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Original Investigation

Association of Predialysis Calculated Plasma Osmolarity With Intradialytic Blood Pressure Decline

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Background: The rapid reduction in plasma osmolality during hemodialysis (HD) may induce temporary gradients that promote the movement of water from the extracellular to the intracellular compartment, predisposing to the development of intradialytic hypotension (IDH).

Study Design: Observational cohort study.

Setting & Participants: 3,142 prevalent patients receiving thrice-weekly HD from a single dialysis provider organization.

Predictor: Predialysis calculated plasma osmolarity (calculated after the 2-day interval as 2 × serum sodium + serum urea nitrogen/2.8 + serum glucose/18).

Outcome: Magnitude of systolic blood pressure (SBP) decline (predialysis SBP − nadir intradialytic SBP) and risk of IDH (SBP decline > 35 or nadir SBP < 90 mm Hg).

Measurements: Unadjusted and multivariable-adjusted generalized linear models were fit to estimate the association of calculated osmolarity with intradialytic SBP decline and the odds of developing IDH.

Results: Mean age of participants was 62.6 ± 15.2 (SD) years, 57.1% were men, and 61.0% had diabetes. Mean predialysis calculated osmolarity during follow-up was 306.4 ± 9.5 mOsm/L. After case-mix adjustment, each 10-mOsm/L increase in predialysis calculated osmolarity was associated with 1.48 (95% CI, 0.86-2.09) mm Hg ($P < 0.001$) greater decline in intradialytic SBP and 10% greater odds of IDH (OR, 1.10; 95% CI, 1.05-1.15). In adjusted models, lower predialysis sodium and higher serum urea nitrogen and serum glucose levels were associated with greater decline in intradialytic SBP.

Limitations: Measured serum osmolality, timing of changes in intradialytic osmolality, dialysate osmolality, and dialysate temperature were not available.

Conclusions: Higher predialysis calculated osmolarity is associated with greater decline in intradialytic SBP and greater risk of IDH in maintenance HD patients. Strategies to minimize rapid shifts in osmolality should be tested prospectively to minimize excess SBP decline in susceptible patients.

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INDEX WORDS: Intra-dialytic hypotension; osmolality; hemodialysis; calculated plasma osmolarity; systolic blood pressure (SBP); hemodynamic instability; end-stage renal disease (ESRD); renal replacement therapy (RRT).

Intradialytic hypotension (IDH), defined as significant and abrupt decline in systolic blood pressure (SBP) during the hemodialysis (HD) procedure that causes symptoms and/or requires an intervention, is estimated to affect up to one-third of outpatient HD sessions.[1-3] IDH events are associated with a greater incidence of myocardial stunning,[4] cerebral atrophy,[5] and greater all-cause mortality.[6] The underlying pathogenesis of intradialytic SBP decline is likely to be multifactorial, including the presence of autonomic neuropathy,[7] higher ultrafiltration rates (UFRs),[8] and temporary changes in osmolality induced by the HD procedure itself.[9]

Mean predialysis serum osmolality in HD patients is reported to range from 291 to 339 mOsm/kg and may decline by up to 33 mOsm/kg during dialysis,[10-13] primarily due to changes in levels of sodium, glucose, and urea (the 3 major constituents of serum osmolality). We previously reported that greater rates of decline in serum urea nitrogen (SUN) levels during HD are associated with a greater risk of developing IDH.[9] Previous studies have reported that use of a higher concentration of dialysate sodium[14] and other hyperosmolar substances[15,16] may limit the development of transient osmotic gradients and thereby promote intradialytic hemodynamic stability.

We wished to determine the association of predialysis calculated osmolarity with the magnitude of decline in intradialytic SBP. We hypothesized that higher predialysis calculated osmolarity would be associated with greater intradialytic SBP decline.

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METHODS

Study Design and Population

The study protocol was deemed exempt by the Partners Healthcare Institutional Review Board. We performed a nonconcurrent cohort study of prevalent patients receiving HD in Satellite Healthcare facilities in 2012. Patients became eligible for participation on the earliest date within this period on which they were at least 18 years of age and had been receiving HD for more than 180 days (n = 3,722). Those not receiving thrice-weekly HD (n = 291), those with session length longer than 5 hours (n = 23), and those without available variables to calculate the predialysis calculated osmolarity (n = 231) or intradialytic SBP decline (SBP readings < 40 or >240 mm Hg or missing; n = 18) were excluded. Because most (97%) laboratory values were measured on the first dialysis day of the week (ie, Monday or Tuesday), we excluded patients with blood drawn on other days (n = 17). The final cohort consisted of 3,142 individuals and 21,646 HD sessions.

Exposures and Outcomes

The primary exposure of interest was calculated osmolarity, equal to (2 × serum sodium) + (SUN/2.8) + (serum glucose/18). Secondary exposures of interest included predialysis serum sodium, glucose, and SUN levels (recorded from routine monthly blood draws). The primary outcome was the magnitude of intradialytic SBP decline, defined as predialysis SBP less the nadir intradialytic SBP. Routine blood pressures were measured every 30 minutes during dialysis; the median number of measurements per session was 8. The secondary outcome of interest was the development of IDH, defined as a decline in SBP > 35 mm Hg or any intradialytic SBP < 90 mm Hg.

Study Data

Demographic data including sex, race, comorbid conditions, and age were recorded at baseline. Dialysis treatment and hemodynamic parameters were recorded at each individual HD session; only sessions with corresponding laboratory data were included in the analyses. Laboratory measurements were obtained prior to the first HD session of the week (after the 2-day interdialytic interval) on a monthly basis and processed in a central laboratory. All patients were assumed to dialyze against a dialysate glucose concentration of 100 mg/dL.[17] Dialysate sodium concentrations used in these treatments ranged from 126 to 148 mmol/L, including 16.1% that used sodium modeling algorithms.

Statistical Analysis

Continuous variables were examined graphically and recorded as mean ± standard deviation for normally distributed data or median with interquartile range for non-normally distributed data. Comparisons were made using analysis of variance or Kruskal-Wallis tests as appropriate. Categorical variables were examined by frequency distribution and recorded as proportions, and comparisons were made using χ^2 test.

Initially, unadjusted generalized linear regression models (using a normal distribution and identity link function) were fit to assess the association of calculated osmolarity with intradialytic SBP decline. Subsequently, in model 1, adjustment was made for age, sex (male vs female), race (black vs nonblack), diabetes, ischemic heart disease, congestive heart failure, access type (fistula, graft, or catheter), predialysis SBP, and UFR (in milliliters per kilogram per hour). Model 2 was adjusted for the same variables as model 1, in addition to predialysis serum calcium, albumin, and bicarbonate levels. Subsequently, further models were fit using a binomial distribution and logit link function to determine the association of calculated osmolarity with the odds of developing intradialytic hypotension. Because extreme hyperglycemia may influence the calculated osmolarity, sensitivity analyses were performed when excluding those with predialysis glucose concentrations > 132 mg/dL. In order to evaluate the individual components that contribute to the calculated osmolarity, secondary analyses were performed in the manner already described to determine the association of predialysis serum sodium, glucose, and SUN levels with the magnitude of intradialytic SBP decline and odds of developing IDH. Finally, by the inclusion of cross-product terms, exploratory analyses were performed to assess for effect modification of the association of calculated osmolarity with SBP decline according to higher (>140 mmol/L or modeling) versus lower (≤140 mmol/L) dialysate sodium use and UFR, with subgroup analyses presented for lower and higher dialysate sodium concentration use and tertiles of UFR.

Covariates for all models were selected on the basis of clinical and biological plausibility, without use of probabilistic selection criteria. Nominal 2-sided $P < 0.05$ was considered statistically significant. Analyses were performed using Stata MP, version 13.1.

RESULTS

Baseline Characteristics

Mean age of the patients was 62.6 ±15.2 years; 12.9% were black, and 61.0% had diabetes. Individuals in the highest tertile of baseline calculated osmolarity tended to be younger and men and have higher predialysis serum sodium, SUN, serum glucose, and albumin levels, but lower predialysis serum bicarbonate concentrations (Table 1). Those in the highest tertile of calculated osmolarity also tended to have higher predialysis SBP, greater ultrafiltration volume and UFR, greater intradialytic SBP decline, and greater frequency of IDH (Table 2). During a median follow-up of 5.3 months, mean predialysis calculated osmolarity was 306.4 ± 9.5 mOsm/L.

Predialysis Calculated Osmolarity and Intradialytic SBP Decline

In unadjusted models, each 10-mOsm/L increment in predialysis calculated osmolarity was associated with a 2.22 (95% confidence interval [CI], 1.51-2.93) mm Hg greater decline in intradialytic SBP. In the fully adjusted model (model 2), the association was attenuated, but remained statistically significant (1.48 [95% CI, 0.86-2.09] mm Hg) even after exclusion of patients with predialysis serum glucose levels > 132 mg/dL (0.98 [95% CI, 0.23-1.70] mm Hg [Table 3]). Effect estimates were qualitatively and quantitatively similar after individual additional adjustment for categories of blood flow, dialysate bicarbonate concentration, and dialysate calcium concentration (data not shown). When analyzed in tertiles of calculated osmolarity, a monotonic association was apparent (Fig 1). Similar patterns of association were evident when IDH was considered as the outcome of interest (Table 3).

Predialysis Serum Sodium, SUN, Glucose, and Intradialytic SBP Decline

In secondary analyses, the associations of serum sodium, SUN, and serum glucose levels with intradialytic