Impact of Sodium and Ultrafiltration Profiling on Hemodialysis-Related Symptoms

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Abstract. Dialysate sodium and ultrafiltration profiling are two methods to reduce symptoms during hemodialysis. The objective of the study was to determine the efficacy of combining these techniques to reduce symptoms in chronic hemodialysis patients. Blood volume changes were measured to determine whether any benefit of profiling could be explained through this mechanism. Patients were randomized to profiled dialysate sodium and ultrafiltration or constant dialysate sodium and ultrafiltration. The study was a two-period, two-treatment, crossover design with repeated measures. The primary outcome was hypotension and/or symptomatic events observed by the dialysis nurse. Secondary outcomes were symptom survey scores, weights, BP, and blood volume changes. Thirty-three patients were randomized. On standard treatment, 30.6% of dialysis sessions were symptomatic compared with 20.4% on profiled treatments. The odds ratio for development of hypotension or symptomatic event on profiled treatments was 0.61 (95% confidence interval, 0.39 to 0.96) compared with standard treatment. Patients had lower symptom scores by questionnaire in both the intradialytic and the interdialytic periods during profiled treatments. Predialysis weight was greater during profiled treatments by 0.3 kg ($P = 0.008$), but there were no differences in postdialysis weight, BP, or thirst. There was no difference in maximum decrease in blood volume during the two treatments (standard, $-11.2\%$; profiled, $-10.0\%$; $P = 0.08$), but there was a significant difference in the rate of change in blood volume (standard, $-2.96\%/h$; profiled, $-1.96\%/h$; $P < 0.001$). Decrease in blood volume, rate of change in blood volume, and predialysis weights were not associated with hypotension or symptomatic dialysis sessions. In conclusion, dialysate sodium and ultrafiltration profiling significantly reduces hemodialysis-related symptoms. Profiling reduces the slope of the blood volume curve during dialysis, but blood volume changes are not predictive of symptomatic events for an individual patient.

Despite technological advances in the field of hemodialysis, treatments are still symptomatic for many patients (1). One technique to reduce symptoms during dialysis is to increase the dialysate sodium concentration. This can be adjusted manually or automatically using computer controlled profiles available on many dialysis delivery systems. Studies of sodium profiling generally have shown a reduction in intradialytic symptoms but at the expense of increased symptoms between dialysis treatments (2–11).

Similarly, ultrafiltration can be profiled such that the majority of fluid is removed early in the dialysis treatment. If dialysate sodium and ultrafiltration profiling are combined, high fluid removal can be matched to high dialysate sodium concentration early in dialysis. This technique should effectively reduce intradialytic symptoms but has undergone limited critical evaluation (12,13).

Monitoring of blood volume change during dialysis may provide further insight into the cause of patients’ symptoms during dialysis. Blood volume changes have been associated with BP changes (14), hypotensive events (15), and hydration status (15). It is unclear whether blood volume changes for an individual patient can reliably predict symptomatic events.

The primary objective of this study was to determine whether the combination of sodium and ultrafiltration profiling was effective in reducing intradialytic symptoms without increasing interdialytic symptoms. Blood volume monitoring was performed to determine the effect of profiling on blood volume and the relationship of blood volume to patient symptoms.

Materials and Methods

Study Group
Patients were recruited from the hemodialysis center at St. Joseph’s Hospital, Hamilton, Canada, from February 1998 to April 1998. This hospital-based outpatient dialysis center serves approximately 400 patients. Patients were approached if they were experiencing symptoms during dialysis. Unstable patients and those who were unable to complete questionnaires in English were excluded. The ethics research committee approved the protocol, and all patients gave informed consent.
**Intervention**

The study was a two-period, two-treatment crossover design with repeated measures. Patients were randomized to begin with either 2 wk of standard dialysis or 2 wk of profiled dialysis. At the end of the first 2 wk, the patients immediately crossed over to the other treatment for 2 wk. The randomization schedule was generated by random number tables and was concealed in opaque envelopes. During the profiled treatments, the initial dialysate sodium concentration of 152 mmol/L was decreased exponentially over the first 150 min to 142 mmol/L and thereafter kept constant (148, 146, 144, 143, 142 mmol/L at 30, 60, 90, 120, and 150 min, respectively). The ultrafiltration rate automatically decreased exponentially so that fluid removal was greatest during the period of high sodium concentration. During standard dialysis treatment, the dialysate sodium was held constant at 142 mmol/L and the ultrafiltration rate was constant.

In both periods, treatments were 4 h in duration and used dialysate with calcium 2.5 mmol/L, bicarbonate 35 mmol/L, and temperature of 36.5°C. Euvolemic weight was determined clinically by each patient’s primary nephrologist and was not altered during the study. Antihypertensive and cardiac medications did not change during the study. All treatments were performed on Althin System 1000 dialysis machines (Althin Medical Inc., Ronnaby, Sweden).

**Outcome Assessment**

Patients were assessed at each dialysis session (6 per period) and at weekly intervals (2 per period). During each dialysis session, the dialysis nurse recorded any hypotension or symptoms and interventions used to treat them. Events were classified as hypotension if the systolic BP was less than 100 mmHg, or as dizziness, cramps, nausea, headache, or other. Interventions were at the nurses’ discretion but generally followed the sequence of Trendelenburg position followed by decreasing or stopping ultrafiltration followed by normal saline infusion. Dialysis was rarely discontinued. The dialysis nurses were not blinded to the protocol because they believed that knowledge of ultrafiltration rates was required to respond appropriately to hypotension or symptoms during dialysis. Dialysis system monitors were not concealed during treatments, but nurses and technicians were repeatedly instructed not to reveal the treatment protocol to the patients. Patient weight, supine BP, and heart rate were recorded before and after each treatment. Ultrafiltration volume was calculated as the difference in weight before and after dialysis or by measured ultrafiltration volume if weights were unavailable. Blood volume was recorded at 20-s intervals throughout the dialysis treatment using a Crit-line monitor (In-line diagnostics, Salt Lake City, UT); blood volume monitoring was suspended during infusions of intravenous iron or blood products.

At the end of each week, patients completed a questionnaire grading the severity of intradialytic and interdialytic symptoms experienced during that week. Intradialytic symptoms evaluated were muscle cramps, dizziness, headaches, nausea, and overall symptoms. Interdialytic symptoms were fatigue, muscle cramps, nausea, thirst, headache, dizziness, shortness of breath, swelling, and overall symptoms. Serum electrolytes, calcium, complete blood counts, and urea reduction ratios were measured weekly.

At the completion of the study, patients were grouped according to frequency of symptoms (asymptomatic, occasional, frequent, and very frequent) for descriptive purposes.

**Estimation of Blood Volume Parameters**

Blood volume measurements were calculated as a percentage reduction from the start of dialysis and were relative, not absolute. Blood volume was plotted versus time to generate blood volume curves for each treatment. Visual inspection of these curves revealed that blood volume occasionally changed rapidly (usually over 1 to 2 min) and return to baseline without a clinical explanation. These data were judged to be artifact and censored using a standard algorithm.

![Figure 1](image.png)

*Figure 1.* Methods used to calculate minimum blood volume and rate of change in blood volume. Blood volume data were first censored for artifact and after any intervention to treat a symptom. The minimum blood volume usually occurred immediately before a symptom, but if the treatment was asymptomatic, then the minimum blood volume usually occurred at the end of the dialysis treatment. A regression line that is drawn approximately represents the rate of change. The actual regression analysis accounts for the related nature of the values and does not assume independence of observations like traditional regression.
Blood volume would also rise rapidly after an intervention (e.g., saline bolus), so blood volume data were censored after an intervention. An example of this censoring process is displayed in Figure 1. After censoring, the maximum decrease in blood volume (nadir) and rate of change in blood volume (slope of the blood volume curve) were calculated as an average over each dialysis session. The mean maximal decrease in blood volume and rate of change in blood volume for profiled and standard treatments were estimated from mixed models that accounted for the repeated measures within individuals.

**Statistical Analyses**

Longitudinal analysis techniques were used to account for repeated measures within individuals over time (16). Mixed models were used to analyze continuous outcomes, and the generalized estimating equation approach (17) was used to analyze binary outcomes. Both of these techniques adjust for the correlation of measurements made within patients over time and allow for the testing of period, sequence, and carryover effects that may occur during crossover studies.

In the primary analysis, the relationship between the dialysis treatment (standard/profiled) and whether the dialysis session was symptomatic (yes/no) was modeled. In a secondary analysis, maximum decrease in blood volume, rate of change in blood volume, predialysis weight, and postdialysis weight were added as covariates to the model to determine whether they independently predicted whether the treatment was symptomatic.

Total symptom scores for the intradialytic and interdialytic periods were calculated by summing the separate symptom scores in each period and modeled using the same techniques. The paired t test and the Wilcoxon signed-ranks test were used to compare paired differences when appropriate. All analyses were conducted using SAS software version 6.12 (SAS Institute Inc., Cary, NC).

**Results**

**Data Collection**

Thirty-three patients were enrolled in the study (15 women, 18 men). Four patients did not complete the protocol. One patient had a myocardial infarction and was withdrawn before randomization; two patients withdrew from standard dialysis because of cramps; one patient died from a cardiac arrest during the period of profiled treatments. After review, the death was believed to be unrelated to the dialysis treatment. Data from both standard and profiled treatments were available from 32 patients. Baseline patient characteristics according to frequency of symptoms are presented in Table 1.

Nurses monitored patients for hypotension or symptomatic events during 369 dialysis treatments (188 standard, 181 profiled). Data were not collected from six treatments because they were performed at unscheduled times. One patient received a standard dialysis treatment instead of the intended profiled session, so this session was included in the standard group. Of the 369 treatments, blood volume data were available for 86% of standard sessions and 91% of profiled sessions. The primary reason for missing blood volume data was improper use of the Crit-line monitor. Iron infusion or transfusion invalidated blood volume measurement during three treatments.

**Intradialytic Symptomatic Events and Interventions**

Patients in 96 of 369 (26%) dialysis treatments experienced events of either hypotension or symptoms. Within these 96 treatments, 130 individual events were observed. Seventy-two, 14, and 10 dialysis treatments were complicated by one, two, or three events, respectively. Of standard treatments, hypotension or symptoms occurred in 30.6%, compared with 20.4% of the profiled treatments ($P = 0.03$). The odds of experiencing an event during profiled treatments was 0.61 (95% confidence interval, 0.39 to 0.96), and the odds of receiving an intervention during a profiled treatment was 0.62 (95% confidence interval, 0.38 to 0.99) compared with standard dialysis. Hypotension was the most commonly observed event, but specific events and interventions were not statistically different between the groups (Table 2). The average time to the first event in the profiled group was 147 min compared with 182 min in the standard group ($P < 0.001$). Sequence of treatment, period of treatment, and day of treatment were not significant. The

<p>| Table 1. Baseline patient characteristics according to symptomatic profilea |
|-----------------------------|----------------|----------------|---------------- |</p>
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>None</th>
<th>Occasional</th>
<th>Frequent</th>
<th>Very Frequent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>7</td>
<td>10</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Age (y)</td>
<td>71.5</td>
<td>72.8</td>
<td>67.8</td>
<td>65.8</td>
</tr>
<tr>
<td>No. women</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Diabetic (%)</td>
<td>14</td>
<td>30</td>
<td>50</td>
<td>26</td>
</tr>
<tr>
<td>Antihypertensive or cardiac medications (%)</td>
<td>86</td>
<td>40</td>
<td>75</td>
<td>43</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>123</td>
<td>110</td>
<td>110</td>
<td>117</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>2.3</td>
<td>2.2</td>
<td>2.2</td>
<td>2.3</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>37.3</td>
<td>36.0</td>
<td>35.3</td>
<td>37.3</td>
</tr>
</tbody>
</table>

a Patients are classified into symptomatic group on the basis of frequency of symptomatic treatments that occurred over the course of 12 hemodialysis sessions. Those with 1 to 2 symptomatic treatments were classified as occasional, 3 to 5 symptomatic treatments were classified as frequent, and $\geq$6 symptomatic treatments were classified as very frequent.
Intradialytic Blood Volume Changes

The maximum decrease in blood volume during the dialysis treatment was \(-11.2\%\) on standard treatments and \(-10.0\%\) on profiled treatments \((P = 0.08)\). On average, the blood volume decreased at 2.96%/h during standard treatments and 1.96% during profiled treatments \((P < 0.001)\). Blood volume changes at hourly intervals are presented in Table 3. During standard dialysis, the slope of the blood volume curve was relatively constant but the slope decreased over the course of dialysis during profiled dialysis. Early in dialysis, the overall decrease in relative blood volume was less on standard treatments but by the end of dialysis was greater than profiled treatments.

Interdialytic Symptom Scores and Other Outcomes

Interdialytic symptoms were modestly reduced during profiled treatments. The total interdialytic survey score was 20.3 on standard treatments and 19.0 on profiled treatments \((P = 0.05)\). Individual symptoms were not significantly different between profiled and standard treatments. These include patient-reported thirst, shortness of breath, and edema. Postdialysis serum sodium was greater during profiled treatments (140.8 mmol/L) compared with standard treatments (139.6 mmol/L; \(P = 0.002\)). Predialysis weight was greater by a mean of 0.3 kg during profiled dialysis \((P = 0.008; \text{Table 4})\). There was no
Table 4. Patient weights, ultrafiltration volume, serum sodium, and urea reduction ratios according to dialysis treatment profile

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standard</th>
<th>Profiled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predialysis weight (kg)a</td>
<td>71.7</td>
<td>72.1</td>
</tr>
<tr>
<td>Postdialysis weight (kg)</td>
<td>69.1</td>
<td>69.2</td>
</tr>
<tr>
<td>Net ultrafiltration (L)b</td>
<td>2.6</td>
<td>2.9</td>
</tr>
<tr>
<td>Predialysis supine BP (mmHg)</td>
<td>151/79</td>
<td>149/78</td>
</tr>
<tr>
<td>Postdialysis supine BP (mmHg)</td>
<td>134/74</td>
<td>137/76</td>
</tr>
<tr>
<td>Predialysis sodium (mmol/L)c</td>
<td>137.0</td>
<td>137.3</td>
</tr>
<tr>
<td>Postdialysis sodium (mmol/L)c</td>
<td>139.7</td>
<td>141.0</td>
</tr>
<tr>
<td>Urea reduction ratio (%)</td>
<td>69.9</td>
<td>69.9</td>
</tr>
</tbody>
</table>

a \( P = 0.008 \)

b \( P = 0.002 \)

c \( P = 0.001 \)

Discussion

This study demonstrated that a combination of dialysate sodium and ultrafiltration profiling reduced hypotension and symptoms related to hemodialysis with minimal adverse effects. Patients on profiled dialysis were 39% less likely to experience an adverse event and 38% less likely to require an intervention to treat the event. Profiling significantly reduced the rate of blood volume decline but not the nadir of blood volume. These results differ from other studies of high dialysate sodium because the majority of these studies demonstrated adverse effects—particularly in the interdialytic period. Patients who are exposed to a high dialysate sodium concentration throughout dialysis have shown increased serum sodium, serum osmolality, weight gain, and hypertension (2–5). Patients who were exposed to a high dialysate sodium concentration early in the dialysis treatment (sodium profiling) experienced similar effects with the addition of increased fatigue, thirst, and overall symptom scores (6–11).

Studies of combining sodium and ultrafiltration profiling suggest that adverse effects may be less than when constantly high or profiled sodium dialysis is used. Dumler \textit{et al.} (13) exposed 10 patients to 150 mmol/L of sodium for the first 3 h of a 4-h dialysis treatment and performed all ultrafiltration in the first 3 h. Levin and Goldstein (12) exposed 29 patients to decreasing dialysate sodium from 155 to 160 mmol/L to 140 mmol/L over the first 3 h of a 4-h dialysis treatment, and 12 of 29 received decreasing ultrafiltration rates. Both studies report reduced intradialytic symptoms. Dumler \textit{et al.} reported only increased serum sodium during dialysis; Levin and Goldstein found increased serum sodium and thirst but no significant weight gain. Our results support these observations by demonstrating a clear benefit of combination profiling with acceptable levels of adverse effects. Our patients had small but significant increases in postdialysis serum sodium and predialysis weight but no changes in postdialysis weight or BP. Moreover, these changes were not reflected in increased symptom scores during the interdialytic period; in fact, scores were modestly reduced. This overall adverse effect profile likely is acceptable, in the short-term, because patients received significant reductions in intradialytic morbidity during combination profiling. Worsening of adverse effects has not been reported when sodium profiling has been used for months (5,12), but further long-term study of combination profiling is necessary before this technique can be recommended chronically.

The study also provides insight into the relationship between symptomatic events and blood volume. Although the cause of intradialytic symptoms is multifactorial, blood volume changes likely play a role. Patients with large decreases in blood volume are more likely to be hypotensive during dialysis, and interventions that are based on blood volume changes have reduced patient symptoms (14,15,18). However, for an individual patient, whether blood volume changes closely correlate to symptomatic events is less certain. In this study, neither the rate of change in blood volume nor the maximal decrease in blood volume correlated significantly with symptomatic dialysis sessions. Also, blood volume changes did not explain the benefit of profiling when profiling clearly reduced symptoms. These results suggest that using blood volume changes to predict symptoms or target interventions may be more difficult than first suspected. Part of the difficulty arises from the complexity of analyzing blood volume. In this study, we were able to include all of the blood volume data, excluding censored values, but it was still necessary then to generate an average over the course of the dialysis treatment. Using these methods, we found no relationship, but we accept that correlation between blood volume changes and symptoms may improve if the relationship between time on dialysis and blood volume is examined further. Ideally, factors such as patient age, diabetes, and left ventricular function should also be considered.

Combination profiling modestly altered the rate of change but not the maximal decrease in blood volume. Other inves-
gators have found more dramatic differences in blood volume change during profiled and standard dialysis. Coli et al. (19) in a one-session crossover study of 12 patients found that the maximum blood volume change was −17% during standard dialysis and −10% during sodium profiled treatments. Notably, patients in that study did not receive profiled ultrafiltration.

The results of this study may also be limited because of observer bias from lack of blinding. The intention of the study was to observe differences in clinically meaningful symptoms that dialysis nurses typically would respond to during usual care. Indeed, nurses intervened for most symptoms in this study, and the most common event was hypotension, which is objective. Nonetheless, the recording of these events may have been biased because of unblinding. Blinding of nurses was not considered practical because knowledge of ultrafiltration rates was believed to be important for patient care. Similarly, although the treatment allocation was not revealed to patients, an astute patient could have deduced it from ultrafiltration rates displayed on the dialysis monitor. If either the nurses or the patients had been biased in favor of profiling and had under-reported symptoms, then the true benefit of profiling would be less. We believe that these effects are minimal because the most common event was hypotension, events generally required intervention, and the two treatments were presented to patients and nurses as equivalent. However, formal assessment of blinding was not done and therefore we cannot completely rule out a large effect of bias.

In conclusion, we demonstrated that combined dialysate sodium concentration and ultrafiltration profiling reduces intradialytic symptoms compared with standard dialysis with constant dialysate sodium and ultrafiltration. Profiling slowed the rate of blood volume decline, but these changes did not fully explain the benefit of profiling. Future research should evaluate how dialysate sodium concentration, ultrafiltration rates, and blood volume can best be altered to minimize patient morbidity.

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References

Access to UpToDate on-line is available for additional clinical information at http://www.jasn.org/