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Impact of Drugs on Intradialytic Hypotension: Antihypertensives and Vasoconstrictors

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Abstract

Intradialytic hypotension (IDH) is a common complication of hemodialysis and is associated with numerous adverse outcomes including cardiovascular events, inadequate dialysis, loss of vascular access, and death. It is estimated that approximately 20%–30% of all dialysis sessions are affected by IDH. In seeking ways to reduce the occurrence of IDH, dialysis providers often turn to pharmacological approaches: withholding antihypertensive medications prior to hemodialysis or administering vasoconstrictor medications. This review will focus on what is known about the relation between antihypertensive medications and IDH, and summarize studies that have examined the efficacy of vasoconstrictor medications on IDH, including midodrine, arginine vasopressin, and droxidopa. However, there is currently scant evidence that any pharmacological approach is particularly effective in reducing IDH. Additional studies of potential treatments for IDH are needed, and should examine not only hemodynamic effects such as changes in nadir blood pressure during dialysis, but also on patient-centered and clinical outcomes such as symptoms of IDH, quality of life, and cardiovascular events.

Nearly all patients with end-stage renal disease (ESRD) are affected by high blood pressure (BP), and a majority of patients on hemodialysis require treatment with antihypertensive medications. However, the treatment of high BP in patients with ESRD can be limited by the occurrence of intradialytic hypotension (IDH), which affects an estimated 20–30% of all dialysis sessions[1]. In turn, IDH is associated with numerous adverse outcomes, including decreased quality of life, inadequate dialysis, loss of vascular access, myocardial dysfunction and death.[2–6] Therefore, providers of dialysis care often use pharmacological strategies such as withholding antihypertensive medications prior to dialysis and/or administering vasoconstrictor medications in an effort to reduce the frequency of IDH.

Effects of Antihypertensive Medications on IDH

Antihypertensive medications could theoretically mitigate or exacerbate IDH. On the one hand, patients with ESRD commonly have left ventricular hypertrophy and impaired left ventricular relaxation, [7] and thus certain classes of antihypertensive medications that can improve these cardiac parameters might be expected to reduce IDH. For example, non-

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dihydropyridine calcium channel blockers like verapamil can improve left ventricular compliance,[8] and they have been tested for an effect on IDH. Ten patients on hemodialysis (including 8 patients with evidence of left ventricular hypertrophy) were randomly assigned to alternating two-week periods of verapamil 40 mg administered thrice weekly prior to dialysis or to placebo.[9] There were no differences in the frequency or severity of symptomatic IDH during the verapamil *versus* placebo weeks in that study ($p > 0.05$). As another example, beta-blockers, by slowing the heart rate, could increase left ventricular filling time and improve cardiac output. A study of 8 patients on hemodialysis tested the hemodynamic effect of atenolol 25 mg administered thrice weekly at each dialysis session for three weeks.[10] That study showed that the addition of atenolol reduced mean systolic 44-hour ambulatory BP (144 mm Hg at baseline, 127 mm Hg at end of study, $p < 0.001$), but had no effect on IDH. The recent Beta-Blocker to Lower Cardiovascular Dialysis Events (BLOCADE) pilot study[11] randomly assigned patients on hemodialysis to receive carvedilol *versus* placebo. Systolic BP was similar between the carvedilol and placebo groups at baseline and follow-up, as were the rates of IDH (7 *versus* 2 per 100 sessions, respectively, $p=0.1$).

On the other hand, the negative chronotropic and/or vasodilatory effects of antihypertensive medications could impair the ability to respond appropriately to fluid removal and other hemodynamic changes during the dialysis session, thereby increasing the frequency of IDH. Perhaps for these reasons, patients are commonly told to withhold their antihypertensive medications prior to dialysis, sometimes for as long as 12 hours before their scheduled sessions.[12, 13] Unfortunately, to date there are no studies that systematically tested whether such a strategy of antihypertensive medication withholding prior to dialysis actually reduces the frequency of IDH. Conversely, several studies have demonstrated that the administration of antihypertensive medications to patients on dialysis reduces pre-dialysis BP without causing IDH. For example, a study in Japan showed that administering more antihypertensive medications to patients on hemodialysis with uncontrolled hypertension (from a mean of 2.8 to 4.0 medications) reduced pre-dialysis systolic BP from an average of 175 mm Hg to 154 mm Hg, but had no impact on the frequency of IDH. [14] Another study randomly assigned 251 prevalent patients on hemodialysis to receive amlodipine 10 mg daily *versus* placebo for 30 months to assess the effects on death and cardiovascular events. [15] The mean pre-dialysis systolic BP, which had been similar between the two groups at baseline, dropped significantly during follow-up in the amlodipine group (140 mm Hg to 130 mm Hg, $p < 0.01$) and was unchanged in the placebo group (141 mm Hg to 140 mm Hg, $p > 0.05$). Despite the significant differences in the change in pre-dialysis systolic BP, there was no significant difference in the frequency of IDH between the amlodipine and placebo groups (7% *versus* 13%, respectively, $p = 0.21$). Of note, patients with persistent hypotension, defined as systolic BP <90 mm Hg, were excluded from that trial.

Taken together, the limited evidence from prospective studies does not support the use (or avoidance) of any particular antihypertensive medication class for IDH. There is also little support for the routine practice of withholding antihypertensive medications in patients on hemodialysis, since lower pre-dialysis systolic BP did not translate into more frequent episodes of IDH. Moreover, withholding antihypertensive medications is associated with longer periods of uncontrolled hypertension during the interdialytic period, [12, 13] which

could lead to poorer cardiovascular outcomes. However, there are several important caveats to consider: 1) an overall paucity of studies on the effect of antihypertensive medications on IDH, with only a minority of trials reporting on IDH, even as a safety outcome; 2) the definition of IDH varied among studies, hampering comparisons across studies; 3) patients prone to IDH were generally excluded from the trials; and 4) most trials were designed to examine outcomes such as cardiovascular morbidity or death, rather than to study IDH specifically. Even when data on IDH were available, the studies may have lacked sufficient statistical power to detect meaningful differences by treatment group. Of note, several randomized clinical trials of antihypertensive medications in ESRD (*e.g.*, beta-blockers, [16] ACEIs, [17–20] and ARBs [21, 22]) did not collect or report on IDH at all. Given how difficult it is to study patients on hemodialysis (for example, in BLOCADE, of the 1443 patients screened, only 49 [3%] were successfully randomized[11]), not collecting data on IDH represents an important missed opportunity that should be avoided when designing future trials.

Observational studies using existing data have examined antihypertensive medications in patients on hemodialysis, but few reported on IDH since most administrative databases do not contain detailed intradialytic BP information. For example, several studies used data from the United States Renal Data System (USRDS) Dialysis Morbidity and Mortality Study (DMMS) Wave II to compare the effects of various antihypertensive medications on cardiovascular morbidity and mortality, but none provided information relating antihypertensive medication use with IDH due to lack of these data. [23–27] Analyses using other administrative databases from Canada[28] or the Dialysis Outcomes and Practice Patterns Study (DOPPS)[29] faced similar limitations. However, a recent observational analysis harnessed data from 44,801 treatments in 1137 patients undergoing hemodialysis in a large dialysis organization. [30] Although that analysis did not include information on antihypertensive medications, it was able to provide fairly granular information about patient demographics and dialysis-related correlates of IDH, such as dialysis temperature, treatment time, and sodium bath concentration. Similarly, a separate analysis used data from 28,628 patients undergoing treatment in a large dialysis organization. [31] Although not strictly an analysis of IDH, the authors showed that initiation of ACEI *versus* ARB was associated with no significant differences in the occurrence of orthostatic hypotension (adjusted HR 1.00, CI 0.97-1.03).

Together, these observational studies reflect the growing availability of detailed clinical data from large patient cohorts that are broadly representative of the general hemodialysis population. These data, derived from electronic health records, now often include information on intradialytic BP, and may provide novel opportunities to gain insights into the association of antihypertensive medications with IDH.

Effects of Vasoconstrictor Medications on IDH

Another pharmacological strategy to prevent IDH is the use of vasoconstrictor medications. The most commonly used medication of this type is midodrine, a prodrug that is converted into desglymidodrine, an alpha-1 adrenergic receptor agonist. Data on the efficacy of midodrine to treat IDH come from small single-center studies. For example, one crossover

study enrolled 11 patients with severe resistant IDH, defined as a decrease in systolic BP of ≥20 mm Hg to < 100 mm Hg during hemodialysis, which did not improve with other adjustments to the dialysis prescription, antihypertensive medications or diet.[32] The study compared hemodynamic parameters during three weeks in the control phase (no treatment) *versus* three weeks in the midodrine phase (midodrine 10 mg, administered as a single oral dose 15–30 minutes before the hemodialysis session). The nadir systolic BP improved from a mean of 90 mm Hg during the control phase to 104 mm Hg during the midodrine phase ($P < 0.001$). The number of interventions for IDH (saline infusion, reduction of ultrafiltration volume, Trendelenburg positioning) also decreased from an average of 29 per patient during the control phase to 7 per patient during the midodrine phase. There were no adverse effects of midodrine reported and dialysis adequacy was unaffected.

In 2004, a systematic review identified a total of 10 studies that examined the effect of midodrine on IDH [33]; no additional trials of midodrine have been published since that review was completed. Using a fixed effects model, they found that the nadir systolic BP improved by an average of 13 mm Hg (CI 9-18 mm Hg, $P < 0.0001$), and 6 of the 10 studies reported an improvement in symptoms associated with IDH with use of midodrine *versus* control. However, it is important to note that the included studies were all of fairly short duration, had small sample sizes (ranged from 6 to 21 patients), and none examined hard clinical endpoints such as death or cardiovascular events. Interestingly, in 2010 the U.S. Food and Drug Administration (FDA) proposed to withdraw approval for midodrine, citing a lack of required post-approval studies to verify clinical benefit rather than just improved hemodynamic parameters. [34] The proposed withdrawal garnered opposition from various groups including the American Society of Nephrology, [35] and in 2012 the FDA and Shire came to an agreement: the pharmaceutical company would conduct two clinical trials to verify a clinical benefit of midodrine and midodrine would remain FDA-approved and on the market in the meantime.

The role that arginine-vasopressin (AVP) plays in IDH has also been subject to investigation. This nonapeptide hormone is normally secreted from the posterior pituitary in response to increased serum osmolality and mild-to-moderate hypovolemia and hypotension, and may also contribute to maintaining BP under normal physiologic conditions. [36] During hemodialysis, ultrafiltration and BP lowering should stimulate AVP release. However, a recent meta-analysis of 496 patients from 26 studies showed that plasma AVP levels did not significantly change from pre- to post-hemodialysis (mean difference in AVP 0.13 pg/mL, 95% confidence limit −0.82 to 1.07),[37] even in patients prone to IDH, suggesting a relative AVP deficiency. Reasons for the relative AVP deficiency are not entirely elucidated, but may be due at least in part to reductions in serum osmolality during dialysis. In a study of 42 patients on hemodialysis with frequent IDH, hypertonic saline was infused during the dialysis session in amounts that were too small to increase plasma volume.[38] However, the hypertonic saline did increase serum osmolality, leading to increased endogenous AVP secretion and an increase in BP; a similar increase in BP was observed with direct exogenous AVP infusion in that study as well.[38] Two other studies examined the administration of exogenous intranasal AVP analogues *versus* placebo administered just prior to the dialysis procedure in patients prone to IDH. [39, 40] Both studies showed that patients in the AVP group had fewer episodes of IDH and higher nadir BP compared with

placebo. A randomized, double-blinded study of 22 patients on hemodialysis administered a continuous infusion of AVP at a dose below the threshold that normally induces a vasopressor effect (*versus* placebo) during a single dialysis session. [41] Patients in the AVP group had lower proportion experiencing symptomatic IDH (9% *versus* 64%, P=0.024), lower maximal fall in systolic BP (16 *vs.* 34 mm Hg, p=0.008), and more fluid removal (520 mL *vs.* 64 mL above baseline ultrafiltration volume). Of note, these studies of exogenous AVP administration were limited by their relatively small sample sizes and short duration, so the long-term benefits or harms of AVP remain unknown at present. The use of AVP to treat IDH, therefore, remains experimental.

Droxidopa is a prodrug that is converted to norepinephrine, leading to vasoconstriction. It is currently FDA-approved to treat neurogenic orthostatic hypotension, and was recently studied in a randomized, placebo-controlled phase 2 study for treatment of IDH. [42] That trial randomized 85 patients prone to IDH (defined as a decrease in systolic BP of ≥20 mm Hg or in mean arterial pressure [MAP] ≥10 mm Hg with associated symptoms of hypotension) in a 1:1:1 fashion to receive droxidopa 400 mg daily, 600 mg daily or placebo for 4 weeks. The primary outcome was the mean change in intradialytic MAP from baseline to the last 2 weeks of treatment; droxidopa showed no significant benefit compared with placebo (mean change in MAP: −0.1, 2.0, and 1.6 mm Hg in the droxidopa 400 mg, 600 mg and placebo groups, respectively; p=0.7 and 0.8 *versus* placebo). There were also no significant differences in the number of hypotension-induced interventions such as changes in body position, reduction of ultrafiltration rate, and saline or albumin infusion among the groups. In addition, more patients in the droxidopa groups experienced adverse events compared with placebo (proportion having at least 1 adverse event: 83%, 81%, and 61% in the droxidopa 400 mg, 600mg and placebo groups, respectively), including nausea, fatigue, and headache. Thus the efficacy of droxidopa for treating IDH remains unproven.

Adenosine A1 receptor antagonists have also been tried as a treatment for IDH. The hypothesis is that local adenosine released in response to hypotension leads to inhibition of norepinephrine and subsequent vasodilation, thus worsening the hypotension. A randomized crossover trial of FK352, an adenosine A1 receptor antagonist, enrolled 30 patients with frequent IDH to receive intravenous FK352 *versus* placebo after 1 hour of hemodialysis for four weeks.[43] Use of the adenosine receptor antagonist improved the rates of IDH and patients had fewer early hemodialysis discontinuations due to hypotension. Despite the positive results from this small, short-term study, no further studies on this class of medication for treatment of IDH have been conducted, and the use of adenosine receptors as drug targets has generally struggled.[44]

In summary, IDH remains a vexing problem that cannot be easily prevented with pharmacological treatments – either withholding antihypertensive medications or administering vasoconstrictor medications – alone. Given the relatively scant amount of evidence available to guide treatment decision-making, more studies focused on IDH are clearly needed. The optimal timing of antihypertensive medication administration for patients on hemodialysis, including whether withholding these medications is appropriate for patients with IDH, requires clarification. In addition, future studies of potential pharmacological treatments should examine not only hemodynamic effects such as nadir BP

and intradialytic MAP, but also patient-centered outcomes such as symptoms of IDH or quality of life, as well as other important clinical outcomes such as cardiovascular events.

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