

Preventing dialysis hypotension: A comparison of usual protective maneuvers

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Background. Intradialytic hypotension (IH) is a common adverse event. Currently, there are several commonly utilized therapies of IH, but they have not been compared directly in the same group of patients. We performed the present study in order to learn which of these techniques is most effective so that a rational approach to treating IH could then be formulated.

Methods. A single-blinded, crossover study design of five different protocols was undertaken in 10 hemodialysis patients with a prior history of IH. Each patient first underwent one week (three dialyses) of standard dialysis (dialysate sodium 138 mEq/L). Then each patient was subjected to one week each (three dialyses) of the four test protocols, performed in random order in a blinded fashion. The specific protocols were as follows: high sodium dialysate, in which the patient was dialyzed using a dialysate sodium of 144 mEq/L; sodium modeling, during which the dialysate sodium declined from 152 to 140 mEq/L in the last half hour of dialysis; one hour of isolated ultrafiltration followed by three hours of isovolemic dialysis; and cool temperature dialysis in which the dialysate was cooled to 35°C.

Results. Weight loss in each of the five protocols was essentially identical, varying between 2.9 and 3 kg. There were significantly fewer hypotensive episodes per treatment in the sodium modeling, high sodium, and cool temperature protocols as compared with the standard protocol ($P < 0.05$). Ultrafiltration followed by dialysis was associated with a significantly greater number of hypotensive episodes per treatment than any of the three test protocols ($P < 0.05$). Similarly, the number of nursing interventions required for IH per treatment was significantly greater in the standard dialysis and in the isolated ultrafiltration protocols compared with sodium modeling and cool temperature protocols ($P < 0.05$). The number of hypotensive signs and symptoms per treatment was also significantly reduced during the sodium modeling and cool temperature protocols compared with the standard protocol ($P < 0.004$ and $P < 0.02$, respectively). Again, the isolated ultrafiltration protocol resulted in significantly more hypotensive symptoms and signs

than the three test protocols ($P < 0.005$). Finally, the nadir mean arterial pressures were significantly lower in the standard and isolated ultrafiltration protocols when compared with the three test protocols ($P < 0.05$). The upright postdialysis blood pressure was best preserved in the sodium modeling and cool temperature protocols compared with the standard and isolated ultrafiltration protocols ($P < 0.05$).

Conclusion. This study supports the use of sodium modeling as a first step in combating IH. Also effective were the use of cool-temperature dialysate and a high-sodium dialysate. All three test protocols were well tolerated. As applied in this study, isolated ultrafiltration followed by isovolemic dialysis was notably less effective in reducing IH.

Intradialytic hypotension (IH) is a common adverse event that occurs in 15 to 25% of all dialysis treatments [1, 2]. Hypotension is a major clinical problem not only because of its frequency, but also because it contributes to the unwell feelings experienced by dialysis patients, limits rehabilitation, and consumes a disproportionate amount of dialysis staff time and resources. Dialysis hypotension has a multifactorial etiology, including such disparate causes as autonomic dysfunction [3–8], decreased plasma osmolality [9, 10], a decrease in extracellular fluid volume with inadequate plasma [11], impaired venous compliance [12], decreased cardiac reserve [13], changes in serum potassium and calcium concentrations, and, perhaps, an accumulation of nitric oxide [14–16].

There are several commonly utilized therapies of dialysis hypotension, and each of these has been developed to counter the specific derangements that lead to the disorder. Thus, an increase in plasma osmolality has been achieved by the use of either a high-sodium dialysate [17] or a sodium modeling protocol [18]. Cooling the dialysate to 35°C (from the usual 37°C) induces catecholamine release and thereby leads to peripheral vasoconstriction and an increase in cardiac inotropy [19, 20]. Isolated ultrafiltration followed by isovolemic dialysis enhances plasma refilling and maintains a steady plasma osmolality [21]. Each of these strategies has been at least partly successful in preventing dialysis hypotension

Key words: hemodialysis, sodium modeling, cool temperature dialysis, ultrafiltration, intradialytic hypotension.

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Table 1. Patient characteristics

Patient Number	Age years	Sex	Cause of ESRD	Length of time on hemodialysis months
1	27	Female	Chronic GN	112
2	51	Male	Diabetes	38
3	67	Female	Diabetes	25
4	68	Female	Diabetes	24
5	79	Male	Diabetes	36
6	68	Female	Diabetes	24
7	84	Male	Unknown	24
8	54	Female	Diabetes	11
9	63	Female	Diabetes	29
10	50	Female	Diabetes	21
Mean \pm SEM	61.1 \pm 12.5	30% Male 70% Female		34.4 \pm 16.6

[17–21]. However, currently there is not a consensus among practitioners as to which of these strategies is most effective, in part because a direct comparison of these maneuvers has not been performed previously. Thus, in order to learn which of the techniques is most effective as a therapy for IH, we performed the present study to learn whether there was an advantage of one particular therapy versus another so that a rational approach to therapy could be elucidated.

METHODS

Patients

Informed consent was obtained from all patients, and the protocol was approved by the Institutional Review Board at the Medical College of Ohio. A total of 10 patients was recruited from the outpatient hemodialysis facility at the Medical College of Ohio; inclusion criteria were that the patient had to have suffered frequent bouts of hypotension (four episodes per week or one or more episodes of hypotension in >75% of treatments) during dialysis despite standard adjustments in dry weight and changes in antihypertensive medicine that would be initially instituted to treat the problem. In most dialysis units, dry weight is clinically determined and is defined as the lowest weight a patient can tolerate without the development of intradialytic symptoms (for example, cramping, nausea, vomiting, or lightheadedness) and hypotension in the absence of overt fluid overload. In the study cohort, dry weight was increased, but there was no change in frequency of hypotensive episodes in these 10 patients. Patients were excluded if they had uncontrolled hypertension, unstable angina, a history of non-compliance, variable weight gains, or if they required frequent hospitalization. The patients' clinical characteristics are shown in Table 1. As can be seen, 7 of the 10 patients were women, and the average age was 61 years (range 27 to 84 years). The population was dominated by diabetics (8 of the 10 patients), and they had spent a total of an average of 34.4 months on dialysis (range 11 to 112 months). The patient's usual medications were

unchanged in dose or frequency during the study; Table 2 depicts the medicines consumed by the patient group.

Experimental protocol

A single-blinded, crossover design of five different dialysis protocols was undertaken in this study. Each patient began the study by undergoing a standard dialysis with a sodium bath of 138 mEq/L. The patient underwent one week (three dialysis sessions) of standard dialysis. Following the completion of this week, each patient then was subjected to one week each (three dialyses) of the four test protocols performed in random order in a blinded fashion. Data were collected on all dialyses during the week. The ultrafiltration followed by dialysis protocol required several adjustments of the dialysis machine at the one-hour mark, and this made "blinding" the patients impractical for this particular maneuver. The specific test protocols were as follows: High sodium dialysate in which the patient was dialyzed using a dialysate sodium of 144 mEq/L; sodium modeling (step function design) during which the dialysate sodium was 152 mEq/L at the onset of dialysis and then declined to 140 mEq/L in the last 30 minutes of dialysis; ultrafiltration (one hour of isolated ultrafiltration in which 50% of the target weight loss was removed not to exceed a total of 1.5 kg) followed by three hours of isovolemic dialysis; and cool-temperature dialysis in which the dialysate was cooled to 35°C. The dialysate sodium concentration was 140 mEq/L in the cool-temperature protocol. During the ultrafiltration followed by isovolemic dialysis protocol, all patients underwent three hours of dialysis in addition to the first hour of ultrafiltration only. Thus, for patients on 3.5 or 4.0 hours of dialysis, this was less dialysis time than usual.

Other aspects of each of the dialysis treatments such as the dialysate composition (other than the sodium concentration), the quantity of dialysis, and the duration of dialysis were comparable in each of the protocols. The standard dialysate potassium was 2.0 mEq/L in nine of the patients and 3.0 mEq/L in one patient; the dialysate

Table 2. Patient medications

Patient Number	Antihypertensive/anti-anginal medications	Other medications
1	None	Phenytoin, conjugated estrogens, levothyroxine, bromocriptine, warfarin, cisapride
2	Isosorbide mononitrate 60 mg qhs	Testosterone IM, salmeterol, albuterol, ipratropium, ASA, ranitidine, cisapride
3	Enalapril 15 mg qhs	Amiodarone, levothyroxine, warfarin, insulin
4	Isosorbide dinitrate 10 mg tid, Hydralazine 50 mg tid, Metoprolol 50 mg bid	ASA, warfarin, albuterol, hydroxyzine
5	Amlodipine 10 mg qd	Famotidine, ASA, simethicone
6	Amlodipine 5 mg qd, TTS#3	Insulin, quinine
7	None	Dipyrimadole
8	None	Insulin
9	Isosorbide dinitrate 10 mg tid, Atenolol 25 mg qd	Metoclopramide, coated ASA, insulin
10	None	Carbamazepine, conjugated estrogens, warfarin, cisapride, omeprazole, insulin

calcium concentration was 3.0 mEq/L, and the dialysate bicarbonate concentration was 35 mEq/L in all patients. In addition, the same amount of weight was removed in each of the protocols. Studies in which there was >0.6 kg intraindividual weight variance in weight removal were considered experimental failures and were not analyzed. Food intake was not allowed during any of the maneuvers. The temperature of the dialysate and the sodium concentration of the dialysate were verified to insure that the desired sodium concentration and dialysate temperature were actually being delivered. In the sodium modeling program, the dialysate sodium concentration was sampled twice, once at the beginning of dialysis and then again in the last 20 minutes of dialysis to document that the dialysate sodium had, in fact, decreased from 152 to 140 mEq/L. Hemoglobin and hematocrit measurements and the urea reduction ratio were measured in each patient weekly to make certain that these parameters had not changed. The identical dialysis machine (Fresenius USA, Inc., Walnut Creek, CA, USA) and a polysulfone dialyzer membrane (Fresenius F-80) were used in all maneuvers. The dialysate flow rate was 500 mL/min for all of the patients, and the blood flow rates were adjusted individually to achieve the usual prescription for each patient (range 250 to 450 mL/min). The blood pressure was recorded by an automated cuff every 15 minutes.

Intradialytic hypotension (IH) was defined as an abrupt (over 10 to 15 min) decrement in blood pressure accompanied by symptoms or a decline of blood pressure requiring a nursing intervention. In addition, an abrupt decrement (again, over 10 to 15 min) of greater than 40 mm Hg in systolic blood pressure (SBP) or greater than 20 mm Hg in diastolic blood pressure (DBP) was considered a significant intradialytic hypotensive change. Finally, a SBP of less than 100 mm Hg or a DBP of less than 40 mm Hg accompanied by symptoms was also considered as hypotension. In this study, a total of 131 episodes of IH were recorded; 64 of these (49%) were

characterized by an abrupt >40 mm Hg decline in SBP. These were not serial decrements in blood pressure over the course of an entire treatment. Rather, in the majority of cases the SBP had fallen to 100 mm Hg or there was a 60 mm Hg drop in SBP and/or 30 mm Hg drop in DBP. Of these 64 episodes, 20 (31%) were accompanied by symptoms. Another 47 occurrences (36% of the total) were IH due to a SBP <100 mm Hg accompanied by symptoms. Finally, 20 of the 131 (15%) episodes of IH were characterized by a blood pressure decline accompanied by adverse patient symptoms.

Orthostatic blood pressure recordings were obtained predialysis and postdialysis as follows: The patient was placed in the supine position, and the access was cannulated. The patient remained in the supine position for two minutes, after which a blood pressure and pulse were recorded. Following this, the patient was asked to stand or, if unable, to sit upright for two minutes, at which time another blood pressure and pulse were obtained. The same procedure was performed following the dialysis after the patient had been disconnected from the dialysis machine but still had the dialysis fistula cannulated. In addition to the predialysis and postdialysis supine and upright blood pressures and heart rates, the number of hypotensive episodes per treatment (defined as mentioned previously in this article), the number of nursing interventions required (data obtained from the dialysis record), and the lowest blood pressure during a treatment were recorded. Nursing interventions included the implementation of the routine maneuvers employed by the nursing staff to combat dialysis hypotension. These included placing the patient in the Trendelenberg position, saline and hyperoncotic albumin boluses, decreasing the transmembrane ultrafiltration pressure, and early termination of treatment. All patient symptoms of hypotension during dialysis were also recorded and included nausea, vomiting, sweating, dizziness, weakness, and cramping. The patients were also questioned during each of the treatments for any adverse symptoms

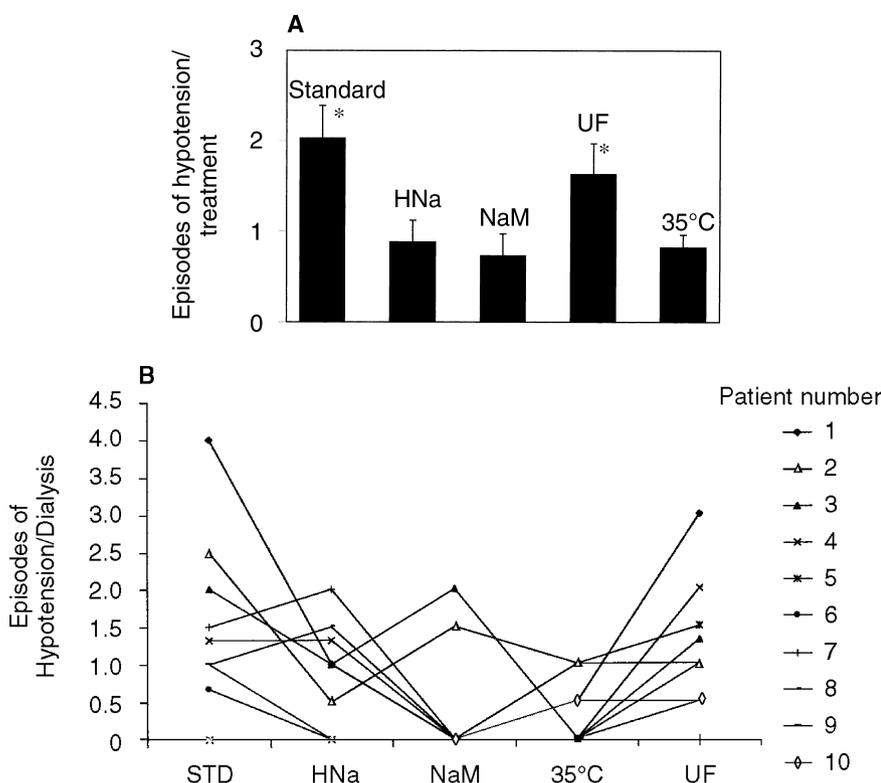


Fig. 1. (A) Number of episodes of hypotension per dialysis treatment. Note the significant reduction in hypotensive episodes with the HNa, NaM, and 35°C procedures. * $>$ HNa, NaM, and 35°C, $P < 0.05$. (B) The number of hypotensive events for each individual during each of the maneuvers. Abbreviations are: STD, standard; HNa, high-sodium dialysis; NaM, sodium modeling; UF, ultrafiltration followed by isovolemic dialysis; and 35°C, cooler temperature dialysis. All data in this and the other figures are mean \pm SEM.

related to the therapeutic maneuvers such as excessive thirst or shivering. The mean arterial pressure in this study was calculated as $1/3 \times (\text{SBP} - \text{DBP}) + \text{DBP}$.

Data analysis

For each of the five experimental protocols in the patients, there were three hemodialysis treatments to analyze. Comparisons of values between dialysis sessions were performed by repeated-measures analysis of variance (ANOVA), and a $P < 0.05$ was considered significant. The data are expressed as the mean \pm SEM.

RESULTS

Changes in urea reduction ratio and hemoglobin concentration during each protocol

There were no significant differences in the urea reduction ratio between any of the protocols. The urea reduction ratio range was $71 \pm 5\%$ (in the cooler temperature and ultrafiltration protocols) to $78 \pm 5\%$ (in the high-sodium protocol). Similarly, the hemoglobin concentrations ranged between 10 and 10.5 g/dL in each of the protocols and were also not significantly different between maneuvers.

Delivered dialysate sodium and verification of cool-temperature dialysis

In the standard dialysis protocol, the measured dialysate sodium concentration was 138 ± 1.2 mEq/L. In the

sodium modeling protocol, the initial sodium concentration was 152 ± 1.2 mEq/L, and the ending dialysis sodium concentration was 139 ± 1.8 mEq/L. In the high-sodium dialysate protocol, the mean dialysate sodium concentration was 144 ± 1.4 mEq/L. The dialysate temperature in the cool-temperature dialysis protocols was 35°C.

Changes in weight during the dialysis protocols

As by design, the changes in absolute weight loss achieved during each of the protocols was essentially identical and varied between 2.9 and 3.0 kg. Similarly, the percentage weight loss in each of the protocols was between 3.7 and 3.8% for each of the protocols. Thus, each patient was subjected to an equivalent amount of volume depletion during each of these protocols.

Number of hypotensive episodes, frequency of nursing interventions, and hypotensive signs and symptoms during each of the protocols

The number of hypotensive episodes per treatment for each of the five dialysis maneuvers is shown in Figure 1A. As can be seen from Figure 1, there were significantly fewer hypotensive episodes per treatment when the patients were dialyzed on the high-sodium, sodium-modeling, and cool-temperature dialysis protocol as compared with the standard bath. In contrast, the ultrafiltration followed by dialysis protocol was associated with a significantly greater number of episodes of hypotension

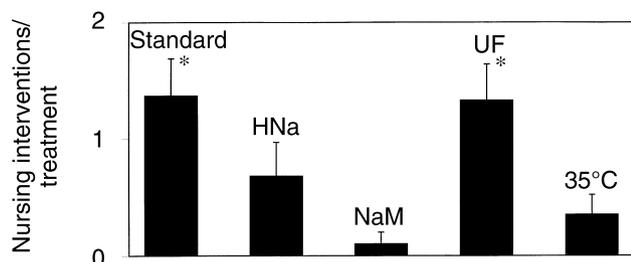


Fig. 2. Number of nursing interventions per treatment for all five protocols. The NaM and 35°C procedures required significantly fewer interventions than the other maneuvers. Abbreviations are: HNa, high-sodium dialysis; NaM, sodium modeling; UF, ultrafiltration followed by isovolemic dialysis; and 35°C, cooler temperature dialysis. * $>35^{\circ}\text{C}$, $P < 0.05$; $>\text{NaM}$, $P < 0.01$.

than any of the three test protocols. Figure 1B depicts each individual patient's number of hypotensive episodes during each of the protocols. Similarly, as shown in Figure 2, the number of nursing interventions required per treatment was significantly greater in the standard dialysis protocol and in the ultrafiltration protocol when compared with the sodium modeling and cool-temperature protocols. Finally, as shown in Figure 3, the number of hypotensive symptoms and signs per treatment was also significantly reduced during the sodium-modeling and 35°C protocols as compared with the standard bath. Again, the ultrafiltration protocol resulted in significantly more hypotensive signs and symptoms than the three test protocols. This reduction in the number of hypotensive symptoms and signs was particularly notable in the sodium-modeling protocol in which no adverse symptoms or signs were recorded during the study.

Changes in blood pressure during each protocol

As shown in Table 3, the mean blood pressure in the upright position postdialysis was lower in the standard and ultrafiltration procedures. The upright postdialysis blood pressure was best preserved in the sodium-modeling and cooler temperature dialysis protocols. Interestingly, the high-sodium dialysis procedure was associated with a lower upright postdialysis blood pressure than sodium modeling or cooler temperature despite the fact that there was a similar reduction in the number of hypotensive events observed in the high-sodium, sodium-modeling, and cooler temperature procedures (Fig. 1). The nadir in arterial pressure in the five protocols was also significantly lower in the standard and ultrafiltration followed by dialysis procedures. The nadir blood pressure was 64 ± 8 mm Hg in the standard dialysis procedure and 66 ± 8 mm Hg in the ultrafiltration procedure. The nadir blood pressure was 80 ± 14 mm Hg in sodium modeling, 72 ± 9 mm Hg in high-sodium dialysis, and 76 ± 11 mm Hg in cool-temperature dialysis. The nadir blood pressures were significantly lower ($P < 0.05$) in the standard and ultrafiltration protocols as compared with the other three maneuvers.

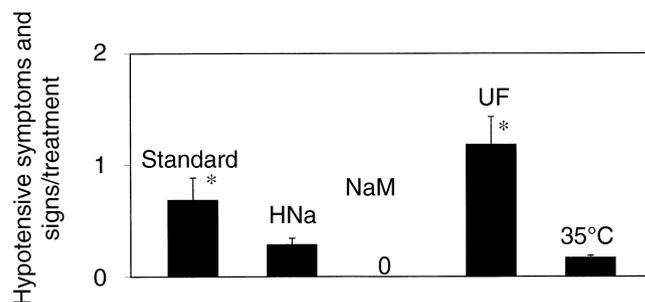


Fig. 3. Hypotensive symptoms and signs per dialysis treatment. A significant reduction in hypotensive symptoms and signs was noted in the NaM and 35°C protocols as compared with the other maneuvers. Abbreviations are: HNa, high-sodium dialysis; NaM, sodium modeling; UF, ultrafiltration followed by isovolemic dialysis; and 35°C, cooler temperature dialysis. * $>35^{\circ}\text{C}$, $P < 0.02$; $>\text{NaM}$, $P < 0.004$.

DISCUSSION

In this population of hypotension-prone patients, the results of this direct comparison of maneuvers commonly used to treat dialysis hypotension show that sodium modeling using a step-wise protocol and cooler temperature dialysate is most effective in stabilizing blood pressure throughout the dialysis procedure. The results also demonstrate significant hemodynamic benefits of a higher sodium dialysate concentration (144 mEq/L). Surprisingly, the popular procedure of performing isolated ultrafiltration followed by dialysis proved to be ineffective in preventing the occurrence of dialysis hypotension, and was also associated with hypotensive symptoms and signs more frequently than might have been expected. It should be acknowledged that the isolated ultrafiltration followed by isovolemic dialysis procedure was designed to remove 50% of the goal weight loss in the first hour of dialysis (not to exceed a total of 1.5 kg). This amount of volume reduction in one hour may be excessive for some patients. However, it is common for patients to have weight loss requirements in excess of the amount removed in this group of hypotension-prone patients so that the protocol design is reflective of the circumstances that occur in usual dialysis practice.

In the last several years, there have been a number of studies that have addressed the etiology of dialysis hypotension and sought remedies to reduce its frequency and severity. Dialysis hypotension usually presents in one of two ways: as episodic hypotension in which a sharp fall in the blood pressure (usually later in dialysis) accompanied by signs and symptoms of hypotension are noted, and chronic, persistent hypotension in which the SBP is less than 90 to 100 mm Hg at the initiation of dialysis. The latter condition is characterized by high circulating angiotensin II levels and maximal vasoconstriction predialysis [22, 23] and is more commonly recognized in individuals who have been on dialysis for a number of years. Both of these conditions are therapeutic

Table 3. Mean supine to upright blood pressures pre- and post-hemodialysis for the five protocols

	Supine MAP pre-HD	Upright MAP Pre-HD	Supine MAP Post-HD	Upright MAP Post-HD
<i>mm Hg</i>				
Standard	100 ± 15	101 ± 13	88 ± 11	78 ± 9 ^a
HNa	99 ± 12	102 ± 11	92 ± 6	80 ± 8 ^a
NaM	99 ± 13	104 ± 13	94 ± 11	91 ± 9
UF	98 ± 15	100 ± 14	86 ± 10	80 ± 8 ^a
35°C	102 ± 12	102 ± 13	94 ± 9	86 ± 11

Abbreviations are: HNa, high sodium; NaM, sodium modeling; UF, ultrafiltration followed by dialysis; 35°C, cool temperature dialysis; MAP, mean arterial pressure. ^a<NaM and 35°C protocols, *P* < 0.05

tic challenges because ultrafiltration requirements are difficult to achieve in the context of hemodynamic instability. Hemodynamic instability is particularly troublesome because it contributes to the morbidity associated with dialysis. Patients who are frequently hypotensive often feel unwell and spend the interdialytic period “recovering” from the preceding dialysis. In addition, such patients often have their dialysis procedure interrupted with delays that result in a decrease in the dialysis prescription. If dialysis hypotension occurs frequently, the patient may be chronically underdialyzed, and this may result in a further increase in morbidity and mortality [24, 25]. Chronic persistent hypotension is estimated to occur in 3 to 5% of the dialysis population, whereas episodic hypotension occurs in between 15 and 25% of all dialysis encounters [22].

Episodic hypotension has multiple etiologies. Several studies have shown that a fall in plasma osmolality as ultrafiltration proceeds compounds extracellular volume depletion because fluid moves intracellularly. This has led to the routine use of a higher sodium dialysate concentration (140 to 144 mEq/L) with reported favorable outcomes [26]. Moreover, the use of a higher sodium dialysate has been shown to be safe, although it does increase thirst and results in higher interdialytic weight gains [27]. Also helpful in combating the problem of excessive volume depletion is the routine use of volumetric dialysis machines that are able to remove volume evenly over the course of a dialysis. These machines may be adjusted to remove disproportionate amounts of volume at different times in the dialysis and thereby allow the physician to tailor the dialysis to an individual patient’s tolerance. The use of sodium modeling protocols has become more popular in the last five years and also is designed to maintain a stable plasma osmolality during the course of ultrafiltration on dialysis. Several recent studies have addressed the design of the sodium modeling protocol and have suggested that the step-wise design has advantages over linear and logarithmic sodium modeling [18]. In addition, the sodium modeling studies have also supported the use of the higher sodium dialysate at the beginning rather than at the conclusion

of the procedure [28, 29]. Hence, in the present study, we selected a step-wise pattern of sodium modeling with the higher sodium dialysate concentration at the initiation of the procedure. Of note is the fact that not all work has supported the use of sodium modeling as best tolerated by patients. In one recent study, even though blood pressure was well supported during sodium modeling protocols, patients complained of excessive thirst in the interdialytic period [29].

This study was designed to learn which of several commonly employed protective maneuvers was most effective in a population of patients in whom dialysis hypotension was frequent and disabling. Physicians and dialysis units familiar with this syndrome typically have developed individual algorithms used to treat dialysis hypotension, and the aim of the study was to provide insight into which of the procedures is actually most effective when tested under rigorous conditions. The results support the use of sodium modeling as a first step in combating dialysis hypotension. As noted previously in this article, the tolerance of patients to sodium modeling may be idiosyncratic, and therefore, it should not be surprising if all individuals are unable to tolerate a modeling protocol routinely. In this study, sodium modeling was well tolerated, with most patients (6 out of 10) reporting increased thirst that did not, in the short term, translate into larger interdialytic weight gains. Only one patient out of 10 did not tolerate it well, becoming hypertensive with nausea and headache (mean arterial pressure postdialysis 122 mm Hg). Based on the results of this and other studies [18], our results support the use of a step-wise protocol starting with the higher sodium dialysate at the beginning of dialysis.

Also effective in preventing hypotension was the use of a higher sodium dialysate and cooler temperature dialysis. Excessive thirst may occur in some patients upon exposure to the higher sodium dialysate and is roughly proportional to the concentration of dialysate sodium employed. Cooler temperature dialysis is also tolerated by most patients [19, 30, 31]; shivering and cramping occur in some patients and limit use. In the present study, 7 of 10 patients noted a “cold” sensation, and shivering

was seen in two patients. The use of isolated ultrafiltration followed by dialysis was notably ineffective in this study. As previously noted, isolated ultrafiltration may be more effective in patients who have a smaller weight loss requirement during the procedure. It is interesting to note that the majority (8 of 10) of hypotension-prone patients in this study were diabetics, which is not surprising given the high prevalence of diabetes as an etiology of end-stage renal disease and the frequency of autonomic disorders in this group of patients. We surmise that these maneuvers will be efficacious in nondiabetic hypotension-prone patients as well, but this will require further testing.

In summary, our study supports the use of sodium modeling and cooler temperature dialysis as first options in treating hypotension-prone patients; a higher sodium dialysate is also a reasonable therapeutic option. The use of midodrine as an adjunctive modality is also rational in patients with repeated bouts of dialysis hypotension [32]. Finally, the current study did not address the therapeutic efficacy of combinations of these maneuvers. The rigorous testing of several combination maneuvers would be of interest and is meritorious of future investigation.

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