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Resistant Hypertension in Chronic Renal Failure

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Abstract

Background Several factors involved in the pathogenesis of hypertension among chronic renal failure patients including sodium and water retention, increased activity of vasoconstrictive systems, decrease activity of vasodilatory systems, increased intracellular calcium, increased arterial stiffness, sleep apnea, hyperparathyroidism, erythropoietin and renovascular disease and dialysate composition and prescription.

Objective To assess the prevalence of resistant hypertension in chronic renal failure patients and to study the relation between primary causes of renal failure, smoking, non-steroidal anti-inflammatory drugs, body mass index and hepatitis C positive with resistant hypertension.

Methods A case-control study of five hundred patients with hypertension and on antihypertensive drugs was conducted during the period from August 2013 to December 2014. Three hundred of them are complaining chronic renal failure. All patients underwent a history and physical examination at baseline. Blood pressure measurement was done for them and blood urea, serum creatinine, serum electrolytes, hemoglobin level and random blood sugar were estimated.

Results Patients with office blood pressure 140/90 mmHg or those treated with antihypertensive drugs are considered as hypertensive, which made up 87.9% of patients with chronic renal failure. The prevalence of resistant hypertension is 31%; all of them are receiving more than three drugs. Resistance hypertension in chronic renal failure associated with high body mass index, left ventricular hypertrophy, and symptom complaint and non-steroid anti-inflammatory drugs but not related to urea level.

Conclusion Resistant hypertension in chronic renal failure is almost always multifactorial in etiology, may be more sensitive to sodium than the general hypertensive population. Resistance to diuretic in chronic renal failure contributes mainly to resistant hypertension.

Keywords Hemodialysis, resistant hypertension, chronic renal failure

List of Abbreviation: RH = resistant hypertension, BP = blood pressure, ABPM = ambulatory blood pressure measurement, CRF = chronic renal failure, OFB = office blood pressure, GFR = glomerular filtration rate, NSAID = non-steroidal anti-inflammatory drugs.

Introduction

Resistant hypertension (RH) is a common clinical problem faced by both primary care clinicians and specialists. While the exact prevalence of resistant hypertension is unknown, clinical trials suggest that it is not rare, involving perhaps 20% to 30% of study participants. As aging and obesity are two strongest risk factors for uncontrolled hypertension, the incidence of resistant hypertension will likely increase as the population becomes more elderly and heavier. The prognosis of RH is unknown but cardiovascular risk is undoubtedly increased as patients often have a history of long-standing severe hypertension complicated by multiple other cardiovascular risk factors such as obesity, sleep apnea, diabetes, and chronic kidney disease [(1)].

RH is defined as blood pressure (BP) above a goal despite adherence to at least 3 optimally dosed antihypertensive medications of different classes, one of which is a diuretic. Evaluation of possible RH begins with an assessment of adherence to medications [(2)].

Relevant factors involved in the pathogenesis of hypertension in dialysis patients include sodium water retention, dialysate composition and prescription, increased activity of vasoconstrictive systems (sympathetic nervous system, renin-angiotensin system, endothelin and vasopressin), decreased activity of vasodilatory systems (nitric oxide, kinins), increased intracellular calcium, increased arterial stiffness, sleep apnea, hyperparathyroidism, erythropoietin and renovascular disease [(3)].

Clinic BP measurements may not indicate the 'real' BP load in the fluctuating BP profile of hemodialysis patients. Indeed, interdialytic ambulatory BP monitoring is agreed by most as the best method to estimate BP in haemodialysis patients, mostly due to its better reproducibility [(4)].

Furthermore, ambulatory BP measurement (ABPM) provides PB during sleep, where most dialysis patients fail to experience a drop in BP (non-dipping) [(5)].

RH is almost always multifactorial in etiology. Treatment is predicated on identification and reversal of lifestyle factors contributing to treatment resistance; accurate diagnosis and appropriate treatment of secondary causes of hypertension; and use of effective multi-drug regimens. Lifestyle changes, including weight loss; regular exercise; ingestion of a high-fiber, low-fat, low-salt diet; and moderation of alcohol intake should be encouraged where appropriate. Potentially interfering substances should be withdrawn or down-titrated as clinically allowable. Obstructive sleep apnea should be treated if present [(6)].

Inaccurate measurement of BP can result in the appearance of treatment resistance. Two of the most common mistakes—measuring the BP before letting the patient sit quietly and use of too small cuff—will result in falsely high BP readings [(7)].

In recent years, there has been growing interest in nonpharmacologic interventions to treat RH. Electrical stimulation of the carotid sinus baroreceptor has been shown to decrease BP. A few small studies have demonstrated that an implantable baroreflex stimulator is feasible and may be quite effective [(8)].

Catheter-based radio-frequency renal denervation is another promising approach that currently is being studied [(9)]. Renal sympathetic activity contributes to hypertension in part through simulation of renin release, increased sodium reabsorption, and neurogenic mechanisms. Selective denervation of the renal nerves responsible for these effects has been shown to reduce BP. In the Symplicity HTN-2 Trial, resistant hypertension patients (with mean baseline BP of 178/96 mm Hg) randomized to catheter-based radio-frequency denervation had a 6-month mean reduction of office BP that was 31/12 mm Hg greater than controls [(10)].

An expansion in extracellular volume, which can be either relative or absolute, frequently contributes to RH. Volume overload may be related to a high-sodium diet, chronic kidney disease (leading to sodium retention), or both. Volume overload may not manifest as peripheral edema detectable on physical examination, yet it should be considered in the patient with persistently elevated BP despite multiple medications, even when one of the medications is a low-dose thiazide diuretic.

Patients with RH may be more sensitive to sodium than the general hypertensive population. In one study in which patients with RH were randomized to low-salt versus high-salt diets, mean office BP was reduced to 23/9 mm Hg more in the low-salt diet group [(10)].

The objectives of this study was to assess the prevalence of resistant hypertension in chronic renal failure patients and to study the relation between primary causes of renal failure, smoking, non-steroidal anti-inflammatory

drugs, body mass index and hepatitis C positive with resistant hypertension.

Methods

This case-control study was performed in Al-Imamain Al-Kadhimain Medical City during the period from August 2013 to December 2014. Five hundred patients (250 males and 250 females) complaining of hypertension were involved in this study with different age groups ranging from (15 to 70) years (mean of age 47.6 year). Three hundred patients are known cases of chronic renal failure (CRF) with glomerular filtration rate (GFR) ≤ 60; one hundred and fifty of them were on regular hemodialysis.

Each patient in end stage renal disease was subjected to hemodialysis for period of 4 hours in two or three sessions per week. All patients underwent a history and physical examination at baseline. The investigations include blood urea, serum creatinine, serum calcium, phosphorus, sodium, potassium, hemoglobin level and random blood sugar. BP was measured before, during and after dialysis in the dialysis unit as well as its measurement at home depending on patient's readings.

The BP has been measured accurately using an appropriately sized cuff, with the patient correctly positioned and after at least a 5-minute rest. Hypertension was determined according to European Society of Hypertension criteria: office BP (OBP) = BP 140/90 mmHg, ABPM 125/80 mmHg [(10)].

The patients were instructed on how to perform home BP measurements and were observed to make sure that they performed it correctly. Lastly, a systematic approach to collecting of measurements should be used. Those who missed three hemodialysis sessions or more, bleeding complication, infectious disease, secondary hypertension and chronic atrial fibrillation, white coated hypertension and pseudo resistance hypertension (including lack of BP control secondary to poor medication adherence) are excluded from the study. Statistical analysis was performed using chi-square test. At level of significance p≤o.o5 regarded as statistically significant.

Results

The number of patients who completed BP measurement in the home with a percentage of valid measurements > 80%. Two hundred patients are excluded from this study due to normal renal function, three hundreds were complaining of CRF. The patients on regular hemodialysis were 150 (64 women and 86 men). They were 55.8 ± 16.2 years old, on hemodialysis for 28±12 months; and spKt/V was 1.2±0.34. Patients with OBP 140/90 mmHg or those treated with antihypertensive drugs are considered as hypertensive, which made up of 87.9% in CRF of the study population as shown in table 1.

The prevalence of RH in this study as mentioned in table 2 is 31%; all of them are receiving more than three drugs including diuretic, angiotensin converting enzyme inhibitor, calcium channel blocker, beta blocker and angiotensin receptor blocker.

There are many factors associated with RH in CRF include body mass index, hepatitis C virus infection, staging of renal impairment, smoking, non-steroidal anti-inflammatory drugs (NSAID), symptom complaint such as (headache and dizziness) and complication such as cardiovascular disease and stroke (Table 3).

Discussion

Most of the patients with chronic kidney disease have hypertension especially elderly patients. In this research, 264 patients (87.9%) have hypertension either as a cause of renal failure or as manifestation of CRF. Among them, 30% were patients taking only one drug, mostly angiotensin receptor blockers or angiotensin converting enzyme inhibitors and 27% patients taking two drugs mostly a combination of calcium channel blocker (CCB) and diuretics, and 33% patients taking three or more drugs, one of which is a diuretic, among them 31% patients are RH.

Table 1. Baseline data of patients with chronic renal failure

Characteristics		number	percentage
Number	Total	500	100
	Hypertension + Chronic renal failure	300	87.9
	On regular hemodialysis	150	50
Age range (yrs)	17-76		
Sex	Males	166	
	Females	134	
Diabetes mellitus		190	38
Body mass index	< 18.9	48	16
	19-24.9	117	39
	25-29.9	94	31.4
	≥ 30	41	13.6
Smoking		125	28
Alcoholics		20	4
On NSAID		65	8
Family history of hypertension		58	58
Left ventricular hypertrophy		290	97
Hepatitis positive in hemodialysis	C	59	38
	B	14	9.5

Table 2. Relation between resistance hypertension and causes of chronic renal failure

Causes of CRF	patients with CRF No. (%)	Patients with RH No. (%)
Diabetes mellitus	105 (35)	24 (8)
Hypertension	96 (32)	36 (12)
Obstructive uropathy	33 (11)	6 (2)
Glomerulonephritis	30 (10)	15 (5)
Polycystic kidney	18 (6)	3 (1)
Vasculitis	12 (4)	6 (2)
Hereditary	6 (2)	3 (1)
Total	300 (100)	93 (31)

CRF = chronic renal failure, RH = resistant hypertension

RH is more in CRF in comparison to general population such as in a recent study in Spain which had found a rate 12 % [12]. This result is due to many mechanisms of hypertension in CRF such as resistance to diuretics and …etc. as mentioned previously.

Examination survey data suggests that among hypertensive adults treated with medication, approximately 13% have RH [13].

RH in CRF patients of the current study is present in approximately 31%. The high prevalence of RH in CRF is due to secondary causes and resistance to diuretic and other mechanism as mentioned previously.

In this study, RH is more common in patients who are already hypertensive before development of CRF in comparison with renal failure due to other causes such as vasculitis and obstructive uropathy (12% versus 2%). This could be multifactorial including long duration of hypertension which affects multi systems in the body such as increase stiffness of the

arterial wall, left ventricular hypertrophy, more glomerular sclerosis, lower GFR and increase activity of the renin angiotensin system.

Table 3. Relationship between resistance hypertension and many factors

Factors		Number of patients with			*P* Value
		CRF + hypertension	Controlled hypertension	Resistant hyoertension	
Hepatitis	C	65	42	23	0.881
	C and B	14	12	2	
	negative	221	177	54	
Body mass index	< 18.9	48	46	2	< 0.001
	19-24.9	117	105	12	
	25-29.9	94	85	9	
	≥ 30	41	13	28	
Renal impairment	< 100	42	39	3	< 0.305
	100-150	84	79	5	
	150-200	108	102	6	
	≥ 250	66	52	14	
Smoking		28	20	8	0.156
NSAD		24	17	7	0.8396
Complain symptom		132	110	22	≤ 0.001
Complications (CVS, stroke)		243	187	56	< 0.001

CRF = chronic renal failure, CVS= cardiovascular system, NSAID=non-steroid anti-inflammatory drugs

In an analysis of Framingham study data, the strongest predictor of lack of BP control was older age, with participants > 75 years being less than one fourth as likely to have systolic BP controlled compared with participants <60 years of age [(14)].

RH has significant effect on cardiovascular complication such as left ventricular hypertrophy and stroke.

The next strongest predictors of RH which are significant were the presence of diabetes mellitus and obesity (body mass index more than 30 Kg/m^2) (due to disregulation of endothelial factors regulating contractility of the smooth muscle of blood vessels, hyperlipidemia and other endocrine abnormalities such as secondary hyper-parathyroidism) which is similar to other studies such as in ALLHAT [(15)].

Most of the patients with RH complain from headache, dizziness, cardiovascular complication (heart failure, ischemic heart disease or stroke). Blood urea level does not correlate with RH which could be due to effect on contractility of the heart and impairment of left ventricular dysfunction in CRF. Hepatitis C and B infection and smoking in CRF have no effect on RH.

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Conflict of interest

The author declares no conflict of interest.

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