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Association of intradialytic blood pressure changes with hospitalization and mortality rates in prevalent ESRD patients

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The relationship between blood pressure (BP) and clinical outcomes among hemodialysis patients is complex and incompletely understood. This study sought to assess the relationship between blood pressure changes with hemodialysis and clinical outcomes during a 6-month period. This study is a secondary analysis of the Crit-Line Intradialytic Monitoring Benefit Study, a randomized trial of 443 hemodialysis subjects, designed to determine whether blood volume monitoring reduced hospitalization. Logistic regression was used to estimate the association between BP changes with hemodialysis (Δsystolic blood pressure = postdialysis–predialysis systoic BP (SBP) and the primary outcome of non-access-related hospitalization and death. Subjects whose systolic blood pressure fell with dialysis were younger, took fewer blood pressure medications, had higher serum creatinine, and higher dry weights. After controlling for baseline characteristics, lab variables, and treatment group, subjects whose SBP remained unchanged with hemodialysis ($N = 150$, ΔSBP −10 to 10 mm Hg) or whose SBP rose with hemodialysis ($N = 58$, ΔSBP $\geqslant$10 mm Hg) had a higher odds of hospitalization or death compared to subjects whose SBP fell with hemodialysis ($N = 230$, ΔSBP $\leqslant -10$ mm Hg) (odds ratio: 1.85, confidence interval: 1.15–2.98; and odds ratio: 2.17, confidence interval: 1.13-4.15). Subjects whose systolic blood pressure fell with hemodialysis had a significantly decreased risk of hospitalization or death at 6 months, suggesting that hemodynamic responses to dialysis are associated with short-term outcomes among a group of prevalent hemodialysis subjects. Further research should attempt to elucidate the mechanisms behind these findings.

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Significant controversy surrounds the issue of hypertension and outcomes among hemodialysis (HD) patients. Unlike the general population,[1] a direct association between elevated blood pressure (BP) and cardiovascular mortality has not been clearly identified in dialysis patients.[2–12] Although long-term studies are required to define the association between hypertension and outcomes,[11] pronounced mortality rates and the presence of comorbid conditions that contribute to high mortality among HD patients may limit the ability to detect an independent association between hypertension and outcomes.

A number of studies have been published investigating the associations between BP and outcomes among end-stage renal disease (ESRD) patients.[2–6,8–14] The available observational studies suggest that the relationship between BP and outcomes is complex and differs from the general population. Unfortunately, there are a number of difficulties associated with studying the association between BP and outcomes among HD patients. First, it remains unclear which BP parameter to use in these studies: predialysis, postdialysis, and intradialytic changes in BP are all available, yet which parameter is most strongly associated with detrimental outcomes remains uncertain. Second, clinician's ability to change BP is limited in HD patients due to high frequency[15] and severity[16] of BP, as well as due to changes in BP associated with interdialytic weight gain, which is directly related to mortality risk.[17–19]

Clinically, physicians are carefully balancing the relationship between intradialytic weight loss and BP. In some ESRD patients, BP is unaffected by ultrafiltration and hemodialysis, where as other patients experience a more pronounced hemodynamic response with hemodialysis. Differences in clinical characteristics between such patient groups have not been fully described nor has the relationship between BP responses to ultrafiltration with hemodialysis and outcomes been characterized to date.[20,21]

Owing to the complex relationship between BP, weight gain, and mortality, we postulated that the association

between hemodynamic changes and outcomes might be best assessed using other parameters such as hospitalization. Herein, we undertook a secondary analysis of CLIMB (the Crit-line Intradialytic Monitoring Benefit Study) to assess whether BP responses to hemodialysis are associated with differential short-term outcomes while controlling for interdialytic weight gain, case-mix, and other BP parameters.

RESULTS

Baseline characteristics

Baseline characteristics of subjects enrolled in the CLIMB study have been previously reported.[22] Two hundred and thirty subjects (52.5%) had a fall in systolic blood pressure (SBP) associated with HD (ΔSBP $\leqslant -10$ mm Hg), 150 subjects (34.2%) did not have a significant change in SBP from pre- to post-HD (ΔSBP -10 to 10 mm Hg), and 58 subjects (13.2%) exhibited a paradoxical rise in SBP with HD (ΔSBP $\geqslant 10$ mm Hg) (Table 1). Subjects whose SBP fell with HD were younger and were on less antihypertensive medications. They also had higher predialysis systolic and diastolic BP, lower postdialysis systolic and diastolic BP, higher serum creatinine, and higher dry weights. There was a trend toward a higher prevalence of male subjects and a higher prevalence of diabetes mellitus among subjects whose SBP decreased during HD. Subjects whose SBP were unchanged with dialysis had the lowest prevalence of diabetes mellitus and the highest rates of catheter use compared to subjects whose SBP fell with HD or whose SBP rose with HD.

Unadjusted outcomes

During the 6-month follow-up, 132/438 (30.1%) subjects had a primary event (either non-access-related hospitalization ($N=108$) or death ($N=5$) or both ($N=19$)) (Table 2). Compared to subjects whose SBP fell with HD, subjects whose SBP was unchanged with HD or who had a paradoxical rise in SBP with HD had an increased risk of non-access-related hospitalization or death at 6 months (odds ratio (OR): 1.89, confidence interval (CI): 1.20–2.96, ΔSBP: -10 to 10 mm Hg vs ΔSBP $\leqslant -10$ mm Hg; OR: 2.14, CI: 1.17–3.93, ΔSBP $\geqslant 10$ mm Hg vs ΔSBP $\leqslant -10$ mm Hg, $P=0.0056$). Annual non-access-related hospitalization rates were 0.96 (± 2.96 hospitalizations/year) among subjects whose SBP fell with HD compared to 1.55 (± 3.33) among subjects whose SBP was unchanged with HD and 1.90 (± 3.86) among subjects whose SBP rose with HD ($P=0.0083$).

When ΔSBP was modeled as a continuous variable, every 1 mm Hg increase in ΔSBP following HD was associated with an increased odds of a non-access-related hospitalization or death at 6 months (OR: 1.02, CI: 1.01–1.03, $P=0.0009$). Thus, a 10 mm Hg increase in SBP with HD was associated with a 20% increased odds of hospitalization or death at 6 months among subjects. The relationship between 10 mm Hg increments of ΔSBP and annual non-access-related hospitalization is plotted in Figure 1.

Multivariable analysis

After adjusting for relevant confounders, subjects whose SBP was unchanged with HD or whose SBP rose with HD had an increased risk of non-access-related hospitalization or death compared to patients whose SBP fell with HD ($P=0.012$) (Table 3).

In adjusted models with ΔSBP as a continuous variable, every 1 mm Hg increase in ΔSBP following HD was associated with a 2% increased odds of non-access-related hospitalization or death (OR: 1.02, CI: 1.01–1.03, $P=0.0022$).

In multivariate analyses, other variables associated with an increased risk of hospitalization or death included lower dry weight ($P=0.018$), history of coronary artery disease or congestive heart disease ($P=0.018$), CLIMB treatment group ($P=0.033$), and increasing phosphorus ($P=0.049$). There was a trend toward improved outcomes among black subjects ($P=0.084$). Variables not associated with an increased risk of the primary outcome included increasing age; % of interdialytic weight gain; dialysis vintage; number of BP medications; access type; history of arrhythmia, diabetes mellitus, hypertension, left ventricular hypertrophy, or peripheral vascular disease; and baseline creatinine, albumin, calcium, or urea reduction ratio.

ΔSBP category did not interact with age ($P=0.76$), race ($P=0.92$), % of interdialytic weight gain ($P=0.55$), history of coronary artery disease or congestive heart failure ($P=0.25$), diabetes mellitus ($P=0.42$), left ventricular hypertrophy ($P=0.25$), peripheral vascular disease ($P=0.33$), predialysis SBP ($P=0.14$), or predialysis diastolic BP ($P=0.999$).

Sensitivity analysis

Four separate models were tested, which included the addition of predialysis systolic and diastolic BP, postdialysis systolic and diastolic BP, predialysis pulse pressure, and postdialysis pulse pressure. In each model performed, none of the BP parameters were associated with an increased risk of the primary outcome, nor did they significantly modify the effect of ΔSBP on outcomes (data not shown).

Further sensitivity analyses were performed, which excluded subjects without KDOQI-(Kidney Disease Outcomes Quality Initiative) defined hypertension (predialysis SBP <140 and postdialysis SBP <130, and predialysis diastolic <90 and postdialysis diastolic <80). According to these standards, 343/431 (79%) subjects had hypertension in our cohort. After adjustment for relevant covariates, ΔSBP remained a strong predictor of outcomes among subjects with KDOQI-defined hypertension (Table 4).

Separate analyses included only subjects on antihypertensive medications to assess the impact of medication class on outcomes and to determine if specific antihypertensives modified the effect of ΔSBP on outcomes. In our cohort, 76% of subjects were on antihypertensive medications. None of the classes of antihypertensive agents were associated with the primary outcome (alpha blocker ($P=0.88$), angiotensin-converting enzyme-1 ($P=0.30$), β blocker ($P=0.85$),