Reducing Symptoms During Hemodialysis by Continuously Monitoring the Hematocrit

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- Previous studies have demonstrated that patients on hemodialysis develop intradialytic symptoms when the blood volume decreases to a critical level. Using a continuous monitor (CRIT-LINE; In-Line Diagnostics, Riverdale, UT) to determine the instantaneous hematocrit and blood volume, we observed that certain intradialytic symptoms occurred at a patient-specific hematocrit. In the present study, we exploited this hematocrit threshold concept to decrease the occurrence of lightheadedness, cramping, and nausea, regardless of blood pressure changes. In the first phase of the study, hematocrit threshold was established in six hypotension-prone patients. Five patients entered into the second phase in which ultrafiltration rates were increased 25% above prescribed values at the beginning of the experimental sessions. Subsequently during the experimental sessions, ultrafiltration rates were manipulated to maintain the instantaneous hematocrit value 2 units below the established hematocrit threshold. Sessions without ultrafiltration rate adjustments based on hematocrit served as controls. There were no differences between experimental (n = 27) and control (n = 28) sessions with respect to treatment time (230 minutes ± 229 minutes), fluid volume removed (3,351 mL ± 3,383 mL), and maximum percentage change in systemic blood pressure (–26% ± –24%). However, there were less symptoms during the experimental sessions (25% ± 57%; P = 0.038). These data suggest that a twofold reduction in intradialytic symptoms can be achieved using continuous hematocrit monitoring without altering treatment times or volume removed in hypotension-prone patients.

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INDEX WORDS: Hemodialysis; intravascular volume; symptoms; hematocrit; blood pressure.

HYPOVOLEMIA has been implicated as a major causal factor of morbidity during hemodialysis. Despite the use of bicarbonate dialysate, ultrafiltration controllers, sodium modeling, and automated blood pressure monitoring, the incidence of hypotension has been reported to be approximately 20%. Unfortunately, the morbidity associated with hypovolemia is not limited to hypotension, nor is it limited to unstable patients. Stewart et al suggest that the major cause of leg and muscle cramping is dialysis-induced hypovolemia.3 We have recently demonstrated that cramping and lightheadedness occurred in 28% of all treatment sessions, and in all cases those symptoms were preceded by a pronounced reduction in blood volume.4 Paradoxically, the majority of the symptoms (73%) in that study occurred in patients who were characterized as stable (ie, not hypotension prone). These findings suggest that the total incidence of hypovolemic morbidity during dialysis therapy is more extensive than is indicated by the incidence of hypotension alone.

It therefore appears that maintaining blood volume is a key to prevention of many intradialytic symptoms. Previous studies have suggested that during hemodialysis there exists a critical blood volume level below which hypotension occurs. Kim et al, using a radiolabeled erythrocyte technique, showed that approximately 77% of hypertensive episodes occurred below a blood volume of 50 mL/kg body weight. Similarly, Daugirdas and colleagues, using labeled albumin, observed the same phenomenon in dogs, ie, a subject-specific blood volume indicative of the onset of hypotension.6,9 Unfortunately, these aforementioned methods of measuring blood volume require radiolabeling techniques and are not practical for routine clinical use.

Several less invasive means of measuring changes in blood volume have been developed. Some have used photometry or electrical conductivity in the extracorporeal circuit to monitor hemoglobin concentration, which correlates inversely with intravascular volume.10 Other investigators have used sonography to assess the inferior vena cava diameter, which has a positive relationship with intravascular volume.11 Using

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these techniques, other investigators have shown that both the rate of decline and the magnitude of the remaining blood volume are predictive of intradialytic hypotension.\textsuperscript{12,13}

We recently developed a convenient and accurate instrument to measure hematocrit in the extracorporeal circuit.\textsuperscript{14} Assuming that the total circulating red blood cell mass remains constant for a given patient over a certain period of time and that the red blood cell mass is evenly distributed within the intravascular compartment, the peripheral blood hematocrit would vary inversely with the intravascular volume. Using the changes in hematocrit to monitor intravascular volume during hemodialysis, we have demonstrated in 12 patients that the blood volume (or hematocrit) is a reliable indicator of intradialytic morbidity events, such as hypotension, lightheadedness, and muscle cramps. Furthermore, these events occurred when the hematocrit reached a certain patientspecific threshold value, which appeared to be consistent (average standard deviation of 1.4 hematocrit units) over the observation period of several weeks.\textsuperscript{4} In this present study, we exploited this critical hematocrit threshold concept to design strategies that might reduce intradialytic morbidity without altering treatment times or volume removed.

\textbf{MATERIALS AND METHODS}

\textbf{Study Patients}

Six patients at the University of Utah-affiliated Bonneville Dialysis Unit (Ogden, UT) were enrolled in this study after giving informed consent. They were asked to participate only on the basis that they were considered by the dialysis staff as being hypotension prone according to previous clinical experiences. Each patient was studied on 12 to 29 separate occasions for a total of 106 treatment sessions. The entire study was conducted within a period of 4 months.

\textbf{Hemodialysis Procedure}

Hemodialysis was performed using a 2008E machine (Fresenius, Concord, CA), bicarbonate dialysate, and cellulose acetate membrane hollow fiber dialyzer (CA series; Baxter Healthcare, Round Lake, IL). Dialysate flow rate was fixed at 500 mL/min. The blood flow rate and treatment time were prescribed individually for each patient using urea kinetic modeling according to routine dialysis unit protocols to ensure a delivered single pool Kt/V of 1.2 or greater. The dialysate sodium concentration started at 150 mEq/L and decreased linearly to 140 mEq/L at the end of the session. This dialysate sodium concentration profile remained constant from session to session for all patients. Body weight was determined by standing on the same scale before and after each session. Fluid volume removed was recorded by the dialysis machine and was compared with the prescribed fluid removal goal. Blood pressure and pulse rate were monitored by automated cuff measurement (Fresenius) every 30 minutes throughout the session.

\textbf{Blood Volume (Hematocrit) Monitoring}

With the assumption that the red blood cell mass was essentially constant during hemodialysis, blood volume and hematocrit should be inversely and linearly related to each other. Hematocrit was monitored noninvasively and continuously using the CRIT-LINE Instrument (In-Line Diagnostics; Riverdale, UT) during all treatment sessions. Before hemodialysis, a sterile plastic disposable blood chamber was placed between the arterial blood tubing and the dialyzer. The CRIT-LINE Instrument uses a transmissive photometric technique to determine the absolute hematocrit based on both the absorptive and scattering properties of the erythrocytes as they pass through the blood chamber.\textsuperscript{14} Although dialyzers were reused, the blood tubing and blood chambers were discarded after each treatment.

\textbf{Experimental Protocol}

The study was conducted in two phases. During the first phase, each patient was monitored during consecutive treatment sessions (43 total sessions). A designated research staff person who was not involved in the care of the patients monitored symptoms but was blinded to the hematocrit tracing generated by the CRIT-LINE Instrument, which was covered during this phase. In this manner, the hematocrit threshold value at which the patient experienced intradialytic symptoms was established for each participant in the study. There were no manipulations of ultrafiltration rate (UFR) based on the hematocrit values during this initial phase.

The second phase was designed to determine whether manipulation of the intradialytic blood volume to avoid the hematocrit threshold would decrease morbidity. Each patient was monitored during control sessions alternating with experimental sessions in which the UFR was manipulated based on the protocol described below. During the control sessions, the UFR was set at a constant rate to achieve the target dry weight for the individual patient. If significant symptoms occurred, the UFR was usually decreased to the lowest setting (ie, 70 mL/hr) until such symptoms were relieved spontaneously or with other interventions. Patient symptoms were monitored throughout all sessions by the research staff. The decisions to intervene and how to intervene (including changing UFRs), however, were made by the clinical staff according to routine clinical practice and their experiences with those particular patients; intradialytic hematocrit values from the CRIT-LINE Instrument were ignored.

During the experimental sessions, the hematocrit from the CRIT-LINE Instrument was used as a guide. At the start of these sessions, the research staff calculated the UFR that should have been prescribed on the basis of the patient’s target dry weight. The treatment was then started at a UFR 25% higher than the prescribed UFR. This accelerated rate was maintained until the patient’s hematocrit increased to or exceeded the hematocrit limit (defined as hematocrit threshold minus 2 units). The hematocrit threshold was previously
established in the first phase. Whenever this hematocrit limit was achieved or exceeded, the dialysis staff was instructed to change the UFR rate by decrements of 25% of the prescribed value to maintain the hematocrit at or below the hematocrit limit. For example, if the patient’s prescribed UFR was 1,000 ml/hr, the starting rate would be 1,250 ml/hr and changed by decrements of 250 ml/hr whenever the hematocrit limit was encountered. Once the hematocrit had stabilized or decreased below the hematocrit limit (in the event the limit was inadvertently exceeded), the UFR was again increased. It would be necessary, at times, for the staff to increase or decrease the UFR within 15-minute intervals in an attempt to maintain the actual hematocrit at or near the hematocrit limit for the prescribed session duration. If, during the experimental session, the patient’s original ultrafiltration goal was achieved prior to the end of the prescribed treatment period, the staff was instructed to continue to remove fluid at the same rate as long as the hematocrit was not greater than the hematocrit limit. The research staff noted patient symptoms while all UFR manipulations were carried out by the dialysis center staff.

There were a total of 63 sessions. However, one patient was eliminated from the analysis because of a lack of significant symptoms, reducing the number of sessions analyzed in the second phase to 55 (28 control and 27 intervention sessions).

**Intradialytic Symptoms**

Intradialytic symptoms, regardless of the presence or absence of blood pressure changes, were chosen as the outcome measures of this study. An intradialytic symptom was defined a priori as the occurrence of one or more of the following: muscle cramping, lightheadedness, and nausea. These particular symptoms were chosen because they are often associated with hypovolemia. Other symptoms were noted but excluded a priori from the analysis. Changes in blood pressure alone, without accompanying symptoms, were not considered to be intradialytic symptoms because our objective was to reduce patient symptoms. Nonetheless, blood pressures were recorded and analyzed. Mean arterial pressure (MAP) was defined as $\frac{1}{3}$ systolic blood pressure plus $\frac{2}{3}$ diastolic blood pressure. Maximum percentage change in MAP during a session was defined as (predialysis MAP minus the greatest MAP change observed during the entire session)/predialysis MAP $\times$ 100%. Continuous hematocrit was plotted versus time for each patient during all treatment sessions, and the patient symptoms were contemporaneously noted in relation to the time, blood pressure, and hematocrit values.

**Data Analysis and Statistics**

All values are presented as mean ± SD. Data from the experimental and control sessions were grouped separately and the grouped data were compared with each other. Data regarding treatment durations, weights, volumes removed, and MAP were compared using the unpaired Student’s t-test. Data regarding frequency of symptoms were compared using the comparison of two proportions test. $P < 0.05$ was considered significant.

**RESULTS**

There were fluctuations in the predialysis hematocrit values, but the overall trend remained relatively stable for each patient during the course of the study. The average value of the mean predialysis hematocrits from the five study patients at the beginning of the first phase was 35.9; at the beginning of the second phase, which was approximately 2 months later, the mean value was 35.3. It should be noted, however, that predialysis hematocrit is affected not only by red blood cell mass, but also by hydration status. Nonetheless, there was no clinically noticeable blood loss (other than that related to blood sampling and the usual small residual amounts left in the dialyzers) during the observation period. No transfusion was given to any of the patients. Total red blood cell mass, however, was not determined.

In the first phase of the study, the hematocrit at which hypovolemic symptoms occurred (hematocrit threshold) was determined for individual patients. These hematocrit threshold values for patients no. 1 through 5 were 52.2, 40.0, 38.8, 35.6, and 40.8 and were determined during the course of 15, 8, 11, four, and five separate sessions, respectively. The hematocrit thresholds during the second phase of the study ranged from 35.8 to 51.0 (Table 1). The consistency of the threshold value for a given patient can be depicted by the standard deviation of the values observed over several sessions. The standard deviations ranged from 0.4 to 1.3 hematocrit units for the five study patients (Table 1). Figure 1

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>No. of Sessions</th>
<th>Hct at IDS ± SD</th>
<th>No. of IDS Events</th>
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<tr>
<td>1</td>
<td>14</td>
<td>51.0 ± 1.2</td>
<td>6*</td>
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<tr>
<td>2</td>
<td>11</td>
<td>40.9 ± 1.3</td>
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<tr>
<td>4</td>
<td>8</td>
<td>36.7 ± 1.2</td>
<td>2</td>
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<tr>
<td>5</td>
<td>10</td>
<td>41.4 ± 0.4</td>
<td>6*</td>
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$^*$ There were two morbid events in the session (for both sessions, lightheadednesses was noted first followed later by cramping).
Fig 1. Hematocrit values at which symptoms occurred (diamonds) during six separate dialysis sessions in the same patient with differing UFRs (total volume removed from beginning of dialysis up to the symptomatic event divided by time). The mean value of this hematocrit threshold was 40.9 \pm 1.3 (SD). Pre-dialysis hematocrit values of the corresponding sessions (circles) are presented for reference.

plots hematocrit versus UFR during six separate sessions for patient no. 2. The data demonstrate a consistent hematocrit threshold of 40.9 \pm 1.3 when the patient developed symptoms, despite mean UFRs (total volume removed divided by time from beginning of dialysis up to the symptomatic event) ranging from 590 to 1,190 mL/hr.

After the hematocrit threshold had been established for individual patients in the first phase, a trial was conducted to determine whether maintaining blood volume by avoiding this threshold would diminish intradialytic symptoms. The protocol for the experimental sessions was designed to remove fluid rapidly at the beginning and subsequently avoid the hematocrit limit by decreasing the UFR later in the session. Presumably because of this design, there were more than twice as many manipulations of UFR during the experimental sessions than during the control session (Table 2). Eighty-nine percent and 94% of the UFR manipulations in the experimental and control sessions, respectively, were downward adjustments. A small percentage (11%) of the UFR manipulations were upward adjustments and were made to maintain the hematocrit at or near the hematocrit limit.

There were no differences between experimental and control sessions with respect to treatment duration, predialysis, and postdialysis weight, fluid volume removed, and predialysis and postdialysis MAPs (Table 2). When individual patient data were analyzed, there was also no difference between the intradialytic weight loss during the experimental and control sessions.

Intradialytic symptoms usually occurred when the blood pressure decreased. Overall, the maximum percentage change in MAP during symptomatic sessions (−32% \pm 19%) was greater than that for asymptomatic sessions (−21% \pm 14%; \( P = 0.02 \); Fig 2). However, 22% of the time (five of 23 cases), symptoms developed even when the MAP decreased only mildly or actually increased. During all five of these occurrences, the blood volume decreased (mean change, −13%

<table>
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<th>Table 2. Comparisons Between Control and Experimental Sessions in the Second Phase</th>
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<tr>
<td>No. of sessions</td>
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<td>Predialysis weight (kg)</td>
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<tr>
<td>Postdialysis weight (kg)</td>
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<tr>
<td>Volume removed (mL)</td>
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<td>Postdialysis MAP (mm Hg)</td>
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<tr>
<td>%MAP change (max)</td>
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Abbreviations: %MAP change (max), (predialysis MAP − greatest MAP change during the entire session)/predialysis MAP \times 100%; IDS, intradialytic symptoms.
± 5%) while the mean MAP remained essentially unchanged (+1% ± 11%). These observations indicate that the development of symptoms did not correlate well with hypotension and that reliance of blood pressure measurements alone may not permit the detection of all impending hypovolemia-related adverse reactions.

The maximum percentage change in MAP was not different between the experimental and control sessions (−24% ± 18% vs. −26% ± 16%; \( P = \text{NS} \)). Despite the similar changes in MAP, intradialytic symptoms occurred in 57% (16 of 28) of control sessions, but in only 26% (seven of 27) of the experimental sessions (\( P = 0.038; \) Table 2). In all seven instances during the experimental sessions in which symptoms occurred, the hematocrit exceed the hematocrit limit set for the individual patients (which was determined as the result of the first phase of the study). However, in only two of the seven instances did the hematocrit exceed the hematocrit threshold. When the five study patients were analyzed individually, four patients were found to have less symptoms while one patient experienced no benefit during the experimental sessions.

Of the 23 total sessions in which patients had intradialytic symptoms, there were 11 sessions with cramps, six sessions with lightheadedness, and six sessions with nausea. The types of symptoms occurring during the control sessions were cramps (eight sessions), lightheadedness (four sessions), and nausea (four sessions). The types of symptoms that occurred during the experimental sessions were cramps (three sessions), lightheadedness (two sessions), and nausea (two sessions).

Figure 3 shows an example of the real time tracing of hematocrit changes during a control session with severe cramps compared with an experimental session for the same patient without symptoms. It demonstrates the usefulness of avoiding the hematocrit threshold by adjusting the UFR.

DISCUSSION

In previous studies of the relationship between intradialytic blood volume reduction and morbidity, the primary focus has been on the occurrence of hypotension. However, in our earlier attempts to use blood pressure as a predictor of morbidity, we found that there were other symptoms which correlated with hypovolemia but were not consistently reflected by blood pressure.
changes, as evidenced in the present study (Fig 2). This variability is presumably due to the effect of predialysis hydration status, physical exertion, mental state, and neurohumoral compensatory responses to volume changes on blood pressure. Hence, directly monitoring blood volume appears to be more useful than monitoring blood pressure in predicting and preventing hypovolemia-induced morbidity. The present data also support the findings of our previous study, which suggest that patients develop intradialytic symptoms at a hematocrit threshold specific for the individual. The earlier study, which included blood pressure as an endpoint of intradialytic morbidity, showed hematocrit thresholds with an average standard deviation of 1.4 hematocrit units. However, using only intradialytic symptoms as the endpoints without regard to blood pressure changes in the present study improved the standard deviations of hematocrit thresholds to an average of 1.0 hematocrit units (Table 1).

Cramping, lightheadedness, and nausea were chosen a priori because they are often associated with hypovolemia. Other symptoms, such as headaches, itching, chest pain, backache, chills, tremors, dyspnea, and agitation, were not specifically studied. Further investigations will be required to determine if any of the above symptoms have a temporal relationship with hypovolemia.

Predialysis hydration status and intravascular volumes often vary substantially from session to session, as reflected by fluctuating predialysis hematocrit values. Consequently, in the present study the blood volume loss at which intradialytic symptoms occurred also varied, ranging from 8% to 20% of the predialysis volumes. Furthermore, the intradialytic blood volume–time profile varied from session to session for a given patient, perhaps because the factors that govern vascular refilling rates also changed. For example, patient no. 2 lost 8% of her initial blood volume on 1 day, but incurred a 20% blood volume loss at the time symptoms developed in a subsequent session. Despite this variability, the hematocrit value at which symptoms occurred (hematocrit threshold) was relatively constant for a given patient (Table 1). The consistency of the hematocrit threshold can be further illustrated by the values in the second phase compared with the corresponding values (determined 2 months earlier) in the first phase.

High UFRs portend a shorter symptom-free dialysis session, but UFR and time do not accurately predict intradialytic symptoms. In a preliminary study, Leyboldt et al showed in three of five patients that hematocrit was more predictive than ultrafiltration volume or time. This point is illustrated by Fig 1, which shows that even though UFRs varied substantially from session to session depending on the interdialytic weight gain, the hematocrit threshold was a stable indicator of when hypovolemic symptoms would occur. This preliminary finding, if validated in a larger patient population, suggests that dialysis time can be more effectively managed without an increased risk of developing intradialytic symptoms.

There are caveats associated with blood volume monitoring using this technique. The first relates to a change in red blood cell mass, which may occur as a result of erythropoietin therapy, hemorrhage, transfusions, etc. These conditions would necessitate the re-establishment of the hematocrit threshold for an individual patient, as it would be necessary to re-establish the dry weight periodically. Under these circumstances, however, the intradialytic changes in hematocrit still reflect changes in blood volume.

A second caveat relates to recirculation of blood in the arteriovenous fistula. Although red blood cell volume remains essentially constant during hemodialysis, mixing of dialyzer effluent blood that has been hemoconcentrated by ultrafiltration of water with dialyzer afferent blood would change the relationship between peripheral blood volume and the hematocrit measured in the dialyzer afferent tubing. The magnitude of this problem would depend on both the recirculation rate and the UFR.

Our results indicate a twofold improvement (Table 2) in patient outcome by manually reducing the UFR to avoid the intradialytic hematocrit threshold. Four of the five patients benefited by having fewer symptoms as a result of hematocrit-guided UFR manipulations during their experimental sessions. All symptoms in the experimental sessions occurred when the hematocrit exceeded the patients’ individually preset hematocrit limit, although only two of seven exceeded the hematocrit threshold (which is, by definition, two hematocrit units above the hematocrit limit). The fact that symptoms occurred in five instances
in which the hematocrit was below the hematocrit threshold is not surprising since the threshold was defined as the mean value at which symptoms occurred during the first phase of the study. Thus, targeting the hematocrit at the hematocrit limit instead of the hematocrit threshold would provide a wider margin of safety. These observations also suggest that by refining the protocol or increasing the alertness and responsiveness of the dialysis personnel, a further reduction in symptoms can potentially be achieved. It should be noted that in an attempt to avoid the hematocrit limit in the experimental sessions, there were more than twice as many manual UFR manipulations compared with the control sessions in which there were no UFR adjustments based on hematocrit. Development of an autofeedback system that connects the continuously obtained hematocrit data to the ultrafiltration controller in the dialysis machine may eventually allow continuous and convenient adjustments of the intravascular volume and further success in preventing hypovolemic symptoms.

Many dialysis patients are still fluid overloaded at the end of the dialysis session. Maintenance of the correct dry weight can eliminate interdialytic hypertension in the majority of patients. A preliminary report suggests that continuous blood volume monitoring can conveniently detect appropriately high dry weights. In another study, Baranski and Mehta observed a significant reduction in dry weight of patients when ultrafiltration was adjusted based on blood volume monitoring. In addition to more reliable dry weight determinations, using blood volume monitoring, Stiller et al showed a 50% reduction ($P < 0.025$) in symptomatic hypotension. Thus, hematocrit-guided dialysis appears to be a promising technique to maximize fluid removal and readjust dry weights while reducing interdialytic symptoms.

In summary, the results of the present study suggest that the hematocrit threshold concept is valid. By continuously monitoring the hematocrit and using the hematocrit threshold as a guide, a twofold reduction in volume-related symptoms was achieved without extending treatment times or reducing fluid removal in these hypotension-prone patients. Further large-scale studies will be necessary to determine what proportion of the hemodialysis population may benefit from this technique and how to identify such patients.

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REFERENCES

16. Maeda K, Morita H, Shimizato T, Vega BV, Kobayakawa H, Ishihara T, Inagaki H, Igarashi I, Kitano T: Role of


