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Original Research Article

Nephro protection property of double blockade versus single blocked of RAAS in delaying the progression of CKD

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ABSTRACT

Background: Dual renin angiotensin aldosterone system blockade using angiotensin receptor blockers in combination with angiotensin converting enzyme inhibitors is reported to improve proteinuria in non-diabetic patients.
Methods: A prospective observational study was done on 810 non-diabetic chronic kidney disease patients during July 2012 to August 2014 to compare the nephro protection property of double blockade and single blocked of renin angiotensin aldosterone system in delaying the progression of chronic kidney disease.
Results: At the end of 24 months urinary protein excretion rate of group I and group III were compared by using student t-test and p value (0.0001) was found significant. Similarly, on comparing group II and group III, p value (0.003) was again significant. Mean arterial blood pressure of group I and group III were statistically significant (<0.0496) while comparing group II and group III, p value (0.0419) was again significant.
Conclusions: The study concludes that the use of double renin angiotensin aldosterone system blockade therapy is more effective than monotherapy at reducing albuminuria and proteinuiria, and in decreasing blood pressure at the same time not causing significant deterioration in glomerular filtration rate. Newer potassium lowering therapies can effectively and safely correct hyperkalemia and maintain normokalemia in patients receiving background treatment with renin angiotensin aldosterone system blockade. However, the use of new potassium binders for cardiovascular and renal risk reduction with combined renin angiotensin aldosterone system blockade therapy will require phase III trials.

Keywords: CKD, Double blockade, Hyperkalemia, Non-diabetic, RAAS, Single blockade

INTRODUCTION

In patients with chronic kidney disease (CKD), proteinuria and high blood pressure (BP) predict cardiovascular morbidity, mortality and progression to end stage kidney disease (ESKD).[1-3]

Control of BP and proteinuria are the cornerstone of preservation of renal function and prevention of complications associated with renal dysfunction in patients with CKD. Blockade of the rennin-angiotensin-aldosterone system (RAAS) using either angiotensin-converting-enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) is the most effective pharmacological strategy for this purpose. Accordingly, RAAS blockade with ACE inhibitors or ARBs is the first-line therapy for renoprotection in non-diabetic and diabetic patients with CKD, as recommended by current guidelines.[4-5] The objective of the study is to compare the nephro protection property of double blockade and single blocked of RAAS in delaying the progression of CKD.

METHODS

An observational prospective study was undertaken at SRN Hospital, Allahabad from July 2012 to August 2014. After detailed examination and exclusion criteria, 810 patients of non diabetic CKD were selected for the study who was attending the nephrology OPD. After an informed consent these patients were divided into 3 groups of 270 patients each. Group I was prescribed Ramipril, Group II were Telmisartan and Group III were prescribed both Ramipril + Telmisartan respectively. Follow-up action was done on monthly basis. At every visit a complete clinical examination was done, which included BP, 24 hour urinary protein excretion, serum urea, serum creatinine, serum potassium and glomerular filtration rate (eGFR).

All diabetic patients of stage 4 and stage 5 patients whose last 6 months eGFR was seen unstable, serum potassium value was >5.0, patients who had potentially reversible and rapidly progressing renal diseases, systemic diseases, severe cardiac or hepatic dysfunction, ankle edema or proteinuria greater than 5 gm/day, glomerulonephritis patients being treated with steroids, non-steroidal anti inflammatory drugs and cytotoxic drugs were excluded from the study.

Statistical analysis was performed using chi square test, student unpaired t-test and contingency coefficient. Data were expressed as mean±standard deviation. Statistical significance was defined at a p value of 0.05.

RESULTS

Patients in group I were in the age range of 22 years to 55 years with a mean age of 38.1±12.8 years and a male female ratio of 7:8. Patients in group II were in the age range of 28 years to 55 years with a mean age of 43.47±9.86 years and a male:female ratio of 10:5. Patients in group III were in the age range of 23 years to 65 years with a mean age of 43.53±12.42 years and a male:female ratio of 9:6.

Table 1: Comparison of eGFR between group I and group III at the start and at the end of 24 months.

	Group I		Group II				
Weeks	**Mean**	**S.D.**	**Mean**	**S.D.**	**t**	**DF**	**P value**
Start of study	21.360	3.584	26.180	8.512	2.0212	28	0.0529
End of study	21.823	3.881	25.633	7.584	1.6004	23	0.1232

Out of 810 patients 12 were discontinued from the study due to adverse drug reactions, 9 patients could not complete the study, leaving a total number of 789 patients who were effectively enrolled in the study. Table 1 and 2 showed the comparison of eGFR between group I and III and group II and III respectively.

Table 2: Comparison of eGFR between group II and group III at the start and at the end of 24 months.

	Group I		Group II				
Weeks	**Mean**	**S.D.**	**Mean**	**S.D.**	**t**	**DF**	**P value**
Start of study	24.220	5.718	26.180	8.512	0.7403	28	0.4653
End of study	21.220	5.031	25.633	7.584	1.5760	23	0.1287

Table 3: Comparison of 24 hour urinary protein excretion between group I and group III at the start and at the end of 24 months.

	Group I		Group II				
Weeks	**Mean**	**S.D.**	**Mean**	**S.D.**	**t**	**DF**	**P value**
Start of study	871.33	246.75	846.33	221.99	0.2917	28	0.7727
End of study	713.31	156.49	408.67	121.60	5.4014	23	<0.0001

As per Table 1 and 2 creatinine clearance remained stable in all the patients throughout the study and did not change in all the groups during the study period (21.360±3.584 ml/min in group I vs 24.220±5.718 ml/min in group II vs 26.180±8.512 ml/min in group III) but at the end of 24 months of study creatinine clearance was like this way (21.823±3.881 ml/min in group I vs 21.608±5.031 ml/min in group II and 25.663±7.584 ml/min in group

III). When we compared the p value (>0.05) by using t test between group I and group III it was found insignificant and it remained the same while comparing group II and III at the end of 24 months. Table 3 and 4 shows the comparison of 24 hour urinary protein excretion between group I and III and group II and III respectively.

Table 4: Comparison of 24 hour urinary protein excretion between group II and group III at the start and at the end of 24 months.

	Group I		Group II				
Weeks	**Mean**	**S.D.**	**Mean**	**S.D.**	**t**	**DF**	**P value**
Start of study	830.33	286.14	846.20	222.16	0.1696	28	0.8665
End of study	751.38	255.82	408.67	121.60	4.2170	23	0.0003

In Table 3 and 4, 24 hours urinary protein excretion of group I, group II and group III patients were 871.33±246.75 mg/24 hours, 830.33±286.14 mg/24 hours and 846.20±222.16 mg/24 hours respectively. When 24 hour urinary protein excretion of group I and group III were compared at the start of study, p value (>0.05) was not significant. Similar results were also noticed while comparing group II and group III. Follow-up was done for 24 months and at the end of 24 months urinary protein excretion rate of group I and group III were compared (713.31±156.49 mg/24 hour and 408.67±121.60 mg/24 hour respectively) by using student t-test. P value was observed <0.0001, which was significant. Statistically significant (0.003) results were also obtained while comparing group II and III. Table 5 and 6 shows the comparison of arterial BP between group I and III and group II and III respectively.

Table 5: Comparison of arterial blood pressure between group I and group III at the start and at the end of 24 months.

	Group I		Group II				
Weeks	**Mean**	**S.D.**	**Mean**	**S.D.**	**t**	**DF**	**P value**
Start of study	115.80	6.46	118.80	6.17	1.3009	28	0.2039
End of study	111.62	7.41	104.58	9.50	2.0727	23	0.0496

Table 6: Comparison of arterial blood pressure between group II and group III at the start and at the end of 24 months.

	Group I		Group II				
Weeks	**Mean**	**S.D.**	**Mean**	**S.D.**	**t**	**DF**	**P value**
Start of study	115.60	8.18	118.80	6.17	1.2095	28	0.2366
End of study	112.15	8.06	104.58	9.50	2.1541	23	0.0419

In Table 5 and 6 mean arterial BP of group I, group II and group III patients were (115.80±6.46 mm hg, 115.60±8.18 mm hg and 118.80±6.17 mm hg respectively). When mean arterial BP of group I and group III was compared p value was >0.05, which was insignificant. Similar results were obtained while comparing group II and group III.

At the end of 24 months the mean BP of group I and group III were compared (111.62±7.41 mm hg and 104.58±9.50 mm hg respectively) using student t-test p value (<0.0496) was significant. Similarly, on comparing group II and group III, significant p value (0.0419) was found. Table 7 and 8 revealed the comparison of serum potassium values between group I and III and group II and III respectively.

As per Table 7 and 8 the mean serum potassium levels (meq/l) at the start (0 week) were 3.820±0.514 for group I, 4.053±0.372 for group II, 3.933±0.523 for group III patients.

The mean serum potassium levels (meq/l) after the end of 24 months were 3.831±0.477 for group I, 3.969±0.312 for group II, 4.042±0.493 for group III. On comparing serum potassium levels of group, I and group III the p value (>0.05) was not significant.

Table 7: Comparison of serum potassium values between group I and group III at the start and at the end of 24 months.

	Group I		Group II				
Weeks	**Mean**	**S.D.**	**Mean**	**S.D.**	**t**	**DF**	**P value**
Start of study	3.820	0.514	3.933	0.523	0.5982	28	0.5545
End of study	3.831	0.477	4.042	0.493	1.0876	23	0.2881

Table 8: Comparison of serum potassium values between group II and group III at the start and at the end of 24 months.

	Group I		Group II				
Weeks	**Mean**	**S.D.**	**Mean**	**S.D.**	**t**	**DF**	**P value**
Start of study	4.053	0.372	3.933	0.523	0.7239	28	0.4751
End of study	3.969	0.312	4.042	0.493	0.4430	23	0.6619

Similarly, on comparing group II and group III again the p value was not significant (>0.05). During the study period four patients in group III developed hyperkalemia (serum potassium values >5.5 meq/l). ACEI and ARBs therapy were withdrawn in these patients and they were given alternative antihypertensives i.e. diuretics and b-blockers (Metoprolol 50 mg and Furosemide 40 mg). Antihyperkalemia treatments were given to all of them and advised to bring their serum potassium reports weekly thereafter. Serum potassium values of two patients were normalized within a week and subsequently both ACEI and ARBs were reintroduced in the lowest dose with gradual withdrawing of other antihypertensive agents. In subsequent two weeks serum potassium values remained normal and ACEI and ARBs were escalated to the normal doses with complete withdrawing of b-blockers and Furosemide. Serum potassium levels of the third patient normalized in 3rd week and he was subsequently started on ACEI and ARBs. No rise in serum potassium levels were reported subsequently till the completion of study (24 months).

Fourth patient achieved normal serum potassium values after 4th week but on subsequent introduction of ACEI and ARBs serum potassium showed a tendency to raise and hence had to be discontinued from the study.

DISCUSSION

Hypertension and proteinuria are well-known predictors of the progression of CKD.[6] For the same decrease in systemic BP, agents that block the RAAS exert a stronger antiproteinuric effect than other antihypertensive drugs such as calcium-channel blockers.[7-9] Due to of this, current clinical-practice guidelines recommend using blockers of the RAAS as preferred agents for treating kidney disease.[10,11]

Previous meta-analyses of dual RAAS blockade with an ACEI and ARB demonstrated a significant decrease in proteinuria but no clinically meaningful changes were observed in eGFR.[12-14] This systematic review included a smaller number of trials.[14] In the present study after 24 months creatinine clearance was found this way (21.823±3.881 ml/min in group I vs 21.608±5.031 ml/min in group II and 25.663±7.584 ml/min in group III). At the end of the study when we compare eGFR values between stage I and stage III the p value was <0.05 (not significant) and it remained the same for group II and III too.

In a 2005 meta-analysis, Doulton et al concluded that use of dual blockers in hypertensive patients reduced BP by 4.7/3.0 mm Hg (1 mm Hg = 0.133 kPa), in contrast with 3.8/2.9 mm Hg reduction achieved with ACEI/ARB monotherapy treatment.[15,16] As shown in a more recent meta-analysis, combination therapy outperforms monotherapy in reducing the systolic BP, diastolic BP, and mean arterial pressure, or in controlling the rate of BP in CKD.[16] Some studies have reached similar conclusions also.[17-18]

In current study when mean arterial blood pressure of group I and group III was compared at the beginning of the study p value (>0.05) was not significant. Similar results were also obtained while comparing group II and group III. At the end of 24 months the mean blood pressure of group I and group III were compared (111.62±7.41 mm hg and 104.58±9.50 mm hg respectively) by using student t-test. P value was <0.0496, which was found significant. Similarly on comparing group II and III, p value (0.0419) was significant.

Some early studies suggested that ACEI combined with ARB could further reduce proteinuria and the result be in 20% reduction in albuminuria.[17,19-23] A meta-analysis showed that as compared with ACEI or ARB alone, combination therapy results in 20-30% additional reduction in proteinuria.[24,25] The "Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint" trial (ONTARGET) involved the largest cohort of patients to date (n = 25,620).[26] Patients were assigned to receive Telmisartan alone, Ramipril alone, or a

combination of the both. After 56 month follow-up, it was reported that the risks of development and progression of microalbuminuria and macroalbuminuria were lower for those receiving combination therapy (hazard ratio [HR] = 0.88, P = 0.003 and HR = 0.76, P = 0.019, respectively), as compared to the Ramipril alone treatment.[26]

In present study when 24 hour urinary protein excretion of group I and group III were compared at the start of the study (0 week) p value was observed >0.05, which was insignificant. Similarly, on comparing group II and group III, p value was again found insignificant. Follow-up was done for 24 months and at the end of 24 months urinary protein excretion rate of group I and group III were compared (713.31±156.49 mg/24 hour and 408.67±121.60 mg/24 hour respectively) by using student t-test. P value was observed <0.0001, which was significant. Statistically significant (0.003) results were obtained while comparing group II and III.

In addition to the above, the premature termination of some RCTs evaluating the potential renal benefits of dual RAAS blockade due to an increased risk of hyperkalemia and acute kidney injury indicates that in the absence of a more effective treatment of hyperkalemia, the use of RAAS blockade for renoprotection in proteinuric CKD may have reached its limit.[27-29] In present study hyperkalemia was also observed in few patients casually.

The study clearly states that the use of double RAAS blockade therapy is more effective than monotherapy at reducing albuminuria and proteinuiria, and in decreasing BP at the same time not causing significant deterioration in eGFR. Newer potassium-lowering therapies can effectively and safely correct hyperkalemia and maintain normokalemia in patients receiving background treatment with RAAS blockade. However, the use of new potassium binders for cardiovascular and renal risk reduction with combined RAAS blockade therapy will require phase III trials.

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