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Narrative Review

Intensive Hemodialysis, Blood Pressure, and Antihypertensive Medication Use

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Hypertension is a cardinal feature of end-stage renal disease (ESRD). Hypertensive nephropathy is the primary cause of ESRD for nearly 30% of patients, and the prevalence of hypertension is >85% in new patients with ESRD. In contemporary hemodialysis (HD) patients, mean predialysis systolic blood pressure (SBP) is nearly 150 mm Hg, and about 70%, 50%, and 40% use β-blockers, calcium channel blockers, and renin-angiotensin system inhibitors, respectively. Predialysis SBP generally exhibits a U-shaped association with mortality risk. Interdialytic ambulatory SBP is more strongly associated with risk. Hypertension is multifactorial; key causes include persistent hypervolemia and elevated peripheral resistance. With 3 HD sessions per week, blood pressure (BP) climbs during the interdialytic interval, in step with interdialytic weight gain, particularly among elderly patients and those with higher dry weight. Elevated peripheral resistance can be attributed to inappropriate activation of the sympathetic nervous system due to higher plasma norepinephrine concentrations. Multiple randomized clinical trials show that intensive HD reduces BP and the need for oral medications indicated for hypertension. In the first 2 months of the Frequent Hemodialysis Network trial, the short daily schedule reduced predialysis SBP by 7.7 mm Hg, whereas the nocturnal schedule reduced predialysis SBP by 7.3 mm Hg, both relative to 3 sessions per week. Improvements were sustained after 12 months. Both schedules reduced antihypertensive medication use relative to 3 sessions per week. In FREEDOM (Following Rehabilitation, Economics, and Everyday-Dialysis Outcome Measurements), a prospective cohort study of short daily HD, the mean number of prescribed antihypertensive agents decreased from 1.7 to 1.0 in 1 year, whereas the percentage of patients not prescribed antihypertensive agents increased from 21% to 47%. Nocturnal HD appears to markedly reduce total peripheral resistance and plasma norepinephrine and restore endothelium-dependent vasodilation. In conclusion, intensive HD reduces BP and the need for antihypertensive medications.

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Hypertension is intertwined with chronic kidney disease (CKD). As endogenous kidney function declines, the prevalence of hypertension increases inexorably. For example, in KEEP (Kidney Early Evaluation Program) participants from 2000 to 2006, prevalences of hypertension were 61%, 64%, 68%, 72%, 86%, 91%, and 94% in those with estimated glomerular filtration rates of 90 to 99, 80 to 89, 70 to 79, 60 to 69, 50 to 59, 40 to 49, and 30 to 39 mL/min/1.73 m^2, respectively; in those with estimated glomerular filtration rates $<$ 30 mL/min/1.73 m^2 (ie, with either CKD stage 4 or 5), the prevalence of hypertension was 96%.[1] Here, hypertension was defined as systolic blood pressure (SBP) $\geq$ 130 mm Hg or diastolic blood pressure (DBP) $\geq$ 80 mm Hg in participants with diabetes or self-reported kidney disease and SBP $\geq$ 140 mm Hg or DBP $\geq$ 90 mm Hg in all other participants. In KEEP, the degree of blood pressure (BP) control was strongly associated with the incidence of end-stage renal disease (ESRD).[2] Analysis of concurrent NHANES (National Health and Nutrition Examination Survey) participants revealed a

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similar gradient of prevalence across the spectrum of kidney function, with overwhelming prevalence (98%) in the sample of those with CKD stage 4 or 5.[1] Not surprisingly, hypertension is an important complication in patients who progress to ESRD (ie, requiring either dialysis therapy or kidney transplantation).

The pharmacologic armamentarium for the treatment of hypertension notably includes β-blockers, (dihydropyridine) calcium channel blockers, and renin-angiotensin system (RAS) inhibitors. Less commonly used classes in dialysis patients comprise central α agonists, peripheral α antagonists, and direct vasodilators. Diuretics constitute another antihypertensive modality in patients with normal urine output or mild oliguria, but their utility is limited in ESRD; aside from loop diuretics (in patients with residual kidney function), class members are infrequently prescribed. In dialysis patients, hypertension can be managed with agents in one or more classes; for patients who have also been diagnosed with heart failure, β-blockers and RAS inhibitors may be efficacious through mechanisms other than BP reduction.

Antihypertensive agents lower BP by inhibiting renin release (β-blockers and aliskiren), inhibiting the RAS (angiotensin-converting enzyme [ACE] inhibitors and angiotensin II receptor blockers [ARBs]), inhibiting the sympathetic nervous system (central α agonists and peripheral α antagonists), dilating the vasculature (vasodilators), or eliminating sodium (diuretics). Thus, these agents fail to address the most proximal cause of hypertension in dialysis patients: excess intravascular volume. In the absence of residual kidney function (and setting aside the possibility of limiting fluid intake), the only method by which to lower volume is dialysis itself. If more dialysis, in the form of either greater session frequency or duration, can effectively address persistent hypervolemia, hypertension might be more adequately addressed, as has been observed with increasing treatment duration on conventional in-center hemodialysis (HD).[3]

In this review, we examine the epidemiology of hypertension, pathogenesis of hypertension, efficacy and limitations of antihypertensive agents, and effects of intensive HD on both BP and antihypertensive agent use. We show that both short daily HD and nocturnal HD can effectively lower BP and reduce the use of antihypertensive agents.

EPIDEMIOLOGY OF HYPERTENSION

Prevalence at Dialysis Initiation

According to the US Renal Data System, hypertension was the second leading cause of ESRD among incident patients with ESRD in 2013.[4] Specifically, in each year since the beginning of the century, hypertension has constituted the primary cause of ESRD for ~28% of incident patients with ESRD. The prevalence of hypertension as merely a comorbid condition is much higher. As described previously, data from KEEP and NHANES both suggest that the prevalence is >95% in patients with estimated glomerular filtration rates < 30 mL/min/1.73 m^2.[1] Because hypertension is a risk factor for cardiovascular death in non−dialysis-dependent CKD (NDD-CKD) and because death and ESRD are competing outcomes in NDD-CKD, the prevalence of hypertension may be modestly lower in incident patients with ESRD (ie, those who survived NDD-CKD). According to the ESRD Medical Evidence Report (CMS [Centers for Medicare & Medicaid Services] form 2728), the prevalence of hypertension was 86% in incident patients with ESRD from 2010 to 2012.[4] In an analysis of more than 16,000 patients who initiated HD therapy in a not-for-profit dialysis provider organization, mean predialysis SBP during the second, third, and fourth months of HD therapy was 150 ± 19 (standard deviation) mm Hg, and mean predialysis DBP was 78 ± 12 mm Hg.[5] In a more recent study of more than 3,400 patients who initiated HD therapy in Renal Research Institute facilities, the prevalence of SBP of 140 to 159 mm Hg during the first week of treatment was 38%, whereas prevalences of SBP of 160 to 179 mm Hg and >180 mm Hg were 21% and 6%, respectively.[6]

Prevalence After Dialysis Initiation

In the aforementioned study of Renal Research Institute facilities, mean SBP declined sharply between the first and second weeks of treatment, from 150.5 to 147.7 mm Hg, before increasing during the rest of the first 12 weeks of treatment.[6] However, the aggregate pattern belies heterogeneity in SBP trends by initial SBP. In patients with severe hypertension (ie, initial SBP > 180 mm Hg), mean SBP actually increased during the second, third, and fourth weeks of treatment, before gradually decreasing to a plateau of ~170 mm Hg by the middle of the first year of treatment. In patients with initial SBPs of 140 to 159 mm Hg, mean SBP was very stable at nearly 150 mm Hg during the first year. Finally, in patients with relative hypotension (ie, initial SBPs < 120 mm Hg), mean SBP initially decreased further, to 110 mm Hg during the first month, before steadily increasing to almost 130 mm Hg at the end of the first year.

As of December 2015, in the DOPPS (Dialysis Outcomes and Practice Patterns Study), mean predialysis SBP among prevalent HD patients was 148 mm Hg, with 75th and 90th percentiles of 163 and 179 mm Hg, respectively.[7] Alternatively, 32%, 21%, and 9% had predialysis SBPs of 140 to 159, 160 to 179, and >180 mm Hg, respectively (Fig 1).[7] Thus,