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Original Research Article

Comparison between the efficacy of double blockade and single blockade of RAAS in diabetic kidney disease

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ABSTRACT

Background: Diabetic kidney disease is associated with high morbidity and cardiovascular mortality. A number of guidelines and recommendations have been issued over the years recommending the use of renin angiotensin aldosterone system blockade in the management of diabetic kidney disease.
Methods: A prospective observational study was done on 750 diabetic chronic kidney disease patients during July 2012 to August 2014 to compare the efficacy of double blockade and single blocked of renin angiotensin aldosterone system in diabetic 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 (0.0268) was found significant. Similarly, on comparing group II and group III, p value (0.0278) 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 mono-therapy at reducing albuminuria and proteinuiria, and in decreasing blood pressure at the same time not causing significant deterioration in glomerular filtration rate in diabetic kidney disease patients. Novel potassium-lowering therapies are shown to effective compensate the hyperkalemia risk associated with renin angiotensin aldosterone system blockade use in people with diabetic kidney disease, offering promise for more adequate therapy and greater renal and cardiovascular risk protection in the future.

Keywords: CKD, Double blockade, Diabetic, Hyperkalemia, RAAS, Single blockade

INTRODUCTION

Blockade of the renin-angiotensin-aldosterone system (RAAS) is a proven cornerstone of therapy for the prevention and treatment of diabetic kidney disease (DKD). An elegant body of scientific accomplishment from basic science through clinical trials has solidified the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and other RAAS inhibitors in patients with diabetes. The simultaneous use of two RAAS inhibitors (i.e., dual RAAS blockade) is supported by strong biologic rationale, and such therapy has been recommended by experts and frequently used in clinical practice.[1]

Albuminuria is a major and early clinical finding in DM, with renal and cardiovascular implications. It often, but not invariably, heralds the onset of progressive diabetic nephropathy.[2] Moreover, the severity of albuminuria is not significantly linked with the progression of the disease in both type 1 and type 2 DM.[3-5] Nevertheless, the use of RAAS blockers, to control hypertension and

reduce albuminuria, remains one of the cornerstones of the management of diabetic nephropathy; assuming that the added control of albuminuria by these agents may impact favourably on the subsequent progression and outcome of the nephropathy. Therefore, the main objective of the study is to compare the efficacy of double blockade and single blocked of RAAS in DKD.

METHODS

An observational prospective study was undertaken at SRN Hospital, Allahabad from July 2012 to August 2014. After detailed examination and exclusion criteria, 750 patients of diabetic chronic kidney disease (CKD) were selected for the study who was attending the nephrology OPD. After an informed consent these patients were divided into 3 groups of 250 patients each.

Group I was prescribed Ramipril, Group II was Telmisartan and Group III were prescribed both Ramipril + Telmisartan together respectively. Follow-up action was done on monthly basis. At every visit a complete clinical examination was done, which included BP, 24 hours urinary protein excretion, serum urea, serum creatinine, serum potassium and glomerular filtration rate (eGFR).

All diabetic patients of stage 4 and stage 5 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

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 58 years with a mean age of 38.1±12.8 years.

Table 1: Showing age, mean arterial pressure, eGFR, 24 hours urinary protein excretion of group I, II and III patients at the start and at the end.

		At 0 week			After 24 months		
Group	**Age**	**Mean arterial pressure (mm Hg)**	**eGFR (ml/mt)**	**24 hours urinary protein excretion (mg/24 hrs)**	**Mean arterial pressure (mm Hg)**	**eGFR (ml/mt)**	**24 hours urinary protein excretion (mg/24 hrs)**
Group I	38.1±12.8	115.80±6.46	21.7±5.68	871.5±266.4	111.62±7.41	22.0±6.04	698.73±319.9
Group II	45.1±13.1	115.60±8.18	21.2±4.5	870.9±350.8	112.15±8.06	22.0±6.0	708.0±349.20
Group III	43.6±12.2	118.80±6.17	19.8±5.0	736.66±308.0	104.58±9.50	20.8±8.4	430.0±310.21

Table 2: Comparison of eGFR of group I and III and Group II and III.

Group I		**Group III**				
Mean	**SD**	**Mean**	**SD**	**t-difference**	**Df-t**	**P value**
22.0	6.04	20.8	8.4	0.449	24.9	0.6534
Group II		**Group III**				
22.0	6.0	20.8	8.4	0.45	24.8	0.6522

Table 3: Comparing 24 hours urinary protein excretion of group I and III and Group II and III.

Group I		**Group III**				
Mean	**SD**	**Mean**	**SD**	**t-difference**	**Df-t**	**P value**
698.73	319.9	430.0	310.2	2.335	27.5	0.0268
Group II		**Group III**				
708.0	349.2	430.0	310.2	2.305	27.1	0.0278

Patients in group II were in the age range of 26 years to 58 years with a mean age of 45.1±13.0 years. Patients in group III were in the age range of 22 years to 60 years with a mean age of 43.6±12.2 years.

Out of 750 patients 16 were discontinued from the study due to adverse drug reactions, 5 patients could not complete the study, leaving a total number of 729 patients who were effectively enrolled in the study. Table 1 depicts age, mean arterial pressure, eGFR, 24 hours urinary protein excretion of group I, II and III patients at the start and at the end and Table 2 shows the comparison of eGFR between group I and III and group II and III.

As per Table 2 eGFR was similar in all patients at the 0 week of the study (21.7±5.68 ml/min in group I vs. 21.2±4.5 ml/min in group II vs. 19.8±5.0 ml/min in group III). It did not change significantly in all the three groups during the duration of the study. At the end of 24th month of study it was 22.0±6.04 ml/min in group I vs. 22.0±6.0 ml/min in group II and 20.8±8.4 ml/min in group III. When we compare p value (by using t-test) between group I and group III, it was 0.6534 (not significant). Same findings we obtained while comparing group II and III (p value is 0.6522). Table 3 shows the comparison of 24 hours urinary protein excretion between group I and III and Group II and III.

As per Table 3, at the 0 week of study 24 hours urinary protein excretion of group I patients were similar to that of group II patients (871.5±266.4 mg/24 hours in group I, 870.9±350.8 mg/24 hours in group II and 736.66±308.0 mg/24 hours in group III). After 4 weeks of treatment with Ramipril it declined significantly. This decline in albuminuria for group I patients was maintained throughout the duration of study. At the end of 24th month of study it was 698.73±319.9 mg/24 hours in group I, 708.0±349.20 in group II and 430.0±310.21 in group III.

Table 4: Comparing arterial blood pressure of group I and III and group II and III.

Group I		Group III				
Mean	**SD**	**Mean**	**SD**	**t-difference**	**df-t**	**P value**
111.62	7.41	104.58	9.50	2.0727	23	0.0496
Group II		Group III				
112.15	8.06	104.58	9.50	2.1541	23	0.0419

Table 5: Comparing serum potassium values of group I and III and group II and III.

Group I		Group III				
Mean	**SD**	**Mean**	**SD**	**t-difference**	**df-t**	**P value**
3.831	0.477	4.042	0.493	0.5982	23	0.2881
Group II		Group III				
3.969	0.312	4.042	0.493	0.4430	23	0.6619

So, when we compare 24 hours urinary excretion in group I and III we get significant p value <0.05 suggestive of significant decline in albuminuria in group III. Similar findings we get in comparing group II and group III. Table 4 shows the Comparison of arterial blood pressure between group I and III and Group II and III respectively.

In Table 4, at the end of 24 months the mean BP of group I and group III were statistically compared (111.62±7.41 mm hg and 104.58±9.50 mm hg respectively) by using student t-test and significant p value (<0.0496) was observed. Similarly, on comparing group II and group III, significant p value (0.0419) was found. Table 5 revealed the comparison of serum potassium values between group I and III and group II and III respectively.

In Table 5, at the end of 24 months the serum potassium value of group I and group III were statistically compared (3.831±0.477 meq/l and 4.042±0.493 meq/l respectively) by using student t-test and insignificant p value (<0.2881) was observed. Similarly, on comparing group II and group III, insignificant p value (0.6619) was found.

During the study we encountered two major adverse drug reactions hyperkalemia and worsening renal function. Three patients in the third group had serum potassium >5.5 during the follow up period, and their ACEI were stopped and followed up next week with potassium report and were given anti-hyperkalemia measures. Two of them were found to have normal potassium next week and in them the ACEI was started in the lowest dose. In the next two visits one week apart, they had normal potassium values, and this was the same till the end of the study. In the remaining patients the potassium normalized in the 3rd week and did not have hyperkalemia in the subsequent follow-ups. One patient in the second group also has serum potassium >5.8 at 8th week follow-up. He was withdrawn of ACEI for 1 week and again restarted at the lowest dose. The patient's potassium remained stable and gradually over a period of four weeks his ACEI does was increased to the maximum without any adverse

effects. His normal potassium was continued till the end of the study.

Significant deterioration in the renal function was noted in just one patient in the third group at fourth month and he was put off both the drugs and watched for 2 weeks till his creatinine stabilized and reached the pre-treatment value and was restarted on both the drugs during the third week of follow-up after the acute event. This patient also did not report any deterioration of renal function vis a vis eGFR n subsequent follow-up visits.

DISCUSSION

A meta-analysis suggests that combined RAAS blockade therapy is associated with a decline in GFR, especially in diabetic patients, patients with preserved kidney function (GFR ≥ 60 ml/min or ml/min/1.73 m^2), and patients in whom GFR was measured rather than calculated or estimated. They hypothesize that stricter BP goals in studies of diabetic patients might have induced the upward titration of antihypertensive medications. In the present study eGFR was similar in all patients at the 0 week of the study.[6] It did not change significantly in all the three groups during the complete duration of the study. When authors compared p value (by using t-test) between group I and group III, it was >0.05 (not significant). Same findings we obtained while comparing group II and III (p value >0.05).

The effect of reducing proteinuria by using ACEI or ARB alone has been established among the DKD patients; at the highest tolerable dosage, the effect is even more pronounced among the patients whose level of proteinuria is at least 300 mg/d, independent of BP control.[7-10] ACEI or ARB agents are thus the first line choices for DKD patients with hypertension. In present study after the 4 weeks of treatment with Ramipril it declined significantly. This decline in albuminuria for group I patients was maintained throughout the duration of study and was 698.7±298.5 mg/24 hours. In the Telmisartan group, at the start of study the 24 hours urinary excretion of albumin was 870.9±350.8. It progressively decreased during the course of study and became 708.0±349.20 at the end of study. Similar findings were also observed in group III. Initial protenuria was 736.66±308.0 which progressively decreased to 430.0±310.2 mg/24 hours at 24th month of study. So, when we compare 24 hours urinary excretion in group I and III authors obtained significant p value <0.05 suggestive of significant decline in albuminuria in group III. Similar findings we get in comparing group II and group III.

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), contrasting with a 3.8/2.9 mm Hg reduction achieved with ACEI/ARB mono-therapy treatment. Further subgroup analysis showed an even more effective reduction - by 6.8/4.7 mm Hg - in the patients with diabetes.[11] According to our study at the end of 24 months the mean BP of group I and group III was significant. Similarly, on comparing group II and group III, significant p value (0.0419) was also found.

A meta-analysis of dual blockade among the DKD patients found an only slightly increased incidence of hyperkalemia; the increase in the level of potassium was limited to 0.2 mmol/L, and the decrease in renal function to 3 ml/min.[12] In present study, at the end of 24 months the serum potassium value of group I and group III were statistically compared (3.831±0.477 meq/l and 4.042±0.493 meq/l respectively) which was found insignificant. Similarly, on comparing group II and group III, insignificant p value (0.6619) was found. In present study hyperkalemia was also observed in few patients casually.

CONCLUSION

The study clearly states that the use of double RAAS blockade therapy is more effective than mono-therapy at reducing albuminuria and proteinuiria, and in decreasing blood pressure at the same time not causing significant deterioration in glomerular filtration rate in diabetic kidney disease patients. Novel potassium-lowering therapies are shown to effective compensate the hyperkalemia risk associated with RAAS blockade use in people with DKD, offering promise for more adequate therapy and greater renal and cardiovascular risk protection in the future.

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REFERENCES

1. Pichler RH, de Boer IH. Dual renin-angiotensin-aldosterone system blockade for diabetic kidney disease. Curr Diab Rep. 2010;10(4):297-305.
2. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR; UKPDS Group. Development and progression of nephropathy in type 2 diabetes: The United Kingdom prospective diabetes study (UKPDS 64). Kidney Int. 2003;63:225-32.
3. Perkins BA, Ficociello LH, Roshan B, Warram JH, Krolewski AS. In patients with type 1 diabetes and new-onset microalbuminuria the development of advanced chronic kidney disease may not require progression to proteinuria. Kidney Int. 2010;77:57-64.
4. MacIsaac RJ, Panagiotopoulos S, McNeil KJ, Smith TJ, Tsalamandris C, Hao H, et al. Is nonalbuminuric renal insufficiency in type 2 diabetes related to an increase in intrarenal vascular disease? Diabetes Care. 2006;29:1560-6.
5. Caramori ML, Fioretto P, Mauer M. Low glomerular filtration rate in normoalbuminuric type

1 diabetic patients: An indicator of more advanced glomerular lesions. Diabetes. 2003;52:1036-40.
6. Susantitaphong P, Sewaralthahab K, Balk EM, Eiam-ong S, Madias NE, Jaber BL. Efficacy and Safety of Combined vs. single renin- angiotensin-aldosterone system blockade in chronic kidney disease: a Meta-Analysis. Am J Hypertension. 2013;26(3):424-41.
7. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med. 1993;329:1456-62.
8. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345:851-60.
9. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345:861-9.
10. De Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: Lessons from RENAAL. Kidney Int. 2004;65:2309-20.
11. Doulton TW, He FJ, MacGregor GA. Systematic review of combined angiotensin-converting enzyme inhibition and angiotensin receptor blockade in hypertension. Hypertension. 2005;45:880-6.
12. Jennings DL, Kalus JS, Coleman CI, Manierski C, Yee J. Combination therapy with an ACE inhibitor and an angiotensin receptor blocker for diabetic nephropathy: a meta-analysis. Diabet Med. 2007;24:486-93.

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