$t = end$	98 (18) ^{b,c}	98 (14) ^b	107 (14) ^{d,e}
Diastolic blood pressure			
$t = 0$	74 (12)	64 (8)	68 (10)
$t = iv$	64 (11)	52 (10)	53 (8)
$t = end$	58 (16) ^b	55 (6) ^b	61 (6) ^f

^aData are given as mean (SD). Blood pressure course before the start of the dialysis ($t = 0$), before the intravenous fluid administration ($t = iv$), and at the end of the dialysis session ($t = end$). Systolic and diastolic blood pressure are given in mmHg. HES, hydroxyethylstarch.

^b $P < 0.05$, $t = end$ versus $t = 0$.

^c $P < 0.05$, saline versus albumin and saline versus HES, $t = end$ versus $t = 0$.

^d $P < 0.05$, $t = end$ versus $t = iv$.

^e $P < 0.05$, HES versus saline, $t = end$ versus $t = iv$.

^f $P = 0.075$, HES versus saline, $t = end$ versus $t = iv$.

test. A P value < 0.05 was considered significant. All values are expressed as mean \pm SD.

Results

The predialysis weights in the three treatment sessions (saline [3%], albumin [20%], and HES [10%]) were 64.71 ± 14.94 , 65.16 ± 12.55 , and 65.71 ± 12.79 kg, respectively (NS). The mean UF rate was 0.72 ± 0.20 , 0.66 ± 0.19 , and 0.71 ± 0.14 L/h in the three treatment sessions (NS). The mean dialysate temperature during all three treatment sessions was $36.66 \pm 0.42^\circ\text{C}$.

BP Course

Data are listed in Table 1. Time of intravenous infusion of saline (3%), albumin (20%), and HES (10%) was 137 ± 48 , 134 ± 60 , and 151 ± 52 min, respectively (NS). SBP decreased significantly versus baseline ($t = 0$) during UF and HD in all three treatment sessions ($P < 0.05$). The decrease was significantly higher when using saline compared with albumin ($P < 0.05$) and when using saline compared with HES ($P < 0.05$). Between HES and albumin there were no significant differences (NS).

When we compared the values at $t = iv$ with those at $t = end$, SBP decreased with saline (change in SBP, -8.71 ± 16.63 mmHg; NS), increased with albumin (change in SBP, $+8.66 \pm 16.61$ mmHg; NS), and increased significantly with HES (change in SBP, $+16.11 \pm 19.37$ mmHg; $P < 0.05$). The change in SBP at $t = end$ versus $t = iv$ was significantly greater when using saline compared with HES ($P < 0.05$) and tended to decrease more when using saline compared with albumin ($P = 0.09$). Between albumin and HES there were no significant differences.

DBP (Table 1) decreased significantly versus baseline ($t = 0$) during UF and HD with saline and albumin ($P < 0.05$) but not with HES. When we compared the values at $t = iv$ with those at $t = end$, DBP decreased with saline (change in DBP,

-5.71 ± 16.70 mmHg; NS), increased with albumin (change in DBP, $+2.89 \pm 10.05$ mmHg; NS), and increased significantly with HES (change in DBP, $+7.55 \pm 10.38$ mmHg; $P < 0.05$). The change in DBP at $t = end$ versus $t = iv$ tended to decrease more when using saline compared with HES ($P = 0.075$). Between albumin and HES and between albumin and saline there were no significant differences.

Changes in Relative BV

Data are presented in Figure 1. BV decreased significantly versus baseline during UF and HD in all three treatment sessions ($P < 0.05$). The decrease in BV at $t = end$ versus $t = 0$ was significantly higher when using saline compared with albumin ($P < 0.05$) and when using saline compared with HES ($P < 0.05$). Between albumin and HES there were no significant differences.

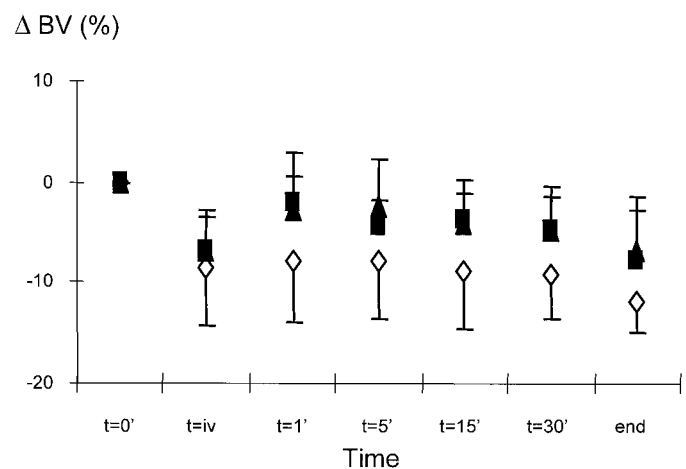


Figure 1. Blood volume course: percent changes in blood volume versus baseline. ■, study with intravenous albumin; ◇, study with intravenous saline; ▲, study with intravenous hydroxyethylstarch.

Table 2. Laboratory parameters^a

Parameter	Saline (3%)		Albumin (20%)		HES (10%)	
	<i>t</i> = 0	<i>t</i> = end	<i>t</i> = 0	<i>t</i> = end	<i>t</i> = 0	<i>t</i> = end
Sodium (mmol/L)	138.2 (4.6)	135.8 (2.2)	135.6 (3.2)	136.8 (3.1)	137.5 (3.9)	136.4 (3.8)
i-Ca (mmol/L)	1.20 (0.07)	1.31 (0.03) ^b	1.24 (0.11)	1.31 (0.07) ^b	1.20 (0.07)	1.34 (0.08) ^b
BUN (mmol/L)	24.23 (4.81)	7.03 (1.34) ^b	29.30 (5.78)	8.77 (2.27) ^b	26.78 (4.78)	7.88 (2.06) ^b

^a Data are given as mean (SD). Laboratory data before the start of the dialysis (*t* = 0) and at the end of the dialysis session (*t* = end). BUN, blood urea nitrogen; i-Ca, ionized calcium.

^b *P* < 0.05, *t* = end versus *t* = 0.

When we compared the values, before fluid administration, at *t* = iv with those at *t* = end, BV decreased, although not significantly, with saline (change in BV, $-3.19 \pm 2.88\%$; NS) and albumin (change in BV, $-1.04 \pm 6.91\%$; NS), but remained stable with HES (change in BV, $+0.14 \pm 4.7\%$; NS).

Laboratory Parameters

The laboratory data are presented in Table 2. The change in serum sodium was comparable between the three treatment sessions. During all sessions there was a significant increase in ionized calcium and a significant decrease in BUN. Among the three sessions there were no significant differences in the change in ionized calcium and BUN.

Other Parameters

The interdialytic weight gain after the treatment sessions with saline (3%), albumin (20%), and HES (10%) was 2.63 ± 0.38 , 2.43 ± 0.34 , and 2.63 ± 0.71 kg, respectively. Between the three treatment sessions there were no significant differences in interdialytic weight gain. Three patients experienced a hypotensive episode when using saline, and one patient experienced a hypotensive episode when using albumin. However, UF could be continued when the patients were placed in the Trendelenburg position.

Discussion

In this study we compared the efficacy of hypertonic saline (3%), albumin (20%), and HES (10%) on SBP during UF and HD in cardiac-compromised dialysis patients who often experienced hypotensive episodes. Our results show that HES is an effective solution in maintaining the SBP course, similar to albumin but superior to hypertonic saline.

It has been shown that preventing the reduction in plasma osmolality during HD could improve hemodynamic instability because it avoids or decreases the water inflow into the intracellular compartment and preserves the available amount of interstitial fluid to compensate for intravascular hypovolemia (9). Limiting the reduction in extracellular osmolality by injecting hypertonic fluids is generally advocated as an efficient treatment of symptomatic hypotension (10). However, repeated intravenous injections of saline may lead to an increase in the exchangeable sodium pool and, as a consequence of thirst, may lead to an increase in interdialytic weight gain and hypertension, which may be of great clinical importance in vulnerable

cardiac-compromised dialysis patients (11,12). In an earlier study of stable dialysis patients, we showed a superior preservation of BV with HES compared with isotonic saline, without any side effect (21). Therefore, in this study we compared two hypertonic fluids (HES [10%], which is also a hyperoncotic fluid, and saline [3%]) and albumin, a hyperoncotic fluid with an osmolality between 260 and 280 mosmol/L, with respect to their effect on SBP and BV. Saline (3%) and HES (10%) were administered in such amounts that a similar osmolar load was given. We found that SBP was better maintained with HES compared with saline, which suggests that it is not only the effect on osmolality, but also the additional oncotic effect of HES that is responsible for the distinct and prolonged effect on SBP course. This has also been observed by Gong *et al.* (40), who compared hypertonic saline solutions with dextran, which also has oncotic effects. They found that the BP response was more prolonged with 23% saturated hypertonic saline and dextran compared with hypertonic saline alone (7.5%) (40). However, in their study, in a great number of patients, repeated intravenous infusions were needed to maintain SBP, whereas we administered only one infusion. This difference could be explained by differences in the UF rates between their study and ours. Unfortunately, data regarding the UF rate are lacking in the study of Gong *et al.* (40).

In this study, SBP was also better maintained with albumin compared with hypertonic saline, which could be caused by the oncotic effects of albumin. These data are also comparable with the results of our previous study, in which we showed that SBP, although not significant, was better maintained with albumin compared to isotonic saline (21). When we compared the effect of HES with that of albumin, we found that there were no significant differences in SBP course after the intravenous infusion of either of the two fluids. However, the increase in SBP, although not significant, was greater with HES compared to albumin. It cannot be excluded that the higher sodium concentration of HES compared with albumin has an additional beneficial effect on the SBP course (21). Nevertheless, this difference in sodium concentration does not appear to introduce untoward clinical effects, because the change in serum sodium during dialysis and interdialytic weight gain during the days after treatment were comparable between the three sessions.

Regarding the decrease in BV from baseline to the end of the dialysis treatment, the decrease in BV was significantly more

pronounced with hypertonic saline compared to HES and albumin, which could also be explained by the oncotic effect of HES and albumin. When we compared the changes in BV from the time of infusion *versus* the end of the dialysis session, BV also decreased with saline and albumin, and remained unchanged with HES. However, these differences did not reach statistical significance.

Similar to our previous study (21), in this study none of the patients experienced side effects with either of the fluids during or after the dialysis session. HES also did not cause intravascular volume overload in these cardiac-compromised patients, because BV declined gradually to the preinfusion values during the rest of the dialysis session.

From these data, we conclude that HES is an effective fluid in maintaining SBP and in preserving BV in hypotensive-prone dialysis patients, comparable to albumin but superior to hypertonic saline. Given the costs and side effects of albumin, HES is preferred.

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