Impact of sodium profiling on ambulatory blood pressure in patients on maintenance hemodialysis

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SUMMARY
Introduction/Objective Most patients with end-stage renal disease (ESRD) have hypertension. However, dialysis-related strategies to optimize blood pressure in these patients remain controversial. The current study aims to investigate the influence of dialysate sodium profiling on ambulatory blood pressure (ABP) in patients on maintenance hemodialysis, when there are no adequate dialytic and economic resources or high patient compliance.

Methods This prospective, single-center study enrolled 60 hypertensive ESRD patients. Subjects received maintenance dialysis with regular dialysate sodium concentration (140 mmol/L) during the initial three months after the enrollment, and were randomly assigned to continue regular sodium dialysate (group A) or switch to sodium profiling (group B) for duration of three months. ABP, heart rate (HR), pre-/postdialysis serum sodium levels, antihypertensive treatment dosages, and interdialytic weight gain (IDWG) etc. were recorded after treatment assignment.

Results Thirty patients each were enrolled in groups A and B. The characteristics at baseline were not significantly different between the two groups. Compared to patients in group A three months later, patients in group B had lower systolic ABP (p = 0.00), HR (p = 0.04), IDWG (p = 0.04), and antihypertensive medication dosages (p = 0.04). Throughout the treatment duration, no significant inter-group differences were observed for pre-/post-dialysis serum sodium and intra-dialytic complications. Additionally, no significant correlations were found between systolic or diastolic ABP and other variables studied in this study.

Conclusion In this study, we found that dialysate sodium profiling successfully ameliorated hypertension and reduced BP medications without altering natremic levels or increasing complications among patients on maintenance hemodialysis during the three months. Dialysate sodium profiling was relatively safe in this duration.

Keywords: ambulatory blood pressure; end-stage renal disease; sodium profiling; hemodialysis

INTRODUCTION
Hypertension is frequently observed in patients with advanced chronic kidney disease (CKD) and end-stage renal disease (ESRD). More than 90% of patients with advanced CKD have hypertension, which persists even after progression to ESRD [1]. In addition, blood pressure (BP) variability is a risk factor for adverse outcomes among hypertensive patients; patients on maintenance dialysis are more susceptible to adverse impact of BP fluctuations due to increased vascular stiffness and dialysis-related body fluid shift. In 2009, a meta-analysis mostly incorporating randomized controlled trials found that reduction of BP is closely associated with lower risk of cardiovascular events, better all-cause mortality, and cardiovascular mortality among patients on maintenance dialysis [2].

Rahman et al. [3] found that hypertensive ESRD patients had significantly higher blood volume, plasma volume, and extracellular fluid levels than normotensive patients with ESRD. In ESRD patients undergoing maintenance hemodialysis, it is now recognized that refractory hypertension and sodium and fluid retention might result from impaired homeostasis associated with loss of renal function. Sodium and fluid retention plays an important role in the pathogenesis of hypertension in ESRD patients, and the sodium-potassium balance is crucial to endothelium-dependent vascular dilatation. Determinants of salt and water retention in ESRD patients primarily include dietary sodium intake, sodium gain from high-sodium dialysate, and the dialytic modality and schedule (usually thrice weekly) for sodium clearance [4, 5].

Greater ultrafiltration during dialysis and dry weight lowering is beneficial for BP reduction, decreasing predialysis systolic BP, left ventricular volume, and antihypertensive medication dosage. A recent study lends support to this theory by showing that enhanced dialysis sodium removal can ameliorate arterial stiffness, left ventricular hypertrophy, and interdialytic weight gain (IDWG) [6]. Thus, maintaining the balance of sodium and extracellular fluid plays an important role in IDWG modulation. Del Giudice et al. [7] found that
The primary endpoints of this effective study were changes on maintenance dialysis, to instruct clinical intervention. Lytic ABP, and we sought to investigate this issue in patients. Therefore, we performed this study and tried to find a suitable way to relieve their hypertension in our center. Thus believe that such procedures are beneficial to patients facing difficulty in reaching dry weight due to the adverse effects of dialysis.

In addition, recent studies suggest the superior prognostic importance of ambulatory BP (ABP) monitoring compared to single BP measurement and its facilitation of adequate BP control in patients on dialysis [9]. Guidelines from the American Heart Association and European Hypertension Society recommend ABP monitoring in all hypertensive patients [10].

People in Chinese Shandong province usually have a dietary habit of high salt, and the IDWG of our patients was in the range of 0.5–3.5 kg or more. Large IDWG requires high ultrafiltration rate, which is always followed by dialysis instability, some patients even could not eliminate the superfluous fluid in one dialysis course. But according to Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, patient's IDWG should not exceed 1 kg during the week and 1.5–2 kg during the weekend. IDWG of more than 4.8% (i.e. 3.4 kg in a 70 kg person) is a reflection of excessive sodium and water intake, and is associated with increased mortality.

A large percentage of patients in our dialysis center comprised refractive hypertension, probably because of superfluous fluid and sodium. Although we prescribed them with restricted sodium and water diet, tried to use 138 mmol/l or lower dialyzate sodium, tried to normalize Kt/V and to increase the frequency of dialysis etc., there was no ideal result, which might be due to low compliance with clinicians' advices. Additionally, as a result of our country's limitations in dialytic and economic resources, we neither have enough dialysis machines to meet longer dialysis session time nor can we afford high flux dialyzers every time. Subjects were included when mean systolic ABP levels were above 150 mmHg. Patients with a history of arrhythmia (atrial fibrillation or frequent premature complexes), major cardiovascular or cerebrovascular events within three months preceding the enrollment, active infection or concurrent malignancy, and prominent subcutaneous edema or pericardial effusion on cardiac ultrasonography were excluded.

Study procedure

All participants underwent a washout period of three months with a regular dialysate sodium concentration (140 mmol/L) before commencing study treatment. All patients were prescribed low salt, limited fluid intake before this trial, and did not perform any alterations in dietary habits or new dietary instructions. All subjects underwent maintenance hemodialysis using polysulphone-based membrane thrice weekly for four hours, low flux dialyzers routinely and high dialyzers twice a month. Subjects were randomly assigned to either regular sodium dialysate (group A) or sodium profiling (group B) groups. Dialysate for group A patients comprised a bicarbonate-based formula, with a fixed sodium, potassium, and calcium levels of 140 mmol/L, 2.5 mmol/L, and 1.5 mmol/L, respectively. Dialysate for group B patients consisted of an adjustable formula, which comprised an initial sodium level of 148 mmol/L and a linear reduction to 132 mmol/L over the treatment period, and potassium and calcium levels of 2.5 mmol/L and 1.5 mmol/L, respectively. The blood flow rate for each patient ranged between 200 mL/min. and 280 mL/min.; dialysate flow rate and temperature were 500 mL/min. and 37°C, respectively, with anticoagulation using unfractionated or low–molecular-weight heparin.

In study subjects, pre- and post-dialytic serum sodium and urea were measured once a month at the central laboratory of the hospital. The formula Kt/V was utilized.
to evaluate the adequacy of each dialysis session. Kt/V was calculated according to a natural logarithm formula 
\[ Kt/V = \ln (R - 0.008 \times t) + (4 - 3.5 \times R) \times UF/W, \]
where R is postdialysis blood urea nitrogen and predialysis blood urea nitrogen, t is session length in hours, UF is ultrafiltration volume in liters, and W is postdialysis weight in kg [11].

**Study endpoints**

Parameters included in primary and secondary endpoints were monitored. On the interdialytic day of the first week of each month, sitting BP and HR were measured after patients rested for 10 minutes at three time points (morning, noon, and evening) and the mean of the three measurements was recorded as the value for that day. Mean values of ABP and HR were documented from data obtained on consecutive interdialytic days in that week. The patients were censored if their ABP decreased to less than 130/80 mmHg during the intervention period or after three months of treatment.

Antihypertensive medication dosage was quantified with the defined daily dose (DDD) approach for each type of medication [6]. For patients on more than one antihypertensive medication, we calculated the sum of DDD from all medications to represent the antihypertensive dosage. IDWG was calculated from the difference between body weight measured after one dialysis and that measured before the next session, which was divided by their dry weight and the mean of measurements from consecutive interdialytic days of the first week of each month was calculated.

Safety endpoints included intradialytic hypovolemia-related complications. We recorded the monthly frequency of dialysis-related hypotension and muscle cramping. Dialysis-related hypotension was defined as a decrease in systolic BP of more than 20 mmHg or a decrease in mean BP of more than 10 mmHg, accompanied by symptoms of hypotension requiring clinical interventions. Muscle cramping referred to intradialytic painful muscle contractions unaccompanied by hypotension, amenable to improvement by a local massage and saline infusion.

**Statistical analysis**

We used SPSS Statistics for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA) for statistical analysis. Continuous variables are expressed as mean ± standard deviation; normal distributions of the variables were examined. Comparison of data normal distributions was done by Student's independent t-test. Blood urea nitrogen, DDD, IDWG were not normal distributions and were tested by Mann–Whitney U-test. Categorical data were analyzed by \( \chi^2 \) test. Pearson analysis and multi-factor regression analysis were performed to find the correlation between ABP and other variables. A p-value of less than 0.05 was considered statistically significant.

**RESULTS**

Sixty patients [male, 27; mean age 45 ± 12.3 (range 25.5–65) years] on maintenance hemodialysis were enrolled. The mean duration of dialysis was 5.7 ± 2.6 years (range 1.5–10.5 years). ESRD etiologies in these patients were: 35 (58.3%) chronic glomerulonephritis, 10 (16.7%) diabetic nephropathy, and 15 (25%) hypertensive glomerulosclerosis.

**Baseline parameters: inter-group comparison**

Of the 60 participants, 30 were assigned to group A (46.7% male) and 30 to group B (43.3% male). Mean age and duration of dialysis were 45.4 ± 13.1 and 5.8 ± 2.7 years for group A, 44.7 ± 11.6 and 5.7 ± 2.6 years for group B. No significant inter-group differences existed for baseline characteristics, including hemoglobin, total protein, albumin, calcium, phosphates, potassium, urea, creatinine, total protein, antihypertensive medication dosage, IDWG status, intradialytic hypotension, and muscle cramping (Table 1). Pretreatment ABP, HR, pre- and postdialysis
serum sodium, and Kt/V did not differ between group A and B patients.

**Endpoints**

After dialysate sodium profiling for three months, group B patients did not have significant alterations in their pre-/postdialysis serum sodium, dialysis adequacy measures, IDWGs, and intradialytic hypotension / muscle cramping compared to group A (Table 2).

However, group B patients had significantly lower systolic (p < 0.01), diastolic ABP (p < 0.01) and HR (p = 0.04) compared to patients in group A. Antihypertensive medication dosage also decreased significantly in group B patients compared to group A (p = 0.04) (Table 1).

IDWG for group B patients decreased from 4.4 ± 1.5 kg at baseline to 3.8 ± 1.2 kg at three months, with a significantly lower level at three months than in patients in group A (p = 0.04) (Table 2).

**Correlation analysis**

We performed Pearson analysis and multi-factor regression analysis, but did not find any significant relation between systolic or diastolic ABP and other variables (data not show).

**DISCUSSION**

This is an effective study designed to compare the effect of sodium profiling with sodium dialyzate concentration of 140 mmol/L, which is the routine sodium dialyzate concentration in our dialysis center, as well as many centers in our country, maybe some other countries as well. This study tried to use adjustable sodium dialysis, adjusted the ultrafiltration according to the IDWG and the tolerance of each patient, to exclude more fluid in one dialysis course, get near to the dry weight, lowering the ABP, without increasing dialysis adverse events. We previously found that dialysate sodium profiling can reduce postdialysis BP in hypertensive patients on maintenance hemodialysis [12]; in the current study, we further identified that dialysate sodium profiling, compared to regular dialysate sodium status, effectively decreases intradialytic ABP and use of antihypertensive medication. Another study similarly showed that low-sodium dialysate can reduce morning and night ABP over a period of six months [13]. Inrig et al. [14] conducted a randomized study, comparing hemodialysis patients receiving low- and high-sodium dialysate for three weeks, and found that low-sodium dialysate leads to a mean 9-mmHg decrease in systolic BP, consistent with our findings. Our study extends their findings by demonstrating the similarly favorable effect of dialysate with adjustable sodium on ABP parameters, antihypertensive medication dosages, and IDWG in patients on maintenance hemodialysis.

In sodium profiling, hypernatremic dialysates are used at the beginning of the dialysis process. Sodium content of the dialysate is then gradually reduced to allow excess sodium to be removed from the blood. High sodium concentration in this method facilitates the movement of water from the interstitial space into the intravascular space and results in better maintenance of intravascular volume and fewer adverse effects during dialysis. In this study, we used high-sodium dialysate (148 mmol/L) initially during each session, and linearly reduced dialysate sodium concentrations over time (finally to 132 mmol/L) to facilitate removal of excessive sodium. This maneuver did not affect serum sodium and intradialytic BP after three months; the systolic and diastolic ABP and HR all significantly improved after dialysate sodium profiling, whereas these parameters did not alter in the control group.

Intradialytic complications such as hypotension and muscle cramping are frequently associated with dialysis intolerance, the reduction of blood flow and dialysis duration, leading to lower dialysis adequacy (Kt/V) [15]. From this study, we found that, compared to regular dialysate sodium group, dialysate sodium profiling did not increase these complications significantly, which is consistent with results from previous studies [11]. However, despite the fact that there are already multiple studies addressing the effect of dialysate sodium profiling on improving hypertension in patients on maintenance hemodialysis, some believe that high concentrations of sodium in sodium profiles will lead to not only increased thirst and intradialytic weight gain (which means the need for removing greater volumes of fluids to reach dry weight and higher frequency of hypotension) but also hypertension [11]. Thus, sodium in sodium profiles nowadays should only be used in short time, with adequate assessment of patients’ response. Once there is improvement in fluid load and ABP, dialysis mode should be back to the routine mode.

**Table 2. Inter-group comparison of parameters at post-assignment**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A</th>
<th>Group B</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kt/V*</td>
<td>1.38 ± 0.10</td>
<td>1.40 ± 0.10</td>
<td>0.442</td>
</tr>
<tr>
<td>Pre-dialysis serum sodium (mmol/L)*</td>
<td>139.5 ± 2.8</td>
<td>138.7 ± 2.9</td>
<td>0.281</td>
</tr>
<tr>
<td>Post-dialysis serum sodium (mmol/L)*</td>
<td>136.5 ± 2.8</td>
<td>136.3 ± 3.0</td>
<td>0.790</td>
</tr>
<tr>
<td>Antihypertensive medication dosage (DDD)#</td>
<td>4.4 ± 2.3</td>
<td>3.3 ± 1.7</td>
<td>0.039</td>
</tr>
<tr>
<td>Intradialytic hypotension (events/month)**</td>
<td>20</td>
<td>12</td>
<td>0.156</td>
</tr>
<tr>
<td>Intradialytic cramping (events/month)</td>
<td></td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Interdialytic weight gain (%)#</td>
<td>4.44 ± 1.17</td>
<td>3.80 ± 1.18</td>
<td>0.039</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)†</td>
<td>154.67 ± 18.32</td>
<td>138.00 ± 18.19</td>
<td>0.000</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)‡</td>
<td>109.47 ± 14.88</td>
<td>85.34 ± 12.90</td>
<td>0.000</td>
</tr>
<tr>
<td>Heart rate (beats/min.)*</td>
<td>78 ± 6</td>
<td>75 ± 8</td>
<td>0.039</td>
</tr>
</tbody>
</table>

DDD – daily defined dose;
*Data were normal distributions and comparisons were made using Student’s independent t-test; #Data were not normal distributions and comparison were made using Mann–Whitney U-test;
**Data were categorical and comparisons were made using χ² test; p-value of less than 0.05 was considered statistically significant.
Therefore, more studies, especially those with large sample size, conducted at multiple centers, and of longer duration, are needed to verify the benefit of this approach. Other issues such as ultrafiltration profiling and individualized sodium profiling regimens also await further investigation. Our study is limited in several aspects. The case number is modest, and cardiac as well as vascular stiffness parameters were not collected during the study. However, our findings have merit because adjustable sodium dialysate for BP control is scarcely addressed in the literature.

CONCLUSION

This study found that, in patients on maintenance hemodialysis, adjustable sodium dialysis can reduce ABP, HR, antihypertensive medication dosage, and IDWG. These findings contribute to the current literature by showing that adjustable dialysate sodium has a beneficial effect on hemodynamic parameters similar to that with low-sodium dialysate in patients on hemodialysis, and we did not increase dialysis adverse events in the three months. Further study is needed to confirm our results.

NOTE

Zhang Yue-yue and Zhai Li-hui have equally contributed to this paper and should be considered to be first co-authors.

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REFERENCES

Увод/циљ
Већина болесника са терминалном болешћу бубрега (ТББ) има хипертензију. Међутим, стратегија за дијализу везана за оптимизацију крвног притиска код ових болесника остаје контроверзна. Циљ овог рада је да испита утицај подешавања натријума у дијализату на крвни притисак (КП) мерен целог дана код болесника на дугорочну хемодијализу у условима неодговорајућих дијализних и економских ресурса.

Методе
Проспективна студија у једном дијализном центру обухватала је 60 хипертензивих болесника са ТББ. Прва три месеца сви су били су на дијализи са натријумом у дијализату од 140 mmol/L, а потом насумично подељени у групу А (иста дијализа) и групу Б (подешен натријум у дијализату). Групе су дијализиране три месеца, када су им праћени следећи параметри: целодневни КП, пулс, натремија пре и после дијализе, дозе антихипертензивних лекова (АЛ) и међудијализни прираст телесне масе (МДТМ).

Резултати
Почетне вредности контролисаних параметара нису се значајно разликовале између група. После три месеца болесници групе Б су у односу на групу А имали значајно нижи систолни КП (p = 0,02) и пулс (p = 0,03) у односу на њихове почетне нивое, мањи прираст МДТМ (p = 0,04) и мање дозе АЛ (p = 0,04). Између група нису уочене значајне разлике у натремијама пре и после дијализе, као ни у учесталости интразијализних компликација. Такође, нису пронађене значајне везе између систолног и дијастолног КП и других праћених варијабли у овој студији.

Закључак
Подешавање натријума у дијализату успешно смањује хипертензију и дозе АЛ, без мењања натремије и повећања учесталости компликација хемодијализе.

Кључне речи: холтер крвног притиска; крајњи стадијум бубрежних болести; натремија; хемодијализа