Effect of Intravenous Saline, Albumin, or Hydroxyethylstarch on Blood Volume during Combined Ultrafiltration and Hemodialysis

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Abstract. It is generally advocated to use saline or albumin infusions during symptomatic hypotension during dialysis. However, because of their side effects and/or costs, they are of limited use. Hydroxyethylstarch (HES), a synthetic colloid with a long-standing volume effect, is used in the management of hypovolemia. In this study, the efficacy of three fluids (isotonic saline [0.9%], albumin [20%], and HES [10%]) was assessed during three treatment sessions with combined ultrafiltration and hemodialysis, which differed in the type of fluid given intravenously. Changes in relative blood volume (BV), systolic BP (SBP), and vascular reactivity (venous tone [VT]) were compared. An intravenous infusion of 100 ml of fluid was given when the decrease in BV versus baseline was more than 10% as measured by a continuous optical reflection method. The ultrafiltration was continued. BV decreased significantly versus baseline independent of the intravenous fluid administration in all three treatment sessions. However, when we compared BV values at the end of the dialysis session with those at the time of infusion, BV continued to decrease significantly with saline (change in BV −4.56 ± 2.75%; P < 0.05) and albumin (change in BV −2.13 ± 2.51%; P < 0.05), but not with HES (change in BV −0.15 ± 2.17%; NS). Between albumin and HES there were no significant differences in changes in BV (NS), whereas between HES and saline (P < 0.05) and between albumin and saline (P < 0.05) the differences in BV changes were significant. SBP remained unchanged within each session. Although SBP tended to decrease more with saline compared to albumin and HES, the difference was not significant. The higher decrease in BV and SBP with saline was counterbalanced by a significantly higher increase in VT, while VT remained unchanged in the other two sessions. It is concluded that HES is a promising fluid in preserving blood volume, comparable to albumin, but superior to saline.

Symptomatic hypotension is a common complication of hemodialysis, occurring in 20 to 30% of patients (1). It will not only endanger the patient, but will also reduce the efficacy of the dialysis therapy. Particularly in patients with a compromised cardiovascular system, the risk of hypotension is high (2). The immediate cause is intravascular hypovolemia related to the dialysis procedure, although other factors such as autonomic neuropathy, left ventricular dysfunction, inappropriate activation of cardiovascular reflexes, and abnormal vascular compliance can also be of importance (3–8).

Nevertheless, the acute management of intradialytic hypotension has depended on volume expansion regardless of the underlying mechanism. Volume expansion is frequently performed by infusions of saline, a practice that frustrates attempts to attain dry weight by increasing the fluid burden, thus necessitating greater ultrafiltration and further hypotension. The use of hypertonic or hyperoncotic solutions during symptomatic hypotension has also been proposed, although none of the studies investigated the effect on blood volume (9). The most commonly used fluids are saline, albumin, dextran, and mannitol. However, because of the side effects of hypertonic saline (thirst, interdialytic weight gain, hypertension), dextran (acute anaphylactic reactions, prolonged bleeding time, intracellular deposition, especially in macrophages, and interstitial deposition of dextran in various tissues), and mannitol (hyponatremia, hyperkalemia, metabolic acidosis, and deposition in tissues), these are of limited clinical use (10–15). The effect of albumin infusion in the management of hypovolemia is well known. Compared with other solutions, albumin is expensive and can cause side effects (allergic reactions). Also, it was recently reported that there was an increased risk of death in patients treated with albumin because of hypovolemia (16). So, the ideal fluid would be inexpensive, rapid in onset, prolonged in duration, and associated with no side effects. In intensive care wards, hydroxyethylstarch (HES), a relatively inexpensive synthetic colloid, is used in the management of hypovolemic disturbances (17,18). Compared with albumin, HES is much cheaper: $3 (US$) for 100 ml of HES 10% versus $52 for 100 ml of albumin 20%. Because of its physicochemical properties,
HES has a long-standing volume effect up to 4 h (19). It can therefore be expected that hyperoncotic HES 10% might also be of clinical importance in dialysis patients. In this study, the efficacy of saline (0.9%), albumin (20%), and HES (10%) on blood volume (BV), hemodynamic parameters, and vascular reactivity during combined ultrafiltration and hemodialysis (UF + HD) was compared.

**Materials and Methods**

**Patients and Dialysis**

After giving informed consent for participation in the study, approved by the Ethics Committee of the Maasricht University Hospital, 10 patients (4 women, 6 men) on chronic intermittent hemodialysis were included. The patient group had a mean age of 61.4 yr (range, 40 to 75) and the mean time on hemodialysis was 13.7 mo (range, 5 to 60). All were stable dialysis patients who rarely suffered from intradialytic hypotension. Exclusion criteria were severe coronary (NYHA II or more) heart disease and compromised left ventricular function (ejection fraction ≤50%). The etiology of the renal failure was nephrosclerosis (n = 4 patients), diabetic nephropathy (n = 1), IgA nephropathy (n = 1), chronic transplant dysfunction (n = 1), oxalosis nephropathy (n = 1), adult polycystic disease (n = 1), and antiglomerular basement membrane nephritis (n = 1). By adjusting fluid intake, patients were able to achieve a predialysis weight that was similar in the three sessions. The optimal dry weight was estimated by echography of the inferior caval vein (20).

Each patient was studied on the regular day of his or her dialysis schedule with a weekly interval during UF + HD. Each patient served as his or her own control and was studied during three hemodialysis sessions that differed only in the type of intravenous fluid given. Dialysis was performed with a Gambro AK-100 module (Gambro, Lund, Sweden) using hemophane membranes (GFS-16; Gambro). To prevent the effect of a salt load on changes in blood volume (21) and the effect of dialysate temperature on hemodynamic parameters and vascular reactivity (22), the composition of the dialysate was individualized. Dialysate sodium is serum sodium, chloride depending on dialysate sodium, bicarbonate individualized (between 32 and 36 mmol/L), potassium 2.0 mmol/L, acetate 3.0 mmol/L, magnesium 0.5 mmol/L, calcium 1.5 mmol/L, and glucose 2.0 mmol/L. The dialysate temperature was adjusted according to the core temperature of the patient, measured with an ear thermometer (Genius First Temp Model 3000A; Sherwood Medical, Sussex, United Kingdom), which correlates well with intra-arterial measured temperature (r² = 0.999, P = 0.0001) (23). The blood flow was 250 ml/min and dialysate flow 500 ml/min.

**Study Protocol**

The study was started with the insertion of the needles, after which patients were allowed supine rest for 30 min. An intravenous infusion of 100 ml of saline (NaCl 0.9%; Baxter, Utrecht, The Netherlands), albumin (Cellb-20%; CLB, Amsterdam, The Netherlands), or HES (Haes-steril 10%; Fresenius, Den Bosch, The Netherlands) was given at room temperature (22°C) when the decrease in relative blood volume (BV) was more than 10% measured with an optical reflection method. The ultrafiltration was continued at the same rate. The order of the intravenous infusions was randomized. Measurements were performed just before the start of UF + HD (t = 0), when the decrease in BV was more than 10% (t = iv), and after 1 (t = 1), 5 (t = 5), 15 (t = 15), and 30 min (t = 30) after t = iv, and at the end of UF + HD (t = end).

**Methods**

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 hemodialysis 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 %BV (versus time) were logged over the entire treatment period. It is known from previous studies that relative changes in BV can reliably be determined during hemodialysis by the serial monitoring of hematocrit (24–26). Most of the automatic devices to measure continuous BV are derived from the serial hematocrit method. All methods measure a physical phenomenon that is a function of BV relative to its initial volume. Measurements of hematocrit by optical devices correlate well with those determined by centrifugation (r = 0.89 to 0.996, P < 0.05) (24–26). The baseline value was obtained after 2 min of extracorporeal circulation at a blood flow of 250 ml/min without ultrafiltration to exclude the influence of saline (recirculation) present in the extracorporeal circuit at the start of dialysis.

Bioimpedance measurements were performed using a Xitron® 4000B bioimpedance analyzer (Xitron Technologies, San Diego, CA). The electrodes were placed contralateral to the site of vascular access. A range of frequencies between 5 and 500 kHz was used. Estimations of extracellular and intracellular volume and fat-free and fat mass were calculated by equations provided by the manufacturer. Bioimpedance measurements were validated to measure intracellular and extracellular conductivity and consequently transcellular fluid shifts, and the reproducibility was in healthy subjects r = 0.975 and in dialysis patients r > 0.987, although it must be cautiously applied to the measurement of absolute volume changes in dialysis patients (27,28).

Before as well as at the end of dialysis, a blood sample was taken for the determination of sodium (Beckman CX-7; Brea, CA), ionized calcium (ABL 505 radiometer), total CO₂, colloid osmotic pressure (COP), and osmolality (Fiske 2400; Copenhagen, Denmark). Arterial BP (BP) and heart rate (HR) were measured with the Finapres method (Finapres, Ohmeda 2300; Lamers, The Netherlands). The mean value of 3 min was calculated. With the Finapres device, arterial BP and HR are measured beat to beat at zero transmural pressure by the use of a small finger cuff that is equipped with an infrared photoplethysmograph (29). The Finapres cuff was applied to the third finger.

Vascular reactivity was studied at the nonfistula arm that was positioned just above heart level using strain-gauge plethysmography as described by Whitney (Periflow; Janssen Scientific Instruments, Beerse, Belgium) (30). An inflatable cuff was applied to the upper arm while the mercury-filled strain gauge was positioned at the thickest part of the forearm. In addition, an antecubital vein was cannulated (Venflon, 1 mm diameter) for the recording of direct intravenous pressure (Hewlett-Packard 7820SC pressure monitor). Venous tone (VT) (active venous constriction) and forearm vascular resistance (FVR) were measured as described previously by van Kuik et al. (22). The coefficient of variation of consecutive measurements is 11.9% (8).

**Statistical Analyses**

Changes in hemodynamic parameters within each session as well as within patient differences between sessions were analyzed by repeated measurements MANOVA (SPSS-PC version 6.1) (31). If the sphericity of the variance-covariance matrix of repeated measurements appeared to be violated, degrees of freedom in the univariate
MANOVA tests were corrected by the Greenhouse–Geisser epsilon to avoid type I error in testing the F-ratio. Reversed Helmert contrasts were used to test between sessions, and orthogonal polynomial contrasts within time were made taking $t = 0$ as well as $t = iv$ as baselines. Predialysis weights, ultrafiltration rate, and dialysate temperature were analyzed by the $t$ test. All laboratory parameters were analyzed by Friedman ANOVA and, if appropriate, by the Wilcoxon signed-rank test. $P < 0.05$ was considered significant. All values are expressed as mean $\pm$ SD.

Results

Patient Characteristics

The predialysis weights in the three treatment sessions, saline (0.9%), albumin (20%), and HES (10%), were 79.22 $\pm$ 10.50, 78.87 $\pm$ 10.60, and 79.08 $\pm$ 10.80 kg, respectively (NS). The mean ultrafiltration rate (UF rate) was 0.94 $\pm$ 0.11, 0.94 $\pm$ 0.10, and 0.94 $\pm$ 0.10 L/h, respectively, in the three treatment sessions (NS). Dialysate temperatures were, respectively, 36.56 $\pm$ 0.56, 36.41 $\pm$ 0.69, and 36.56 $\pm$ 0.56°C in the three treatment sessions (NS).

Changes in Relative Blood Volume

Data are given in Figure 1. Time of intravenous infusion of saline (0.9%), albumin (20%), and HES (10%) was, respectively, 2.20 $\pm$ 0.55, 2.35 $\pm$ 0.49, and 2.31 $\pm$ 0.49 h (NS).

BV decreased significantly versus baseline during UF + HD in all three treatment sessions ($P < 0.05$). The decrease was significantly higher when using saline compared with albumin (NS) and saline compared with HES ($P < 0.05$). Between albumin and HES, there were no significant differences, although BV tended to decrease less versus baseline with HES compared to albumin.

When we compared the values at $t = end$ with those at $t = iv$, BV decreased significantly with saline (change in BV $-4.56 \pm 2.75\%$; $P < 0.05$) and albumin (change in BV $-2.13 \pm 2.51\%$; $P < 0.05$), but not with HES (change in BV $-0.15 \pm 2.17\%$; NS). The decrease in BV in $t = end$ versus $t = iv$ was again significantly higher when using saline compared to albumin ($P < 0.05$) and using saline compared to HES ($P < 0.05$); between albumin and HES there were no significant differences. After the intravenous infusion of albumin and HES there was an immediate and sustained effect on BV.

Extracellular and Intracellular Volume

Changes in extracellular (VECF) and intracellular (VICF) volume are shown in Table 1. VECF decreased and VICF increased significantly in all of the sessions. Among the three sessions there were no significant differences.

Systolic BP

Figure 2 shows the results of the systolic BP course (SBP) in the three sessions. There were no significant differences in SBP course within each session. With saline, SBP tended to decrease more compared with albumin and HES, although the difference was not significant.

Venous Tone and Forearm Vascular Resistance

In Table 2, the results of changes in VT and FVR in the three sessions are shown. VT increased significantly with isotonic saline and remained unchanged with albumin and HES, and was significantly higher with isotonic saline compared to albumin but not to HES. FVR increased significantly in the three sessions, and there were no significant differences between saline, albumin, and HES.

Laboratory Parameters

The laboratory data are presented in Table 3. Plasma sodium was comparable before as well as after the three sessions, which could be expected because the dialysate sodium was adjusted according to the serum sodium concentration of the patient. At all sessions there was a significant increase in COP. Osmolality decreased significantly in all of the sessions. Ionized calcium increased significantly in the three sessions. Among the three sessions there were no significant differences in laboratory parameters.

Discussion

In this study, we compared the efficacy of isotonic saline (0.9%), albumin (20%), and HES (10%) on BV during UF + HD in stable dialysis patients. The fluids were infused when the decrease in BV was more than 10%. The ultrafiltration was continued. After infusion of HES and albumin, there was an immediate and sustained effect on BV, while BV continued to decrease with saline. Intra- and extracellular volume changed comparably during each treatment session. This could be expected because only 100 ml of intravenous fluid was given, which is approximately 0.6% of the intracellular and 0.5% of the extracellular volume. Our results show that HES is an effective solution in preserving BV, being comparable to albumin but superior to saline.

The larger decrease in BV and SBP after treatment with isotonic saline, as shown in our data, was counterbalanced by a higher level of VT. During BV decrease, compensatory mechanisms arise to maintain cardiac output. Because the
venous system is a very important blood reservoir (containing approximately 60 to 80% of total BV), increasing VT by vеноconstriction is of utmost importance to maintain venous return and in consequence cardiac output and BP, as was supported by our data (32,33).

It has been shown that the vascular refilling rate is related to the level of COP (34). It can be expected that in dialysis patients with symptomatic hypovolemia (i.e., symptomatic hypotension), an intravenous infusion of an albumin solution or other hyperoncotic fluid will enhance vascular refilling and improve hemodynamic stability. In our study, COP was measured before and at the end of dialysis and increased comparably between the three treatment sessions, probably due to hemoconcentration. However, it is conceivable that BV was better preserved with HES and albumin because of the immediate effect of an increase in COP after intravenous infusion of the colloid fluid and its attendant water binding effect. This is supported by the fact that in another study an immediate increase in COP after infusion of 500 ml of HES 10% in hypovolemic volunteers was found (35). The water binding capacity of HES is 20 ml of H2O/g HES. So, 100 ml of HES 10% binds approximately 200 ml of water. It is known that after infusion of a hyperoncotic albumin infusion, COP increases immediately. Albumin has a water binding capacity of 18 ml of H2O/g albumin, and 100 ml of albumin 20% binds approximately 360 ml of water, which is predominantly due to an increase in COP. Nevertheless, the effect of HES on BV preservation was at least as effective compared with albumin. The immediate increase in BV after treatment with the three different kinds of fluid in our study could also be due to an immediate increase in osmolality; however, we did not perform measurements of osmolality just before and after initiation of the intravenous fluid. Kohler et al. found no changes in osmolality in the previously mentioned study, in which 500 ml of HES 10% was given to healthy volunteers (35). In our study, there were no differences in plasma sodium concentration or plasma osmolality before as well as at the end of the dialysis between isotonic saline, albumin, and HES. One liter of HES contains 154 mmol NaCl and has an osmolality of 308 mosmol/L. Albumin contains 145 mmol NaCl per liter and has an osmolality between 260 and 280 mosmol/L. It cannot be excluded that the higher sodium concentration of HES compared to albumin has an additional beneficial effect on the preservation of BV.

HES (10%) is a solution of hydroxyethylstarch with a mean

Table 1. Intra- and extracellular volume

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Intracellular Volume</th>
<th>Extracellular Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t = 0</td>
<td>t = iv</td>
</tr>
<tr>
<td>Saline (0.9%)</td>
<td>15.16 (1.93)</td>
<td>16.33 (2.08)</td>
</tr>
<tr>
<td>Albumin (20%)</td>
<td>15.74 (2.58)</td>
<td>16.19 (2.00)</td>
</tr>
<tr>
<td>HES (10%)</td>
<td>15.88 (2.29)</td>
<td>16.56 (2.01)</td>
</tr>
</tbody>
</table>

a Data are given as mean (SD). Intra- and extracellular volume are given in liters. HES, hydroxyethylstarch.
b P < 0.05, t = end versus t = 0.

table 2. Forearm vascular resistance and venous tone

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Forearm Vascular Resistance</th>
<th>Venous Tone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t = 0</td>
<td>t = iv</td>
</tr>
<tr>
<td>Saline (0.9%)</td>
<td>29.66 (15.68)</td>
<td>48.94 (30.85)</td>
</tr>
<tr>
<td>Albumin (20%)</td>
<td>26.78 (15.27)</td>
<td>46.90 (33.20)</td>
</tr>
<tr>
<td>HES (10%)</td>
<td>30.00 (14.55)</td>
<td>38.17 (17.64)</td>
</tr>
</tbody>
</table>

a Data are given as mean (SD). Forearm vascular resistance is given in mmHg/ml per dl per min. Venous tone is given in mmHg/ml per dl.
b P < 0.05, t = end versus t = 0.
c P < 0.05, saline versus albumin.
molecular weight of 200,000 daltons and a molar substitution of 0.5 (HES 200/0.5) and was selected because of its prolonged intravascular volume effect (13–15). The substitution rate of starches is very important for their pharmacodynamics because the hydroxyethyl side chains markedly decelerate the intravascular breakdown by amylase (36). Although HES may lead to anaphylactic reactions in isolated cases, of all the available colloids it has the lowest incidence of adverse reactions (37,38). Long-term, daily administration of HES in medium and high doses, and at high molecular weight (400,000 daltons), could lead to prolonged bleeding time, deposition in the reticular endothelial system, and itching (39–42). This seems to be related to storage of HES in the skin and appears to be dose-dependent, as has been shown in a recent study in which pruritis did occur only if more than 150 g of HES (1500 ml of HES 10%) was given every week (42). In another study, in which the cumulative dose did not exceed the 300 g in 14 d, the incidence of HES-induced pruritis was very low and comparable with Ringer’s solution (43). Therefore, there appears to be no elevated risk of pruritis if low molecular weight HES is applied in amounts typical for volume substitution (44). The pharmacokinetics of HES in patients on hemodialysis and hemofiltration were studied by Steinhoff et al. (45). They infused 300 ml of HES 10% in 10 patients on hemodialysis and nine patients on hemofiltration and compared the elimination half-life period of HES in these patients with renal healthy people. In patients on hemodialysis, the elimination half-life period was prolonged threefold and in patients on hemofiltration it was twice as long compared with renal healthy people. Considering their results, 300 ml of HES 10% can be given to hemodialysis patients after every second dialysis, whereas application to hemofiltration patients is possible after every hemofiltration. Therefore, based on the pharmacokinetic results of Steinhoff et al. in patients on dialysis and the fact that side effects only occur if high doses of HES are given, it seems to be safe to give 100 ml of HES 10% (10 g) to dialysis patients as we did in our study.

We conclude that blood volume was better preserved with albumin and hydroxyethylstarch compared to saline, whereas the efficacy of hydroxyethylstarch was at least comparable to albumin. Therefore, hydroxyethylstarch seems to be a promising fluid in preserving blood volume, comparable to albumin but less expensive. In our study, the effect of 100 ml of hyperoncotic hydroxyethylstarch was rapid in onset, prolonged in duration, and associated with no side effects. Additional studies in hypotensive-prone patients and cardiac-compromised dialysis patients are needed to look at the clinical effect of hydroxyethylstarch on BP course during hemodialysis.

Table 3. Laboratory parametersa

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Saline (0.9%)</th>
<th>Albumin (20%)</th>
<th>HES (10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t = 0</td>
<td>t = end</td>
<td>t = 0</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>137.9 (3.25)</td>
<td>138.3 (3.5)</td>
<td>136.6 (2.88)</td>
</tr>
<tr>
<td>Osmolality (mosmol/kg)</td>
<td>305.1 (9.39)</td>
<td>288.0 (4.76)b</td>
<td>304.1 (7.13)</td>
</tr>
<tr>
<td>COP (kPa)</td>
<td>3.34 (0.43)</td>
<td>4.30 (0.48)b</td>
<td>3.22 (0.32)</td>
</tr>
<tr>
<td>iCa (mmol/L)</td>
<td>1.12 (0.10)</td>
<td>1.25 (0.08)b</td>
<td>1.14 (0.12)</td>
</tr>
</tbody>
</table>

aData are given as mean (SD). COP, colloid osmotic pressure; iCa, ionized calcium.
bP < 0.05, t = end versus t = 0.

References

29. Penaz J: Photoelectric measurement of blood pressure, volume and flow in the finger. 10th International Conference of Medical and Biological Engineering, Dresden, 1973