Prospective Comparative Study of the Effects of Clonidine and Moxonidine as Add on Therapy in Patients of Chronic Kidney Disease with Hypertension in a Tertiary Carecenter

Chandresh Kumar Gupta[1], Pradeep Kumar Yadav[2], Laxman Verma[3], Divya R.[4], Sanjay Kumar Bhatt[4], Rajiv Ratan Singh[4]

[1]Senior Resident, Department of Pharmacology, [2]Senior Resident, Department of Forensic Medicine and Toxicology, [3]Associate Professor, Department of Surgery, [4]Associate Professor, Department of Emergency Medicine, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, UP, India

Abstract

Objectives: To compare the effects of clonidine and moxonidine as add on therapy in patients of chronic kidney disease with hypertension.

Method: It is an observational study of duration of one year. Patient who fall under the diagnostic criteria of chronic kidney disease with hypertension were selected randomly from those attending the routine medicine outpatient department and medicine wardat S.N. Medical College and associated hospital.

Result and Conclusion: Study shows a slightly greater reduction in various parameters of chronic kidney disease like systolic BP, diastolic BP, pulse rate, blood urea, and serum creatinine with moxonidine group than clonidine group. But statistically there was no significant difference was found in both groups.

Keywords: *Chronic kidney disease, hypertension, moxinidine, clonidine.*

Introduction

Hypertension is a "life time" condition and, if left untreated, leads to lethal complications. High blood pressure went from being the 4th leading risk factor in 1990 and 1st risk factor in 2010 as quantified by DALYs.[1] According to a WHO report on Global Status of Non-Communicable Diseases 2010, 33% of the adult Indian men and 30% of adult Indian women have high blood pressure, implying that one in every three adult Indian is hypertensive.[2] Hypertension is a one of the cause of chronic kidney disease (CKD). Hypertension in CKD increases the risk of important adverse outcomes, including loss of kidney function and kidney failure, early development and accelerated progression of cardiovascular disease (CVD), and premature death. CKD is an internationally recognized public health problem affecting 5–10% of the world population.[8,9]

Clonidine is classified as a centrally acting α_2 adrenergic agonist and imidazoline receptor agonist that has been in clinical use for over 40 years.[10] Clonidine suppresses sympathetic outflow resulting in lower blood pressure, but sudden discontinuation can cause rebound hypertension due to a rebound increase in sympathetic outflow. Treatment of clonidine withdrawal hypertension depends on the severity of the condition.[11,12] Moxonidine is widely approved central antihypertensive drug that acts primarily by reducing central sympathetic nervous system activity via activation of imidazoline I-1 receptors in the rostral ventro-lateral medulla (RVLM). It is an orally administered imidazoline compound with selective agonist activity at imidazoline I-1 receptors, for which it has affinity >30 fold than α-2 adrenoreceptors. [15]Thus, the unique profile of moxonidine and clonidine

Corresponding Author:
Dr. Pradeep Kumar Yadav
Senior Resident, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, UP, India
e-mail: dctrprdp@gmail.com
Phone No.: 9410662955

provides an opportunity to simultaneously cover a large number of factors crucially involved in the patho-physiology of the Chronic kidney disease associated with elevated blood pressure.

Aim: To compare the effects of clonidine and moxonidine as add on therapy in patients of chronic kidney disease with hypertension.

Objectives:

1. To study the efficacy and safety of clonidine and moxonidine in chronic kidney disease with hypertension.
2. To compare the efficacy and safety of clonidine and moxonidine during the study period.

Material and Method

Patient who fall under the diagnostic criteria of chronic kidney disease with hypertension were selected randomly from those attending the routine medicine outpatient department and medicine wardat S.N. Medical College and associated hospital after having taken approval from institutional ethical committee. It is an observational study of duration of one year. Informed consent was taken from all patients and strict compliance of prescription was ensured during the study.

Inclusion Criteria: Patients of either sex with following parameter:

1. Patients age >30 years and <60 years.
2. Patient who were diagnosed of chronic kidney disease by biopsy, USG, GFR or DMSA scan.
3. Patients whose systolic blood pressure is ≥ 140 mmHg or diastolic blood pressure is ≥ 90 mmHg

Exclusion Criteria:

1. Patients age <30 years and >60 years.
2. Patient who were not diagnosed of chronic kidney disease by biopsy, USG, GFR or DMSA scan.
3. Patients whose systolic blood pressure is <140 mmHg or diastolic blood pressure is <90 mmHg.
4. Patients who require renal transplant (Grade-5 CKD).

Drugs: Clonidine, Moxonidine

In this study patients were selected randomly on the basis of inclusion and exclusion criteria. These patients were already on standard treatment CCB(AMLODIPINE) +THIAZIDE DIURETICS+B BLOCKERS. Selected patients were divided randomly into two groups:

Group-I: Comprises 94 Chronic kidney disease patients with hypertension who were given Clonidine 0.1mg BD as add on therapy and dose was titrated to achieve target level along with their standard treatment.

Group-II: Comprises 87 Chronic kidney disease with hypertension who were given Moxonidine 0.2mg BD as add on therapy and dose were titrated to achieve target level along with their standard treatment.

Although study was started with 100 cases in each group but there was drop out of 6 cases in group A and 13 cases in group B after 8 weeks due to unknown reasons. These patients were excluded from the study.

Observations: One hundred eighty one cases of chronic kidney disease with hypertension attending Medicine OPD, and admitted in Medical wards in post graduate Department of Medicine, S.N. Medical College& hospital Agra, fulfilling the inclusion criteria constituted the material for the present study.

Overall incidence of distribution of cases is maximum in 41-50 years, followed by 30-40 years and least no of cases in 51-60 years. Youngest person in this study was 31 years and oldest person in this study was 58 years.

In group-I the male/female ratio was 1.3:1, and in group- II the male/female ratio was 1.48:1. This could be due to a larger number of male being treated.

Table 1: Systolic blood pressure values (mmHg) before and after treatment

	Group I (n =94)				Group II (n=87)			
	Before treatment	After treatment			Before treatment	After treatment		
		4wk	8wk	12wk		4wk	8wk	12wk
Mean	173.43	166.87	164.57	159.43	171.29	166.87	161.47	155.06
SD	14.81	16.57	13.35	11.92	20.17	16.57	14.49	15.03
% change baseline		-3.783	-1.378	-3.12		-2.580	-3.236	-3.97
T value		2.8619	1.048	2.7855		1.5426	2.235	2.7972
P		0.0047	0.2961	0.0059		0.1249	0.0268	0.0058

Table -1 Illustrates the baseline value of systolic blood pressure before and after 4 weeks, 8 weeks and 12 weeks of therapy in group I and group II. With clonidine therapy fall in systolic BP was statistically significant at 4 week in group I ($t=2.8619$, $p< 0.01$) insignificant thereafter. With moxonidine therapy, the fall in systolic BP was statistically insignificant at 4 weeks ($t=1.542$, $p>0.05$), but was significant at 8 weeks ($t=2.235$, $p<0.05$) and 12 weeks ($t=2.797$, $p<0.05$).

Table 2: Diastolic blood pressure values (mmHg) before and after treatment

	Group I (n =94)				Group II (n=87)			
	Before treatment	After treatment			Before treatment	After treatment		
		4wk	8wk	12wk		4wk	8wk	12wk
Mean	99.09	95.19	91	87.79	99.36	96.02	92.23	87.79
SD	6.67	6.49	6.73	6.44	8.93	9.58	8.39	6.44
% change baseline		-3.94	-4.40	-7.77		-3.36	-3.95	-8.57
T value		4.063	4.345	3.3411		2.3234	2.7114	3.6415
P		0.0001	0.0001	0.001		0.0214	0.0074	0.0004

Table 2 illustrates the mean baseline value of Diastolic blood pressure before and after 4 weeks, 8 weeks and 12 weeks of therapy in group I and group II. With both clonidine and moxonidine therapy, decrease in diastolic BP was statistically significant at all time intervals.

Table 3: Pulse rate (BEATS/min) CHANGE before and after treatment

	Group I (n =94)				Group II (n=87)			
	Before treatment	After treatment			Before treatment	After treatment		
		4wk	8wk	12wk		4wk	8wk	12wk
Mean	84.13	85.98	84.04	83.72	84.37	85.11	84.11	83.44
SD	7.94	6.9	5.65	5.49	8.90	5.05	4.26	5.18
% change baseline		+0.37	-0.40	-0.71		+0.23	-0.34	-0.28
T value		1.0599	2.1091	0.3938		1.8134	0.976	2.9825
P		0.2906	0.161	0.6942		0.217	0.3305	0.3301

Table 3 Illustrates the baseline value of pulse rate before and after 4 weeks, 8 weeks and 12 weeks of therapy in group I and group II. With both clonidine and moxonidine therapy,there was increase in pulse rate which was statistically insignificant at all time intervals.

Table 4: Blood urea (mg/dl) level before and after treatment

	Group I (n =94)				Group II (n=87)			
	Before treatment	After treatment			Before treatment	After treatment		
		4wk	8wk	12wk		4wk	8wk	12wk
Mean	165.61	153.94	138.8	138.04	165.22	153.27	138.59	132.29
SD	31.68	24.91	17.69	19.78	34.49	25.59	17.48	16.89
% change baseline		-7.05	-9.84	-0.55		-7.23	-9.58	-4.55
T value		2.8075	4.8045	0.2777		2.535	4.3156	2.3613
P		0.0056	0.0001	0.7816		0.0123	0.0001	0.0194

Table -4 Illustrates the mean baseline value of blood urea before and after 4 weeks, 8 weeks and 12 weeks of therapy in group I and group II. There was decrease in blood urea in both groups. In group I, the decrease however was significant at 4 weeks ($t=2.8075$, $p<0.05$) and 8 weeks ($t=4.8045$, $p<0.05$) and was insignificant at 12 weeks ($t=0.2777$, $p>0.05$). The decrease in blood urea level was significant at all intervals in group II.

Table 5: Serum creatinine (mg/dl) level before and after treatment

	Group I (n =94)				Group II (n=87)			
	Before treatment	After treatment			Before treatment	After treatment		
		4wk	8wk	12wk		4wk	8wk	12wk
Mean	11.04	10.31	9.84	9.69	11.24	10.65	9.91	9.45
SD	2.20	2.12	2.39	2.19	2.60	2.48	2.48	2.41
% change baseline		-6.61	-4.56	-1.52		-5.25	-6.95	-4.64
T value		2.3166	1.4263	0.4486		1.496	1.9222	1.2119
P		0.0216	0.1555	0.6542		0.1366	0.563	0.2273

P value at 12 weeks, Group- I Vs Group-II $P>0.05$

Table 5- Illustrates the mean baseline value of serum creatinine value before and after 4, 8, and 12 weeks of treatment. Serum creatinine value decreases in both groups. However in group I, the decrease in serum creatinine was significant at 4 weeks ($t=2.3166$, $p<0.05$) and was insignificant at 8 weeks ($t=1.4263$, $p>0.05$) and 12 weeks ($t= 0.4486$, $p>0.05$) and in group II, it was insignificant at all intervals.

Table 6: Side effects comparison in both groups

Side effects	Clonidine v(N=94)		Moxonidine (N=87)	
	No.	%	No.	%
Dry mouth	63	67.02	27	32.53
Sedation	75	79.79	51	61.45

Side effects	Clonidine v(N=94)		Moxonidine (N=87)	
	No.	%	No.	%
Dizziness	51	54.26	36	43.37
Tiredness	15	15.96	24	28.92
Headache	24	25.53	12	14.46
Pallor	15	15.96	18	21.69

Table 6 demonstrates the most commonly seen side effect was sedation in both groups. Other side effects were more common in group I as compared to that seen in group II.

DISCUSSION: The prevalence of chronic kidney disease has been increasing worldwide during the past years and is reaching epidemic proportion in industrialized countries. This problem represents an enormous burden on health care systems and most importantly, the quality of the affected individuals is substantially lowered. Even though extensive research and public awareness efforts have been made over the previous decades the proportion of people affected is still rising. Chronic kidney disease (CKD) is an important source of long term morbidity and mortality. It has been estimated that CKD affects more than 20 million people in the United States. Most patients were asymptomatic until the disease had significantly progressed, they remain unaware of the condition. Thus it is essential to have clinical practice guidelines aimed at early detection evaluation, diagnosis and treatment of this condition. Hypertension was found in approx. 80 % of the chronic kidney disease patients. Treatment of hypertension significantly reduces the progression of chronic kidney disease.

Clonidine therapy (Group-I): In clonidine therapy (group-I) there was significant reduction in mean systolic blood pressure and mean diastolic blood pressure. Our finding are similar to those of G. J. A. MACPHEE (1992) and V. Planitz (1984) who observed significant reduction in systolic blood pressure and diastolic blood pressure[9, 10]. With clonidine therapy there was insignificant change in mean pulse rate while V. Planitz (1984) crossover comparison study found that there was no significant change in pulse rate after clonidine therapy[10]. After clonidine treatment major side effects observed are dry mouth and sedation and tiredness. V. Planitz (1984) observed that out of 20 hypertensive patients treated with clonidine 17 patients complained of dry mouth and tiredness[10].

Moxonidine therapy (group-II): In moxonidine therapy (group-II) There was significant reduction in mean systolic blood pressure and mean diastolic blood pressure. Our finding are similar to those of G. J. A. MACPHEE (1992) and V. Planitz (1984) who observed significant reduction in systolic blood pressure and diastolic blood pressure[9,10]. With moxonidine therapy, there was insignificant change in mean pulse rate. These findings concurred with the observation of V. Planitz (1984)[10]. Our study demonstrate that the decrease the mean baseline value of serum creatinine,however V. Planitz (1984) observed that there was no significant change in s. creatinine level after moxonidine treatment[10]. After moxonidine treatment main adverse effect was sedation, tiredness, pallor and dry mouth. Planitz, V. et. al. (1987) reported that moxonidine produces a hypotensive response similar to that of clonidine, at an equivalent dose, but with a significant reduction in adverse effects particularly sedation and xerostomia[11].

Conclusion

Study shows a slightly greater reduction in various parameters of chronic kidney disease like systolic BP, diastolic BP, pulse rate, blood urea, and serum creatinine with moxonidine group than clonidine group.Side effects like dry mouth, sedation, dizziness, and headache are more common with clonidine group than moxonidine group. Moxonidine was better tolerated by patients.

Conflict of Interest: There is no conflict of interest.

Funding: Self.

References

1. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2013; 380 (9859):2224–60.

2. Joshi SR, Saboo B, Vadivale M, Dani SI, Mithal A, Kaul U, et al. Prevalence of diagnosed and undiagnosed diabetes and hypertension in India – Results from the screening India's Twin Epidemics (SITE) study. Diabetes Technol Ther. 2012; 14:8-15.
3. Eknoyan G, Lameire N, Barsoum R; et al. "The burden of kidney disease: improving global outcomes". Kidney (2004).
4. A Martínez-Castelao, JL. Górriz, J Bover; et al. "Consensus document for the detection and management of chronic kidney disease". Nefrologia(2014),34 (2):243
3. CDC. Prevalence of Chronic Kidney Disease and Associated Risk Factors - United States, 1999-2004 accessed on 11 May 2011.
4. National Kidney Foundation. KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. Am J Kidney Dis 2002;39 (supp 1):S1-S266.
5. Neil, MJ "Clonidine: clinical pharmacology and therapeutic use in pain management.". Current Clinical Pharmacology (2011), 6 (4):280-7.
6. Parker, K; Brunton, L; Goodman, LS; Lazo, JS; Gilman, A . Goodman & Gilman's - the pharmacological basis of therapeutics. New York: McGraw-Hill. (2006), Pp. 854-855 86
7. Vitiello, B. "Understanding the Risk of Using Medications for ADHD with Respect to Physical Growth and Cardiovascular Function". Child AdolescPsychiatr Clin N Am (2008), 17 (2):459-474
8. Emsberger P. Pharmacology of moxonidine: an I_1-imidazoline receptor agonist. Journal cardiovascular Pharamcol 2000;359(7 SUPPL.4):S27-41.
9. G. J. A. MACPHEE, C. A. HOWIE, H. L. ELLIOTT & J. L. REID Department of Medicine and Therapeutics, Stobhill General Hospital, Glasgow G21 3uwbr. J. Clin. Pharmac. (1992), 33, 261-267.
10. Planitz, V. Crossover comparison of moxonidine and clonidine in mild to moderate hypertension. Eur. J. Clin. Pharmac.,(1984), 27, 147-152.
11. Planitz, V. Comparison of moxonidine and clonidine in treating patients with hypertension. J. Clin. Pharmac., (1987)27, 46-51. 39.