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Original Article

First Indian study to correlate dose of Moxonidine and incidence of dry mouth in patients with chronic kidney disease

Vikash Khandelia[1*], Pavankumar Pyarsabadi[2*], Saurabh Chittora[2] and Umashankar Nama[1]

[1]Department of Nephrology, [2]Department of Medicine, Government Medical College, Rajasthan University, Kota, India.

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ABSTRACT

The sympathetic nervous system is known to play a central role in the pathophysiology of hypertension in CKD patients. A centrally acting sympatholytic drug would not only help reduce blood pressure but also intervene in multiple disease processes. Moxonidine differs from other available centrally acting antihypertensive by exhibiting only low affinity to central α_2-adrenoceptors compared to I1-imidazoline receptors. The aim of the study was to evaluate whether moxonidine would result in dry mouth in patients of chronic kidney disease (CKD) and evaluate the presence of a dose dependent response. 55 adult hypertensive patients with CKD were included in the study. The patients were treated with moxonidine at different doses (0.2 mg/day 0.3 mg/day, 0.4 mg per day, 0.6 mg day and 0.9 mg/day) depending on the serum creatinine and eGFR. The highest incidence of dry mouth with moxonidine occurs at the dose of 0.4 mg and a ceiling effect is observed regarding the prevalence of dry mouth at doses above 0.4 mg.

Key words: CKD; moxonidine; eGFR

Address for Correspondence: Dr. Pavankumar Pyarsabadi, Department of medicine, Government Medical College, Kota, Rajasthan, India; E-mail: pavankumarp145@gmail.com

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INTRODUCTION

Systemic hypertension is often accompanied by chronic renal failure and can accelerate its progression to end-stage renal disease (ESRD).[1] The sympathetic nervous system is known to play a central role in the pathophysiology of hypertension, other cardiovascular diseases and metabolic disorders such as disturbances of glucose and lipid homeostasis. A centrally acting sympatholytic drug would not only help reduce blood pressure but also intervene in multiple disease processes. The older centrally acting sympatholytic drugs such as clonidine and guanabenz have several limiting side effects such as sedation and dry mouth that reduce their acceptability to patients. The control of salivary secretion and also the effects of alpha (2)-adrenoceptor activation are mediated through an area present in the lateral hypothalamus .[2]

Moxonidine is considered to differ from the other centrally acting sympatholytic drugs. Moxonidine acts primarily through a novel cellular site, termed the I (1)-imidazoline receptor [3].This receptor subtype is observed to be present in both the rostral ventro-lateral pressor and ventromedial depressor areas of the medulla oblongata. 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 [4].

Moxonidine differs from other available centrally acting antihypertensive by exhibiting only low affinity to central α2-adrenoceptors compared to I1-imidazoline receptors; α2-adrenoceptors are considered the molecular target through which the most common side effects of centrally acting antihypertensive namely sedation and dry mouth are mediated. Peripheral I1 receptors in the renal proximal tubules may also be responsible for the long-term control of blood pressure, as stimulation of I1 receptors increases osmotic clearance**,** diuresis and natriuresis .This may be a direct renal effect or a combined, central plus peripheral one

Chronic kidney disease is a complication of hypertension. 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 [5]. 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.

Sympathetic hyperactivity is associated with poor cardiovascular outcomes; hence a reduction might be beneficial to the patients. Hence, central modulation of the sympathetic nervous system has re-emerged as an important target for lowering blood pressure. Recently, moxonidine was observed to have preventive effects on ischemic acute kidney injury by suppressing the excitation of renal sympathetic nervous system after reperfusion. [5.] The addition of moxonidine to angiotensin II antagonist treatment might be appropriate [6]. Moxonidine can modulate the central sympathetic activity. Moxonidine has an anti-hypertensive efficacy which is comparable to that of angiotensin -converting enzyme inhibitors (eg, enalapril and captopril), b-blockers (e.g., atenolol), calcium-channel blockers (e.g., long-acting nifedipine), and diuretics (eg, hydrochlorothiazide) in lowering blood pressure. Moxonidine may be preferred due to its superior tolerability profile and its ability in to prevent target organ dysfunction such as CKD [7.]

The current study was conducted to evaluate the incidence of dry mouth in patients of CKD treated with different doses of moxonidine. This was postulated to help guide the appropriate effective and safe dose of moxonidine in CKD patients.

Aim: The chief aim of the study was to evaluate whether moxonidine would result in dry mouth in patients of CKD and evaluate the presence of a dose dependent response be observed in this patient population in order to guide the appropriate dose to be used in clinical practice

MATERIALS AND METHODS

55 adult hypertensive patients with CKD were included in the study. The patients were treated with moxonidine at different doses (0.2 mg/day 0.3 mg/day, 0.4 mg /day, 0.6 mg/ day and 0.9 mg/day) depending on the serum Creatinine and eGFR. The study was conducted over the period of 6 months (NOV'16 TO APRIL'17).

Serum creatinine was measured using standard Jaffe method and eGFR was estimated with CKD-EPI equation. Dry mouth was categorized clinically into mild, moderate and severe.

Statistical analysis: The Spearman's rank-order correlation was used to estimate the correlation between the dose of moxonidine and the eGFR (glomerular filtration rate) and serum Creatinine. The Spearman's correlation determines the strength and direction of the monotonic relationship between the two variables.

RESULTS AND DISCUSSION

CKD patients often complain of dry mouth and the prevalence of dry mouth in these patients has been reported to be as high as 12.22% [8]. Dry mouth may be attributed to fluid restriction, electrolyte imbalance, and use of medications, such as frusemide and hydrochlorothiazide. Secondly, the aetiological factors implicated in CKD such as diabetes mellitus, hypertension, amyloidosis and autoimmune disease not only cause renal disease but also independently initiate salivary gland disease. CKD patients have lower mean stimulated and unstimulated salivary production (2.34 ml/5 min and 4.07 ml/5 min) as compared to the controls (3.82 ml/5 min and 8.05 ml/5 min). Another consistent finding in CKD patients is reduced salivary flow rate. This may be ascribed to the effects of drugs, emotional stress and neuropathy in CKD patients[8] .Altered saliva composition in patients with Stages 4 and 5 CKD may be associated with uraemic upper gastrointestinal symptoms. Lower saliva concentrations of bicarbonate are associated with dry mouth and retching. Higher saliva calcium levels are also implicated in causing dry mouth whilst higher saliva sodium levels and a greater sodium/potassium ratio are associated with nausea [9].

A clinician's dilemma increases when the patient complains of dry mouth and the physician advises restricted fluid intake. The use of drugs which further increase dry mouth can reduce patient compliance. Hence the physicians choosing treatment regimens to treat hypertension, diabetes or other co-morbid disorders in CKD patients must consider this fact and choose drugs with care.

In CKD patients with hypertension, a centrally acting sympatholytic drug would not only help reduce blood pressure but also intervene in multiple disease processes. Moxonidine overcomes the drawbacks of the older centrally acting sympatholytic drugs such as clonidine and guanabenz[2]. Moxonidine is a good option in the treatment of patients with mild to moderate hypertension, particularly as adjunctive therapy in patients with the metabolic syndrome.[10.] Moxonidine may be a preferred drug due to its unique effects in patients with metabolic syndrome and CKD[10.] Moxonidine treatment is conventionally initiated at 0.2 mg once daily (in the morning).

If blood pressure needs further lowering after 2 weeks, the dose is increased to 0.4 mg/day (either as a single morning dose or as 2 divided doses). The dose may be escalated to a maximum of 0.6 mg/day after a further 2 weeks, if required. Any single dose should not exceed 0.4 mg.[2]The dose can be reduced in patients with renal impairment. But, in the real life setting the dose of moxonidine commonly used is 0.4 mg or higher rather than the lower doses .A dose dependent increase in side effects is commonly observed with drugs.

But, in the current study we found the highest incidence of dry mouth with the 0.4 mg /day dose (42.1%) and there was a reduction in the prevalence of dry mouth at doses higher than 0.4 mg /day (0.6 mg/day and 0.9 mg/day). This may be ascribed to the development of tolerance to the side effect of dry mouth after about a week. [11]. There was no significant correlation between the eGFR levels and incidence of dry mouth .These facts must be considered in the real life setting .Dose defining studies have indicated the safety of doses of moxonidine up to 1.5 mg twice a day. [12] The phenomenon of tolerance to the dry mouth observed with moxonidine may be reassuring to both the physician and the patient in the clinical practice.

CONCLUSION

The highest incidence of dry mouth with moxonidine occurs at the dose of 0.4 mg. Since a ceiling effect is observed regarding the prevalence of dry mouth at doses above 0.4 mg and tolerance develops to this side effect of dry mouth, the patient can be reassured to continue the medication in order to improve compliance.

Conflict of interest: This is the first study attempted to correlate dose of moxonidine with incidence of dry mouth**;** maximum incidence of dry mouth was found at dose 0.4mg and with higher dose the incidence was unaltered or even decreased. Hence, large scale studies are necessary to address this dose-side effect relationship.

Table 1: Dry mouth prevalence with Moxonidine dose /day (mg)

Moxonidine dose /day(mg)	No Dry mouth		Dry mouth		p value
	N	%	N	%	
0.2	2	11.8	0	0.0	0.01*
0.3	8	47.1	7	18.4	
0.4	2	11.8	16	42.1	
0.6	5	29.4	13	34.2	
0.9	0	0.0	2	5.3	
Total	17	100.0	38	100.0	

Table 1→The highest prevalence of dry mouth was observed with the dose of 0.4 mg day (42%). A trend of reduction of the incidence of dry mouth was observed as the dose increased beyond 0.4 mg /day to 0.6 mg/day (34.2%) and 0.9 mg/day (5.3%). The highest prevalence of all the grades of dry mouth (mild , moderate and severe) were observed in the 0.4 mg /day dose of moxonidine.

Table 2: Distribution of Dry mouth levels with Moxonidine dose /day(mg)

Moxonidine dose /day(mg)	No Dry mouth		Mild		Moderate		Severe		p value
	N	%	N	%	N	%	N	%	
0.2	2	11.8	0	0.0	0	0.0	0	0.0	0.055
0.3	8	47.1	5	29.4	1	8.3	1	11.1	
0.4	2	11.8	6	35.3	6	50.0	4	44.4	
0.6	5	29.4	6	35.3	5	41.7	2	22.2	
0.9	0	0.0	0	0.0	0	0.0	2	22.2	
Total	17	100.0	17	100.0	12	100.0	9	100.0	

Mild, moderate and severe dry mouth prevalence was highest at Moxonidine dose of 0.4 mg/day.

Table 3: Spearman Correlation coefficient between Level of Dry mouth and selected parameters

Parameters	Correlation Coefficient (ρ)	p value
S.creatinine	0.487	<0.001**
eGFR(ml/min/1.73m2)	-0.361	0.007**
dose of moxonidine/day(mg)	0.342	0.011*

Note: **significant at 1% level of significance, *significant at 5% level of significance

Table 3→There was a positive correlation between serum creatinine, dose of moxonidine and levels of dry mouth while a negative correlation was observed between eGFR and levels of dry mouth. All correlations were statistical significant ($p<0.05$).

Table 4: Spearman Correlation coefficient between Level of Dry mouth and selected parameters by dose of moxonidine/day (mg)

Dose of moxonidine/day (mg)	S.creatinine		eGFR(ml/min/1.73m2)	
	Correlation Coefficient (ρ)	p value	Correlation Coefficient (ρ)	p value
0.2	-	-	-	-
0.3	0.429	0.11	-0.174	0.534
0.4	0.678	0.002**	-0.554	0.017*
0.6	0.486	0.041*	-0.449	0.061
0.9	-	-	-	-

Note: **significant at 1% level of significance, *significant at 5% level of significance, - less or no observations

Table 4→The Moxonidine dose of 0.4 mg/day demonstrated a higher incidence of dry mouth and demonstrated the highest positive correlation with serum creatinine and highest negative correlation with eGFR as compared to that at other doses of Moxonidine.

Table 5: Mean S. Creatinine and eGFR by Moxonidine dose /day (mg)

Moxonidine dose /day(mg)	S. Creatinine			eGFR (ml/min/1.73m2)		
	N	Mean	SD	N	Mean	SD
0.2	2	6.33	0.95	2	8.65	1.77
0.3	15	4.33	2.90	15	17.17	9.77
0.4	18	6.03	3.00	18	13.54	9.04
0.6	18	4.74	3.26	18	19.99	19.89
0.9	2	5.55	4.74	2	16.25	15.06
Total	55	5.14	3.06	55	16.56	13.73

Table 5→Mean S. Creatinine was 6.03 and eGFR was 13.54 at 0.4 mg/day Moxonidine where the highest dry mouth prevalence was observed.

Table 6: Mean values of S.cr. and eGFR according to Level of Dry mouth

Level of Dry mouth	S. creatinine		ANOVA p value	eGFR(ml/min/1.73m2)		ANOVA p value
	Mean	SD		Mean	SD	
No Dry mouth	3.8	1.7	<0.001**	20.6	19.4	0.095
Mild	3.8	2.3		19.4	10.1	
Moderate	6.4	2.9		13.1	9.3	
Severe	8.5	3.6		8.2	7.2	

Note: **significant at 1% level of significance, *significant at 5% level of significance

Table 6→Mean value of Serum Creatinine was observed to significantly increase and mean eGFR decreased with the rise in the incidence of dry mouth.

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