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Review Article

Nephrology Section

High Blood Pressure in Dialysis Patients: Cause, Pathophysiology, Influence on Morbidity, Mortality and Management

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ABSTRACT

Dialysis is initiated in a patient with End stage renal disease. The recent guidelines suggest the initiation of dialysis when symptoms and signs of kidney failure are present and not merely a decrease in GFR. The most common complication postdialysis is the occurrence of hypotension. However many dialysis patients are found to be hypertensive. In this article, we mention the cause and pathophysiology of hypertension in dialysis patients and its management.

Keywords: Blood pressure, Chronic kidney disease, Dialysis, Hypertension, Mortality

INTRODUCTION

The latest KDIGO 2013 guidelines define Chronic kidney disease (CKD) by the presence of kidney damage or decreased kidney function (GFR) for three or more months, irrespective of the cause [1] [Table/Fig-1]. The term End Stage Renal Disease (ESRD) is used to refer to a chronic kidney disease which requires renal replacement therapy. This term came up with the widespread use of KDOQI guidelines introduced in 2002 [2]. These staged CKD into five categories [3] [Table/Fig-2]. ESRD was defined as CKD stage 5 requiring dialysis [3]. However the latest KDIGO guidelines suggest that dialysis be initiated when one or more of the following are present: symptoms or signs attributable to kidney failure (serositis, acid-base or electrolyte abnormalities, pruritus); inability to control volume status or blood pressure; a progressive deterioration in nutritional status refractory to dietary intervention; or cognitive impairment [1].The KDIGO staging of CKD is different from the KDOQI staging and it is worthwhile to have a look at it [Table/Fig-3]. Hypotension is the most common complication observed in dialysis patients [4] and is observed in 15-50% of the cases [5]. The other complications include muscle cramps, itching, fever, chills, pyrogen reactions, disequilibrium syndrome, nausea and vomiting, itching, headache and hypertension [6].

HYPERTENSION IN DIALYSIS PATIENTS

It is a known fact that the presence of hypertension in the population is directly proportional to cardiovascular morbidity and mortality [7]. However it is surprising and interesting to know that CKD patients demonstrate what is known as an 'inverse epidemiology' [8,9]. Higher longevity of hypertensive patients receiving dialysis has been noted in many studies [10]. Both higher and lower blood pressures have been found to be detrimental in these group of patients and therefore recommendations to achieve a target blood pressure have been set forth. `However there are no strict guidelines and they vary from patient to patient [11].

Markers of Kidney Damage (One or more)	Albuminuria (AER<30mg/24 hours; ACR<30mg/g [=3mg/mmol] Urine sediment abnormalities Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	GFR<60ml/min/1.73m^2 (GFR categories G3a–G5)

[Table/Fig-1]: Criteria for diagnosis of chronic kidney disease [3]

How to measure Blood Pressure in dialysis patients. In a US study on 2535 hemodialysis patients, 86% were found to be suffering from hypertension. Even in those patients who received antihypertensive medications, 58% had poorly controlled Blood Pressure and 12% had refractory hypertension [12].The bloodpressure in these patients can be assessed by taking blood pressures pre-dialysis, during dialysis and post-dialysis. In most cases, the pre-dialysis and post-dialysis systolic blood pressure are found to be 10 mm Hg more and 10 mm Hg less than the interdialytic blood pressure respectively [13]. The other way is to educate the patient to routinely measure blood pressure at home, and look for a composite reading over 1-2 weeks [14,15]. But by far the best way to monitor the blood pressure in these patients would be at home by the patient by an automatic ambulatory blood pressure monitoring [16,17].

TARGET BLOOD PRESSURE

Till now there have been no randomized prospective trials evaluating the target blood pressure in dialysis patients.Some studies suggest that the goal of bloodpressure be a pre-dialysis value of below 140/90 mmHg and a post-dialysis value of 130/80 mmHg [18-23]. In patients undergoing dialysis; a normal blood pressure may be defined as the mean ambulatory blood pressure less than 135/85 mmHg during the day and less than 120/80 mmHg by night. Some studies have postulated keeping the systemic blood pressure low leads to enhanced mortality so a J or U shaped curve has been observed [19,24-27].

Hypertension: protective or not: Effect on morbidity and mortality

Fifty percent deaths in CKD stage 5 patients are found to be from cardiovascular diseases [28]. The complications from CKD such as anemia, hyperhomocysteinemia, hyperparathyroidism, oxidative stress, hypoalbuminemia, chronic inflammation, prothrombotic factors are all responsible for high morbidity and mortality in these group of patients. Furthermore, in patients who receive dialysis, there is higher risk of cardiovascular diseases and mortality than the general population. Patients who receive renal transplantation have been shown to have improved cardiovascular survival [29]. When studying the effect of high blood pressures, 50 to 60 percent of the patients on hemodialysis are hypertensive and the value can be as high as 85 % as seen in various studies [12,30,31]. Persistent

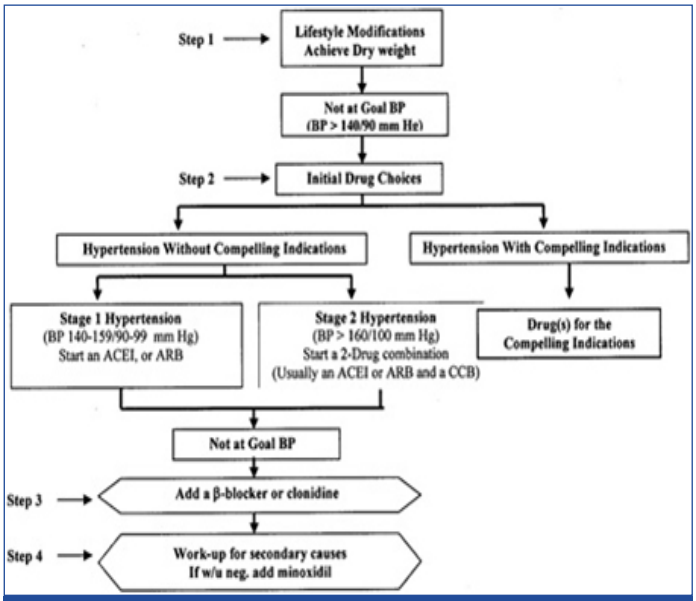
CKD Stage	GFR
Stage 1	>90
Stage 2	60-89
Stage 3	30-59
Stage 4	15-29
Stage 5	<15

[Table/Fig-2]: KDOQI Guidelines for staging of CKD [3]

GFR STAGE	GFR (mL/min/1.73 m^2)
G1	>90
G2	60-89
G3a	45-59
G3B	30-44
G4	15-29
G5	<15
ALBUMINURIA STAGE	AER (mg/day)
A1	<30
A2	30-300
A3	>300

Low risk =G1A1, G2A1
Moderately increased risk=G1A2, G2A2, G3aA1
High risk=G3A1, G3A2, G3bA1, G3aA2
Very high risk =G4A1, G5A1, G3bA2, G4A2, G5A2,G3aA3, G3bA3, G4A3, G5A3

[Table/Fig-3]: KDIGO guidelines for CKD classification [1]



[Table/Fig-4]: Management algorithm (KDOQI Guidelines) [3]

hypertension reflects imperfect volume control despite initiation of dialysis [12,31-33].

Lower blood pressures (pre dialysis systolic Blood Pressure <110 mm Hg) was found to be associated with higher mortality whereas higher blood pressures (pre dialysis systolic Blood Pressure 150-159) have also been reported to have higher mortality [9,26]. Kalantar-Zadeh et al., studied a cohort of 40,933 hemodialysis patients for a 15 months period and found that the hazard ratio was 1.60 in the patients with pre-dialysis systolic blood pressure <110 mmhg and pre-dialysis diastolic blood pressures <50 mmHg was 2.00 [8]. Another study in 16,939 patients followed for 1-2 years found an increased mortality with a systolic blood pressure greater than 150 mm Hg [34]. Another retrospective study in peritoneal dialysis patients found that higher blood pressures were protective [35].

PATHOPHYSIOLOGY

Concept of Dry Weight : DW is the post-dialysis weight in which the patient remains normotensive without antihypertensive medication until the next dialysis [36], or as that body weight at the end of dialysis below which further reduction results in hypotension [37]. Dry weight is measured by biochemical markers, bioimpedence analysis, bioimpedence spectroscopy, and vena caval diameter. Biochemical markers include cyclic guanidine monophosphate and ANP. Chronic kidney disease is a catabolic state and is associated with progressive nephron destruction. The progressive nephron loss causes extra cellular volume enlargement and sodium retention. This leads to weight gain but paradoxical reduction in lean body mass.

Hypervolemia occurs in chronic renal disease because of decrease in GFR, which results in positive sodium balance and extracellular fluid expansion. This is coupled with excessive dietary sodium and fluid intake. There is also secretion of ouabain like inhibitors of Na-K ATPases, which lead to elevation of intracellular calcium; causing increase in vascular resistance [38].

Other causes include renin angiotensin system overactivity. It occurs due to regional renal ischemia and scarring due to CKD which consequently causes increased renin release; further increasing systemic vascular resistance. Increased sympathetic activity, due to increased levels of Angiotensin 2; also plays important role by increasing vascular resistance and systemic Blood Pressure. It is also attributed to asymmetric dimethyl arginine; the role of which is not properly understood [39-41]. The other implicated factors include uremia,endothelin-1, administration of erythropoietin for the treatment of anemia of chronic kidney disease, hyperparathyroidism and increased pulse pressure. Uremia due to the Chronic Kidney disease causes a neural reflex which stimulates cardiovascular centers in brainstem. Endothelin-1; a potent vasoconstrictor; accumulates as a result of decreased renal clearance. Erythropoeitin administered subcutaneously in chronic anemia is known to increase blood pressure by 10 mm Hg in patients with chronic renal failure [42]. Hyperparathyroidism is another cause of increase Blood Pressure in patients with CKD. Calcification of arterial tree causes an increase in vascular resistance, causing increased pulse pressure, which also has an important role in pathogenesis of hypertension.

MANAGEMENT

The management is centered on the control of volume status, lifestyle modification, dialysis and antihypertensive agents.

Lifestyle modifications include weight reduction to achieve dry weight, salt and fluid restriction and adherence to strict salt diet (1000-1500 mg salt/day) [43]. Physical exercise decreases blood pressure, reduces peripheral vessel resistance and reduces vessel rigidity [Table/Fig-4]. Alcohol abuse as documented by MAST study (Michigan Alcohol Screening test); which studies the effect of alcoholism in patients undergoing hemodialysis found that alcohol abuse was associated with lower serum albumin levels and increased dialysis dependence so alcohol abuse must be adequately treated [44,45].

If during the interdialytic period blood pressure remain normal and it does not exceed 160/95 mmHg immediately before the next dialysis session, it is reasonable to keep antihypertensive therapy withheld [45]. Diuretics are not commonly used because of lack of efficacy. The choice of antihypertensive depends upon the coexsisting comorbidities, patient demographic characterstics, risk profile and lifestyle [45-48]. The K/DOQI guidelines suggest that the ACE inhibitors or angiotensin II receptor blockers provide greater benefits in terms of reducing left ventricular mass [49]. A recent observational study stated that there was no significant blood pressure eduction between the treated and untreated groups on ACE inhibitors. However in the treated patients, the mortality was significantly decreased with a risk reduction of 52%.The postulated mechanism of action maybe reducing the mean arterial pressure,

pulse wave velocity and aortic systolic pressure and left ventricular hypertrophy.The adverse effects include hyperkalemia due to inhibition of excretion of potassium in the colon or cellular uptake of potassium [50]. However more evidence is required that ACE inhibitors decrease mortality among chronic haemodialysis patients and younger patients as well [49].

Recommendation from the KDOQI also suggest that the large interdialytic weight gains should be discouraged which can be accomplished by low sodium intake, increased dialysis treatments [49]. Other interventions include the fixed lower dialysate sodium concentration in combination with dietary salt restriction will help in controlling hypertension [51].

In cases of refractory hypertension,minoxidil may be effective. However bilateral nephrectomy may be considered in the rare non compliant individual with life threatening hypertension, this can be seen in a study in which it was found that after nephrectomy the diastolic blood pressure dropped to less than 90 mm Hg ; 3 to 6 months after nephrectomy [52]. Refractory hypertension may be observed due to altered nitric oxide/endothelin-1 balance and/or endothelial dysfunction [53]. The drug carvedilol may be effective in this setting to decrease the blood pressure, as suggested by a pilot study done in a 12 week period in which initiation of carvedilol titrated to 50 mg twice daily was associated with a decrease in the frequency of intradialytic hypertensive episodes from 77 to 28 percent .

CONCLUSION

The most important management strategy in these patients is the attainment of dry weight. A combination of lifestyle changes, antihypertensives and management of the comorbidities is to be achieved. The lack of any cardiovascular events until blood pressure reaches 180 mm Hg is puzzling. Poor ventricular function in patients with lower blood pressure may be the cause of higher mortality, whereas higher risk hypertensive patients may not have survived to enter the study thus leading to a survival bias.

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