Original Research Article

Comparison of the efficacy of triple blockade, double blockade and single blockade of RAAS in non diabetic chronic kidney disease

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ABSTRACT

Background: Although dual blockade of the renin-angiotensin-aldosterone system with the combination of an angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker is generally well established as a treatment for nephropathy, this treatment is not fully effective in some patients.

Methods: A prospective observational study was done on 600 chronic kidney disease patients during July 2012 to August 2014 to compare the efficacy of triple blockade, double blockade and single blockade of renin-angiotensin-aldosterone system in non diabetic chronic kidney disease.

Results: At the end of the study, 24 hours 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 (0.0160) was again found significant.

Conclusions: Triple blockade of the renin-angiotensin-aldosterone system was effective for the treatment of proteinuria in patients with non-diabetic nephropathy whose increased urinary protein had not responded sufficiently to a dual blockade.

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

INTRODUCTION

Dual blockade with an angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin II receptor blocker (ARB) has been reported to be superior to single blockade both in reducing proteinuria and in slowing the progression of renal disease.[1-3] However, some patients do not respond adequately to the conventional renin-angiotensin system (RAS) blockade, raising a clinical problem that remains to be solved. This therapeutic inadequacy might be attributable to such putative mechanisms as non-renin-angiotensin-aldosterone system (RAAS) stimulators, aldosterone breakthrough, or a vicious cycle within the RAAS in which aldosterone perpetuates both the expression of ACE and that of AII type 1 receptor.[4-12]

Several pharmacological intervention have been introduced targeting rennin angiotensin aldosterone axis e.g. ACE inhibitor (Rampril), ARB receptor blockers (Telmisartan), aldosterone antagonists (Eplerenone) and direct Renin inhibitors (Aliskiren). Although use of ACE inhibitors and ARB receptor blockers have been associated with favourable outcome in both diabetic and non diabetic chronic kidney disease (CKD) patients, it has been suggested that addition of an aldosterone antagonist may further slow the disease progression by decreasing proteinuria and having favourable effect on blood pressure.[4,5] Therefore, the objective of this study is

to compare the efficacy of triple blockade, double blockade and single blockade of RAAS in non diabetic chronic kidney disease.

METHODS

An observational prospective study was undertaken at SRN Hospital, Allahabad from July 2012 to August 2014. After detailed examination and exclusion criteria, 600 patients of CKD were selected for the study who was attending the nephrology OPD.

After an informed consent these patients were divided into 3 groups of 200 patients each. Group I were prescribed Ramipril, Group II was prescribed both Ramipril + Telmisartan together and Group III was prescribed Ramipril + Telmisartan + Eplerenone 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 CKD 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 26 years to 60 years with a mean age of 40.30±11.8 years. Patients in group II were in the age range of 27 years to 59 years with a mean age of 41.07±11.44 years. Patients in group III were in the age range of 25 years to 56 years with a mean age of 38.38±11.25 years.

Out of 600 patients 9 were discontinued from the study due to adverse drug reactions, 2 patients could not complete the study, leaving a total number of 589 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. 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 21.68±3.98 ml/min in group I vs. 21.23±2.00 ml/min in group II and 20.99±2.35 ml/min in group III. When we compare p value (by using unpaired t-test) between group I and group III, it was 0.6147 (not significant). Same findings we obtained while comparing group II and III (p value is 0.7797). 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. After 24 months of treatment with Ramipril in group I, Ramipril + Telmisartan in group 2 and Ramipril + Telmisartan + Eplerenone in group 3, 24 hours urinary protein excretion declined to 771.64±231.15, 716.54±214.48 and 526.17±140.45 mg/24 hours respectively.

So, when we compare 24 hr urinary protein excretion in group I and III we obtained significant p value (0.0268) suggestive of significant decline in proteinuria in group III. Similar findings we obtained in comparing group II and group III (p value 0.0160).

According to Table 4, arterial blood pressure changes significantly in third group during the study. 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 (4.16±0.27 meq/l and 4.34±0.37 meq/l respectively) by using student t-test and insignificant p value (<0. 2129) was observed. Similarly, on comparing group II and group III, insignificant p value (0. 4056) was found.

During the study, hyperkalemia was observed. Four patients in third group had developed serum potassium level more than 5.5 during the follow up period and we had to stop Eplerenone and followed further with potassium report subsequently they were treated for hyperkalemia. Two of them were back to normal potassium levels in the next week and Eplerenone was started again in the lowest dose. These patients did not develop hyperkalemia on further follow up and in remaining two patients the potassium normalized in the 24 month and did not developed hyperkalemia in the subsequent follow ups.

One patient was found in the second group with raised serum potassium levels more than 5.5 at 3 months of follow up. Telmisartan was withdrawn for 1 week and again restarted at the lowest dose, potassium level remained normal during follow up.

Table 1: 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	40.30±11.83	115.80±6.46	21.19±4.29	1015.15±211.89	111.62±7.41	21.68±3.98	771.64±231.15
Group II	41.07±11.44	115.60±8.18	20.40±2.46	1023.77±170.91	112.15±8.06	21.23±2.00	716.54±214.48
Group III	38.38±11.25	118.80±6.17	19.90±2.47	1039.15±178.49	104.58±9.50	20.99±2.35	526.17±140.15

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

Group I		Group III		
Mean	sd	Mean	sd	P value
21.68	3.98	20.99	2.35	0.6147
Group II		Group III		
21.23	2.00	20.99	2.35	0.7797

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	P value
771.64	231.15	526.17	140.45	0.0268
Group II		Group III		
716.54	214.48	526.17	140.45	0.0160

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

Group I		Group III		
Mean	sd	Mean	sd	P value
111.62	7.41	104.58	9.50	0. 0496
Group II		Group III		
112.15	8.06	104.58	9.50	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	P value
4.16	0.27	4.34	0.37	0.2129
Group II		Group III		
4.22	0.32	4.34	0.37	0.4056

DISCUSSION

Blockade of the RAAS with ACEI and/or ARBs may also be incomplete because both classes of compounds interrupt the normal feedback inhibition of rennin release, leading to a reactivation of the downstream effects of ANG-II, including aldosterone release.[13-16]

In clinical trials of ACEIs and ARBs, aldosterone levels, after an initial decline, increase toward baseline in roughly 30-40% of patients by 6-12 months.[17] This phenomenon, called aldosterone breakthrough or escape, likely has important clinical consequences that may explain, in part, the failure of the ACEI/ARB combination. Aldosterone's classical epithelial effects of salt retention and volume expansion are well known with regard to their effects on blood pressure and, consequently, cardiac and renal function.

Many studies revealed that blockade of the RAAS lowers blood pressure in patients with chronic kidney disease.[18-21] In present study at the end of 24 months the mean blood pressure of group I and group III were compared, and significant p value was observed <0496. Similar results were obtained while comparing group II and III (p value 0. 0419). Thus, present study findings revealed that by adding aldosterone antagonist significant results will be obtained.

A number of small, short-term, clinical studies have examined the effects of adding spironolactone or eplerenone to ACEI and/or ARB therapy in patients with proteinuric kidney disease, typically patients with diabetic nephropathy.[22-31] These studies have consistently shown that adding MRB therapy reduces proteinuria in patients on long-term ACEI or ARB therapy and persistent proteinuria. In a systematic review 72 of 15 studies of 436 patients with proteinuric kidney disease, ranging from randomized controlled trials to case reports, the addition of an MRB to ACEI and/or ARB therapy resulted in a 15-54% reduction in proteinuria from baseline. In the present study, when we compared 24 hr urinary protein excretion in group I and III we obtained significant p value (0.0268) suggestive of significant decline in proteinuria in group III. Similar findings we obtained while comparing group II and group III (p value 0.0160).

The potential adverse effects of MRB therapy on serum potassium levels must also be considered. The overall incidence of clinically significant hyperkalemia in the aforementioned 15 renal studies was 5.5% and ranged from minimal to 17.2% of the patients receiving the MRB

combination.[32,33] In present study, hyperkalemia was also observed in few cases and was found statistically insignificant while comparing group I and II and group II and III, which was subsequently corrected by adding potassium lowering compounds.

CONCLUSION

Our study clearly states that triple blockade of the RAAS with an aldosterone antagonist plus an ACE-I and ARB might be more effective than the dual blockade both in reducing proteinuria and in slowing the progression of renal disease, especially in patients whose proteinuria did not respond sufficiently to the dual blockade. Newer potassium lowering therapies can effectively and safely correct hyperkalemia and maintain normokalemia hence it should be added with in patients receiving background treatment with triple blockade.

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