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Review Article

Hypertension in End-Stage Renal Disease

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Abstract

Hypertension is one of the leading causes of End Stage Renal Disease (ESRD) worldwide. The diagnosis and true prevalence estimates remain variable and challenging due the lack of a standardized definition. Most of the recommendations are based on expert opinions rather than high quality data. Ambulatory blood pressure measurement (ABPM) is the preferred method of diagnosing hypertension in this population but may not be readily available. Multiple factors are involved in the pathogenesis of hypertension ESRD including volume overload and impaired sodium balance, activation of the sympathetic nervous system and activation of the renin angiotensin aldosterone system. Management of hypertension in dialysis patients involves adjustment to dialysis prescription with meticulous attention to salt and water balance and dry weight. Pharmacological therapy is subsequently added if the blood pressure remains uncontrolled. There is no evidence supporting the use of one agent over another and the decision is generally individualized and made on the basis of any accompanying comorbidities. This review focuses on the current state of diagnosis and treatment of hypertension in ESRD patients.

Key words: Blood pressure, dialysis, end stage renal disease, hypertension

Introduction

Hypertension is both a leading etiology of end-stage renal disease (ESRD) and a well-recognized cardiovascular risk factor in ESRD patients on dialysis. Despite this, hypertension remains highly prevalent and is often inadequately controlled in this population.[1,2] The prevalence estimates of hypertension in ESRD are quite variable, due to the lack of a standard definition for diagnosis as well as the setting and technique of blood pressure (BP) measurement. Hypertension and chronic kidney disease (CKD) are indeed closely interrelated clinical conditions such that sustained uncontrolled hypertension can cause worsening of renal function and vice versa. Here, we will consider the diagnosis and treatment of hypertension in ESRD patients on renal replacement therapy including both non-pharmacologic and pharmacologic approaches.

Diagnosis of hypertension in ESRD

The diagnosis of hypertension in ESRD patients on dialysis is challenging due to the absence of an accepted definition and different methods of BP measurement. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines suggest targeting a pre-dialysis BP of <140/90 mmHg and a post-dialysis BP of <130/80 mmHg.[3] However, this recommendation is expert opinion and not based on high-quality evidence. Improper measurement techniques may result in significantly higher BP readings both pre- and post-dialysis.[4] BP is highly dependent on extracellular fluid volume in hemodialysis (HD) patients in particular, and BP measurements can vary widely during and between HD treatments based on rapid changes in volume status.[5,6] As a result, before and after dialysis BP measurements might not be the best values on which to base a diagnosis of hypertension.

In one meta-analysis, Agarwal *et al.* showed that both pre- and post-dialysis BP readings have poor diagnostic accuracy and correlate poorly with mean interdialytic BP as determined through 44 h ambulatory BP monitoring (ABPM).[7] ABPM can also identify nocturnal non-dippers, a subgroup with a higher cardiovascular morbidity and mortality.[8] Although ABPM may

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be the preferred method for the diagnosis of hypertension in HD patients, it is expensive, impractical, and may not be available to all patients.

Standardizing the technique of BP measurement may lead to more accurate BP readings in hemodialysis patients both pre- and post-dialysis.[4] Adding the average of intradialytic blood pressures to those obtained before and after treatment can improve reproducibility and accuracy compared with using either pre- or post-dialysis readings alone.[9] If ABPM is not feasible or available, home BP measurements may be a reasonable compromise. Home BP readings correlate better with 44 h ABPM compared with either pre- or post-dialysis values, with home BP readings ≥150 mmHg being the best predictor in diagnosing systolic hypertension in hemodialysis patients.[10] In addition, home readings may help recognize patients with masked and white coat hypertension-diagnoses which would be missed if one relied only on in-center BPs.[11]

Both ABPM and home measurements are especially useful in patients with large swings in dialysis unit BP measurements and can help to guide management. In general, it is suggested that home measurements should be performed for a week with two readings in the morning before medications and in the evening pre-dinner, although this has not been validated in the ESRD population.[12]

Prevalence and control of hypertension in ESRD

The prevalence of hypertension in ESRD is difficult to define because of different definitions (i.e., at what level of BP is hypertension determined) and the fluctuation of BP with respect to timing of dialysis due to volume shifts and removal during the procedure. In a study involving 2535 adult HD patients, hypertension was reported in 86% when defined as use of antihypertensive medications or pre-dialysis average systolic and diastolic BP (SBP and DBP) of >150 mmHg and >85 mmHg, respectively.[13] Among these subjects, BP was adequately controlled in only 30%, untreated in 12%, and inadequately treated in the remaining 58%. A 2011 study by Agarwal examined BP in 369 HD patients using 44 h interdialytic ABPM and found that 82% of patients were hypertensive using an average ambulatory SBP ≥135 mmHg or a DBP ≥85 mmHg, or the use of antihypertensive medications as the definition for hypertension.[14] Despite 88% of these subjects being treated pharmacologically, only 38% of patients had controlled BPs. In this cohort of patients, higher use of hypertension medication and being volume expanded were associated with uncontrolled hypertension.[14] The relationship between hypervolemia and hypertension is strengthened by the finding that end expiration inferior vena cava diameter was independently associated with uncontrolled hypertension.[14]

With respect to patients on peritoneal dialysis (PD), in a cross-sectional analysis of 504 Italian PD patients, 88% had hypertension when defined as SBP > 140 mmHg or DBP > 90 mmHg. Of those who were hypertensive, 81.5% were on antihypertensive therapy.[15]

Comparisons between peritoneal and HD patients are rare and limited to small studies. Rodby *et al.* compared 44 h ABPM among 33 HD and 27 PD patients and reported similar diurnal patterns in both groups.[16] HD patients had significantly higher average systolic BPs and loads (the percentage of systolic BPs > 140 mmHg) compared with those on PD.[16] In a similar study, Tonbul *et al.* compared the results of 44 h ABPM between 22 HD and 24 PD patients and found similar mean systolic and diastolic BPs. HD patients had significantly higher nighttime BPs on the off dialysis day and significantly lower daytime BPs on their dialysis day.[17]

BP targets

As noted earlier, the KDOQI guidelines of 2005 offered an opinion-based recommendation of a pre-dialysis BP of <140/90 mmHg and post-dialysis target of <130/80 mmHg.[3] The 2015 KDOQI Clinical Practice Guideline for HD Adequacy offers no further guidance, stating "the current paucity of clinical trial data does not allow defining the target pre-dialysis, post-dialysis, or ambulatory BP for HD patients."[18]

In the absence of clinical trial data, observational studies can provide some guidance. The direct relationship between higher BPs and mortality seen in the non-dialysis population is generally absent in the HD population where there appears to be a reverse J- or U-shaped relationship between pre-dialysis BP and death.[19,20] One study found a higher risk of morality with a pre-HD SBP below 140 mmHg.[19] The other showed the lowest risk of mortality with a pre-HD SBP between 130 and 159 mmHg.[20] It is speculated that the increased mortality risk associated with lower pre-HD SBP may be the results of unmeasured confounding with low BPs being a marker of severe cardiovascular disease.[21]

Several studies provide evidence that home BP readings correlate more strongly with mortality and cardiovascular morbidity than do measurements at the dialysis unit. Alborzi *et al.* studied 150 HD patients who had self BP measurements at home, 44 h ABPM during the interdialytic interval, and BP measurements before and after dialysis. Over a median 24 months of follow-up, higher BPs at home and through ABPM measurements predicted all-cause mortality, whereas in-center measurements did not.[22] In a separate analysis, Agarwal also showed that home systolic BPs and ABPM systolic BPs predicted mortality after a median 29-month follow-up period.[23] The lowest mortality was seen for systolic BPs of 120–130 mmHg for values obtained at home and 110–120 mmHg for ABPM values.[23] Increasing quartiles of BP predicted excess mortality for both home measurements and ABPM values.[23]

Although individual trials have not been powered to suggest a BP target, several meta-analyses may provide some information. Agarwal and Sinha performed a meta-analysis of five studies examining different BP medications and found that in 1202 dialysis patients, pharmacologic treatment of BP led to a 38% risk reduction of cardiovascular events compared to those who received placebo.[24] Mortality in this study did

not differ between groups. A separate meta-analysis done of eight trials encompassing 1679 patients by Heerspink *et al*. demonstrated 29% decrease in cardiovascular events, 29% decrease cardiovascular mortality, and 20% decrease in all-cause mortality.[25] Unfortunately, the included trials did not test specific BP targets so the meta-analyses are unable to offer one.

Non-pharmacological options to treat hypertension in ESRD patients

Volume overload and sodium retention play a central role in hypertension in ESRD patients on dialysis. In healthy individuals, sodium balance is exquisitely regulated, principally through renal sodium loss. In ESRD patients, this natriuresis is typically compromised, and renal replacement therapy is often required for adequate removal of salt and water. Increased dietary sodium in HD patients leads to increased interdialytic weight gain and extracellular volume expansion and is independently associated with higher pre-HD BP and greater mortality.[26] Restoring balance of sodium and volume status is paramount in hypertensive dialysis patients. KDIGO guidelines stress the importance of sodium restriction and recommend salt restriction to <5–6 g/day.[27] In conjunction with reducing salt intake, achieving an appropriate dry weight is also important. A patient's dry weight is defined as the post-dialysis body weight at which extracellular volume (ECV) is in the normal range.[27] Since ECV is difficult to measure, this definition, while accurate, is not of great utility clinically. Nonetheless, based on available evidence, nephrologists should attempt to reduce the dry weight in ESRD patients with high BP. The dry weight reduction in hypertensive HD patients (DRIP) trial reported that a decrease in dry weight by 1 kg at 8 weeks led to a reduction in systolic BP of 6.6 mmHg and diastolic BP of 3.3 mmHg.[6] As most patients in this trial were already being treated for hypertension, this shows that dry weight reduction may work synergistically with medications. While lowering dry weights, practitioners need to keep in mind that intensifying ultrafiltration without increasing dialysis time or frequency may result in intradialytic hypotension, arteriovenous fistula clotting, and cardiovascular morbidity and mortality.[28] It is recommended to limit ultrafiltration rates to <12.4 mL/kg/h as higher rates are associated with increased mortality.[29]

Increasing HD frequency may also help with hypertension management. The Frequent HD Network Trial compared an in-center frequent intensive dialysis regimen to a conventional regimen (3 times a week) and reported improved control of hypertension, although study participants in the frequent HD arm were more likely to require vascular access interventions.[30] Similarly, a randomized crossover trial showed that subjects who underwent short daily HD treatments versus conventional HD required fewer BP medications to maintain a similar BP.[31] Other non-pharmacological interventions include adjusting dialysate sodium and avoiding sodium-containing or sodium exchanging medications.

With respect to PD patients, dietary sodium restriction is also important for the management of volume status and BP. Gunal *et al.* reported a decrease in systolic BP from 158 to 120 mmHg in hypertensive PD patients by strict attention to a low salt diet and more aggressive ultrafiltration when indicated, without pharmacologic intervention.[32] The International Society for Peritoneal Dialysis has recently designated volume management and BP control as a key aspect of high-quality PD care.[33]

The use of low-sodium PD fluid may also enhance sodium removal and help decrease BP in PD patients. One prospective, non-randomized study compared a low-sodium peritoneal dialysis solution with a conventional solution by substituting one 3–5 h exchange/day for 2 months. The osmolality was kept the same in both groups by increasing glucose concentration in subjects using lower sodium fluid. The use of low-sodium dialysate was associated with improved diffusive peritoneal sodium removal and significant reduction in nighttime SBP.[34] Low-sodium dialysate, however, is not available commercially.

Pharmacologic management of hypertension in ESRD patients

Antihypertensive regimens in hypertensive ESRD patients should be tailored to individual patients taking in account efficacy, side effects, dialyzability of the medication, pharmacokinetics, and cardioprotective properties of BP-lowering medications along with any associated comorbidities of the patient. All antihypertensive drug classes can be used in this population with the exception of diuretics in oligoanuric patients. Diuretics may help to limit weight gain between dialysis sessions and volume overload in HD patients with preserved residual kidney function[35] and are commonly used in PD patients as adjunct to volume removal by ultrafiltration.[36]

Another consideration is the pattern of BP during the inter- and intradialytic period. Short-acting antihypertensive medications should be avoided just before dialysis sessions, especially in patients prone to intradialytic hypotension. Patients with sustained hypertension during the interdialytic period would benefit by the use of long-acting agents. Much of the time, hypertension in this population is both unpredictable and difficult to control and may require multiple agents with different mechanisms of action. One strategy suggested to reduce pill burden is to administer antihypertensive agents thrice weekly with HD sessions. The hypertension in HD patients treated with atenolol or lisinopril (HDPAL) trial supported this notion and resulted in better interdialytic BP control with thrice weekly dosing.[37] Another strategy in non-dippers includes switching one of the antihypertensive agents to bedtime dosing.[38]

Without randomized control trials comparing the effects of different antihypertensive agents on end-organ damage in ESRD patients, results from studies done in patients without ESRD have been extrapolated to patients on dialysis. The use of beta-blockers is preferred in patients with previous cardiovascular disease based on their cardioprotective properties including improvement in arterial stiffness and improvement in left ventricular hypertrophy.[39] Excessive activation of the sympathetic nervous system in dialysis patients makes them prone to arrhythmias and sudden cardiac death

and beta-blockers may prove to be an attractive antihypertensive agent in this population. Beta-blockers were associated with a lower risk of sudden death in the Dialysis Outcomes and Practice Patterns Study (DOPPS) study, after adjustment for comorbidities.[40] The HDPAL trial also showed superiority of atenolol over lisinopril for the prevention of serious cardiovascular events.[37] Inrig *et al.* demonstrated that carvedilol led to better intradialytic and interdialytic BP, improvement in endothelial dysfunction and reduced incidence of intradialytic hypertension.[41] It is important to consider renal clearance and dialyzability of beta-blockers in this population subset as a recent study suggested that highly dialyzable beta-blockers do not provide a survival benefit or intradialytic protection against arrhythmias.[42]

Trying to extrapolate cardiovascular benefits of renin–angiotensin system (RAS) blockers in dialysis patients from results obtained in general population can be challenging as randomized trials in dialysis patients with hypertension show contradictory results. In the Fosinopril in Dialysis trial, fosinopril led to a significant reduction of pre-dialysis BP; however, no difference was observed in the occurrence of cardiovascular events (fatal or non-fatal) between the fosinopril and placebo arms.[43] In the Olmesartan Clinical Trial in Okinawa patients under dialysis study, the incidence of all-cause mortality, non-fatal stroke, MI, and coronary revascularization was similar in both intervention and control groups.[44] Small randomized studies and a meta-analysis, however, show a beneficial cardioprotective effect of ACEIs and ARBs,[45,46] although this is not consistent in all studies, and it is difficult to say if the cardioprotective effect was mediated by the ACE-I/ARB or by the improved BP control. In PD patients, ACE-I/ARBs may be among the preferred agents due to small clinical trials showing protection of residual kidney function.[47,48]

Mineralocorticoid receptor antagonists (MRAs) are also used for cardioprotective effects, although the initial concern was the risk of life-threatening hyperkalemia in this population subset. The safety of eplerenone was recently studied in 146 HD patients who were followed for 13 weeks. It was found that eplerenone did increase the risk of serious hyperkalemia, however, there was no associated need for discontinuation of the drug.[49] In the Dialysis Outcomes Heart Failure Aldactone Study, 309 HD patients were randomized to receive either spironolactone (25 mg/d) or no add-on therapy and were followed for 3 years. The spironolactone group had significantly lower cardiovascular morbidity and mortality and a low (1.9%) incidence of serious hyperkalemia requiring stopping of the medication.[50] In another randomized trial of 253 non-heart failure, ESRD patients on chronic dialysis (HD and PD) by Lin *et al.*, low-dose spironolactone as add-on therapy was found to reduce the incidence of the composite primary outcome of cardio or cerebrovascular death, observed cardiac arrest, and sudden death by 58%.[51] A recent meta-analysis supports the use of MRAs in low dose in ESRD patients.[52] Potassium levels should be monitored closely if MRAs are used.

Calcium channel blockers (CCBs) may also be used in managing hypertension in dialysis patients. CCBs are often used as combination therapy in dialysis patients and have been shown to work effectively to lower BP, even in the volume overload state.[53] The pharmacokinetics of CCBs is not altered with dialysis and they are generally non-dialyzable.[54]

Other drug classes that can be used as add-on therapy include centrally acting α-agonists, direct acting vasodilators, and α-adrenergic blockers. The centrally acting *α*-agonist clonidine reduces autonomic activation and is effective in reducing BP in this subset of patients, however, it may lead to significant side effects, such as dizziness, dry mouth, and fatigue. Direct vasodilators such as minoxidil or hydralazine are generally used for resistant hypertension. They usually result in reflex tachycardia, which can be controlled by concomitant use of beta-blockers.[54] Practitioners should be aware that hydralazine may lead to a lupus like syndrome. Minoxidil in rare cases may precipitate a pericardial effusion. Alpha-adrenergic blockers use may be associated with orthostatic hypotension and worsening of intradialytic hypotension.[54]

Conclusion

There is much uncertainty surrounding hypertension in ESRD patients and many questions remain. Clinicians should be aware of the pitfalls of using peridialysis BP measurements for treatment decisions in HD patients. Home BP monitoring and, if available, ambulatory BP monitoring are better choices in this population given stronger associations with clinical outcomes and mortality and should be employed if possible. The target BP in dialysis patients has not been established. Studies using peridialysis BP show associations between lower BPs and mortality, whereas smaller studies using home or ABPM BPs show that lower BPs are protective. Non-pharmacologic approaches, particularly restoration of sodium and water balance, are of paramount importance. With respect to pharmacologic therapy, evidence to support the use of one agent over another is lacking and the choice of which medication to use should be individualized for each patient. Beta-blockers may be a reasonable first choice given the potential cardio-protection that they offer. In peritoneal dialysis patients, ACE-I/ARBs may be preferentially used to preserve residual kidney function.

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