Determinants of Hemodynamic Stability and Patient Reported Outcomes in Hemodialysis

Determinants of Hemodynamic Stability and Patient Reported Outcomes in Hemodialysis

By

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I have reviewed this thesis. It represents work done by the author under my guidance/supervision.

Primary Mentor: Dr. Finnian Mc Causland, MBBCh, MMSc

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Overview

Patients on maintenance hemodialysis (HD) suffer from disproportionately high morbidity and mortality, with up to a 15-fold higher risk death compared to age-matched individuals without end-stage kidney disease.(1–3) This high disease burden is in part related to hemodialysis treatments themselves which induce systemic fluctuations in volume and serum osmoles that can destabilize blood pressure, trigger intracellular fluid shifts, and precipitate end-organ injury.(4–7)

Intradialytic hypotension (IDH) is one of the most frequent complications of HD, with a prevalence of 8-40% and is a major risk factor for cardiovascular disease and mortality.(7–9) IDH can provoke ischemic symptoms such as chest pain and muscle cramps, however there are over a dozen intradialytic symptoms common to HD that can occur independent of blood pressure.(10,11) Intradialytic symptoms occur in up to 75% of patients and are associated with reduced quality of life and risk for depression, which can occur in up to 25% of the HD population(2,3,12,13) Both IDH and intradialytic symptoms can be severe enough to impair the delivery HD, which in turn can predispose patients to additional risk associated with inadequate renal replacement.(7,14,15)

Although the precise pathogeneses of both IDH and intradialytic symptoms is incompletely understood, they are associated with the intensity of hemodialysis itself. This is illustrated by the clinical management of these disease entities, which often involves reducing either the efficiency or duration of the dialysis session.(7,10,16) This underscores the crucial need to identify risk factors for IDH or intradialytic symptoms that a) are high-yield, inexpensive and

modifiable and b) will not negatively impact the adequacy of HD treatments.(17) With this in mind, I have chosen to explore the role of intradialytically-administered iron sucrose and calculated pre-HD serum osmolarity in the manifestation of intradialytic complications.

Manuscript 1:

Associations of Iron Sucrose and Intra-dialytic Blood Pressure

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Abstract

Introduction

Intra-dialytic hypotension (IDH) and intra-HD hypertension (IDHyper), are associated with increased morbidity and mortality for patients on maintenance hemodialysis (HD). Many factors can contribute to extremes of intra-HD blood pressure (BP), including intra-HD medication administration. Intradialytic intravenous iron sucrose is commonly administered for correction of iron deficiency, but its hemodynamic effects remain incompletely understood.

Methods

Using the DaVita Biorepository (n=950), a prospective cohort study unadjusted and adjusted repeated measures models were fit to assess the association of iron sucrose administration with IDH, IDHyper, and systolic BP parameters (pre-HD systolic BP, nadir intra-HD systolic BP, and post-HD systolic BP). Multivariable models adjusted for age, sex, race, access, and pre-HD systolic BP, categories of session length, ultrafiltration volume, diabetes, heart failure, ischemic heart disease, peripheral vascular disease, lung disease, erythropoietin dose were performed. Exploratory models were fit including the prior variables with additional adjustment for hemoglobin and endothelin-1 concentrations.

Results

Mean age was 56 ±20 years, 43% were females, and 38% were Black. Mean pre-HD SBP was

152 ±26 mmHg. Patients who received iron sucrose tended to be younger, diabetic, have higher ultrafiltration volume, and higher frequency of ESA use, compared with those who did not. In fully adjusted models, those with iron sucrose had a 7% lower odds (OR 0.93; 95%CI 0.89 to 0.97) and 8% higher odds (OR 1.08; 95%CI 1.04 to 1.11) of developing IDH and IDHyper, respectively. Further, iron sucrose was associated with a 1.2 (95%CI 1.0 to 1.5) mmHg higher pre-HD systolic BP, 0.6 (95%CI 0.4 to 0.8) mmHg higher nadir systolic BP, and 0.7 (95%CI 0.5 to 1.0) mmHg higher post-HD systolic BP in fully adjusted models.

Conclusions

We observed an independent association of intravenous iron sucrose administration with a lower risk of IDH, higher risk of IDHyper, and higher intra-dialytic systolic BP parameters. Future studies to better understand the mechanisms underlying this pattern are warranted.

Introduction:

Abnormal blood pressure (BP) is a major health concern for the ~485,000 people in the United States receiving maintenance hemodialysis (HD).(1) Intradialytic hypotension (IDH) is one of the most common complications of HD and occurs in up to 68% of HD sessions, depending in the definition used.(2)IDH is associated with end-organ ischemic damage leading to increased risk of myocardial stunning, heart failure, limb ischemia, dementia, loss of renal reserve, and cardiac- and all-cause mortality.(3–6) On the other end of the spectrum, intradialytic hypertension (IDHyper) occurs when systolic BP rises or fails to lower over the course of a dialysis session and is estimated to affect up to 22% of HD sessions.(7,8) IDHyper is associated with higher rates of hospitalization, cardiac and all-cause mortality.(8–10)

Intradialytic BP is affected by multiple patient and treatment-specific factors, including cardiovascular, neurohormonal, and autonomic dysfunction, in addition to blood, dialysate, and ultrafiltration rates.(9,11) Intradialytic medications must be considered carefully, as administration of drugs with vasoactive properties could destabilize an already tenuous BP. One such medication is Intravenous iron sucrose, which is a nondialyzable, polynuclear iron (III)-hydroxide and sucrose mixture, widely used in the HD population to correct iron deficiency.(12,13) There have been concerns raised that iron sucrose infusions generate a bioactive, “labile” iron fraction in the blood that can cause endothelial damage or hypersensitivity reactions.(14) Data on the safety profile of intravenous iron sucrose is not entirely consistent, with some studies reporting an association with up to a threefold higher risk of IDH,(15) while others do not.(16)

Based on prior data suggesting a dose-response relationship between iron sucrose and risk of transient hypotension IDH, we undertook this study with the a priori hypothesis that an association between iron sucrose administration and IDH would be seen in this large cohort. (18)

Methods:

Study Population

The current analyses were performed using a prospective cohort of anonymized samples and statistically de-identified clinical data from a biorepository assembled by DaVita Clinical Research (DCR) and made available to academic organizations through the Biospecimen Research Grant (BioReG) program. Patients who were <18 years old, with Hgb <8.0 g/dL, pregnant, or with any physical, mental, or medical condition which limited the ability to provide written informed consent were excluded from BioReG. The present study only included patients undergoing thrice-weekly HD. The sampling protocol was approved by an Institutional Review Board (Quorum IRB, Seattle, WA, USA) and patients provided written informed consent prior to the initiation of sample collection. All clinical and hemodialysis prescription data were collected from the electronic medical record. A randomly sampled subset of the total cohort was provided to each of four academic institutions by DCR in a deidentified format.

Biospecimen collection and storage

Biospecimens were collected and processed according to a standardized protocol, including shipping on refrigerated packs on the same day as collection, processing, aliquoting, and storage at -80°C. Re-collection was requested for any specimen with cause for rejection (e.g., unspun tubes, insufficient volume, or thawed specimens). Specimens received >48h from the time of collection were also rejected and re-collected. Samples were distributed frozen at -80°C across the four academic medical centers.

Exposure

The primary exposure for this study was the administration of intravenous iron sucrose at the individual HD session. The prescribed dose and confirmation of patient administration were obtained from the electronic medical record.

Outcome Ascertainment

The primary outcome was IDH, defined as either an absolute intradialytic nadir systolic BP<90 mmHg in patients with a pre-HD systolic BP of <160 mmHg or nadir systolic BP<100 mmHg in patients with pre-HD systolic BP ≥160 mmHg. This definition of IDH was selected over alternative definitions due to its potent association with mortality. (2)

Secondary outcomes included other intra-HD blood pressure parameters (pre-HD systolic BP, nadir intra-dialytic systolic BP, and post-HD systolic BP). The development of intra-dialytic hypertension was also considered, defined as any increase in systolic BP from pre- to post-HD.(17) BP was measured at all study sessions per standard clinical guidelines.

Assessment of Other Covariates

Demographic information including age, race, sex, dialysis access and comorbid conditions including diabetes, heart failure, coronary artery disease, cerebrovascular disease, peripheral vascular disease and chronic obstructive pulmonary disease (COPD), were recorded at baseline and updated from the medical record (via ICD-9 codes) throughout the study. Additional information such as the HD prescription, erythropoiesis-stimulating agent (ESA) dose, vascular access, and laboratory data were collected at each session. Dialysis session length was categorized (≤180 mins; 181-209 mins; 210-239 mins; ≥240 mins). Ultrafiltration volume was calculated by subtracting the post-dialysis weight from the pre-dialysis weight. Potential effect

modification by variables determined *a priori* (sex, diabetes, and heart failure) was assessed via the inclusion of cross-product terms.

Statistical Analysis

Continuous variables were summarized using means (±standard deviations) or medians (25^{th}-75^{th} percentiles) and compared with t-test or Wilcoxon Rank Sum tests, according to data distribution. Categorical variables were summarized as percentages and compared with Chi-squared tests.

Initially, unadjusted repeated measures regression models (to account for within person correlation) were fit to determine the association of iron sucrose administration with outcomes of interest. Subsequently, multivariable adjusted linear and logistic random effects regression models were fit, including a random intercept for subject-wise variability. Model 1 was adjusted for age, sex, race, access, and pre-HD systolic BP (the latter was excluded from analyses where pre-HD systolic BP was the outcome of interest); Model 2 was adjusted for the same variables as model 1 with additional adjustment for categories of session length, ultrafiltration volume, diabetes, heart failure, ischemic heart disease (history of coronary artery disease, myocardial infarction, or angina), peripheral vascular disease, lung disease, erythropoietin dose. Two further exploratory analyses were considered: Model 3 adjusted for the same variables as model 2, with additional adjustment for hemoglobin; Model 4 adjusted for the same variables as model 3, with additional adjustment for endothelin-1. Several data imputations were performed: a) Hb was measured inconsistently, and missing values were imputed based on last recorded measurement; b) ET-1 was only measured prior to the first HD session, this value was

imputed for the remaining sessions. Assessment for the presence of effect modification for pre-specified variables (sex, diabetes, heart failure) was performed via the inclusion of cross-product terms in Model 2. Model covariates were selected for inclusion based on clinical and biologic plausibility.

All analyses were performed using Stata MP version 16 (StataCorp LP). A two-sided P-value <0.05 was considered to be statistically significant, without adjustment for multiple testing.

Results

We examined data from 950 subjects and 135,412 HD sessions from the BioReG cohort (Figure 1). Those included were more likely to have a lower baseline pre-HD systolic BP and were more likely to have had an ESA administered during HD, compared with those excluded from the final cohort (Supplementary Table 1).

The mean age of patients included in the study was 56 ±20 years, 43% were females, and 38% were Black. Mean pre-HD systolic BP was 152 ±26 mmHg. At baseline, patients who received iron sucrose tended to be younger, diabetic, have higher ultrafiltration volume, and higher frequency of ESA use, compared with those who did not receive iron sucrose (Table 1).

Iron sucrose and intra-dialytic hypotension

In unadjusted analyses, iron sucrose was associated with 9% lower odds of experiencing IDH (odds ratio [OR] 0.91; 95%CI 0.87 to 0.94). In adjusted models 1 and 2 this association persisted, with 8% lower odds (OR 0.92; 95%CI 0.89 to 0.96) and 7% lower odds (0.93; 95%CI 0.89 to 0.97), respectively. In exploratory model that were adjusted for hemoglobin and endothelin, iron sucrose administration was associated with a 8% lower odds of IDH (0.92; 95%CI 0.88 to 0.97). In an exploratory analysis that looked at doses of iron sucrose, we found an association between iron sucrose administration and lower risk of IDH in doses of iron sucrose >100mg (OR 0.86; 95%CI 0.80 to 0.91; fully adjusted; supplementary table 2).

Iron sucrose and intradialytic hypertension

In unadjusted analyses, administration of iron sucrose during HD was not associated with intradialytic hypertension. However, in adjusted analyses, iron sucrose administration was

associated with an 8% higher odds of developing intradialytic hypertension (OR 1.08; 95%CI 1.05 to 1.12 in model 1 and OR 1.08; 95%CI 1.04 to 1.08 in model 2). This effect estimate persisted in exploratory models that adjusted for hemoglobin and endothelin (Table 2). When analyzed by dose category, we found an association between iron sucrose administration and higher risk of IDHyper in doses of iron sucrose >100mg (OR 1.18; 95%CI 1.13 to 1.24; fully adjusted; supplementary table 2) in fully adjusted and exploratory models.

Effect modification and sub-group analyses

For the IDH outcome, no evidence of effect modification by diabetes, sex, or heart failure was observed (Table 5). In the IDHyper group, there was no evidence for effect modification according to sex or diabetes, but there was according to a history of heart failure at baseline (P-interaction=0.016). Subgroup analyses suggested a stronger association of iron sucrose administration with IDHyper among those with a history of heart failure (OR 1.20; 95%CI 1.09-1.32), compared to those without (OR 1.06; 95% CI 1.02-1.10).

Iron sucrose and HD-related systolic BP parameters

The baseline differences in HD-related BP parameters according to administration of iron sucrose are presented in Table 3. In unadjusted analyses, iron sucrose administration was associated with 1.4 (95%CI 1.2. to 1.7) mmHg higher pre-HD systolic BP (Table 4). In the fully adjusted model (Model 2), iron sucrose administration was associated with 1.2 (95%CI 0.9 to 1.4) mmHg higher pre-HD systolic BP . Overall, in the fully adjusted model, iron sucrose administration was associated with 0.6 (95%CI 0.4 to 0.8) mmHg higher nadir systolic BP and 0.7 (95%CI 0.5 to 0.9) mmHg higher post-HD systolic BP.

Discussion

In this large cohort of patients receiving maintenance HD, we found that the administration of intravenous iron sucrose during HD was associated with a lower odds of developing IDH and a higher odds of developing IDHyper. Similarly, iron sucrose administration was associated with higher pre-HD systolic BP, nadir intra-dialytic systolic BP, and post-HD systolic BP.

Iron deficiency is common among patients receiving maintenance HD and is thought to be related to impaired nutrition, chronic blood loss, and decreased intestinal absorption of iron.(18–20) As an integral component in erythropoiesis, administration of iron has been promoted as a means to correct anemia, reduce the need for transfusions, and to reduce the requirement for erythropoiesis-stimulating agents.(21) In the setting of HD, iron deficiency is associated with adverse symptoms and important clinical outcomes, such as hospitalization and mortality.(22,23) Indeed, proactive administration of IV iron (400 mg per month) was reported to be superior to a reactive IV iron strategy (0-400 mg per month) in the PIVOTAL trial in terms of reducing the risk for cardiovascular outcomes (composite of non-fatal myocardial infarction, non-fatal stroke, heart failure, or all-cause death).(24)

The development of anaphylaxis is perhaps the most feared complication from administration of intravenous iron. In the non-CKD/ESKD population, the reported frequency of serious reactions related to intravenous iron administration appears to be relatively rare. For example, a meta-analysis by Wang et al comparing the safety profiles of different IV iron formulations found that use of iron sucrose carried a very low risk of anaphylaxis (21 per 100,000 persons).(25) Another study by Baile et al. that used a large United States Food and Drug

Administration surveillance database found zero episodes of anaphylaxis/million mg of iron sucrose administered.(26) Iron sucrose is frequently used to correct iron deficiency anemia in ESKD and is widely considered to be safe in HD patients. Given the concern with iron-associated allergic reactions, one might expect adverse blood pressure events to present as hypotension in patients with CKD or HD dependance. This was seen in a trial comparing iron sucrose to oral iron in patients with CKD (n=188) which described transient hypotension in two patients in the context of 500 mg dose administration.(27) The Iron Sucrose Clinical Trial of repletion versus maintenance (n=665 patients on maintenance HD) reported iron sucrose-related nonserious IDH in 0.0004% of exposures and 0.004% of patients.(28) Other studies, including the single-arm North American Clinical Trial (n=77), which looked at the effect of 10 consecutive 100mg doses of iron sucrose, and the Proactive IV Iron Therapy in Haemodialysis Patients (PIVOTAL; n=2141), which compared proactive (frequent) vs reactive (less frequent) doses of iron sucrose, did not raise concerns about hypotension. (24,29)However, it should be noted that these studies did not specifically examine prespecified definitions of IDH.(24,29)

Although FDA labeling for Venofer (iron sucrose) references a 36% prevalence of hypotension among patients in the three, single-arm clinical trials used in the drug approval process, this risk may be overstated. None of the trials used standardized definitions of IDH and instead, events were recorded if a decline in blood pressure was felt to be significant in the investigator's opinion. In the two published trials, all episodes of IDH occurred at least 2 hours after iron sucrose administration and were felt to be unrelated to the drug.(30–32) Van Wyck even observed a higher frequency of IDH among patients during the observation period rather than during sessions when iron sucrose was infused. (31)

Conversely, one study examining different doses of iron sucrose in pediatric patients with CKD observed an adverse event of increased BP in 6.4% of patients in the higher dose arm, but granular information was not available on what definition of IDH was used or when this occurred in relation to the HD session.(33)

In our study, we found that the administration of iron sucrose was associated both with a lower risk of IDH and a corresponding higher risk of IDHyper. This contrasts with the more common clinical concerns related to potential hypotension which are hypothesized to be related to allergic-type responses.(15) In trying to reconcile these differences, it is notable that the maximum dose of iron sucrose administered in our patient population was 200mg at any given session, with previous studies appearing to suggest a higher risk of IDH at higher doses.(27,34) However, this would not account for a potential association of iron sucrose administration with IDHyper. In this respect, intravenous iron sucrose is hyperosmolar (1200 mOsm/L) and is often administered in 100mL of isotonic saline (combined 404 mOsm/L). The addition of even small volumes of hypertonic fluid has been reported to elevate intradialytic BPs, likely through both expansion of the intravascular space and enhanced vasopressin activity.(35) Due to data limitations, we were not able to determine the volume of diluent at each administration in the present analyses. This analysis cannot rule out the possibility that iron sucrose administration is a surrogate marker for another factor associated with higher blood pressures such as more intense/attentive medical care or another unmeasured confounding variable.

While correction of iron deficiency is known to improve cardiovascular outcomes,(24) and may act in part through improved cardiac function,(36) it is not clear if this would explain improved hemodynamic parameters at an individual session level.

Our study has several strengths such as a relatively large sample size, duration of follow-up, and availability of detailed, per-HD session intravenous medication and hemodynamic data. However, several limitations are present, including the non-availability of the precise iron sucrose formulation, nonavailability of laboratory data for each HD session and outpatient medications, limited data on the dialysate temperature, and potential misclassification of covariables secondary to the use of ICD-9 codes. No data is available for other intravenous iron formulations. Although other formulations are generally considered to be better tolerated than iron sucrose, we are unable to address their precise hemodynamic effects in this dataset.(14,37) Other potentially relevant information relating to objective measures of volume status, home medications, and symptom data were not recorded in this study, and it is possible that transient episodes of hypotension or hypertension may have been missed. We used data imputation in our exploratory models to account for a lack of available laboratory values, which carries the risk of introducing bias into the analysis. For all analyses, the potential for residual confounding remains. Although, the patient population and data collection methodology strongly reflect the US in-center hemodialysis population, it is impossible to account for hidden sources of bias and confounding.

In summary, we observed an independent association of intravenous iron sucrose administration with a lower risk of intra-dialytic hypotension and higher intra-dialytic systolic BP parameters. Future studies to better understand the mechanisms underlying this data are warranted.

Table 1. Baseline characteristics according to administration of iron sucrose

Baseline Characteristic*	Iron Sucrose (-) (n=828)	Iron Sucrose (+) (n=122)	P-value
Age, yrs	53 ± 22	52 ± 20	0.53
Female, N (%)	363 (44%)	51 (42%)	0.67
Pre-Dialysis weight, kg	90.3 ±24.1	90.0 ± 24.2	0.88
Ultrafiltration volume, L	2.1 ± 1.5	2.2 ± 1.5	0.35
Race, n(%)			0.88
White	323 (39%)	50 (41%)	
Black	317 (38%)	44 (36%)	
Other	188 (23%)	28 (23%)	
Pre-HD Systolic BP, mmHg	152 ± 27	153 ± 29	0.78
Access, n (%)			0.005
AVF	567 (67%)	77 (63%)	
AVG	108 (13%)	29 (24%)	
Tunneled Catheter	153 (18%)	16 (13%)	
Dialysis Session Length, mins			0.01
<180	203 (25%)	15 (12%)	
>180	134 (16%)	27 (22%)	
≥210	271 (33%)	38 (31%)	
≥240	217 (26%)	41 (34%)	
Diabetes, n (%)	355 (43%)	65 (53%)	0.3
Hypertension, n (%)	247 (30%)	46 (38%)	0.8
Ischemic Heart Disease, n (%)	73 (9%)	9 (7%)	0.6
Heart Failure, n(%)	70 (8%)	14 (11%)	0.27
Serum Albumin, g/dL	3.5 ± 0.5	3.4 ± 0.5	0.15
ESA Dose, units per HD	0 [0, 6600]	5500 [2200, 11000]	<0.001

Abbreviations: BP, blood pressure; AVF, arteriovenous fistula; AVG ateriovenous graft

*the values used to construct this table are from the first recorded hemodialysis session for each patient

Table 2. Association of iron sucrose administration with intradialytic hypotension and hypertension

Odds Ratio (95% CI) for Iron Sucrose administration versus not					
	Unadjusted	**Model 1**	**Model 2**	**Model 3**	**Model 4**
IDH	0.91 (0.87 to 0.94)	0.92 (0.89 to 0.96)	0.93 (0.89 to 0.97)	0.93 (0.89 to 0.97)	0.92 (0.88 to 0.97)
IDHyper	1.00 (0.97 to 1.03)	1.08 (1.05 to 1.12)	1.08 (1.04 to 1.11)	1.08 (1.04 to 1.11)	1.07 (1.03 to 1.11)

Abbreviations: IDH, intradialytic hypotension; IDHyper, intradialytic hypertension

Table 3. Baseline mean HD-related Systolic BP Parameters with Iron Sucrose

	Iron Sucrose (-)	**Iron Sucrose (+)**	**P-value**
Pre-dialysis systolic BP, mmHg	150 ±26	152 ±26	<0.001
Nadir intra-dialytic systolic BP, mmHg	114 ±114	116 ±22	<0.001
Post-dialysis systolic BP, mmHg	139 ±25	141 ±25	<0.001

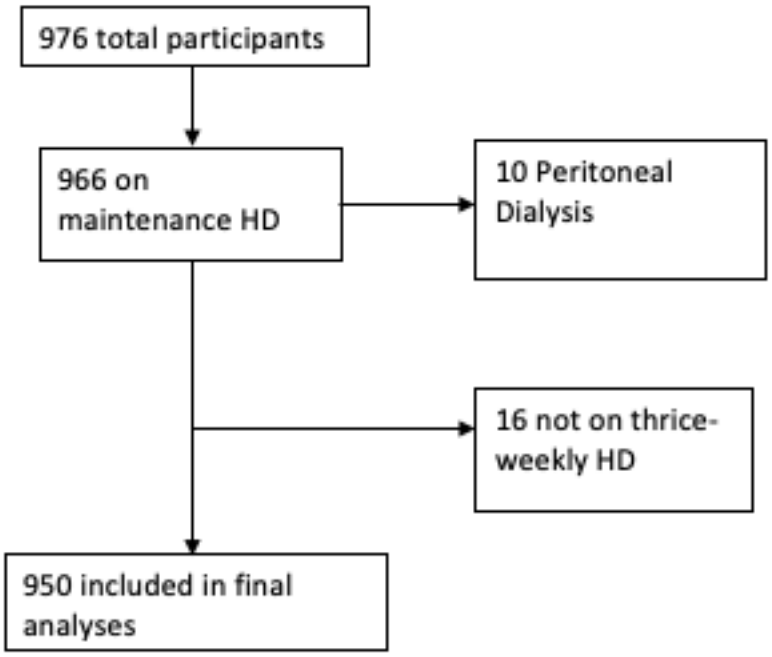
Abbreviations: BP, blood pressure; mmHg, millimeters of Mercury

Table 4. Association of iron sucrose with dialysis-related systolic blood pressure parameters.

SBP Parameter	Model	Difference in Systolic BP (95%CI) for IS vs. non-IS, mmHg	P-value
Pre-HD SBP	Unadjusted	1.4 (1.2-1.7)	<0.001
	Model 1	1.4 (1.2-1.7)	<0.001
	Model 2	1.2 (0.9-1.4)	<0.001
	Model 3	1.2 (0.9-1.4)	<0.001
	Model 4	1.2 (0.9-1.5)	<0.001
Nadir SBP	Unadjusted	1.2 (1.0-1.5)	<0.001
	Model 1	0.7 (0.5-0.9)	<0.001
	Model 2	0.6 (0.4-0.8)	<0.001
	Model 3	0.6 (0.4-0.8)	<0.001
	Model 4	0.7 (0.5-0.9)	<0.001
Post-HD SBP	Unadjusted	1.3 (1.0-1.5)	<0.001
	Model 1	0.8 (0.5-1.0)	<0.001
	Model 2	0.7 (0.5-0.9)	<0.001
	Model 3	0.7 (0.5-1.0)	<0.001
	Model 4	0.7 (0.5-1.0)	<0.001

Abbreviations: BP, blood pressure; mmHg, millimeters of Mercury; CI, confidence interval

Figure 1. Consort Diagram



Supplementary Table 1. Comparison of included and excluded participants

Baseline Characteristic	Included (n=950)	Excluded (n=26)	P-value
Age, yrs	59.3 ± 14.5	60.7 ± 16.8	0.82
Female, N (%)	414 (43.6%)	13 (50%)	0.51
Pre-Dialysis weight, kg	90.3 ± 24.1	97.0 ± 39.1	0.36
Ultrafiltration volume, L	2.1 ± 1.5	1.9 ± 1.3	0.69
Race, n(%)			0.14
White	373 (39.3%)	15 (57.7%)	
Black	38.0 (38.0%)	8 (30.8%)	
Other	226 (22.7%)	3 (11.5%)	
Pre-HD Systolic BP, mmHg	152.2 ± 27.7	159.5 ± 39.9	0.39
Access, n (%)			0.54
AVF	644 (67.8%)	14 (77.8%)	
AVG	137 (14.4%)	1 (5.6%)	
Tunneled Catheter	169 (17.8%)	3 (16.7%)	
Dialysis Session Length, mins			0.49
<180	216 (22.9%)	3 (33.3%)	
>180	163 (17.3%)	0	
≥210	307 (32.6%)	4 (44.4%)	
≥240	257 (27.3%)	2 (22.2%)	
Diabetes, n (%)	418 (44.0%)	6 (33.3%)	0.37
Hypertension, n (%)	293 (30.8%)	3 (16.7%)	0.20
Ischemic Heart Disease, n (%)	82 (8.6%)	1 (5.6%)	0.64
Heart Failure, n (%)	84 (8.8%)	1 (5.6%)	0.63
Serum Albumin, g/dL	3.5 ± 0.5	3.7 ± 0.4	0.56
ESA Dose, units per HD	0 [0, 3300]	2200 [0, 7700]	0.057

Abbreviations: BP, blood pressure; AVF, arteriovenous fistula,; AVG arteriovenous graft

Supplementary Table 2: Association of iron sucrose administration with intradialytic hypotension and hypertension by dose category

Dose of iron sucrose (mg)		None	>0-100	>100
Number of Observations		100,126	20,001	15,765
IDH	Unadjusted	REF	0.99 0.94-1.04	0.80 (0.75 to 85)
	Model 1	REF	1.01 (0.96 to 1.06)	0.81 (0.76 to 0.86)
	Model 2	REF	0.98 (0.93 to 1.03)	0.86 (0.93 to 1.03)
	Model 3	REF	0.98 (0.93 to 1.03)	0.85 (0.80 to 0.91)
	Model 4	REF	0.97 (0.92 to 1.03)	0.86 (0.80 to 0.92)
IDHyper	Unadjusted	REF	0.87 (0.84-0.90)	1.19 (1.15 to 1.24)
	Model 1	REF	0.94 (0.90-0.98)	1.29 (1.23 to 1.35)
	Model 2	REF	1.00 (0.96 to 1.04)	1.18 (1.13 to 1.24)
	Model 3	REF	1.00 (0.96 to 1.04)	1.18 (1.13 to 1.24)
	Model 4	REF	1.00 (0.96 to 1.05)	1.17 (1.11 to 1.23)

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Manuscript 2

Calculated Serum Osmolarity as a Predictor of Intradialytic Symptoms

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Running Title: Serum Osmolarity and Intradialytic Hypotension and Symptoms

Abstract

Introduction

Hemodialysis (HD) is associated with intradialytic hypotension (IDH) and a plethora of often debilitating intradialytic symptoms. Techniques to mitigate these complications often are insufficient or interfere with patients' renal replacement therapy. Solute and water shifts that occur during HD have been linked to both processes, making patient pre-HD serum osmolar state a potentially useful biomarker for both intradialytic hypotension and symptoms.

Methods

We used data collected from the Hemodialysis Trial from 1810 patients and 9036 hemodialysis sessions to examine the association of pre-HD calculated serum osmolarity (cOsm) [by 10mmol/L and by quartile] with rates of five pre-specified intradialytic symptoms collected during the study (muscle cramps, chest pain, headache, nausea, and lightheadedness) and IDH. Multivariate analysis was performed using random effects Poisson regression modeling. In exploratory analyses, we tested for effect modification between cOsm and IDH and analyzed cOsm using an alternative definition of IDH.

Results

Mean age was 58 years old, 62% of patients were black and 56% were female. In fully adjusted models, each 10mOsm/L increase in pre-HD cOsm was associated with a 22% higher rate of muscle cramping (incidence rate ratio [IRR] 1.22; 95%CI [1.13-1.32]), a 42% greater rate of headache (IRR 1.42; 95%CI [1.09-1.85]) and a 19% higher composite symptom score (IRR 1.19; 95%CI [1.10-1.27]). Chest pain, nausea, and lightheadedness failed to achieve statistically

significance individually. Each 10mOsm/L increase in pre-HD cOsm was associated with 9% higher rate of IDH in the fully adjusted model (IRR 1.09; 95%CI [1.03-1.16]). Our analysis did not detect effect modification from IDH on pre-HD cOsm's association with intradialytic symptoms.

Conclusion

We found that greater pre-HD cOsm levels were independently associated with higher rates of muscle cramping, headache, and IDH. Additional studies that incorporate severity scores and a wider range of symptoms are needed.

Introduction

Maintenance Hemodialysis (HD) is a critical life sustaining technology that can condense a week's worth of renal filtration into less than half a day. The rapid shifts in body volume and electrolyte concentrations are create a unique set of physical and emotional challenges. Intradialytic symptoms (IDS) are common and frequently underreported, with up to 75% of patients experiencing symptoms including muscle cramping, dizziness, nausea, chest pain, and fatigue (1–3). In addition to significantly impacting patient quality of life, these symptoms can be severe enough to impede delivery of HD, which predisposes these individuals to excess risk of mortality and morbidity associated with inadequate dialysis(4–6). Presently, there is a paucity of targeted treatments for intra-dialytic symptoms that do not involve the reducing the duration or efficiency of HD treatments. Although the precise pathogenesis of HD-related symptoms is incompletely understood, an interplay between intradialytic serum osmotic shifts and intradialytic hypotension (IDH) may be important.(7)

Rapid clearance of osmoles from the blood during HD may generate transient osmotic gradients between the extracellular and intracellular compartments. These favor the movement of water intracellularly, which can predispose to development of hypotension and adverse symptomatology. This hypothesis is supported by a body of work from our group that has reported on elevated calculated pre-HD serum osmolarity as a risk factor for intradialytic hypotension. (8,9)We have also published on the association of higher pre-HD blood urea nitrogen levels—one of the principle osmoles in the blood-- with higher risk of IDH and certain intra-dialytic symptoms.(9) However, the association of overall serum osmolarity with patient

symptoms, and whether this depends on development of intra-dialytic hypotension, is not clear.

Methods

Study Design: The Hemodialysis (HEMO) study was a multicenter, clinical trial that used a 2-by-2 factorial design to randomize 1846 patients with end stage kidney disease to standard- vs high-flux dialysis membranes and standard- versus high-Kt/V prescriptions. Enrollment occurred from March 1995 to October 2000(10). The mean follow-up was 2.84 ± 1.84 years. A detailed description of the study design and protocol is available on the National Institute of Diabetes and Digestive and Kidney Diseases website [HEMO](11). This is a post-hoc analysis of the prospectively collected data assembled for the HEMO study.

Study Population:

The study enrolled patients 18-80 years of age undergoing thrice-weekly HD, who had an HD vintage of ≥3 months. Patients were excluded if they had a urinary urea clearance >1.5ml/min per 35-liters of urea volume, serum albumin <2.6g/dL, or if they were assigned to the high-dose dialysis arm but failed to achieve an equilibrated Kt/V >1.3 within two of three consecutive monitored HD sessions.

Data Collection:

Detailed demographic data was collected for each patient at baseline, including age, sex, race, medical comorbidities, dialysis vintage, and access. Laboratory and clinical data from HEMO was collected during kinetic modeling sessions which were performed at baseline and weeks 1, 2, 4 & 5, then until the higher equilibrated Kt/V goal was reached in two of three consecutive sessions, then monthly thereafter. Blood urea nitrogen (BUN) was collected at each of these

sessions but serum sodium (Na), serum potassium, serum chloride, serum bicarbonate, serum phosphorous, and fasting blood glucose were collected every 6 months.

Presence or absence of five prespecified patient symptoms (muscle cramps, chest pain, headache, lightheadedness, and vomiting) were recorded by the study coordinator or dialysis unit technician on kinetic modeling days. Symptom severity scores were not included. Episodes of intradialytic hypotension were recorded during these sessions using a prespecified definition: drop in systolic blood pressure that prompted an intervention (saline administration, or reduction in ultrafiltration or blood flow).

Exposures and Outcomes:

The primary exposure was pre-HD calculated serum osmolarity (cOsm) which is derived from the following the formula: 2*[Na] + [BUN]/2.8 + [glucose]/18.

The main outcomes of interest were the five prespecified symptoms: muscle cramps, chest pain, headache, lightheadedness, and vomiting. A composite outcome for the presence/absence of any symptom was also assessed. The presence or absence of intradialytic hypotension was considered as a secondary outcome of interest. Interaction terms were created in relevant models to assess for effect modification of the association of cOsm with patient symptoms, according to presence of intra-dialytic hypotension.

Statistical Analysis

Continuous variables were reported as mean ± standard deviation (SD) if normally distributed or median with 25^{th}-75^{th} percentiles if nonnormally distributed. Categorical variables were reported as frequency and percentages. Baseline laboratory and demographic data was

presented using either first available baseline or kinetic measurement for each patient. Comparisons by quartile of pre-HD cOsm were tested for trend using linear regression, chi-squared trend testing, and Cuzick nonparametric testing, as appropriate.

Relationships between exposures and outcomes were analyzed at the HD-session level. The main analyses were restricted to HD sessions that coincided with per protocol measurement of pre-HD serum sodium, serum BUN and fasting glucose so that cOSM could be determined. To account for nonindependence of repeated measurements from same patient across multiple HD sessions, random effects Poisson regression modeling was used. Three hierarchical models were considered and followed a stepwise inclusion of covariates: Model 1 adjusted for age, sex, race, HD vintage, and HEMO study arms (randomized KT/V allocation, randomized dialysis flux allocation); Model 2 contained the covariates of Model 1 and further adjusted for presence of congestive heart failure, diabetes mellitus, type of HD access, pre-HD systolic blood pressure, and ultrafiltration rate; Model 3 (main) contained the covariates of Model 2 and further adjusted for serum levels of albumin, bicarbonate, phosphorous, creatinine, and hematocrit. For the outcome of IDH an additional sensitivity analysis was conducted using an alternative definition: nadir systolic blood pressure <90mm Hg if pre-HD systolic blood pressure was ≤160 mm Hg or nadir <100mm Hg if pre-HD systolic blood pressure was >160mm Hg.(12)

An interaction term was created to test for effect modification between intra-dialytic hypotension and pre-HD cOsm and evaluated using Wald tests for Model 3.

P-values less than 0.05 were considered statistically significant, without correction for multiple hypothesis testing. Missing data was not imputed. All analyses were conducted using the

STATA IC (version 16.1, STATACorp LP) statistical software package. Data for this study was obtained from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) data repository.

RESULTS

Patient Baseline Characteristics

This study included 1,838 patients and a combined 64,797 HD sessions. After selecting for sessions where pre-HD sodium, blood urea nitrogen, and glucose were available, 1,810 patients and 9,632 observations remained for analysis.

Mean age was 58 years old, 62% of patients were of black race, and 56% were female. When divided by quartiles of pre-HD serum osmolarity, patients in the highest quartile of cOsm were more likely to be male, have diabetes, longer dialysis vintage, greater serum albumin and creatinine levels, and have been assigned to the high KT/V arm (table 1). Serum sodium, BUN, and glucose were positively associated with higher cOSM.

cOsm and Symptoms

Cramping

Greater pre-HD cOsm (per 10 mOsm/L) was associated with a 22% higher rate of cramping in the unadjusted (incidence rate ratio [IRR] 1.22; 95CI [1.12-1.32]) and fully adjusted (IRR 1.22; 95%CI [1.13-1.32]; Table 2) models. In the fully adjusted categorical analysis, the highest quartile of pre-HD cOsm was associated with a 63% greater rate of IDH compared to the lowest quartile (IRR1.63; 95%CI [0.1.26-2.11]).

Headache

Although pre-HD cOsm (per 10 mOsm/L) was not associated with headache in the continuous, unadjusted model, it was was associated with a 42% greater rate in the fully adjusted model

(IRR 1.42; 95%CI [1.09-1.85]). The association of pre-HD cOSM and headache showed a stepwise increase in risk across quartiles of pre-HD cOsm compared to the lowest quartile.

Chest Pain

There was no association between pre-HD cOsm (per 10 mOsm/L) and chest pain in the unadjusted or adjusted models (Table 2). The models in the categorical analysis failed to achieve convergence due to the small number of observations (40) spread across the quartiles. It was therefore omitted.

Vomiting

Pre-HD cOsm (per 10 mOsm/L) was not associated with rate of vomiting in the unadjusted or adjusted models (Table 2). No association between pre-HD cOsm and vomiting was seen in the fully adjusted categorical analysis either.

Lightheadedness

In both unadjusted and adjusted models, pre-HD cOsm (per 10 mOsm/L) was not associated with rate of Lightheadedness. No association between pre-HD cOsm and lightheadedness was seen in the fully adjusted categorical analysis either.

Any Symptom

Greater pre-HD cOsm (per 10 mOsm/L) was associated with a 16% higher rate of reporting any symptom (cramping, headache, chest pain, vomiting, or lightheadedness) in the unadjusted (IRR 1.16; 95%CI [1.09-1.24]; Table 2) and 19% higher rate in the fully adjusted model (IRR 1.19; 95%CI [1.10-1.27]). The categorical analysis of pre-HD cOsm found a stepwise increase in rate of any symptom across quartiles. Patients in the highest quartile of pre-HD cOsm had a 54% higher

rate of experiencing any symptom compared to those in the lowest quartile (IRR 1.54; 95%CI [1.26-1.89]).

cOsm and Intradialytic Hypotension

IDH occurred in 17% (1681 out of the 9632) sessions analyzed, with 55% (898 out of 1810) of patients experiencing at least one episode of IDH. Greater pre-HD cOSM (per 10 mOsm/L) was associated with a 6% higher rate of IDH in the unadjusted model (IRR 1.06; 95%CI [1.01-1.12]; Table 3) and 9% higher rate in the fully adjusted model (IRR 1.09; 95%CI [1.03-1.16]). The highest quartile of pre-HD cOsm was associated with a 24% higher rate of IDH compared to the lowest quartile (IRR 1.24; 95%CI [1.05-1.45]).

A sensitivity analysis was performed using an alternative definition of IDH defined by nadir intradialytic systolic blood pressure cutoff. No association between pre-HD cOsm and rate of IDH (nadir) was seen in either the unadjusted or adjusted analyses [supplemental 1].

Interaction between Hypotension and pre-HD cOsm

Wald tests on Hypotension and pre-HD cOsm in the main adjusted model for cramping, headache, and any symptom had Wald statistics of >0.1.

Discussion

In this post-hoc analysis of the HEMO study, we found that higher pre-HD calculated serum osmolarity was associated with a higher risk of several intradialytic symptoms—specifically, cramping, headache, and lightheadedness. Higher pre-HD calculated osmolarity was also associated with a higher risk of intra-dialytic hypotension, confirming our prior findings in a separate cohort, but the association of cOsm with patient symptoms did not differ according to the presence or absence of intra-dialytic hypotension.

Although the precise pathophysiological etiologies for both intradialytic hypotension and intradialytic symptoms remain unknown, there is evidence to suggest that serum osmolar shifts may play a role in mediating both processes. The rapid clearance of serum solutes during HD is believed to create a transient osmolar gradient between the intra- and extra-cellular spaces, leading to the net movement of water intracellularly.(13,14) The resultant decline in blood volume and cardiac output could, in turn, lead to hypotension and associated ischemic symptoms. A pilot study using bioimpedance technology to monitor transcellular fluid shifts supports this hypothesis, with an observed association of higher drop in serum osmolarity with presence of IDH and intracellular volume expansion.(15) Further, intradialytic blood pressures have been observed to decrease the fastest during the first 25% of a HD session, when osmolar gradients between serum and dialysate fluid are the highest.(16) The present findings confirm our prior reports of an association of higher pre-HD calculated osmolarity with IDH from a separate cohort of patient receiving maintenance HD.(8) Furthermore, research published by our group demonstrated that mannitol appears to improve certain metrics of hemodynamic

stability in patients initiating HD for the first time,(17) with similar association of higher (vs. lower) dialysate sodium in hospitalized patients receiving maintenance HD.(18)

While patient symptoms and intra-dialytic hypotension often go hand-in-hand, it was notable that we did not observe different associations of cOsm with patient symptoms according to the presence or absence of intra-dialytic hypotension. Thus, it may be possible that the association of cOsm with adverse patient symptoms is independent of end-organ hypoperfusion, and may relate more to the consequences of intra-cellular swelling. In this respect, the entity known as dialysis disequilibrium syndrome (DDS) is hypothesized to be caused by rapid correction of a hyperosmolar or uremic state, and can cause neurologic dysfunction independently from end-organ hypoperfusion.(19) DDS presents as a spectrum of symptoms that range from nausea, vomiting, headache, muscle cramping, and dizziness, to life-threatening complications that include seizure and death.(20) The cerebral vasculature is particularly susceptible to sudden changes in serum blood urea nitrogen levels due to a lower transcapillary permeability compared with most other capillary beds.(14) Circumstantial evidence that supports this theory includes observations where administration of hypertonic fluids have reduced the frequency of patient symptoms, including headache and muscle cramps.(21,22)

A major strength of this study is the detailed, session level data included in the analysis. Although pre-HD serum blood urea nitrogen and symptoms were examined by our group in this dataset, this analysis does not use imputation and thus avoids bias from missing data.(9) However, our study also had several limitations. Details on timing of symptoms was not available, limiting our ability to assess the temporal association of IDH in relation to onset of

symptoms. As there are over a dozen common dialysis-related symptoms, this study is limited in its ascertainment of patient symptoms. Further, the severity of the reported symptoms was not recorded, which could have allowed for further subgroup analysis. This is a post-hoc analysis of the HEMO study and thus vulnerable to residual confounding, despite multivariable analysis. Other potentially important variables such as session-level medication administration, other dialysis prescription parameters, and measured osmolality were not available. Further, as we analyzed only sessions where complete laboratory data was available excluded, we only included 16% of the available kinetic modeling sessions.

Although this study was published in the early 2000s, the fundamental technology, pathophysiology, and challenges associated with HD remain the same, underscoring the importance of new therapeutic strategies. In future, prospective studies, eliciting a wider and more detailed range of symptoms, and assessing both calculated and measured osmolality would be helpful. Our findings highlight the need to better understand the mechanistic foundations of intradialytic symptoms while developing strategies to mitigate their effects on patients.

Table 1. Patient baseline demographic, hemodialysis, and laboratory characteristics by cOsm Quartile

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-value
Patients (N)	491	472	446	401	
Age (years)	58 ± 14	58 ± 15	58 ± 14	58 ± 13	0.85
Female sex	295 (60%)	275 (58%)	232 (52%)	218 (54%)	0.02
Black race	303 (62%)	306 (65%)	268 (60%)	250 (62%)	0.78
Dialysis vintage, years	2.4 (1, 6)	2.4 (1, 5)	2.3 (1, 5)	2.1 (1, 4)	0.016
Ischemic heart disease	197 (40%)	177 (38%)	171 (38%)	167 (42%)	0.66
Congestive heart failure	213 (43%)	162 (34%)	174 (39%)	175 (44%)	0.72
Peripheral vascular disease	133 (27%)	105 (22%)	122 (27%)	104 (26%)	0.89
Diabetes mellitus	196 (40%)	196 (42%)	208 (47%)	212 (53%)	<0.001
Cardiac arrythmia	166 (34%)	138 (29%)	138 (31%)	120 (30%)	0.29
HD session length (min)	213 ± 27	214 ± 27	214 ± 29	214 ± 27	0.84
Ultrafiltration rate (ml/kg/hr)	12.4 ± 5.9	11.9 ± 5.9	12.1 ± 5.5	12.7 ± 5.6	0.38
Blood flow (ml/min)	397 ± 62	399 ± 66	396 ± 71	385 ± 73	0.06
Dialysate flow (ml/min)	693 ± 127	682 ± 127	682 ± 128	683 ± 128	0.18
pre-HD SBP (mmHg)	151 ± 28	151 ± 25	153 ± 25	152 ± 24	0.23
High KT/V group	251 (51%)	260 (55%)	206 (46%)	186 (46%)	0.03
High flux membrane group	242 (49%)	236 (50%)	223 (50%)	205 (51%)	0.61
Access Type					0.7

AVG	297 (60%)	285 (60%)	260 (58%)	235 (59%)	
AVF	154 (31%)	153 (32%)	165 (37%)	140 (35%)	
Catheter	40 (8%)	34 (7%)	21 (5%)	26 (6%)	
Creatinine (mg/dL)	9.7 (2.8)	10.4 (2.8)	10.4 (2.8)	10.6 (3)	<0.001
Albumin (g/L)	3.8 ± 0.4	3.9 ± 0.4	3.9 ± 0.3	3.9 ± 0.3	<0.001
Hematocrit (%)	33 ± 4	34 ± 5	34 ± 5	34 ± 4	0.16
Bicarbonate (mEq/L)	22 ± 4	22 ± 4	22 ± 4	21 ± 4	0.81
Sodium (mmol/L)	135 ± 4	138 ± 3	139 ± 3	141 ± 4	<0.001
Blood Urea Nitrogen (mg/dL)	45 ± 13	53 ± 12	61 ± 14	73 ± 17	<0.001
Glucose (mg/dL)	123 ± 60	135 ± 74	149 ± 80	164 ± 98	<0.001
Calculated Osmolarity	294 ± 6	302 ± 2	308 ± 2	318 ± 5	<0.001

Continuous variables are depicted as means ± standard deviation or median (interquartile range); Categorical variables are given as count (%). AVG, arteriovenous graft; AVF arteriovenous fistula.

Table 2. Association of cOSM by unit and by quartile with prespecified symptoms in unadjusted and adjusted models.

	cOsm per 10 mOsm/L		**cOsm by Quartile**							
Category			**Quartile 1**	**Quartile 2**		**Quartile 3**		**Quartile 4**		
	IRR [95% CI]	p		IRR [95% CI]	P	IRR [95% CI]	P	IRR [95% CI]	P	
Cramping										
Univariate	1.22 [1.12-1.32]	<0.001	REF	1.32 [1.05-1.67]	0.02	1.44 [1.14-1.82]	0.002	1.66 [1.32-2.10]	<0.001	
Model 1	1.22 [1.13-1.32]	<0.001	REF	1.32 [1.04-1.67]	0.02	1.44 [1.14-1.82]	0.002	1.67 [1.32-2.11]	<0.001	
Model 2	1.21 [1.12-1.31]	<0.001	REF	1.33 [1.05-1.68]	0.02	1.45 [1.15-1.83]	0.002	1.66 [1.31-2.10]	<0.001	
Model 3	1.20 [1.10-1.31]	<0.001	REF	1.31 [1.01-1.69]	0.04	1.48 [1.15-1.90]	0.003	1.63 [1.26-2.11]	<0.001	
Headache										
Univariate	1.25	0.06	REF	0.98	0.96	0.86	0.67	1.42	0.27	

	[0.99-1.59]			[0.52-1.87]		[0.44-1.69]		[0.77-2.64]	
Model 1	1.27 [1.00-1.60]	0.045	REF	0.98 [0.51-1.86]	0.94	0.88 [0.45-1.72]	0.71	1.45 [0.78-2.69]	0.24
Model 2	1.33 [1.04-1.69]	0.02	REF	1.01 [0.52-1.93]	0.99	0.92 [0.47-1.82]	0.82	1.59 [0.84-3.00]	0.15
Model 3	1.42 [1.09-1.85]	0.01	REF	0.90 [0.43-1.87]	0.77	1.05 [0.51-2.18]	0.89	1.70 [0.84-3.44]	0.14
Chest Pain									
Univariate	1.12 [0.82-1.53]	0.49	REF	-		-		-	
Model 1	1.15 [0.84-1.59]	0.37	REF	-		-		-	
Model 2	1.1 [0.85-1.64]	0.31	REF	-		-		-	
Model 3	1.25 [0.87-1.78]	0.23	REF	-		-		-	

Vomiting									
Univariate	1.02 [0.87-1.21]	0.78	REF	1.07 [0.67-1.71]	0.78	1.15 [0.72-1.82]	0.57	1.13 [0.71-1.81]	0.61
Model 1	1.06 [0.90-1.25]	0.48	REF	1.12 [0.70-1.78]	0.64	1.22 [0.77-1.94]	0.41	1.24 [0.77-1.98]	0.38
Model 2	1.04 [0.22-1.22]	0.69	REF	1.09 [0.68-1.74]	0.72	1.19 [0.75-1.89]	0.46	1.16 [0.72-1.86]	0.54
Model 3	1.05 [0.88-1.27]	0.58	REF	1.13 [0.68-1.88]	0.62	1.23 [0.74-2.03]	0.43	1.24 [0.74-2.08]	0.42
Lightheadedness									
Univariate	1.07 [0.92-1.23]	0.38	REF	0.99 [0.66-1.47]	0.95	1.12 [0.76-1.66]	0.57	1.16 [0.78-1.72]	0.47
Model 1	1.08 [0.93-1.24]	0.31	REF	1.01 [0.68-1.51]	0.95	1.14 [0.77-1.69]	0.52	1.19 [0.80-1.77]	0.4
Model 2	1.0	0.35	REF	1.01	0.96	1.14	0.53	1.17	0.43

	[0.93-1.24]			[0.68-1.51]		[0.76-1.69]		[0.79-1.76]	
Model 3	1.15 [0.97-1.36]	0.11	REF	1.15 [0.71-1.87]	0.56	1.52 [0.96-2.41]	0.07	1.45 [0.89-2.35]	0.13
Any symptom									
Univariate	1.16 [1.09-1.24]	<0.001	REF	1.22 [1.02-1.46]	0.03	1.27 [1.06-1.53]	0.01	1.44 [1.20-1.73]	<0.001
Model 1	1.17 [1.10-1.25]	<0.001	REF	1.23 [1.03-1.47]	0.03	1.29 [1.07-1.54]	0.006	1.47 [1.23-1.77]	<0.001
Model 2	1.17 [1.09-1.24]	<0.001	REF	1.24 [1.03-1.48]	0.02	1.30 [1.08-1.56]	0.005	1.47 [1.23-1.77]	<0.001
Model 3	1.19 [1.10-1.27]	<0.001	REF	1.24 [1.01-1.51]	0.04	1.42 [1.16-1.73]	0.001	1.54 [1.26-1.89]	<0.001

Quartile 1 was used as the reference for the quartile analysis. IRR [95% CI] = Incident rate ratio [95% Confidence interval]. Models for categorical analysis of chest pain outcome failed to converge and were omitted.

Table 3. Association of cOsm by unit and by quartile with hypotension in unadjusted and adjusted models.

Category	**per 10 mOsm/L**		**Quartile 1**	**Quartile 2**		**Quartile 3**		**Quartile 4**	
Unadjusted	1.06 [1.01-1.12]	0.02	REF	0.97 [0.84-1.12]	0.69	1.05 [0.91-1.22]	0.47	1.15 [0.99-1.33]	0.07
Model 1	1.12 [1.05-1.20]	0.001	REF	0.98 [0.85-1.13]	0.77	1.07 [0.93-1.23]	0.36	1.17 [1.01-1.36]	0.04
Model 2	1.08 [1.02-1.14]	0.005	REF	1.0 [0.87-1.16]	0.97	1.10 [0.95-1.27]	0.21	1.19 [1.03-1.38]	0.02
Model 3	1.09 [1.03-1.16]	0.004	REF	1.05 [0.90-1.22]	0.56	1.11 [0.95-1.30]	0.18	1.24 [1.05-1.45]	0.01

Hypotension is defined as drop in systolic blood pressure prompting administration of saline or adjustment of blood flow or ultrafiltration rate; Quartile 1 was used as the reference for the quartile analysis. IRR [95% CI] = Incident Rate Ratio [95% Confidence interval

Supplemental 1: Association of cOsm and intradialytic hypotension using nadir-based definition

Category	**per 10 mOsm/L**		**Quartile 1**	**Quartile 2**		**Quartile 3**		**Quartile 4**	
Unadjusted	1.03 [0.97-1.10]	0.31	REF	0.99 [0.84-1.16]	0.89	0.96 [0.82-1.14]	0.66	1.07 [0.91-1.27]	0.4
Model 1	1.04 [0.97-1.10]	0.27	REF	0.99 [0.84-1.16]	0.9	0.97 [0.82-1.14]	0.7	1.08 [0.92-1.28]	0.35
Model 2	1.04 [0.98-1.11]	0.18	REF	1.01 [0.86-1.18]	0.92	1.00 [0.85-1.18]	0.98	1.09 [0.92-1.29]	0.32
Model 3	1.01 [0.94-1.08]	0.85	REF	0.99 [0.84-1.18]	0.94	0.93 [0.78-1.11]	0.41	1.03 [0.86-1.23]	0.76

Hypotension is defined as nadir systolic blood pressure <90mm Hg (if pre-HD systolic blood pressure was ≤160 mm Hg) or <100mm Hg (if pre-HD systolic blood pressure was >160mm Hg); Quartile 1 was used as the reference for the quartile analysis. IRR [95% CI] = Incident Rate Ratio [95% Confidence interval]

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Summary of Conclusions

The goal of this work was to identify and explore modifiable risk factors for intradialytic hypotension (IDH) and intradialytic symptoms which are two of the most common and overlooked complications of hemodialysis (HD). To this end, we chose to investigate intravenous iron sucrose (Study 1) and pre-HD calculated serum osmolarity (Study 2) as potential predictors.

In Study 1, we used a large, dataset of outpatient HD patients to analyze intradialytic iron sucrose administration and risk of IDH. Contrary to data from older studies which implicate iron sucrose as a risk factor for IDH, we found in our study that iron sucrose administration was associated with **a lower risk of IDH and a higher risk of intradialytic hypertension**. Our results are consistent with several larger trials that also did not observe a hypotensive effect with iron sucrose administration. However, to our knowledge, we are the first to report a negative association with IDH risk or a positive association with intradialytic hypertension risk in adults receiving iron sucrose on HD. (18,19)

While these results should be interpreted with caution as this is a retrospective analysis, our findings are nevertheless intriguing. Given the high prevalence of iron sucrose use in outpatient hemodialysis centers, additional insight into this medication's biological effect is valuable as it has the potential to inform best practice guidelines for tens of thousands of patients.

In Study 2, we analyzed the association of pre-HD calculated serum osmolarity (cOsm) with intradialytic hypotension and five, prespecified intradialytic symptoms using data from a subset of patients enrolled in the Hemodialysis Trial.(20) We observed that greater pre-HD cOsm was associated with higher rates of muscle cramps, headache, and IDH. Our findings build on previous retrospective studies that have reported greater cOsm and blood urea nitrogen as predictors for IDH or intradialytic symptoms.(6,21,22) These data highlight the need for additional research into the clinical implications of a patient's pre-HD osmolar state. Interestingly, our interaction term test did not suggest that IDH was an effect modifier for the association between cOsm and rate of intradialytic symptoms. This supports the notion that large drops in cOsm may contribute to symptoms independent of systemic hypotension.

Discussion and Perspectives

Hemodialysis is a double-edged sword; sessions provide life-sustaining therapy but also place enormous stress on patients' bodies. The high rate of HD-associated complications and the increased long-term morbidity and mortality these episodes confer highlight the urgent need to develop risk mitigation strategies. In this body of work, we identified two modifiable risk factors for intradialytic complications.

Although iron sucrose administration and serum osmolality may affect patients on HD through separate mechanisms, they both represent easily measurable and modifiable risk factors that can be monitored in the outpatient setting. Blood pressure-based holding parameters for iron sucrose would be simple to protocolize, as is already being done with Erythropoiesis-Stimulating Agents.(23) Similarly, hypertonic mannitol and dextrose solutions have been shown experimentally to reduce both intradialytic hypotension and several intradialytic symptoms but are not routinely used in practice(6,16)

It is important to not overinterpret the conclusions from these studies as important data on the precise timing of symptoms, objective measures of volume status, cardiac function, and concurrent medication are unavailable in these datasets.(7,24) Further, as this is a retrospective analysis, there are likely to be multiple unknown confounders.

Still, the results of this body of work remain promising and have the potential to inform future prospective studies focused on developing accurate models of risk and testing therapeutic strategies aimed at reducing intradialytic hemodynamic instability and symptom burden.

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