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Original Article

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Effect of Conductance and Sodium Balance on Inter/Intra-Dialytic Symptoms

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Abstract

Objective: To evaluate Patient Reported Outcomes of intra/interdialytic symptoms and to optimize the ideal conductivity settings maintained for minimal symptom expressions.
Materials and Methods: A prospective observational study, carried out in a south Indian tertiary care teaching hospital. Patient Reported Outcomes Kidney Disease Quality of Life (KDQOLTM) 35 Symptom List Questionnaire was administered to each patient to determine inter/intradialytic symptoms coupled with sodium conductivity measurement during hemodialysis.
Results: Of the 126 study populations, 97 consented were involved, the mean age was 50±11 years, with male predominance of 79%. Of the 31 parameters studied, 9 correlated significantly to conductivity showing some relationship ($p<0.05$). Muscle cramps, muscle soreness, fatigue, trouble sleeping and nausea were least at population conductivity mean of 14.4 mS/m and peaked at the extremes of mean conductivity range of 13.2 and 15.1 mS/m. Whereas hypotensive symptoms and hot & cold spells were lowest at higher extreme of mean conductivity and peaks at lower end due to sodium removal & hyponatremia.
Conclusion: The change in sodium conductivity with response to sodium gradient was associated with significant increases in inter/intra-dialytic symptom rates associated with symptoms like cramps, soreness, fatigue, nausea and trouble sleeping are least severe around a conductivity of 14.5 mS/m.
Keywords: Conductance, intra/interdialytic symptoms, sodium gradient, kidney disease quality of life

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INTRODUCTION

Dialysis is a treatment used for individuals in their late stage kidney failure (chronic kidney disease, CKD) which involves the removal of waste and excess water from the blood (1). A damaged kidney cannot remove excess sodium and fluid from the body that will lead to hypertension and fluid overload. An efficient sodium balance and a controlled rate of volume contraction are prerequisites for maintaining euvolemia throughout the intra and interdialytic periods and preventing complications (2). Positive sodium gradient (dialysate minus pre-dialysis serum sodium) is characterized by diffusive transport of sodium from the dialysate to the blood compartment, reduced intradialytic sodium removal, and hypernatremia, thus resulting in interdialytic symptoms, such as thirst, subsequent increase in interdialytic weight gain (IDWG), and hypertension. Conversely, a negative sodium gradient results in diffusive transport of sodium from the blood to the dialysate, hyponatremia, and intradialytic symptoms, such as muscle cramps, hypotensive episodes, hot and cold spells, and sleep disturbances (2).

Despite the improvement in the techniques of hemodialysis (HD), treatment continues to be complicated by hypotension, muscle cramps, headache, nausea, vomiting, fatigue, hypertension, and excessive thirst. Muscle cramps are a common complication occurring in 33%-86% of patients leading to the early termina-

tion of an HD session and under-dialyzed (3). Volume contraction and hyponatremia are the most likely underlying causative factors; this hypothesis is supported in part by the reduction in the frequency of cramping in association with sodium modeling or ramping (4). Moreover, a change in extracellular volume (due to increased osmolarity and hence increased volume) may have a pressor effect. The associated increase/decrease in plasma sodium itself may also cause the blood pressure (BP) to increase/decrease. In addition, small changes in plasma sodium may directly affect the hypothalamus control of BP through the local renin–angiotensin system (5). Intradialytic hypotension results in dizziness and possibly cessation of dialysis if hypotension progressively worsens. The incidence is approximately 40%. Headache is another common finding, and the incidence is approximately 20% mostly due to BP changes (6). Thirst increases the risk of IDWG which further necessitates a long and extensive duration of dialysis to re-render euvolemia, reducing patient compliance and increasing morbidity (7-9).

Currently, dialysate conductivity is used as surrogate for sodium concentration based on the fact that electrical conductivity of solutions reflects the concentration of solute. In addition, sodium is the major electrolyte present in dialysate, and ion exchange resin traps other cations, except sodium, thus providing an easy, accurate and real-time estimation of dialysate sodium concentration (1 mS/m (unit of conductivity)=10 Na mEq/L) (2, 4, 6). Hence, there is a need for study to identify the relationship between dialysate conductivity, which is reflected by dialysate Na^+ concentration, with that of the various intra/interdialytic symptoms experienced related to HD

The aim of the present study was to (1) identify and study the various intra/interdialytic symptoms experienced by patients with CKD as a complication of HD and (2) establish a relationship between dialysate conductivity with the symptoms experienced and derive an optimal dialysate conductivity rendering lesser intra/interdialytic symptoms.

MATERIALS AND METHODS

A cross-sectional study for a period of 6 months was conducted in a dialysis center at a south Indian tertiary care teaching hospital. The study was approved by the Institutional Ethics Committee (IEC 485/2013). Of the 129 patients with end-stage renal disease (ESRD) actively undergoing HD reviewed, 97 consented and were enrolled in the study. Each patient was followed up for two consecutive dialysis sessions. Inclusion criteria were as follows: (1) patients (age ≥18 years) with CKD and ESRD (estimated glomerular filtration rate <15 mL/min/1.73 m^2) who were anuric (urine output <100 mL/day) as per the NKF KDOQI guidelines and (2) patients undergoing maintenance HD >3 months and at least twice per week. Exclusion criteria were as follows: (1) patients with polycystic kidney disease, human immunodeficiency virus infection, cirrhosis, active cancer, or cancer treatment within the past 2 years, (2) pregnant women, (3) hemodynamically unstable/critically ill patients, and (4) individuals who refuse to provide informed consent.

Assessing the inter/intradialytic symptoms

The occurrence of inter/intradialytic symptoms was determined by employing the well-validated, self-completed *Patient Reported Outcomes Instrument KDQOL 35 Symptom List Questionnaire* (31 out of 35 questions were relevant to the study and were included in the questionnaire). The questions included were about inter/intradialytic symptoms which the patients were bothered off during the past 4 weeks (10-12). The questionnaire was directly addressed to the patient during or soon after his/her dialysis session. The converted Kannada *questionnaire* (local language) was dually evaluated by the Institutional Ethical Committee team and healthcare team (nephrologist and pharmacist) and was made duly available to the patient at the time of performing the study. They were instructed to mark the box with a score of 1 (not at all bothered), 2 (somewhat bothered), 3 (moderately bothered), 4 (very much bothered), and 5 (extremely bothered). Study subjects with symptom scores of 1 and 2 were allocated to group 1, and those with symptom scores of 3, 4, and 5 were assigned to group 2.

Determining the dialysate conductance and volume of fluid removed

Dialysate conductance, transmembrane pressure (TMP), and volume of fluid removed were recorded from the dialysis machine. The values displayed in the dialysis machine were recorded 5 min (to avoid interference from the filter rinsing saline solution) after the start of each dialysis session. Patient demographic details, medical and medication histories, clinical investigations, and laboratory reports were noted from the patient's record file and recorded in pre-designed Case Record Form (CRF) during the dialysis sessions.

Determining IDWG

The patient's weight, both after a session of dialysis and before the next dialysis, were recorded, and the difference between these gives the delta weight or the total weight gain between the consecutive dialysis sessions.

Data collection

Patients with ESRD undergoing maintenance HD during 2014-2015 were identified from patient records available in the dialysis center. Patients with ESRD who have fulfilled the inclusion criteria were selected, and their demographic details, such as age, sex, and weight; medical and medication histories; reports of laboratory investigations; and other details, such as pre- and post-HD weight, delta weight, pre- and post-HD BP, intradialytic weight loss (IDWL), total volume of fluid removed, TMP, and conductivity, were recorded in the CRF. Symptom List Questionnaire was administered in their local language to each patient during the first day of data collection. Questions on trouble sleeping, excessive thirst, cramps after dialysis, and fatigue were asked during their next visit to the dialysis center.

Table 1. Patient demographics of HD patients

Demographic characteristics	Mean±SD/frequency
Age	50.86±11.24 years
Sex	Males 79% (n=77)
Females 21% (n=20)	
Clinical characteristics	Mean/frequency
Hemoglobin level	8.74±1.49 g/dL
Mean pre-dialysis blood pressure	
Systolic	157±22 mm Hg
Diastolic	89±9 mm Hg
Mean post-dialysis blood pressure	
Systolic	162±28 mm Hg
Diastolic	89±12 mm Hg
Mean conductivity	14.47±0.28 mS/m
Mean fluid removed (UF volume)	4.41±1.04 L
Mean dry weight	58.48±10.61 kg
Mean intradialytic weight loss	3.995±1.06 kg
Median transmembrane pressure	100 (73, 119)
Duration of time since on dialysis	1.2±0.8 years
Relevant comorbidities	n (%)
Hypertension	97 (100)
Diabetes mellitus	47 (48.5)
Other kidney diseases, such as PCKD, Alport syndrome, IgA nephropathy, SLE, post-infectious and chronic glomerulonephritis	18 (18.5)

Table 2. Significance of relationships using t-test

SI no.	Symptom	Means		Significance
		Group 1	Group 2	
1	Cramps during dialysis	14.61±0.42	14.41±0.18	0.002
2	Muscle soreness	14.57±0.33	14.43±0.97	0.037
3	Fatigue	14.66±0.43	14.41±0.19	0.001
4	Excessive thirst	14.82±0.17	14.40±0.25	0.001
5	Dry mouth	14.67±0.18	14.38±0.27	0.001
6	Low BP	13.8±0.37	14.51±0.23	0.001
7	Hot and cold spells	14.33±0.39	14.50±0.24	0.014
8	Trouble sleeping	14.58±0.33	14.48±0.22	0.049
9	Nausea	14.54±0.39	14.42±0.22	0.043
10	Headaches	14.5±0.22	14.46±0.30	0.705
11	Dry skin	14.5±0.24	14.46±0.29	0.683
12	Itchy skin	14.50±0.23	14.46±0.29	0.643
13	Lack of strength	14.47±0.28	14.47±0.29	0.984
14	Washed out/drained	14.37±0.35	14.47±0.28	0.48
15	Joint pain	14.41±0.36	14.48±0.26	0.318
16	Easy bruise	14.39±0.28	14.47±0.29	0.416
17	Sleepiness during the day	14.40±0.25	14.47±0.29	0.552
18	Joint stiffness	14.60±0.19	14.46±0.29	0.194
19	Back pain	14.41±0.27	14.48±0.29	0.345
20	Numbness in the hand or feet	14.48±0.12	14.47±0.29	0.936
21	Bone aches	14.52±0.25	14.47±0.29	0.718
22	Lack of appetite	14.50±0.30	14.46±0.28	0.694
23	Trouble with memory	14.22±0.19	14.48±0.28	0.074
24	Shortness of breath	14.45±0.46	14.47±0.26	0.838
25	Cramps after dialysis	14.46±0.24	14.47±0.29	0.912
26	Dizziness	14.44±0.18	14.47±0.29	0.764
27	Trouble concentrating	14.8±0.1	14.47±0.26	0.252
28	Blurred vision	14.46±0.26	14.47±0.29	0.897
29	Chest pain	14.47±0.19	14.47±0.29	0.996
30	Swelling of the ankles	14.48±0.19	14.47±0.30	0.866
31	Loss of taste	14.43±0.26	14.47±0.29	0.629

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 21 (IBM Corp.; Armonk, NY, USA) was used for statistical analysis. Demographic characteristics were analyzed using descriptive statistics, mean (±standard deviation), and frequency (%), as appropriate. Independent samples t-test was used to establish the relationship between each inter- and intradialytic symptom and conductivity. Each symptom severity listed in the questionnaire was divided into two groups (requisite of t-test). The relationship between conductance and each symptom studied was positive if significant ($p \leq 0.05$) and negative if significant ($p > 0.05$). The relationship was confirmed, and the type of correlation between symptom and conductivity was established using ANOVA and obtaining the means plot post ANOVA. The means of severity were plotted against the means of conductivity (corrected by ANOVA), and the trend was observed to establish the type of relationship.

RESULTS

A total of 97 patients were enrolled in the study. There were 77 (79%) male patients. Baseline characteristics of the study population are shown in Table 1. The mean age of the patients was 62.2 years, and the mean dialysis vintage was 1.2±0.8 years. The mean hemoglobin level was 8.72±0.17 g/dL in males, whereas it was 8.83±0.31 g/dL in females. During the study, the mean conductivity was determined to be 14.47±0.28 mS/m; approximately 60% (n=59) of the study population was maintained on a conductivity ranging from 14.2 to 14.6 mS/m. The mean ultrafiltration volume and mean IDWL were determined to be 4.41±1.04 L and 3.995±1.06 kg, respectively.

Relationship between conductivity and symptoms

The mean conductivity across the population was found to be 14.47±0.28 mS/m. The results of the t-test used in determining the presence or absence of a relationship are given in Table 2. Of the 31 parameters studied, the first 9 symptoms listed correlated significantly to conductivity showing some relationship.

The relationship between conductivity and symptoms was established by using ANOVA and deriving the means plots of each

Table 3. One-way analysis of variance between symptoms and conductivity

SI no.	Symptom	ANOVA	
		F value	Significance
1	Muscle cramps during HD	8.431	0.0001
2	Muscle soreness	4.83	0.0001
3	Fatigue	6.895	0.0001
4	Excessive thirst	7.529	0.0001
5	Dry mouth	2.274	0.003
6	Symptoms of low BP	10.365	0.0001
7	Hot and cold spells	1.535	0.012
8	Trouble sleeping	1.526	0.012
9	Nausea	1.57	0.011

Table 4. Conductivity corresponding to least severity of symptoms

SI no.	Symptom	ROC curve		
		Lower limit	Upper limit	Asymptotic sig.
1	Muscle cramps during HD	14.45	14.55	0.005
2	Muscle soreness	14.45	14.55	0.0001
3	Fatigue	14.45	14.55	0.002
4	Nausea	14.45	14.55	0.453
5	Dry mouth	14.35	14.45	0.0001
6	Excessive thirst	14.45	14.55	0.0001
7	Symptoms of low BP	13.85	14.45	0.005
8	Hot and cold spells	14.25	14.55	0.130
9	Trouble sleeping	14.35	14.45	0.404

studied symptom. The results of the same are given in Table 3. A mean plot post ANOVA was also obtained to verify the trends and correlation between symptoms and conductivity (Figures 1-4). Symptoms, such as muscle cramps, muscle soreness, fatigue, trouble sleeping, and nausea, were lowest around the population mean conductivity (14.4 mS/m) and highest at the extremes (13.2 and 15.1 mS/m) (Figures 1 and 2). Excessive thirst and dry mouth follow a similar trend (Figure 3). Both are lowest at the lower end of the population mean conductivity (13.2 mS/m) and increase across the mean to peak at the higher extreme of the mean (15.1 mS/m) as they are mutually inclusive. Figure 4 shows that both symptoms of hypotensive symptoms and hot and cold spells are lowest at the higher extreme of the mean conductivity (15.1 mS/m) and increase across the mean to peak at the lower end of the population mean conductivity

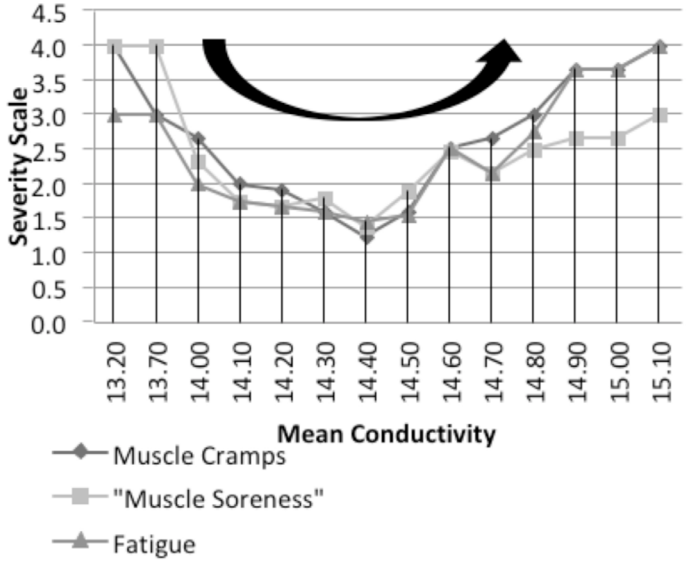

Figure 1. Trends in symptom severity of muscle cramps, muscle soreness, and fatigue.

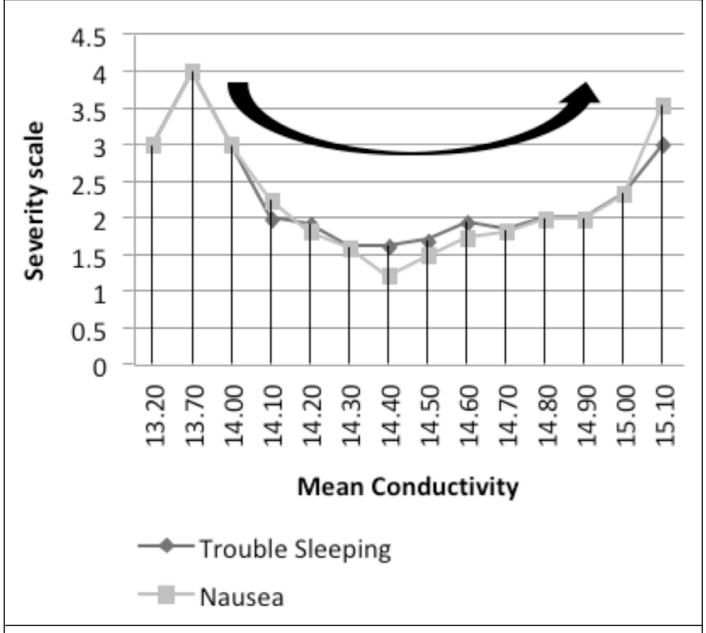

Figure 2. Trends in symptom severity of trouble sleeping and nausea.

(13.2 mS/m). Each of the nine symptoms with an established relationship to conductivity was subjected to an ROC performance (receiver operating characteristic) to derive the optimal range where patients report least discomfort (Table 4). Based on the aforementioned derived limits, the optimal conductivity for minimizing the severity of symptoms was determined to be 14.45-14.55.

DISCUSSION

Despite improvement in dialysis technology, dialysis treatment itself has a number of minor and major complications, mainly

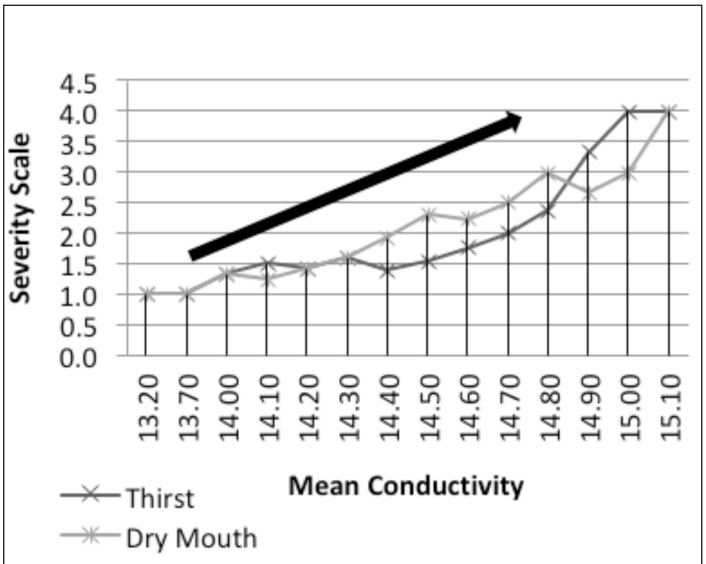

Figure 3. Trends in symptom severity of thirst and dry mouth.

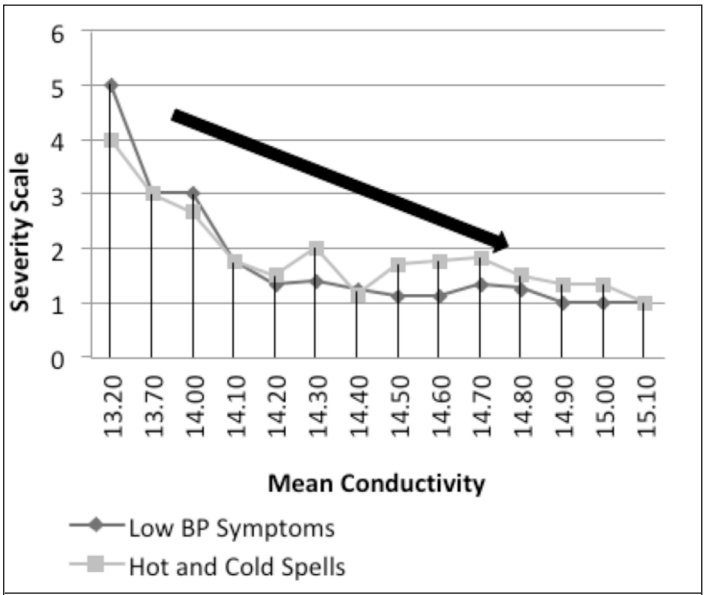

Figure 4. Trends in symptom severity of low BP symptoms and hot and cold spells.

resulting from disturbance in the body's homeostasis. Sodium pooling in the body with dialysis treatment has very important clinical implications, mainly with respect to inter- and intradialytic symptoms depending on the maintenance of constant dialysate sodium concentration (13). To the best of our knowledge, this is the first study attempting to answer the question as to whether a low or high dialysate sodium maintenance is to be advocated in chronic HD for reduced symptoms, reviewed via a Patient Reported Outcomes questionnaire. This study attempted to answer the commonly reported intra/interdialytic symptoms by means of the Patient *Reported Outcomes* using the *KDQOL 35 Symptom List Questionnaire* and tried to establish the relationship between the symptom's severities with dialysate conductivity and also to derive an optimal dialysate conductivity range to be maintained for minimal symptoms expression. The study showed that there was a change in trends of symptoms severity with the changes of the trough and peak value of the sodium conductivity maintained during HD. Sodium homeostasis during HD treatment is important to preserve the patient from clinical events related to hypo- or hypernatremia (4). Our study showed a positive correlation of the symptoms expressed as muscle cramps, muscle soreness, fatigue, trouble sleeping, and nausea with the sodium gradient bothering the patients during inter/intrahemodialytic phases when compared with the value of dialysate conductivity displayed in the dialysis machine. Our study (Figures 1, 2) showed that symptoms are lowest around the study population mean conductivity (14.4 mS/m) and highest at the extremes (13.2 and 15.1 mS/m) consistent with the current literature (14-16). In the DOPPS study, it was observed that lower serum sodium levels are associated with certain HD symptoms and higher adjusted risk of death with serum sodium <137 mEq/L and lower mortality risk in patients with dialysate sodium prescriptions >140 mEq/L. These observations found were to be clinically meaningful because serum sodium measured routinely is rarely interpreted for sodium balancing in HD patients. Thus, dialysate sodium prescriptions are essential for ideal maintenance of sodium conductivity for reduced symptoms in pre- and post-HD of the patients (17). The associations of a high sodium gradient with fluid overload are likely explained by a high dialysate sodium concentration leading to an elevated post-dialysis serum sodium level with the consequence of increased thirst and fluid intake (18). Basile et al. (19) also expressed that the range of 138-140 mmol/L dialysate sodium concentration maintenance is a comfortable target to reduce the impact of mortality or other cardiovascular outcomes in the study. Increased severity of muscle cramps and soreness at the extremes of the study populations mean conductivity range in our study was most likely due to temporary hyponatremic and hypernatremic situations caused by high and low conductivity levels during dialysis. This finding was also observed by Albalate et al. (20) Fatigue has multiple etiologies, but none the less does show a dependence on dialysate conductivity and follows a similar trend as muscle cramps albeit with less severity (21). Fatigue could also be due to mild cerebral edema developed because of rapid urea clearance creating osmotic gradient during dialysis, as cited by Caplin et al. (22) Sleeping problems and nausea severity are also both highest at the extremes and lowest around the population mean conductivity. The prevalence of sleep apnea is >50% in dialysis patients. Resulting fluid overload due to higher dialysate conductivity and overnight shift of fluids from legs to neck soft tissue is considered as the most possible causative factor as mentioned in Murray and Nadel's textbook of respiratory medicine (23). Excessive thirst and dry mouth follow a trend of both lowest at the lower end of the population mean conductivity (13.2 mS/m) and increase across the mean to peak at the higher extreme of the mean (15.1 mS/m) (Figure 3). Thirst is largely dependent on serum osmolality, which increases during hypernatremia and/or rapid and excessive volume contraction.

Figure 4 shows that both symptoms of hypotensive symptoms and hot and cold spells are lowest at the higher extreme of the mean conductivity (15.1 mS/m) and increase across the mean to peak at the lower end of the population mean conductivity (13.2 mS/m). Irrespective of the smallest IDWG, with the lowest ultrafiltration requirements and use of very less number of antihypertensive medications in the study population by Davenport et al. (24), there were more reports of lowest pre- and post-dialysis systolic blood those dialyzing with a median dialysate sodium of <140 mmol/L, but reduced the complaint of low BP with a median dialysate sodium of >140 mmol/L. The similar outcome expressed in our study showed that there were higher complaints with reduced symptoms severity with mean conductance rising near 15.1 mS/m. Hypotensive symptoms and hot and cold spells are lowest at the higher extreme of the mean and increase across the mean to peak at the lower end of the study populations mean conductivity due to hyponatremia as a result of negative sodium gradient between dialysate and plasma as previously shown by Agarwal et al. (25) and Nesrallah et al. (26). However, there was no significant reduction of BP post-dialysis neither were there any correlations to conductivity or volume of fluid lost during HD. The present research demonstrated that of a total of 31 symptoms assessed, nearly 9 correlated significantly to conductivity showing some relationship. These included cramps during HD, muscle soreness, symptoms of low BP, hot and cold spells, thirst, dry mouth, fatigue, nausea, and trouble sleeping. Cramps, muscle soreness, fatigue, nausea, and trouble sleeping showed a similar trend of being least severe around a conductivity of 14.5 mS/m. Thirst and dry mouth severity increased as conductivity increased, whereas hypotensive symptoms and hot and cold spells decreased as conductivity increased. Based on the correlations, an optimal range for conductivity was derived as 14.45-14.55 mS/m for minimizing the sodium gap that may lead to less symptom rates in conventional HD patients.

Ethics Committee Approval: The ethics committee approval was received for this study from the Institutional Ethics Committee, Kasturba Hospital, IEC 485/2013.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – P.K.; Design – P.K., A.D.; Supervision – P.K., R.P.A.; Data Collection and/or Processing - B.S.K., A.D., T.R.; Analysis and/or Interpretation - B.S.K., A.D., T.R.; Literature Search – B.S.K., A.D., T.R.; Writing – B.S.K., A.D., T.R., P.K., A.S., S.N. Critical Reviews – R.P.A.

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