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Original Investigation

Effect of Low Versus High Dialysate Sodium Concentration on Blood Pressure and Endothelial-Derived Vasoregulators During Hemodialysis: A Randomized Crossover Study

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Background: Intradialytic hypertension affects ~15% of hemodialysis patients and is associated with increased morbidity and mortality. While intradialytic hypertension is associated with increases in endothelin 1 relative to nitric oxide (NO), the cause of these imbalances is unknown. In vitro evidence suggests that altering plasma sodium levels could affect endothelial-derived vasoregulators and blood pressure (BP). Thus, we hypothesized that compared to high dialysate sodium, low dialysate sodium concentration would lower endothelin 1 levels, increase NO release, and reduce BP.

Study Design: 3-week, 2-arm, randomized, crossover study.

Setting & Participants: 16 patients with intradialytic hypertension.

Intervention: Low (5 mEq/L below serum sodium) versus high (5 mEq/L above serum sodium) dialysate sodium concentration.

Outcomes: Endothelin 1, nitrite (NO_2^-), and BP.

Measurements: Mixed linear regression was used to compare the effect of dialysate sodium (low vs high) and randomization arm (low-then-high vs high-then-low) on intradialytic changes in endothelin 1, NO_2^-, and BP values.

Results: The average systolic BP throughout all hemodialysis treatments in a given week was lower with low dialysate sodium concentrations compared with treatments with high dialysate sodium concentrations (parameter estimate, −9.9 [95% CI, −13.3 to −6.4] mm Hg; $P < 0.001$). The average change in systolic BP during hemodialysis also was significantly lower with low vs high dialysate sodium concentrations (parameter estimate, −6.1 [95% CI, −9.0 to −3.2] mm Hg; $P < 0.001$). There were no significant differences in intradialytic levels of endothelin 1 or NO_2^- with low vs high dialysate sodium concentrations.

Limitations: Carryover effects limited the power to detect significant changes in endothelial-derived vasoregulators, and future studies will require parallel trial designs.

Conclusions: Low dialysate sodium concentrations significantly decreased systolic BP and ameliorated intradialytic hypertension. Longer studies are needed to determine the long-term effects of low dialysate sodium concentrations on BP and clinical outcomes.

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INDEX WORDS: Intradialytic hypertension; hemodialysis; end-stage renal disease (ESRD); endothelium; vasoregulation; endothelin 1; nitrite; nitric oxide; blood pressure (BP); serum sodium concentration; dialysate sodium concentration; sodium gradient; Mechanisms and Treatment of Intradialytic Hypertension–Sodium (MATCH-NA) Study.

Previously, we demonstrated that patients with intradialytic increases in blood pressure (BP), or intradialytic hypertension, have increased odds of hospitalization and death.[1-3] We and others have shown that patients with intradialytic hypertension have acute intradialytic increases in levels of endothelin 1 (ET-1) relative to nitric oxide (NO; endothelial cell vasoregulators) and chronic impairments in endothelial cell function.[4-7] However, it still is undetermined whether dialysis-specific factors such as dialysate sodium concentration contribute to intradialytic impairments in endothelial cell vasoregulators and intradialytic increases in BP.

In our previous case-control cohort, patients with intradialytic hypertension had a low predialysis serum sodium level (135.8 mEq/L) and a 4.4-mEq/L dialysate-to-serum sodium gradient.[6] Such a high dialysate-to-serum sodium gradient can acutely increase plasma sodium levels.[8,9] In vitro, endothelial cells exposed to small ambient increases in plasma

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media sodium concentration acutely stiffen and have impaired release of NO.[10] Acute decreases in NO bioavailability with increasing plasma sodium levels have the potential in vivo to increase BP. Considering that high dialysate-to-serum sodium gradients acutely increase plasma sodium levels, our findings combined with in vitro evidence raised the question of whether these acute changes in plasma sodium levels could impair NO bioavailability and/or alter BP in vivo.

Thus, this study was performed to test the effects of low versus high dialysate sodium concentrations on intradialytic changes in endothelial-derived vasoregulators (ET-1 and NO) and BP. We hypothesized that compared to high dialysate sodium, low dialysate sodium concentrations would lower ET-1 level, increase NO release, and reduce BP.

METHODS

Trial Design

We prospectively enrolled hemodialysis patients with intradialytic hypertension into a 3-week, randomized, single-blinded, crossover study comparing the effects of low versus high dialysate sodium concentrations on endothelial cell function and BP (Mechanisms and Treatment of Intradialytic Hypertension–Sodium [MATCH-NA] Study).

Participants

Potential participants were screened prospectively using consecutive sampling from 3 hemodialysis facilities affiliated with the University of Texas Southwestern Medical Center in Dallas. Inclusion criteria included patients being on hemodialysis therapy for longer than 30 days, aged 18 to 85 years, ability to provide informed consent, nephrologist deemed patient was at target dry weight, hypertension (predialysis BP $>$ 140/90 mm Hg or postdialysis BP $>$ 130/80 mm Hg), and systolic BP increases $\geq$ 10 mm Hg pre- to postdialysis for at least 4 of the last 6 hemodialysis sessions. Exclusion criteria included active cancer or active wounds, inability to measure BP in the upper extremity, current antibiotic treatment or intravenous antibiotics within the past month, life expectancy less than 6 months, or inability to provide informed consent. Participants were enrolled from June 1 through July 30, 2012, with all study procedures completed by August 30, 2012.

Interventions

After signing informed consent, all participants underwent a thorough history and physical examination with documentation of medical history, medications, and recent laboratory studies. Following enrollment, all participants were randomly assigned by concealed allocation with a 1:1 ratio to either (1) low dialysate sodium followed by high dialysate sodium concentrations or (2) high dialysate sodium followed by low dialysate sodium concentrations. After randomization, all participants had a midweek predialysis blood sample collected for measurement of serum sodium. High dialysate sodium was calculated as serum sodium + 5 mEq/L. Low dialysate sodium was calculated as serum sodium − 5 mEq/L, with a lower limit of dialysate sodium of 134 mEq/L. The week following measurement of the baseline serum sodium level, all participants underwent a 1-week period (3 hemodialysis sessions) of low or high dialysate sodium concentrations followed by a 1-week washout (standard dialysate sodium per local practice, either 140 or 139 mEq/L) during which a midweek predialysis sodium was remeasured to determine the subsequent week dialysate prescription. This was followed by a 1-week period of the alternate dialysate sodium

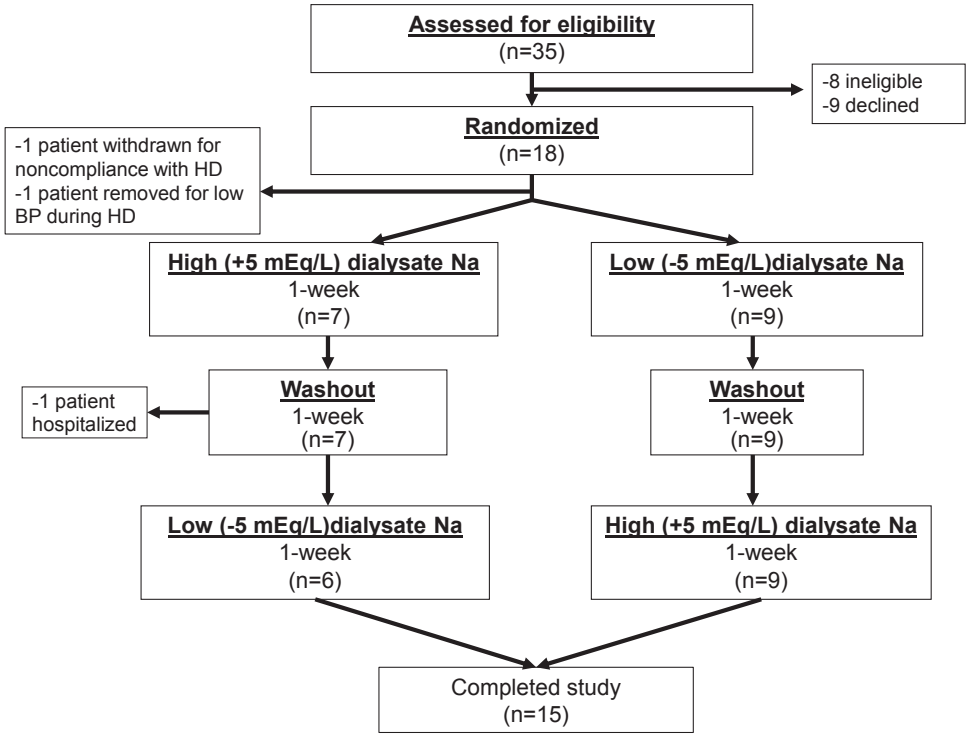

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) study flow chart of Participants in the Mechanisms and Treatment of Intradialytic Hypertension–Sodium (MATCH-NA) Study. Abbreviations: BP, blood pressure; HD, hemodialysis; Na, sodium.