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First Study to Compare the Effect of Moxonidine and Clonidine on Blood Pressure and Kidney Function in Patients with Chronic Kidney Disease

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Abstract
Hypertension is 2-3 times more prevalent in CKD as compared to the general population. Enhancement of renal sympathetic nerve activity during renal ischemia and nor epinephrine overflow from the kidney after reperfusion are responsible for the development of ischemic acute kidney injury. Angiotensin receptor antagonists and Angiotensin -converting enzyme inhibitors are unable to normalize sympathetic hyperactivity in patients with hypertensive chronic renal failure in spite of lowering blood pressure. Moxonidine is considered to differ from the other centrally acting sympatholytic drugs. Fifty patients of CKD were enrolled in the moxonidine group and forty nine patients were enrolled in the clonidine group in this open label randomized study. A significant reduction in SBP and DBP was observed in both the treatment groups as compared to baseline. A significant difference between treatment groups was observed. Moxonidine caused a significantly greater reduction of SBP and DBP as compared to clonidine at the end of 3 months. Serum Creatinine was significantly lower after treatment in the moxonidine group as compared to the clonidine group. eGFR after 3 months of treatment was significantly higher in the moxonidine group. Moxonidine can be a preferred sympatho-inhibitory drug in renal failure patients.

Introduction

Hypertension is 2-3 times more prevalent in chronic kidney disease (CKD) as compared to the general population.[1] The striking burden of hypertension and cardiovascular disease in CKD is a cause of concern. Lowering cardiovascular risk in CKD is a major clinical challenge today. The Systolic Blood Pressure Intervention Trial (SPRINT) was the first trial designed and powered to address this issue. SPRINT was a well designed, randomized, controlled trial which evaluated whether lowering the systolic blood pressure (SBP) to a target of 120 mm Hg would reduce the cardiovascular events as compared to the accepted standard of 140 mm Hg in CKD patients with hypertension .The SPRINT trial showed a clear benefit of an intensive blood pressure lowering in CKD patients. [1] In India in the real life setting, a BP goal of <130/80mmHg is aimed for, by most physicians in patients suffering from CKD with proteinuria as well as without it. In patients with CKD without proteinuria, nearly one-fourth of the physicians aim for a BP goal of <140/90 mm Hg.2 Enhancement of renal

sympathetic nerve activity during renal ischemia and norepinephrine overflow from the kidney after reperfusion are responsible for the development of ischemic acute kidney injury. Angiotensin receptor antagonists (ARBs) and Angiotensin - converting enzyme inhibitors (ACEI) are commonly used for the management of hypertension in CKD patients. Angiotensin - converting enzyme inhibitors such as enalapril and losartan are unable to normalize sympathetic hyperactivity in patients with hypertensive chronic renal failure (CRF) in spite of lowering blood pressure.[3]

Several sympatholytics drugs are available including clonidine and guanabenz but they have several limiting side effects such as sedation and dry mouth that reduce their acceptability to patients. Moxonidine is considered to differ from the other centrally acting sympatholytic drugs.[4] Moxonidine acts primarily through a novel cellular site, termed the I(1)-imidazoline receptor . Moxonidine causes a decrease in sympathetic nervous system activity and a subsequent decrease in blood pressure. Moxonidine not only significantly decreases blood pressure but also reduces fasting glucose, triglycerides, total cholesterol, HOMA-IR. Recently, moxonidine was observed to have preventive effects on ischemic acute kidney injury by suppressing the excitation of renal sympathetic nervous system after reperfusion. The central sympatholytic drug moxonidine has been shown to reduce muscle sympathetic nerve activity in patients of chronic kidney disease[.5,6]. Moxonidine selectivity for imidazoline I receptors over alpha adrenergic receptors may explain why rebound hypertension appears less common with moxonidine than with clonidine. Its long duration of action is attributed to the tight binding to the (1)-imidazoline receptor allows for convenient once a day administration. . Moxonidine has been shown to ameliorate glomerulosclerosis and proteinuria in an experimental model of chronic renal failure The addition of moxonidine to angiotensin II antagonist treatment might be appropriate to achieve intensive blood pressure control in CKD patients.[5,6]

While moxonidine lowers blood pressure effectively, there is inadequate data regarding protection of end organs especially the effect on renal function. The current study was conducted to evaluate and compare the blood pressure lowering efficacy of moxonidine with that of clonidine. Secondly the effects of moxonidine on renal function were also evaluated and compared with clonidine

Materials and Methods

The study was an open label, randomized study to compare the effects of clonidine and moxonidine on kidney disease progression in patients with chronic kidney disease. Clonidine or moxonidine were prescribed as add-on drugs to control blood pressure in patients attending nephrology outpatient clinics. Patient demographics, symptoms, serum creatinine, eGFR and impact on Quality of life were evaluated at baseline and at the end of treatment.

Statistical differences between the groups were assessed using chi-square test for categorical data and Student's t-test for continuous data. A p value<0.05 was regarded statistically significant.

Results

Fifty patients of CKD were enrolled in the moxonidine group and forty nine patients were enrolled in the clonidine group. A significant reduction in SBP and DBP was observed in both the treatment groups as compared to baseline. A significant difference between treatment groups was observed. Moxonidine caused a significantly greater reduction of SBP and DBP as compared to clonidine at the end of 3 months. Serum Creatinine was significantly lower in the moxonidine group as compared to the clonidine group. eGFR after 3 months of treatment was significantly higher in the moxonidine group as compared to the clonidine group.(Table 2, 3,4 and 5)

Table 1: Patient demographics

	Moxonidine (n=50)	Clonidine (n=49)	P value
Patient age	53.8±14.5	50.46±15.12	0.256
Gender			
Males	15 (30.0%)	10 (20.4%)	0.272
Females	35 (70.0%)	39 (79.6%)	0.272
Creatinine(s.cr) at Baseline (mg/dl)	5.36 ± 2.98	5.1096± 2.0	0.622
eGFR at Baseline (mean ± SD)	14.6320 ± 8.44	13.4490 ± 5.514	0.412
SBP at baseline (mm Hg)	166.88 ± 13.47	162.28 ± 19.78	0.179
DBP at baseline (mm Hg)	95.38 ±13.72	91.7755 ± 6.67	0.101

Table 2: Effect on Blood pressure after 3 months of treatment with either moxonidine or clonidine

	Group	N	Mean	Std. Deviation	P value
SBP after 3 months	Moxonidine	50	136.7200	10.62350	
	Clonidine	49	147.0612	7.93833	<0.0001*
DBP after 3 months	Moxonidine	50	83.5400	8.61231	
	Clonidine	49	88.6122	6.14009	0.001*

Table 3: Serum Creatinine after 3 months of treatment with either moxonidine or clonidine

	Group	N	Mean	Std. Deviation	T value	P value
s.creatinine after 3 months	Moxonidine	50	4.5586	2.49202		
	Clonidine	49	5.8863	2.82121	2.483	0.015*

Table 4: eGFR after 3 months of treatment with either moxonidine or clonidine

	Group	N	Mean	Std. Deviation	T value	P value
eGFR after 3 months	Moxonidine	50	16.6600	10.97799		
	Clonidine	49	12.0653	5.42865	2.631	0.010*

Table 5: Changes in parameters after taking moxonidine and clonidine

	Group	N	Mean	Std. Deviation	P value
Reduction in s.creatinine	Moxonidine	50	.8040	1.05042	
	Clonidine	49	-.7767	1.22348	<0.0001*
Increase eGFR	Moxonidine	50	2.0280	3.17516	
	Clonidine	49	-1.3837	2.32928	<0.0001*
Reduction in SBP	Moxonidine	50	30.1600	16.13256	
	Clonidine	49	15.2245	20.39839	<0.0001*
Reduction in DBP	Moxonidine	50	11.8400	11.44706	
	Clonidine	49	3.1633	6.24282	<0.0001*

Discussion

AngII mediated mechanisms are important in the pathogenesis of renal hypertension. But, sympathetic hyperactivity also plays an important role in the pathogenesis of hypertension in Chronic renal failure (CRF) [,7,8,9,10]Sympathetic hyperactivity is also linked with cardiovascular morbidity and mortality independent of its effect on BP (Zoccali C).Hence reduction of sympathetic hyperactivity might be beneficial in controlling hypertension in patients with CRF . The popular drugs of choice for controlling hypertension namely ACEI and ARBs reduce but do not normalize sympathetic hyperactivity[11,12]

Moxonidine is a high affinity agonist of imidazoline I_1 receptors with sympatho-inhibitory effects. Stimulation of these receptors reduces central sympathetic outflow, leading to a reduction of blood pressure and also reduces the peripheral vascular resistance [13,14]

The plasma half-life of moxonidine is 2 h, and this is prolonged in kidney failure[15] .The duration of the antihypertensive effect is longer than that suggested by the plasma half-life, which indicates a possible retention in the central nervous system. Moxonidine has low affinity to central nervous system alpha2 adrenoceptors which results in fewer side effects as compared to the other centrally acting drug like clonidine[13,14] The sympatholytic drug moxonidine causes a significant reduction of blood pressure comparable to the ACEI enalapril in patients with hypertension (24.9 +/- 20.7/13.2 +/- 8.4 mmHg vs 21.9 +/- 17.1/11.9 +/- 7.5 mmHg, respectively)[13] . In end stage renal disease (ESRD patients, low-dose moxonidine causes a sustained and significant reduction in sympathetic outflow without hemodynamic compromise. The inhibition of central sympathetic outflow may improve prognosis in patients with ESRD.[16]

In the current study we compared the antihypertensive efficacy and impact on eGFR and serum Creatinine of moxonidine and clonidine. The results of our current study indicate that moxonidine can be a preferred sympatho-inhibitory drug in renal failure patients. The idea of a sympatholytic drug to be renoprotective is appealing but needs further evaluation.

Conclusion:-Our study suggests that moxonidine can be used widely in CKD patient population because it provides end organ protection. More evidence is needed on possible protection by imidazoline receptor modulation against target organ damage. This is the first study to compare the effect of moxonidine and clonidine on BP, serum Creatinine and eGFR . The findings of the current study lend credence to the efficacy and safety of Moxonidine in CKD patients.

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