Dialysis Dose and Intradiialytic Hypotension: Results from the HEMO Study

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Key Words
Intradialytic hypotension · Urea reduction · Osmolality · Hemodialysis · HEMO study

Abstract
Background: Intradialytic hypotension (IDH) is common and is associated with increased morbidity and mortality in chronic hemodialysis patients. A higher dialysis ‘dose’ may generate transient intradialytic osmotic gradients, predisposing to intracellular fluid shifts and resulting in hypotension. Study Design: We performed a post hoc analysis of the HEMO study, a multicenter trial that randomized chronic hemodialysis patients to high versus standard Kt/V and higher versus lower membrane flux. In order to achieve dose targets, per protocol, adjustments were made in membrane efficiency, blood flow or dialysate flow before changing session length. Detailed hemodynamic and urea kinetic modeling data were abstracted from 1,825 individuals. The primary outcome was the occurrence of hypotensive events necessitating clinical intervention (saline infusion, lowering of ultrafiltration rate or reduced blood flow). Results: Intradialytic hypotensive events occurred more frequently in the higher-Kt/V group (18.3 vs. 16.8%; p < 0.001). Participants randomized to higher-target Kt/V had a greater adjusted risk of IDH than those randomized to standard Kt/V [odds ratio (OR) 1.12; 95% confidence interval (CI) 1.01–1.25]. Higher vs. lower dialyzer mass transfer-area coefficient for urea and rate of urea removal were associated with greater adjusted odds of IDH (OR 1.15; 95% CI 1.04–1.27 and OR 1.05; 95% CI 1.04–1.06 per mg/dl/h, respectively). Conclusions: Higher dialysis dose, at relatively constrained treatment times, may associate with an increased risk of IDH. These findings support the possibility that rapidity of intradialytic reductions in plasma osmolality may play an important role in mediating hemodynamic instability during dialysis.

Introduction
Intradialytic hypotensive events are a common complication of maintenance hemodialysis, affecting up to one third of chronic dialysis treatment sessions [1–3]. Intradialytic hypotension (IDH) can be defined as an abrupt decline in blood pressure that causes symptoms and/or requires an intervention [4, 5]. IDH has been associated with many adverse clinical events, including myocardial stunning [6], cerebral atrophy [7] and increased mortality [8]. Predisposing factors include intrinsic patient-related
factors such as the presence of autonomic neuropathy [9], abnormal cardiac reserve [10] and reduced venous compliance [11] as well as potentially modifiable treatment-related parameters such as ultrafiltration (UF) profiling [12] and changes in serum calcium concentration [13].

The rapidity of removal of urea, sodium and other osmotically active substances from the intravascular compartment, in conjunction with delayed re-equilibration from intracellular compartments, may result in a transient decline in plasma osmolality and intravascular volume depletion secondary to transcellular movement of water. This may predispose to the development of IDH [14]. In support of this concept, investigators have reported that administration of hypertonic glucose or hypertonic saline ameliorates intradialytic blood pressure decline and other dialysis-associated symptoms [15]. In addition, the use of sodium modeling algorithms has been associated with improved hemodynamic parameters in patients with a prior history of IDH [4].

In the HEMO study [16], a multicenter, randomized trial in maintenance hemodialysis, patients were randomized to higher versus standard Kt/V and higher versus lower membrane flux. Study investigators were instructed to increase blood flow (Qb), dialysate flow (Qd) and filter surface area before increasing the session length in order to achieve higher Kt/V targets. Therefore, we used the randomized dose assignment to examine the effect of rapid osmotic shifts during hemodialysis and tested the hypothesis that higher dialysis dose associates with a greater risk of IDH.

**Methods**

**Study Design and Population**

The study protocol was deemed exempt by the Partners Healthcare Institutional Review Board. All data were abstracted from the HEMO study with the permission of the National Institute of Diabetic and Digestive and Kidney Diseases. The design of the HEMO study has been previously reported [16, 17]. Briefly, HEMO was a prospective, multicenter, randomized clinical trial of low-flux versus high-flux membranes and versus standard dialysis dose (target single-pool Kt/V 1.65 vs. 1.25; approx. equivalent to urea reduction ratios of 75 vs. 65%) among prevalent adult subjects receiving thrice-weekly in-center hemodialysis. Exclusion criteria included a baseline serum albumin <2.6 g/dl, residual urea clearance of ≥1.5 ml/min/35 liters of urea distribution volume, inability to consistently achieve an equilibrated Kt/V of >1.3 or the presence of end-stage comorbid conditions other than kidney failure. Of the 1,846 HEMO study participants, we excluded those who did not have available hemodynamic and kinetic modeling data after randomization (n = 20); our final cohort consisted of 1,825 individuals and 62,095 hemodialysis treatment sessions.

**Exposures and Outcomes**

The primary analysis examined the HEMO study randomized Kt/V assignment (higher vs. lower) as the exposure of interest. In secondary analyses, the association of individual components of dialysis ‘dose’ with IDH was examined [Qb, Qd, session length, dialyzer mass transfer-area coefficient for urea (KoAurea) and rate of decline in plasma blood urea nitrogen (BUN)]. In vitro KoAurea values were previously obtained for 22 HEMO study-approved membranes at a Qd of 800 ml/min [18]. The rate of decline in plasma BUN was calculated using BUN measurements as: predialysis BUN to postdialysis BUN/session length, after exclusion of the top and bottom 1% of individual BUN measurements as outliers. Data for all urea-based exposure calculations were abstracted from monthly 2-sample BUN modeling sessions, where post-BUN was taken 15 s (from line disconnect) or 20 s (from sampling port) after dialysis inlet slowing.

The primary outcome was the occurrence of an intradialytic hypotensive event, defined as a hypotensive episode requiring either saline infusion, lowering of the UF rate or reduction in Qb. This was a prespecified outcome of the HEMO study that was assessed and recorded on a monthly basis during monitored hemodialysis sessions by trained study personnel. In sensitivity analyses, an alternative definition of IDH was examined: decline in systolic blood pressure (SBP) of ≥50 mm Hg with headache, cramps or vomiting and requirement for an intervention (lowering of Qb, UF or saline infusion).

**Statistical Analysis**

Continuous variables were examined graphically and recorded as means (± standard deviations) for normally distributed data or medians (with IQRs) for nonnormally distributed data. Comparisons were made using the Student t test, the Wilcoxon rank sum test, analysis of variance or the Kruskal-Wallis test where appropriate. Categorical variables were examined by frequency distribution, recorded as proportions and comparisons were made using the χ2 test. Initially, unadjusted generalized linear regression models (using a binomial distribution and logit link function) were fit to assess the relationship between randomized Kt/V group and hypotensive events (Yes/No). These models used clustered variance estimates to account for nonindependence of covariates within subject. Subsequently, adjustment was made for random-
Results

The primary cohort consisted of 1,825 individuals and 62,095 unique hemodialysis sessions. Mean age was 57.8 ± 14.1 years, 62.6% were black and 44.7% were diabetic. Consistent with other reports from the HEMO study, there was a slightly greater proportion of patients with peripheral vascular disease in those randomized to the higher-Kt/V group [21]; otherwise, no significant baseline differences between randomized groups were evident (table 1). Those in the higher-Kt/V group had significantly longer session length, higher Qb and higher Qd compared with those in the lower Kt/V group (table 2). There were no significant differences in preintervention rates of IDH between randomized Kt/V groups.

At baseline, those with a greater rate of decline in plasma BUN were more likely to be female, not black, of lesser postdialytic weight and have less peripheral vascular disease but have greater serum albumin and creatinine. In addition, they were more likely to have greater UF volume, shorter session length, lower Qb and higher Qd (on-line suppl. tables A, B; for all online suppl. material, see www.karger.com/doi/10.1159/000355958).

HEMO Study Kt/V Assignment

In the higher-Kt/V group, 18.3% of sessions were complicated by hypotensive events, compared with 16.8% of the lower-Kt/V group (p < 0.001; table 3). The mean intradialytic decline in SBP in sessions with IDH was 52.9 ± 27.5 mm Hg, compared with 29.3 ± 22.0 mm Hg in those without (p difference <0.001).

In patient-level analyses, using generalized linear models, the unadjusted and adjusted odds of experiencing a hypotensive event were 11% higher [odds ratio (OR) 1.11; 95% confidence interval (CI) 0.99–1.24; p = 0.07] and 12% higher (OR 1.12; 95% CI 1.01–1.25; p = 0.04), respectively, for the higher-Kt/V vs. the lower-Kt/V group. There was no evidence for effect modification according to randomized flux target (p interaction = 0.19).

In sensitivity analyses, a more restrictive definition of IDH was considered (decline in SBP of 50 mm Hg, with symptoms or need for intervention). In this model, higher Kt/V remained associated with greater odds for IDH (OR 1.10; 95% CI 1.00–1.21; p = 0.049).

Session Length, Blood Flow and

Unadjusted and adjusted models were fit (individually for session length, Qb, Qd and KoA urea) to examine which of these contributors to dialysis dose were independently associated with IDH (table 4). Compared with the reference for each exposure, there was no evidence for an association of greater session length, Qb, Qd or KoA urea with a greater risk for IDH. In fact, greater Qb appeared to be associated with less risk of IDH in adjusted models. However, upon additional adjustment for Qb, Qd and session length in model 2a, higher (vs. lower) KoA urea became significantly associated with a greater risk of IDH (OR 1.15; 95% CI 1.04–1.27).

Rate of Decline in Plasma BUN

In light of the observation that higher KoA urea associates with greater risk of IDH in fully adjusted models, we revisited our original hypothesis that rapid solute removal may generate temporary osmolar gradients and predispose to IDH. Therefore, we considered the rate of decline in plasma BUN as an alternative metric to be examined. In patient-level analyses, using generalized linear models, the unadjusted and adjusted odds (model 1) of experiencing IDH were 4% higher (OR 1.04; 95% CI 1.03–1.06) and
5% higher (OR 1.05; 95% CI 1.04–1.06), respectively, per unit increase in the rate of decline in plasma BUN (mg/dl/h). Of note, this association was independent of Qb, Qd and UF volume (the latter also being significantly associated with IDH (OR 1.05; 95% CI 1.02–1.09; Model 2).

In order to assess for possible nonlinear relationships, the rate of decline in plasma BUN was then considered as quartiles. A progressive increase in the proportion of sessions complicated by IDH was noted for increasing quartiles of rate of decline in plasma BUN (table 3). Of note,

Table 1. Baseline characteristics of the total study cohort according to target Kt/V assignment

<table>
<thead>
<tr>
<th></th>
<th>Total cohort (n = 1,825)</th>
<th>Kt/V assignment</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>standard (n = 915)</td>
<td>higher (n = 910)</td>
<td></td>
</tr>
<tr>
<td>Male, %</td>
<td>43.8</td>
<td>44.0</td>
<td>43.6</td>
</tr>
<tr>
<td>Age, years</td>
<td>57.8±14.1</td>
<td>58.0±14.0</td>
<td>57.6±14.1</td>
</tr>
<tr>
<td>Black, %</td>
<td>62.6</td>
<td>64.2</td>
<td>61.1</td>
</tr>
<tr>
<td>Vintage, years</td>
<td>2.3 (1.1–4.8)</td>
<td>2.4 (1.2–5.0)</td>
<td>2.2 (1.1–4.6)</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>44.7</td>
<td>44.7</td>
<td>44.6</td>
</tr>
<tr>
<td>Ischemic heart disease, %</td>
<td>39.3</td>
<td>39.9</td>
<td>38.7</td>
</tr>
<tr>
<td>Congestive heart failure, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>27.9</td>
<td>27.5</td>
<td>28.3</td>
</tr>
<tr>
<td>Moderate/severe</td>
<td>11.5</td>
<td>11.8</td>
<td>11.2</td>
</tr>
<tr>
<td>Peripheral vascular disease, %</td>
<td>25.6</td>
<td>23.5</td>
<td>27.7</td>
</tr>
<tr>
<td>Arrhythmia, %</td>
<td>30.8</td>
<td>32.4</td>
<td>29.3</td>
</tr>
<tr>
<td>ICED score</td>
<td>2.0 (1.0–3.0)</td>
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<td>2.0 (1.0–3.0)</td>
</tr>
<tr>
<td>Predialysis SBP, mm Hg</td>
<td>152.1±26.3</td>
<td>152.6±26.6</td>
<td>151.6±26.0</td>
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<td>Postdialysis weight, kg</td>
<td>69.4±14.8</td>
<td>69.9±14.9</td>
<td>68.9±14.7</td>
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<tr>
<td>UF requirement, liters</td>
<td>2.9±1.3</td>
<td>2.9±1.3</td>
<td>2.9±1.3</td>
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<td>UFR, ml/kg/h</td>
<td>12.2±5.6</td>
<td>13.1±5.8</td>
<td>11.3±5.3</td>
</tr>
<tr>
<td>Access, %</td>
<td></td>
<td></td>
<td></td>
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<td>AVG</td>
<td>59.9</td>
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<tr>
<td>AVF</td>
<td>33.7</td>
<td>33.5</td>
<td>33.9</td>
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<tr>
<td>Catheter</td>
<td>6.4</td>
<td>6.7</td>
<td>6.0</td>
</tr>
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<td>Serum sodium, mmol/l</td>
<td>138.2±3.9</td>
<td>138.3±4.0</td>
<td>138.1±3.9</td>
</tr>
<tr>
<td>Serum albumin, g/dl</td>
<td>3.8±0.4</td>
<td>3.8±0.4</td>
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<tr>
<td>Serum creatinine, mg/dl</td>
<td>10.3±2.9</td>
<td>10.3±2.8</td>
<td>10.3±3.0</td>
</tr>
<tr>
<td>Serum phosphorus, mg/dl</td>
<td>5.8±1.9</td>
<td>5.8±1.9</td>
<td>5.8±1.9</td>
</tr>
<tr>
<td>Serum bicarbonate, mmol/l</td>
<td>21.4±3.6</td>
<td>21.4±3.7</td>
<td>21.5±3.4</td>
</tr>
</tbody>
</table>

AVF = Arteriovenous fistula; AVG = arteriovenous graft; UFR = ultrafiltration rate.

*p value for difference; significance testing was by Student t test or Wilcoxon rank sum tests for continuous variables or χ² test for categorical variables.

Table 2. Baseline dialysis session characteristics of the total study cohort according to target Kt/V assignment

<table>
<thead>
<tr>
<th></th>
<th>Total cohort (n = 1,825)</th>
<th>Kt/V assignment</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>standard (n = 915)</td>
<td>higher (n = 910)</td>
<td></td>
</tr>
<tr>
<td>Session length, min</td>
<td>210 (180–225)</td>
<td>185 (175–210)</td>
<td>215 (200–240)</td>
</tr>
<tr>
<td>Prescribed Qb, ml/min</td>
<td>400 (300–450)</td>
<td>350 (300–400)</td>
<td>400 (400–450)</td>
</tr>
<tr>
<td>Prescribed Qd, ml/min</td>
<td>700 (500–800)</td>
<td>600 (500–800)</td>
<td>800 (600–800)</td>
</tr>
<tr>
<td>KoAurea ≥1,000 ml/min, %</td>
<td>43.6</td>
<td>36.3</td>
<td>51.1</td>
</tr>
</tbody>
</table>

*p value for difference; significance testing was by Wilcoxon rank sum test.
this pattern was also present in analyses of the preinterventional period. In adjusted analyses, a similar pattern was noted, with increasing odds for IDH associated with increasing quartiles of rate of decline in plasma BUN (fig. 1).

### Discussion

Using data from the HEMO study, the largest study of dialysis dose to date, we found that patients randomized to a higher dose (target single-pool Kt/V 1.65 vs. 1.25)
were more likely to experience IDH during hemodialysis. Notably, these findings occurred despite lower baseline UF rates (11.3 vs. 13.1 ml/kg/h) in the higher-Kt/V group, suggesting that other factors must be involved in the genesis of IDH.

Potential risk factors for IDH may include the presence of autonomic neuropathy [22] and diminished cardiac reserve [10]; however, there were no significant differences in the proportion of individuals with diabetes or heart failure according to higher vs. lower Kt/V groups in our study. We did note a higher proportion of individuals with peripheral vascular disease, as was reported in the HEMO study, but found no difference in effect estimates after additionally adjusting for peripheral vascular disease in multivariable models. Other possibilities include an impaired rate of plasma refilling [23], inflammatory cytokine release [24] and reduced venous compliance [11]. In our secondary analyses, we attempted to further dissect the relationship between ‘dose’ and IDH by examining the individual associations of session length, Qb, Qd and KoA urea. These analyses were informative, in that we found no significant association of greater session length or Qd with IDH, and actually found lower odds of IDH with greater Qb in adjusted models. A potential explanation for this observation may be confounding by patients who are able to achieve higher Qb being less likely to have vascular disease or diabetes, and thus able to tolerate higher flows. However, in line with our original hypothesis, we did note an association of greater KoA urea and greater rate of decline in plasma BUN with greater odds for hypotension (independent of Qb and Qd; model 2), suggesting that this factor is an important determinant in the relationship between dialysis ‘dose’ and IDH.

Experimental data in animals [25, 26] and humans [27] support a role for rapid urea removal by hemodialysis in the generation of temporary osmotic gradients between body compartments. Others argue that the induction of temporary gradients for other molecules, including sodium, are more important [28], but there appears to be a consensus that these gradients contribute to many of the features of dialysis disequilibrium including cerebral edema, mental status changes, seizures and even death [29]. Several investigators have also noted an association between the intradialytic generation of transcellular osmotic gradients and IDH [28, 30, 31]. In order to achieve the higher randomized Kt/V target, the HEMO study investigators were encouraged to increase membrane size, Qd or Qb before increasing treatment time. Therefore, in effect, dialysis session lengths were relatively constrained, which likely increased the rapidity of temporary osmotic gradient generation between the intravascular and extravascular compartments. Our findings, based on the original HEMO targeted Kt/V randomization groups provide evidence for an association between the rapidity of intradialytic plasma osmolality decline and the development of hypotensive events. The absence of differences in the percentage of hypotensive events among preintervention dialysis sessions, according to randomized Kt/V groups, provides supportive evidence that the higher-dose intervention is truly associated with a greater risk of IDH. In the secondary analyses, the association of increasing quartiles of rate of decline in plasma BUN (which are nonrandomized categories) with greater IDH was present for both preintervention and postintervention sessions. These analyses support the presence of a dose-response relationship between the achieved rate of decline in plasma BUN and risk of IDH, irrespective of the randomized trial intervention.

There are numerous reports detailing interventions aimed at minimizing the rate of osmolality decline that may be useful for the treatment of hypotensive-prone patients. Dialysis physicians initially increased the dialysate sodium concentration, finding that this reduced the fre-
quency of dialysis-related symptoms [32], with subsequent studies demonstrating improved hemodynamic stability [33, 34]. Prior reports of increased thirst and interdialytic weight gain tempered the initial enthusiasm of these findings [12, 34], but more recently, the use of biofeedback-controlled sodium profiling appears to have less associated interdialytic weight gain [35]. Other methods include the administration of hypertonic mannitol and other hypertonic solutions [15, 30, 36, 37]. In addition to transcellular fluid shifts due to osmotic changes, a rapid decline of intravascular osmolality may suppress the release of vasopressin, which has pressor-like effects on the vasculature; in support of this concept, infusion of vasopressin during hemodialysis has been associated with improved hemodynamic stability [38]. Given the association of IDH with numerous adverse outcomes (including access failure [39], cerebral atrophy [7], myocardial stunning [40] and death [8]) as well as the promise shown by previous small interventional studies, future research efforts focusing on manipulation of osmolality changes, without compromising clearance, may be fruitful in addressing the unacceptably high morbidity and mortality of our patients.

The major strength of this study is the utilization of the original randomized assignments from the HEMO study, which should minimize the presence of residual confounding in the primary analyses of targeted Kt/V. In this regard, although the HEMO study did not record potentially confounding variables such as dialysate sodium or dialysate temperature, it is likely that randomization produced a minimal imbalance according to these parameters between the targeted Kt/V groups. Furthermore, the HEMO study was performed at a time when the move away from lower sodium dialysate concentrations had already occurred [41]. Other strengths include the large and detailed collection of exposure and outcomes data over the complete duration of follow-up in the setting of a randomized controlled trial. Without the primacy of randomization in secondary analyses, multiple covariates had to be considered in the model-building process, leading to the possibility of residual confounding. There are theoretical concerns of dose-targeting bias in relation to the analysis of rate of decline in plasma BUN as the exposure of interest. For example, in the dose-mortality analyses of the HEMO study, significant associations between higher achieved dose and reduced mortality have been reported (at odds with the original intention-to-treat analyses demonstrating no advantage to higher vs. standard Kt/V) [42]. It is possible that individuals who were able to attain a higher achieved Kt/V were healthier, more compliant and had other beneficial characteristics that could potentially confound the relationship between achieved dose and mortality. The associations we present are less likely to suffer from this bias, as we found that higher rates of urea removal (a metric of clearance, in which higher values may be interpreted as beneficial) were in fact associated with greater odds for hypotension. This is opposite to what we would expect if beneficial dose-targeting bias were an issue. However, on the other hand, a very high rate of decline in plasma BUN can also be achieved in malnourished individuals with low muscle mass or in those with shorter session lengths, who may be at risk for adverse outcomes. This may have contributed to the increased association with hypotensive events which we observed in these individuals. The HEMO study did not record the timing of hypotensive events, prohibiting a more granular assessment of the competing effects of solute removal rate and UF rates, which may be expected to predispose to hypotension at different time points during the dialysis procedure. However, we were able to confirm that both the rate of decline in plasma BUN and UF volume were independently associated with greater risk of IDH. Finally, participants in a randomized controlled setting may not be comparable to the wider chronic hemodialysis population, limiting the generalizability of our results.

In conclusion, a higher dialysis dose appears to increase the risk for intradialytic hypotensive events requiring a clinical intervention. In patients at risk of IDH, targeted strategies to reduce the rapidity of decline in plasma osmolality during hemodialysis may be beneficial. Potential interventions may include selection of lower efficiency membranes, extending the session length, selected use of higher dialysate sodium or infusion of osmotically active substances. While ensuring preservation of hemodialysis adequacy, future studies should assess the potential benefit of these interventions in prospective clinical trials, particularly in patients who suffer from repeated episodes of IDH.

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Portions of this work were presented in abstract form at the American Society of Nephrology annual meeting in San Diego, 2012.
Disclosure Statement

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Dr. Brunelli has served as an advisor to Amgen, C.B. Fleet Company and Proctor & Gamble. Since completing work on this study, Dr. Brunelli has become a full-time employee of DaVita Clinical Research. He has received speaking honoraria from Fresenius Medical Care North America. His spouse is employed by Asta Zeneca. He was supported by DK079056 and Dr. Waikar was supported by DK093574, DK075941 and U01DK085660.

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