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Core Curriculum

Management of hypertension in hemodialysis patients

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The relationship of hypertension with adverse outcomes is uncertain in the hemodialysis population. If hypertension is an etiologically significant cardiovascular risk factor in hemodialysis patients, the first step would be to assess the level of BP accurately. BP obtained at home over a week and averaged using a validated oscillometric automatic device can prove valuable. To the extent BP lowering influences cardiovascular outcomes, home BP of 150/90mm Hg would warrant therapy, since it correlates with target organ damage and hypertension diagnosed by ambulatory BP monitoring. To manage hypertension, limiting dietary sodium intake and individualizing dialysate sodium delivery would be first steps. The magnitude of reduction in BP with dietary sodium restriction and the whether dialysate sodium can be safely limited in those who are hypotension-prone is unclear. Antihypertensive drug therapies can effectively reduce BP and are needed by the vast majority of hemodialysis patients. Whether control of hypertension translates into better outcomes is not known, but collective evidence suggests that hypertension should be controlled in hemodialysis patients.

Keywords: hypertension, hemodialysis, end-stage renal disease, home BP monitoring, ambulatory BP monitoring.

INTRODUCTION

Guidelines on the management of hypertension in hemodialysis patients have been impeded because of cohort studies that show "reverse epidemiology" of hypertension in the hemodialysis population. In contrast to the clear evidence of a continuous, graded, and etiologically significant relationship of hypertension with cardiovascular morbidity and mortality in the general population,[1] studies in hemodialysis patients show that those with the highest blood pressure (BP) have the best survival.[2–4] There are numerous reasons why this may be so that I have discussed elsewhere,[5] but the question for those entrusted with the care of hemodialysis patients is to develop a rational approach to evaluation and management of BP. Available evidence suggests that hypertension should be treated in hemodialysis patients.[5] The purpose of this review is to develop a clinical approach to the management of hypertension in hemodialysis patients.

In a survey of 2535 hemodialysis patients from 69 dialysis units in the United States, the prevalence of hypertension was 86%.[6] Although many patients received antihypertensive drugs, only 30% had well-controlled BP, 58% had poorly controlled BP, and 12% had untreated hypertension. These findings underscore the appropriate recognition of high BP in hemodialysis patients, but poor control despite use of multiple medications.

When ambulatory BP monitoring was used to assess hypertension control in a hemodialysis population, the prevalence of systolic hypertension was 73%.[7] When an unselected hemodialysis population from the same center was evaluated, the prevalence of systolic hypertension was 37%.[8] These data suggest the possibility that hyper-

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tension may not be accurately assessed in the general hemodialysis population.

ASSESSMENT OF BP IN HEMODIALYSIS PATIENTS

There are 3 ways in which we can assess the level of BP in a hemodialysis patient. Blood pressure can be obtained during, before, and after dialysis by the dialysis staff, at home by the patient, or by an automatic ambulatory BP monitor. The value of each of these techniques has been discussed below.

Dialysis unit BP

Single recordings of BP either before or after dialysis are often used to make clinical decisions. Generally, these BP are not obtained using standard procedures.[9] Both predialysis and postdialysis BP are useful in assessing BP.[10] However, these BP need to be obtained over 2 weeks and averaged. Even then, the data are useful only in a qualitative sense and cannot be used to predict ambulatory BP with any degree of accuracy.[7] The correlation of such "routine" measurements of BP with ambulatory BP[7,8] and more importantly target organ damage[11] is weak. As BP falls with dialysis, it is little surprise that the threshold for diagnosing hypertension using predialysis BP is higher than postdialysis BP.[7,8] Whether both BP can provide an incremental value in diagnosing hypertension is less certain, although preliminary data suggest that both may be useful.[12]

Owing to environmental hazards of mercury, mercury sphygmomanometers are fast disappearing and will soon be obsolete. Although there has been a reluctance in using oscillometric devices in hemodialysis patients, the use of validated, automatic, oscillometric sphygmomanometers using standard methods[13] is a good clinical practice. We have evaluated one such oscillometric BP measurement device (HEM 907, Omron Healthcare, Bannockburn, IL, U.S.A.) and have found it to perform well in hemodialysis patients.[14] Standardized measurements of BP around dialysis correlate better with ambulatory BP[8] compared with "routine" BP. Blood pressure of >120 mmHg systolic obtained immediately following dialysis using a standard technique and averaged over 2 weeks has a good sensitivity and specificity in making a diagnosis of hypertension in these patients.[8] The problem of obtaining such measurements due to time constraints is self-evident. Even if BP were to be uniformly obtained using standard techniques, there is little relationship with echocardiographic left ventricular hypertrophy.[11]

In a systematic review,[15] we have found that predialysis systolic BPs generally overestimated ambulatory BP by a variable amount. The heterogeneity between BP differences between dialysis unit BP and ambulatory BP did not allow for pooling the estimates. The agreement limits between the 2 BPs was wide (between 41.7 and -25.2 mmHg). Predialysis diastolic BP also generally overestimated the ambulatory BP with wide agreement limits (23.7, -18.9 mmHg). Postdialysis BPs underestimated average ambulatory BP with wide agreement limits for both postdialysis systolic (33.1, -36.3 mmHg) and diastolic BPs (19.3, -23.9 mmHg). Thus, dialysis unit BP measurements are imprecise estimates of ambulatory BPs. The recent National Kidney Foundation K/DOQI guidelines suggest that predialysis and postdialysis BPs should be $<140/90$ and $<130/80$ mmHg, respectively.[16] These results fail to provide solid data to back the K/DOQI guideline recommendations regarding BP goals in hemodialysis patients. Better methods are needed for the assessment of BP in hemodialysis patients for clinical decision making.

Home BP monitoring

As BP tends to vary over the course of the week depending in part on the intravascular volume status, several measurements should be used to better assess hypertension in hemodialysis patients. This is possible readily with home BP monitoring, which is a useful alternative to assess BP and has been incorporated into national guidelines for the assessment of hypertension.[13] This method is attractive as the peaks and valleys of BP that a typical hemodialysis patient experiences are captured to obtain a time-averaged value. Thus, the approximate barometric load is better reflected by these measurements at home. In a study of nearly 150 patients at one center, BP obtained 3 times daily at home for 1 week, and averaged, correlated better with ambulatory BP[8] and target organ damage as assessed by left ventricular hypertrophy.[11] This study demonstrated that home BP obtained in the morning, afternoon, and evening for 1 week is feasible, even in a relatively uneducated population.[8] When these BP obtained at home over a week are averaged, a BP level of 150/90 mmHg or more was found to be the best determinant of an awake ambulatory BP of 135/85 mmHg that is considered hypertensive in the general population.[8] The diagnostic performance characteristics of home BP monitoring are superior to BP obtained in the dialysis unit in determining ambulatory BP and left ventricular hypertrophy.[11] Thus, home BP monitoring can complement the assessment of hypertension in hemodialysis

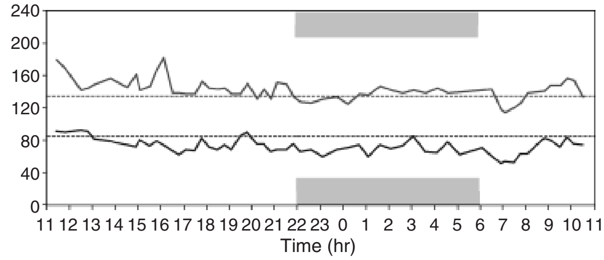

Figure 1 Twenty four-hour ambulatory blood pressure (BP) recording in a patient with chronic kidney disease. Blood pressures are plotted against time over 24 hr. The gray shaded area between 22:00 PM and 06:00 AM represents the sleep time. The dotted lines are placed at 135 and 85 mmHg, indicating the threshold over which the average ambulatory BP is considered high. It is obvious that the patient has systolic hypertension. There is no decline during sleep in this patient, indicating nondipping.

patients. Perhaps, shorter periods of home BP monitoring would provide valuable information as well, but will need to be evaluated in prospective studies.

Ambulatory BP monitoring (ABPM)

Ambulatory BP monitoring involves wearing a small device usually hooked to the belt that is connected via a hose to a BP cuff around the arm. The device automatically inflates at 20–30 min intervals while the patient goes about his usual activity, and records this in its memory. The recordings can then be downloaded to a computer and analyzed. An ambulatory BP recording over 24 hr in a subject without dipping is shown in Figure 1.

Studies utilizing ABPM have demonstrated that hemodialysis patients do not experience lower BP at night, i.e., have a high prevalence of "nondipping."[17–20] This phenomenon of nondipping cannot be detected by other methods and provides a more accurate estimate of the BP burden—also called "BP load"—on the cardiovascular system.[21] Whereas in individuals with essential hypertension nondipping is associated with left ventricular hypertrophy, strokes, and cardiovascular morbidity and mortality, in patients on hemodialysis, nondipping is associated with reduced arterial distensibility[22] and systolic hypertension to left ventricular hypertrophy.[11]

Because of numerous readings obtained by ABPM and the lack of alerting reactions, there is excellent reproducibility between days when duplicate readings are performed.[23] Ambulatory BP monitoring is also more sensitive to change with interventions. For example, whereas routine BP monitoring failed to demonstrate changes in BP with the administration of erythropoietin,[24] ABPM was able to detect a rise in overall BP with just 13 patients.[25] When ABPM was compared with home BP monitoring, again, ABPM was found to be more sensitive in detecting an increase in BP with erythropoietin.[26] We have exploited the reproducibility and sensitivity of ABPM in detecting antihypertensive effects of water-soluble antihypertensive drugs administered to hemodialysis patients 3 times weekly using only a small number of subjects.[27,28]

Ambulatory BP monitoring is required for the diagnosis of the white coat effect. The white coat effect is the elevation in BP due to alerting reactions in the office setting in patients who have preexisting hypertension. Mitra et al. have compared interdialytic ABPM with BP obtained in hemodialysis patients at arrival to the dialysis unit, after 10 min of rest in a quiet room and at other time points.[29] The authors reported that BP on arrival to the hemodialysis unit was $>$20/10 mmHg higher than that in the previous 6 hr recorded by ABPM in 15 of 36 (41%) patients. Even after resting for 10 min, BP was elevated in 19% of the patients, suggesting a true white coat effect. This study suggests that the white coat effect may be common in hemodialysis patients. By comparison, in a population of elderly patients with hypertension but without kidney disease, white coat hypertension was seen in 13%; these patients had a cardiovascular prognosis that was similar to well-controlled hypertension.[30]

Ambulatory BP has been used to predict cardiovascular outcomes in hemodialysis patients in 2 studies. The first study of Amar et al. found a strong relationship of ambulatory pulse pressure with total mortality.[31] The second study from Zocalli's group found that the night/day systolic BP ratio, an index of dipping, was the sole BP indicator associated with all-cause and cardiovascular mortality.[32] Echocardiographic left ventricular hypertrophy was similarly a predictor of these outcomes. These results suggest that nondipping and left ventricular hypertrophy provide overlapping prognostic information that is compatible with the hypothesis that they represent common pathophysiological pathways for cardiovascular damage in patients on hemodialysis.

Systolic vs. diastolic hypertension

Most patients on hemodialysis have systolic hypertension that may or may not coexist with diastolic hypertension.[33] In fact, isolated diastolic hypertension is rare.[8] JNC 7 guidelines designate systolic BP as the primary treatment target in people above 50 years.[34] Most dialysis patients are elderly and even the younger ones have the vascular age of healthy people who are older. A direct relationship between systolic BP and total mortality and systolic BP and cardiovascular events has emerged in the hemodialysis population.[35] An inverse relationship between diastolic BP and these hard end-points is seen.[35] As pulse pressure is the difference between systolic and diastolic BP, it is not surprising that pulse pressure is an excellent marker of total mortality in hemodialysis patients.[35,36] When pulse pressure and systolic BP are compared, Tozawa et al. found that systolic BP is a superior determinant of cardiovascular and total mortality.[35] Thus, it appears reasonable to target systolic BP.

TREATMENT OF HYPERTENSION IN HEMODIALYSIS PATIENTS

Dialysate and dietary sodium restriction

Fluid restriction is often prescribed for hemodialysis patients, but is without physiologic rationale. Free water restriction is a therapeutic option for hypo-osmolar states, not volume overload. A more appropriate therapy for these patients would be to restrict dietary sodium intake. A 2-g sodium diet is commonly recommended. If the patient follows the 2 g sodium diet, an interdialytic weight gain of 1.25 kg would be expected over 2 days or 1.9 kg over the weekend. Only rarely do dialysis patients achieve such small interdialytic weight gains. Limiting weight gain would mitigate the large swings in BP and may ease the intradialytic hypotensive symptoms.

Another, perhaps less recognized, source of sodium excess is the dialysate sodium prescription. In a patient who weighs 72 kg, the total body water is estimated as 43 L. If predialysis sodium concentration is 135 mEq/L and the patient is dialyzed against 145 mEq/L, an estimated 10 mEq/L $\times$ 43 L or 430 mEq Na will be delivered. This will be roughly equivalent to a 3 kg interdialytic weight gain. Individualizing sodium prescription in such patients may be useful and data point to the usefulness of such a strategy in lowering BP in hypertensive subjects.

To evaluate the hypothesis that individualizing dialysate sodium prescription limits interdialytic hypertension, de Paula et al. performed a cross-over study in 27 nondiabetic, nonhypotension-prone hemodialysis patients.[37] In a cross-over design, subjects underwent 9 consecutive HD sessions with the dialysate Na concentration set to 138 mEq/L, followed by 9 sessions wherein the dialysate Na was individualized. To individualize dialysate Na, patients average pre-HD plasma Na was measured 3 times during the standard Na phase and multiplied by 0.95. There was a significant decrease in interdialytic weight gain (2.9 vs. 2.3 kg; $p<0.001$), interdialytic thirst scores, and episodes of intradialytic hypotension in the individualized Na period. Pre-HD BP was lower by 15.6/6.5 mmHg in individualized Na HD in patients with uncontrolled BP at baseline. These data suggest that lowering dialysate Na based on predialysis plasma Na level may reduce interdialytic weight gain, thirst, and may improve BP.

Drug therapies

The majority of patients with end-stage renal disease (ESRD) on chronic dialysis undergoing standard three times a week treatment need antihypertensive drug therapy.[6,38] Several classes of antihypertensive drugs are available and all except diuretics are effective in controlling hypertension in hemodialysis patients. The selection of these agents requires consideration of the comorbidities, pharmacokinetics, and hemodynamic effects of these agents. For example, in patients with left ventricular hypertrophy, angiotensin converting enzyme (ACE) inhibitors may be effective in causing regression, although the trial sizes have been limited.[39,40] Calcium-channel blockers (CCBs) are the most widely prescribed class of drugs in patients on hemodialysis.[6,41] Calcium-channel blockers appear to be more effective when the plasma volume is expanded. As hypertension in hemodialysis patients is thought to be largely a result of volume expansion, these agents may have a unique advantage in ESRD.[42] Both dihydropyridine[43–45] and nondihydropridine calcium channel blockers have unaltered pharmacokinetics in patients with ESRD on hemodialysis and have little dialyzability,[46,47] and therefore require no dose modifications. Sustained-release verapamil could control BP in 21 of 28 hypertensive ESRD patients.[48] Futhermore, a single dose of 40 mg oral verapamil given before hemodialysis to 10 patients with left ventricular hypertrophy did not aggravate intradialytic hypotension.[49] Preliminary studies with verapamil have even suggested a reduction in intradialytic hypotension.[50]

Angiotensin converting enzyme inhibitors and beta-blockers appear to be attractive agents due to their independent cardiovascular benefits. I have tested the utility of an antihypertensive agent from each class administered after dialysis in a supervised manner 3 times weekly to assess the safety and efficacy of these drugs. Atenolol, a water-soluble, renally excreted beta-blocker, was prescribed in 8 hemodialysis patients not receiving any antihypertensive drugs.[27] The half-life of atenolol is prolonged in ESRD; therefore, I reasoned that 3 times weekly administration would suffice. Furthermore, atenolol is removed by hemodialysis; intradialytic hypotension would be mitigated during the time of hemodynamic stress. After confirming hypertension by ABPM, patients were administered atenolol 25 mg following hemodialysis and the dose of the drug was escalated at weekly intervals to 50 mg and finally 100 mg 3 times a week. The efficacy of therapy was judged by ambulatory BP monitoring 3 weeks after instituting atenolol therapy. The mean 44-hr ambulatory BP reduced from 144/80 to 127/69 mmHg ($p<0.001$). The systolic and diastolic BP loads were reduced from 71%/30% to 35%/11%, respectively ($p<0.001$). There was a persistent antihypertensive effect over 44 hr. The BP reduction was achieved without any increase in intradialytic symptomatic or asymptomatic hypotensive episodes, reduction in delivered dialysis, or statistically significant changes in serum potassium or glucose.

I have also assessed the antihypertensive effects of lisinopril, a renally excreted ACE inhibitor administered 3 times weekly following dialysis.[28] Lisinopril was titrated at biweekly intervals at 10, 20, or 40 mg doses. If this was not effective after full titration (lisinopril to 40 mg 3 times weekly), ultrafiltration was added to reduce dry weight. The primary outcome variable was the change in BP from the end of the run-in period to the end of the study. No change in mean ambulatory BP was noted during a 2-week run-in period. However, the average 44-hr ambulatory BP declined from 149/84 to 127/73 mmHg, a decline of 22/11 mmHg ($p<0.001$) at final evaluation. Four patients received 10 mg, five 20 mg, and two 40 mg lisinopril, of which only one required ultrafiltration therapy. There was a persistent antihypertensive effect over 44 hr. Blood pressure reduction was achieved without any increase in intradialytic symptomatic or asymptomatic hypotensive episodes. Therefore, supervised lisinopril therapy was effective in controlling hypertension in chronic HD patients. Some studies have shown that ACE inhibitors induce erythropoietin resistance.[51,52] A small peptide, *n*-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP), is a physiological inhibitor of hematopoiesis and is degraded by ACE. Accumulation of AcSDKP occurs in ESRD patients, and particularly in those treated by ACE inhibitors and may partly explain erythropoietin hyporesponsiveness in ESRD patients.[53] In patients treated with ACE inhibitors, a high incidence of anaphylactoid reactions has been reported during dialysis with AN69 membranes due to bradykinin generation.[54] Thus, ACE inhibitors should not be used in combination with AN69 membranes.

Angiotensin II receptor blockers are also effective in hemodialysis patients. The pharmacokinetics of losartan have been carefully examined and remain unaltered in hemodialysis patients.[55] A multicenter, open-label, 6-month study was performed in 406 patients to test the tolerability and efficacy of losartan in patients on hemodialysis.[56] Fifteen patients discontinued the study owing to adverse reactions related to losartan, and in 7 of them the adverse reaction was hypotension. In 2 patients, a possible anaphylactoid reaction was reported after dialysis with an AN69 membrane, necessitating termination of dialysis and losartan in one patient. In contrast, 9 patients with a history of previous anaphylactoid reaction with ACE inhibitor and AN69 did not show this complication with losartan and AN69. Thus, losartan is a well-tolerated antihypertensive in hemodialysis patients, with a very low incidence of adverse reactions, and a lower incidence of anaphylactoid reactions than those detected with ACE inhibitors and AN69.

Several other options are available to control hypertension. For example, transdermal clonidine applied at weekly intervals can improve hypertension control.[57] In addition, minoxidil, a potent vasodilator, is effective for hypertension control.[58] However, it should be used with beta-blockers to maintain efficacy. The side-effects of hirsuitism, pericardial effusion, and edema should be carefully monitored.[59]

BP TARGETS

To what level BP should be lowered and how is not known. The National Kidney Foundation K/DOQI guidelines suggest that predialysis and postdialysis BPs should be $<140/90$ and $<130/80$ mmHg, respectively.[16] However, these guidelines are opinion based. Although observational studies suggest a mean arterial pressure of <99 mmHg to be associated with best survival, these patients have long-hours hemodialysis unlike most patients in North America. Lowering BP too much may make fluid removal during dialysis difficult and may increase the discomfort associated with dialysis. On the other hand, by reducing BP to a lower level, a cardiovascular benefit may be realized. The balance between risks and benefits will need to be addressed in randomized-controlled trials.

Operationally, an ideal BP in a hemodialysis patient would be associated with hemodynamic stability during dialysis, orthostatic tolerance after dialysis, the best cardiovascular survival, and optimal health-related quality of life. Although some of these goals can be achieved by dietary and dialysate sodium restriction to reduce the amplitude of BP fluctuations, additional factors must be considered. For example, the amplitude of fluctuations in BP for a given level of volume expansion would depend on the vascular compliance. The tolerance to hemodial-

Table 1 Guidelines on assessment and treatment of hypertension in hemodialysis patients

Assessment of hypertension
Use standardized measurements where possible
Use standard equipment. Oscillometric technique may work well
Average several readings: 2 weeks preferable
Both predialysis and postdialysis BP are useful
Home BP is an excellent alternative to assess BP. It correlates best with ABPM and LVH
Treatment of hypertension
Dialysate and dietary sodium restriction is useful
Assess dry weight accurately
Drug therapies: lisinopril or atenolol has the advantage of long half-lives and can be administered 3 times weekly after dialysis

ABPM = ambulatory BP monitoring; BP = blood pressure; LVH = left ventricular hypertrophy.

ysis would then not only depend on the extent of volume excess (sodium intake) but also the cardiovascular state. Thus, a patient with diastolic dysfunction and left ventricular hypertrophy who requires larger filling pressures to maintain an adequate cardiac output may become hypotensive despite minimal fluid shifts. As left ventricular hypertrophy is associated with arterial stiffness, intradialytic hypotension would be associated with interdialytic hypertension. Accordingly, it is likely that tolerance to BP goals will vary by cardiovascular comorbidities. If there is a true association between hypertension and cardiovascular disease in hemodialysis patients, then the lowest possible home BP that is associated with least symptoms on dialysis and best quality of life may be a prudent goal. This BP goal would need to be individualized. As a home BP of >150/90 mmHg correlates with hypertension detected by ABPM, BP targeted to <150/90 mmHg would be a prudent goal.

CONCLUSION

The relationship of hypertension with adverse outcomes is uncertain in the hemodialysis population. If hypertension is an etiologically significant cardiovascular risk factor in hemodialysis patients, the first step would be to assess the level of BP accurately (Table 1). As a paradigm, one may think of BP obtained in the hemodialysis unit as those useful to evaluate hemodynamic stability of the hemodialysis procedure. To better evaluate the time-averaged barometric load, BP obtained at home over a week, and averaged can prove valuable. This is simply a paradigm, not a firm guideline because we do not know whether home BP would correlate better with cardiovascular morbidity and mortality and whether therapy guided by home BP monitoring would lead to superior outcomes. To the extent BP lowering influences cardiovascular outcomes, a home BP of >150 systolic would warrant therapy, as it correlates with target organ damage (left ventricular hypertrophy) and hypertension diagnosed by ambulatory BP monitoring. To manage hypertension, limiting dietary intake, and individualizing dialysate sodium delivery would be the first steps. The magnitude of reduction in BP with dietary sodium restriction and whether dialysate Na can be limited in those who are hypotension prone is unclear. Antihypertensive drug therapies can effectively reduce BP and are needed by the vast majority of hemodialysis patients. Whether control of hypertension translates into better outcomes is not known, but collective evidence suggests that hypertension should be controlled in hemodialysis patients.

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