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CLINICAL RESEARCH

Higher Symptom Frequency and Severity After the Long Interdialytic Interval in Patients on Maintenance Intermittent Hemodialysis

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Introduction: Patients on intermittent hemodialysis (HD) have a high symptom burden. Though studies report higher hospitalizations and mortality after the long interdialytic interval, whether symptoms vary based on the interdialytic interval is unclear.

Methods: This is a prospective observational study of patients over the age of 18 who received in-center HD. Patients were surveyed on the presence and severity of 20 different symptoms at the end of 12 HD sessions. Wilcoxon signed-rank test was used for comparison of severity for each symptom by the interval. Multivariable generalized estimating equation with Poisson regression by repeated measure method was used to determine the association of interdialytic interval and symptom frequency while adjusting for potential confounders.

Results: From the 97 patients enrolled, the most common symptoms were fatigue (60.8%), cramping (58.8%), and dry skin (52.6%). There was large variability in the frequency of symptoms, ranging 0% to 8% of treatments. The most severe symptoms were bone pain (mean severity score 2.2±0.9) and diarrhea (mean severity score 2.2±0.7). Eight of the 20 symptoms were significantly more common after the long interdialytic interval including fatigue (22% vs. 15%, $P < 0.001$) and cramping (21% vs. 16%, $P = 0.003$). The long interval had a 37% higher incidence rate for symptoms compared to the short interval even after adjustment. Results were similar across genders.

Conclusion: Symptoms are more common after the long interdialytic interval. Clinical assessment and research evaluating patient symptoms need to be cognizant of when patients are surveyed or include the length of interdialytic interval as a confounding variable.

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There are over 400,000 people in the United States who are on HD with an additional 100,000 initiated every year.[1] Survey data demonstrates that HD-related patient symptoms (e.g., fatigue, itching, and dry skin) are extremely common and often overlooked.[2,3] Over 50% of patients experience many of these symptoms, with prior data indicating 82% of patients reporting fatigue and 74% reporting cramps.[4] In addition, these symptoms appear frequently, some of which are experienced by patients in almost every HD treatment and they do not resolve until the morning after.[4-6] Patients report an extreme concern about these symptoms, with studies indicating associations between symptom clusters and depressive symptoms and quality of life.[5-9] In addition, patient symptoms are associated with outcomes of hospitalizations and mortality, stressing the importance of assessing patients' perceptions of symptoms.[7-10]

Nevertheless, it is currently unknown whether symptom frequency and/or severity is higher after the long interdialytic interval (the 2-day gap between HD treatments). Previous studies suggest heightened

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mortality risk following this 2-day period, especially cardiovascular complications.[11] Many symptoms, especially intradialytic symptoms, experienced by patients including intradialytic hypotension and cramps are associated with ultrafiltration rates (UFRs), suggesting symptoms may be more severe after the long interdialytic interval when fluid has built up.[12,13] Increased hospital admission and mortality following the 2-day interval is often related to risks of fluid overload before dialysis.[14] Nevertheless, rigorous studies have not been conducted to analyze the frequency and severity of symptoms, both interdialytic and intradialytic symptoms, after different interdialytic intervals. We hypothesized that symptom burden in patients is elevated after the long interdialytic interval, in both frequency and severity, and conducted one of the first prospective cohort studies to assess this.

METHODS

Study Population

This study was conducted at the Mount Sinai Kidney Center from September 14, 2020, to April 1, 2021. Due to the location of the dialysis unit in East Harlem in New York City, the unit serves an ethnically and racially diverse population. Patient data came from surveys and the electronic health records from the Mount Sinai Health System. Written informed consent was obtained from all patients. Patients were included if they were older than 18 years, undergoing in-center HD for more than 30 days, and receiving HD 3 times weekly. Patients were excluded if they started dialysis less than 30 days, because these patients are likely to undergo dry weight probing and changes in medications, which potentially impact patients' symptoms and thus will not be reflective of patients' steady state symptom burden. Only patients who could provide informed consent and were able to answer surveys without assistance (as determined by the patients' treating physician or nurse) were included. Patients who originally consented but were hospitalized, did not complete 12 surveys, or were placed on COVID-19 isolation were excluded from final analysis. For patients who were hospitalized after enrollment, they were included in the study if they were able to complete the remaining surveys after their hospital discharge. In this situation, surveys were resumed after 2 weeks of hospital discharge and restarted on the day of week the survey was due (e.g., if the last survey was Monday prior to hospitalization, the survey was resumed on Wednesday). The Mount Sinai Institutional Review Board approved this study.

Measures

We hypothesized that peri-dialytic symptoms (those occurring on the day of and during dialysis) would be particularly affected by the length of the interdialytic interval. We therefore surveyed patients during the last 15 minutes of their dialysis treatments to ensure capture of intradialytic symptoms and events. Patients were dialyzed on either a Monday-Wednesday-Friday or Tuesday-Thursday-Saturday schedule. Surveys obtained on Mondays for patients on a Monday-Wednesday-Friday schedule and Tuesdays for a patient with Tuesday-Thursday-Saturday schedule were considered surveys from after the long interdialytic interval (2 days between HD) whereas the rest were considered surveys from the short interdialytic interval (1 day between HD sessions).

We surveyed patients at every dialysis treatment over a period of 4 weeks resulting in a total of 12 surveys, 4 surveys after the long interdialytic interval and 8 after the short interdialytic interval. The survey asked whether over the past 24 hours, the patient experienced any of the following symptoms: fatigue, muscle cramps, dry skin, muscle soreness, itching, bone pain, cough, dry mouth, restless leg syndrome, dizziness, shortness of breath, headache, decreased appetite, nausea, constipation, edema, chest pain, difficulty concentrating, vomiting, and diarrhea; which would capture both interdialytic and intradialytic symptoms. The survey was administered by a research coordinator either on paper format or electronically on a laptop with a touch screen as per patient preference. Patients were also asked to assess how much the symptoms bothered them using a 5 point scale; and we used this data to determine symptom severity. A copy of the survey is included as a supplementary file. Because there are no validated symptom surveys specifically focused on the short time frame we were assessing for, we based our survey on the validated Dialysis Symptom Index, which queries for both symptoms and severity.[15] Though the Dialysis Symptom Index asks patients to recall if the symptom was present over the past week, our specific focus was on symptoms after the interdialytic interval and symptoms that occur during the dialysis treatment. Therefore, from the 30 symptoms, we selected 20 symptoms which would vary between dialysis sessions. Patients were asked to report symptoms that occurred over the past 24 hours.

The surveys were administered by a trained clinical research coordinator. The coordinator reads through the list of symptoms and if the patient stated the symptom was present over the past 24 hours, the participant is asked to rate the severity of the symptom from 0 to 4, with 0 being the lowest severity experienced for each symptom and 4 being the highest severity. Surveys were administered in English or Spanish based on the patients' preferences.

In addition to surveys, we asked participants to provide their gender, race, ethnicity, dialysis access, and their medical history. We confirmed this information with a review of the participant's electronic health record. From the electronic health record, we extracted laboratory values of hemoglobin and urea reduction ratio that were obtained on monthly labs during the month of survey participation. In addition, we extracted interdialytic weight gain (IDWG), systolic blood pressure (start, lowest, and post HD), and UFR of every treatment from the electronic health record.

Statistical Analysis

We calculated the prevalence of the symptom as the proportion of patients who reported the symptom on any survey during the 4-week study period. To assess the frequency of each symptom, we calculated the number of treatments where each symptom was reported over the 12 treatments, therefore a value of 0 would mean the patient never reported that symptom, and a value of 100% would mean the patient reported the symptom at every treatment. For symptom severity, a score was generated by summing up the severity across all symptoms for that session. Therefore, each session could have a severity score ranging from 0 where the patient had no symptoms or the lowest severity for all symptoms to 80 where the patient reported maximum severity for all 20 symptoms. A mean severity score was calculated per patient for sessions after the long and short interdialytic intervals. The Wilcoxon signed-rank test was used to compare symptom severity over the long (4 treatments) and short (8 treatments) interdialytic intervals. Subgroup analysis was performed by gender and ethnicity. The comparison was performed using the Wilcoxon Mann-Whitney test.

We used a multivariable generalized estimating equation with Poisson distribution by repeated measures method to determine the association of intervals with total symptom burden. Based on the unadjusted analysis, only the variables with a P-value < 0.1 were added to the adjusted model. The final adjusted model included gender, a combined race/ethnicity variable, comorbidities (congestive heart failure, diabetes mellitus), and urea reduction ratio as covariates. All analysis was performed using R 4.0.3 and SAS 9.4 (SAS Institute, Inc., Cary, NC).[16] A significance level of 0.05 and 2-sided testing were used throughout and 95% confidence intervals were reported.

RESULTS

Patient Characteristics

Of the 209 patients who received HD at Mount Sinai Kidney Center, 166 were eligible for participation, and ultimately 97 patients completed the study (Supplementary Figure S1). Patients who were not included in the study were older (57.9±16 years) and more likely to be male (54%). Recruitment was higher from Monday-Wednesday-Friday shifts (54%) than Tuesday-Thursday-Saturday shifts (39%). The average age of participants was 56±14 years, 53% were female, 49% were black, 41% were Hispanic, and 74% of patients used a fistula for dialysis access. Patients had a high comorbidity burden with 83% having high blood pressure, 26% with a history of coronary artery disease, and 39% with diabetes. Mean hemoglobin was 10.3±1.1 g/dl and average urea reduction ratio was 72±6% (Table 1). Mean IDWG was significantly higher after the long interdialytic interval than after the short interdialytic interval (2.8±1.2 vs. 1.9±0.8 kg, $P < 0.001$). There was no significant difference in mean achieved UFR (8.6±3 vs. 8±3.4 ml/kg/hr, $P = 0.2$) or mean change in systolic blood pressure (29±17 vs. 31±17 mmHg, $P = 0.7$) between long and short interdialytic lengths, respectively.

Table 1. Patient characteristics at study enrollment

Characteristic	N (%)
Gender [%]	
Female	51 (53)
Male	46 (47)
Mean age±SD	56 ±14
Race/Ethnicity [%]	
Black	48 (49)
White	5 (5)
Hispanic	40 (41)
Other	4 (4)
Dialysis access [%]	
Arteriovenous fistula	72 (74)
Arteriovenous graft	13 (13)
Central venous catheter	12 (12.4)
Comorbidities [%]	
Hypertension	80 (83)
Diabetes mellitus	38 (39)
Coronary artery disease	25 (26)
Prior strokes	13 (13)
Liver disease/cirrhosis	10 (10)
Current or past cancer	10 (10)
Congestive heart failure	5 (5)
Depression	2 (2)
Laboratory results (Mean±SD)	
Hemoglobin [mg/dl]	10.3±1.1
URR[a] [%]	72±6
Interdialytic weight gain [Kg]	2.2±0.8
Change in systolic blood pressure [mm Hg][b]	30±16
Achieved ultrafiltration rate [ml/kg/hr]	8.2±3.1

URR, urea reduction ratio.
[a]URR calculated as (pretreatment blood urea nitrogen–post treatment blood urea nitrogen)/pretreatment blood urea nitrogen.
[b]Change in systolic blood pressure is defined as the systolic blood pressure at hemodialysis start minus the lowest systolic blood pressure during the hemodialysis treatment.

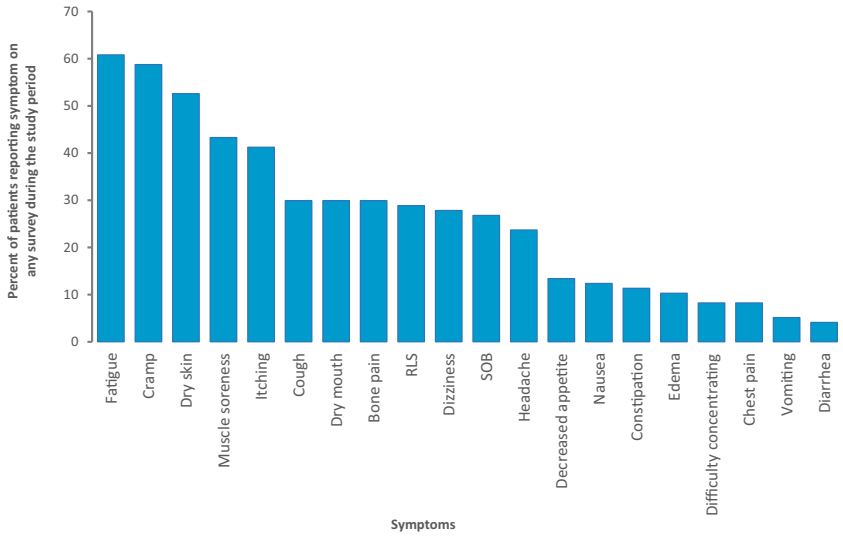

Figure 1. Percent of patients that experienced a symptom on any of the 12 surveys during the study period. RLS, restless leg syndrome; SOB, shortness of breath.

Overall Prevalence, Frequency, And Severity

During the study period, the 6 symptoms most reported by patients on at least 1 survey were fatigue (61%), cramping (59%), dry skin (53%), muscle soreness (43%), itching (41%), and cough (30%). The 6 symptoms least reported by patients were constipation (11.3%), edema (10.3%), decreased concentration (8.2%), vomiting (5.2%), and diarrhea (4.1%) (Figure 1).

The percentage of treatments with the symptom reported over the 12 surveys per person, ranged from a median of 0% of treatments for diarrhea to 8% of treatments for fatigue. However, there was large variability across symptoms with some patients reporting the symptom at nearly every treatment (Figure 2).

In patients who reported symptoms, the overall mean severity was 1.8±0.3. In patients who reported symptoms, symptoms of bone pain (mean 2.2±0.9), diarrhea (mean 2.2±0.7), and muscle soreness (mean 2.2±0.6) were found to be rated with higher severity by participants (Figure 3 and Supplementary Table S1).

Prevalence and Severity by Interdialytic Interval

Considering the proportion of patients who reported symptoms during their HD sessions after their long versus short interdialytic interval, 10 out of the 20 symptoms were significantly more frequent after the long interdialytic interval (Figure 4 and Supplementary Table S2). Notably, symptoms of fatigue (22% vs. 15%, $P < 0.001$) and cramping (21% vs. 16%, $P = 0.003$) were more common after the long interdialytic interval. There were no symptoms that were reported more frequently after the short interdialytic interval compared to the long interdialytic interval. Given a large number of sessions without symptoms, we did not feel that the comparison of individual symptom severity was meaningful (Supplementary Figure S2). Therefore, we calculated a severity score that combined symptoms with severity on a survey level. There was a statistically significant higher mean severity score after the long interdialytic interval than after the short interdialytic interval (6±4.9 vs. 4.6±3.8, $P < 0.001$).

In unadjusted analysis, patients reported a 38% increase in the incidence of symptoms after their long interdialytic interval compared to their short interdialytic interval, incidence rate ratio 1.38 (1.25−1.52) (Table 2). Even after the multivariable adjustment with the aforementioned covariates, the incidence of symptoms remained 37% higher after a long interdialytic interval with a P-value < 0.001 (Table 2 and Supplementary Table S3).

Symptoms by Gender

Overall, more female participants reported all 20 symptoms than male participants, an average difference of 12.5±8.8% (Supplementary Figure S3). Symptom severity was higher in female participants compared to male participants (5.7±4.5 vs. 3.7±2.7, $P = 0.02$). Symptoms were more common after the long interdialytic interval in both females and males (Supplementary Figure S4).

Symptoms by Ethnicity

On subgroup analysis by ethnicity, Hispanic vs. non-Hispanic, some symptoms were more common in Hispanic patients, such as cramps, bone pain, and shortness of breath. Conversely, in non-Hispanic patients, symptoms of fatigue, dry skin, and itching were more common (Supplementary Figure S5). Symptoms were more common after the long interdialytic interval in

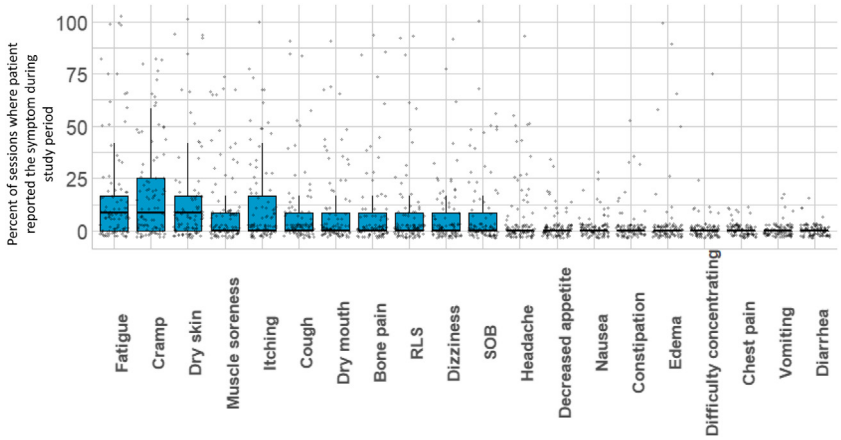

Figure 2. Percent of surveys where the patient reported that symptom. Frequency is calculated as number of surveys where patient reported the symptom divided by 12, the total number of surveys completed. RLS, restless leg syndrome; SOB, shortness of breath.

both Hispanic and non-Hispanic patients (Supplementary Figure S6).

DISCUSSION

In this paper, we describe the high prevalence of 20 symptoms of patients in a cohort of maintenance HD patients. Though overall symptom frequency was low, there was wide variability with some patients reporting a symptom after every session. We found that 10 of these symptoms were statistically significantly more common after the long interdialytic interval compared to after the short interdialytic interval. The multivariable regression analysis found a significant increase in the incidence of symptoms reported after the long interdialytic interval compared to the short interdialytic interval even after adjusting for patient demographics, comorbidities, and laboratory results. Though more female participants reported symptoms, symptoms were more common after the long interdialytic interval in both female and male participants. Though there were some differences in which symptoms were more common in Hispanic and non-Hispanics, all symptoms were more frequent after the long interdialytic interval regardless of ethnicity.

The proportion of patients who reported symptoms in our study is similar to what has previously been reported in the literature with fatigue, cramping, and pruritus being the top symptoms.[3,4] Other studies have predominantly only surveyed patients once, and asked patients the frequency of their symptoms which may be bias due to recall bias. We assessed symptoms 12 times over a 4-week period, which allowed us to accurately assess the frequency of symptoms. In addition, other studies ask patients for their symptoms at any time point during their HD session, whereas we specifically waited until the last 15 minutes to survey patients to ensure capture of intradialytic symptoms. This revealed that though most patients rarely had symptoms, there were subsets of patients who reported certain symptoms during every HD treatment. These findings are particularly useful given the availability of

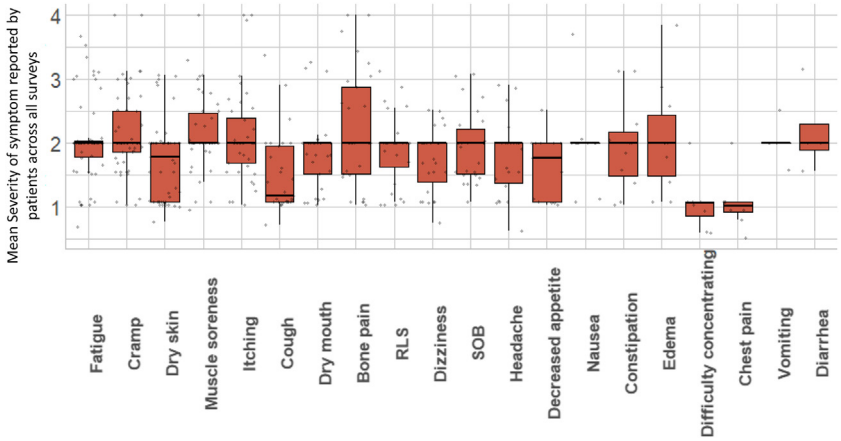

Figure 3. Boxplot of mean severity of each symptoms per patient across all surveys only in patients who reported symptoms. RLS, restless leg syndrome; SOB, shortness of breath.

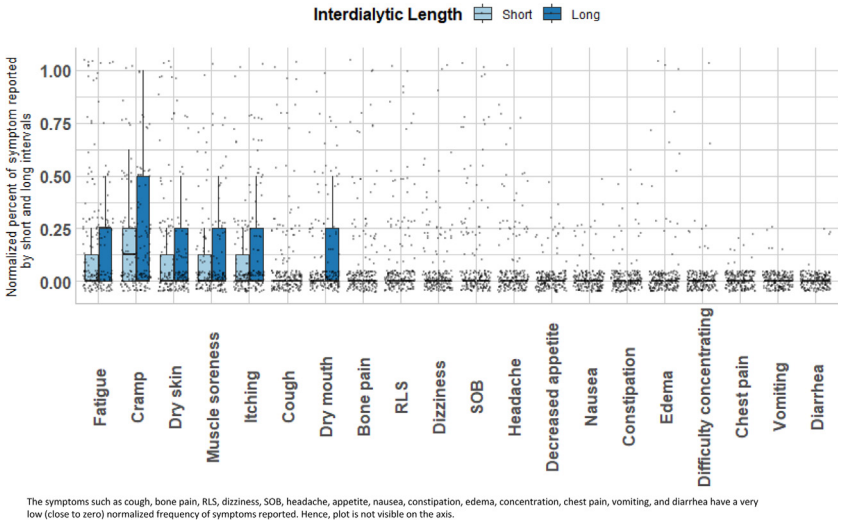

Figure 4. Percent of long and short treatments where patient reported symptoms. This percent was calculated as number of surveys after the long interdialytic interval or short interval where symptom was reported divided by 4 for the long interdialytic interval and 8 for the short interdialytic interval. RLS, restless leg syndrome; SOB, shortness of breath.

new medications and treatments to treat symptoms.[15,17] Currently, in the United States, patients' quality of life, including symptoms, is only assessed on an annual basis and there is no standardization about which day of the week this is done. As our results demonstrate, timing of survey distribution has an impact on symptoms and therefore suggest that symptom surveys be distributed after the long interdialytic interval to capture the maximum symptom burden. In addition, research into patient-centered outcomes need to be cognizant of when surveys are administered and make additional adjustments for the day of week. Clinical trials testing treatments for symptoms would benefit from longitudinal assessment of patient symptom burden to identify patients with the highest symptom burden for more efficient trials.

Though several studies have examined cardiac outcomes, hospitalization, and mortality by interdialytic interval, this is, to our knowledge, the first study to look at the variability of patient symptoms by the interdialytic interval.[11,14,18] Our findings confirmed that symptoms were more common after the long interdialytic interval than after the short interdialytic interval. On analysis of potential patient and treatment characteristics that may be associated with symptoms, we did not find an association between IDWG, change in systolic blood pressure, or hemoglobin and number of symptoms. In addition, multivariable analysis with adjustment for significant patient and treatment characteristics that were significant on univariable analysis did not change the incidence rate ratio. We speculate that symptoms such as cramping, and fatigue may be related to the higher UFR used after the long interdialytic interval.[12,13] We did not find a difference in UFR; we were unable to identify treatments where initial UFR was higher at the start of treatment and stopped or reduced due to symptoms during the treatment, which may be contributing to the lack of difference in achieved UFR despite the significant difference in IDWG. Symptoms of fatigue and itching can be related to build up of uremic toxins.[19,20] Prospective interventional trials testing different dialysis prescriptions are necessary to determine causation.

Interestingly, dry mouth and dry skin were more common after the long interdialytic interval. The pathogenesis of dry mouth is complex and thought to be related to medication use, decreased salivary flow, and fluid restriction.[21] A prior study found that salivary flow increased after HD treatment compared to before the start of the treatment.[22] This finding may partially explain why patients have more dry mouth after a prolonged period without HD. The pathogenesis of dry skin is complex and thought to be related to fluid removal during dialysis, decreased skin perfusion, and loss of sebaceous glands.[23] Given the chronic nature of dry skin and the increased IDWG after the long interdialytic interval; the increase in dry skin was unexpected. Prior studies have found a correlation

Table 2. The results of the generalized estimating equation with Poisson regression by repeated measures analysis for incidence rate ratio between long and short interdialytic interval

Model	IRR (95% CI)	*P*-value
Unadjusted	1.38 (1.25–1.52)	<0.001
Fully adjusted	1.37 (1.24–1.51)	<0.001

CI, confidence interval; IRR, incidence rate ratio.
Fully adjusted model is includes variables for gender, race/ethnicity, comorbidities (congestive heart failure, diabetes mellitus), and urea reduction ratio. In fully adjusted model, patients had a 37% increase in incidence of symptoms after the long interdialytic interval compared to the short interdialytic interval.

between dry skin and pruritus, however, it is unclear how this is affecting dry skin after different interdialytic interval lengths.[24] Future intervention studies examining the effect of modifying ultrafiltration rates and treatment time on patient symptoms are needed.

Symptom severity in patients on HD has previously been reported to be comparable to patients with terminal cancer.[25] In our study, the average symptom severity was mild; and similar to what has previously been reported.[3] The patients in our study also noted bone pain to be one of the most severe symptoms experienced.[3] Not only was symptom frequency higher after the long interdialytic interval but so was symptom severity. Therefore, studies that look to assess symptoms in patients on HD need to be cognizant of the variability of symptoms depending on the day of the week. Given that physicians regularly round on patients weekly, depending on which day of the week the physician evaluates the patient, this can have implications on physician recognition and management of patient symptoms. Dialysis facilities are also mandated by the Centers for Medicare and Medicaid to perform annual quality of life surveys, which also assesses patient symptoms.

Symptoms in patients on HD are generally undertreated, ranging from 20% to 50% depending on the symptom.[2] Whereas some symptoms such as pain may respond to pharmacological interventions, symptoms such as fatigue and cramping are more difficult to treat.[26] Some researchers have found that more frequent dialysis may reduce patient symptoms, however studies so far have been small.[27-29] This is consistent with our findings that patients experience less symptoms after a short interdialytic compared to a long interdialytic interval. Nevertheless, larger studies exploring change to treatment parameters and interdialytic length are necessary to evaluate the effect of interdialytic interval and peri-dialytic symptoms.

On subgroup analysis, we found that female patients reported a higher frequency and severity of symptoms than male patients. This finding supports other research that has documented higher symptom burden and severity in women on dialysis compared to men on dialysis, along with poorer quality of life.[30] Potential contributing factors to this gender difference include differences in prevalence of comorbidities such as depression and differences in social support given the lower proportion of women on dialysis who are married.[31,32] In addition, there are differences in dialysis practice patterns between female and male patients, such as dialysis adequacy and dialysis access, that contribute to differences in symptoms between genders.[32] It remains to be determined if differences in symptoms across genders are due to biological differences or other factors. Nevetheless, despite differences in symptom prevalence and severity, both females and males had a higher frequency of symptoms after the long interdialytic interval. When analysis was performed by ethnicity, we found that some symptoms were more common in Hispanic patients and other symptoms were more common in non-Hispanic patients. Our results add to the literature that there are differences in symptom burden by race or ethnicity groups.[33] Unfortunately, whether these differences are related to biologic differences is unclear.

Our study has the following limitations. We did not collect a blood sample after the different interdialytic intervals, which may provide us information on uremic buildup after different interdialytic lengths. Because residual renal function is not routinely monitored in patients on HD, we are unable to evaluate the potential effect modification of residual renal function on interdialytic interval length and symptom burden. Though our cohort was small, we increased the statistical power of the study by having patients serve as their own controls. Our cohort was predominantly Black and Hispanic, which is not representative of the US HD population. In addition, the proportion of patients with depression is lower than what has been reported in the literature, and there is an association between depression and symptoms.[34,35] Despite the low rate of depression, the symptoms reported by our cohort are similar to other studies.[3,4]

In conclusion, symptom burden and severity were high in a cohort of in-center maintenance HD patients and symptoms varied by the interdialytic interval. Whereas there was large interperson variability in symptoms, a subset of patients experienced symptoms nearly every treatment, a cohort which may benefit from additional symptom management. Clinical care and research on symptoms in patients on HD should consider which day of the week patients are seen and recruited into research studies.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Study flow diagram.

Figure S2. Percent of symptoms reported versus not reported among total number of surveys.

Figure S3. Proportion of patients that experienced a symptom at any point during the study period by gender.

Figure S4. Percent of long or short treatments with symptom reported by gender.

Figure S5. Proportion of patients that experienced a symptom at any point during the study period by ethnicity.

Figure S6. Percent of long or short treatments with symptom reported by ethnicity.

Table S1. Mean and Median severity of symptoms reported on surveys during study period.

Table S2. Mean number of surveys where patient reported symptoms during the short and long interdialytic interval.

Table S3. Results of unadjusted and adjusted generalized estimating equation with Poisson regression.

Survey.

STROBE Statement.

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