

Efficacy of Aldosterone Antagonist with RAAS Blockade in Patients with Diabetic Kidney Disease

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Abstract

Background: The use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker is now standard therapy for patients with diabetic kidney disease. However, this treatment is not fully effective in some patients.

Methods: A prospective observational study was conducted at SRN Hospital Allahabad on 600 diabetic kidney disease patients during July 2015 to August 2017 to compare the efficacy of triple blockade, double blockade and single blockade of renin-angiotensin-aldosterone system.

Results: At the end of the study, 24 hours urinary protein excretion rate was statistically compared between group I & group III and between group II & group III. The rate was found significant with p value (<0.0001) and (0.0003) respectively.

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

Keywords: DKD, RAAS, Aldosterone antagonist, Double blockade, Triple blockade, Hyperkalemia.

INTRODUCTION

Diabetes mellitus (DM) is a pandemic disease affecting 415 million people worldwide. According to the projections of the International Diabetes Federation, the number of affected individuals is expected to increase to 642 million by 2040, the vast majority of which are in developing countries [1]. Diabetic kidney disease (DKD) is the most common cause of end stage kidney disease (ESKD) both in the developed and the developing world accounting for 20-40% of patients starting renal replacement therapy [2]; in India, 31% of the ESKD population have DKD [3]. This figure is likely to rise steadily over the next 2 decades. Unsurprisingly, treatment of diabetics with ESKD incurred very high-the average cost of treatment of diabetics with and without chronic kidney disease (CKD) were INR 100,000 (\$2150) and 30,000 (\$645) respectively.

In DKD patients, the renoprotective effects of RAAS blockade (RAASB) are superior to other antihypertensive drugs. The RAASB using ACE inhibitors or ARB delays both the onset and the increase of albuminuria, and also slows down the deterioration of glomerular filtration rate (GFR) [4-6]. However, presently the level of evidence about the potential beneficial effect of RAASB in DKD patients with advanced CKD is low [7, 5]. Despite the antiproteinuric effects of RAASB, many diabetic patients on this treatment do not show a reduction in the progression of renal disease. Thus, strategies are needed to make the modulation of RAAS more effective. It has been suggested that addition of an aldosterone antagonist may further slows the disease progression by decreasing proteinuria and having favourable effect on blood pressure [8-9]. Therefore, the objective of this study is to compare the efficacy of

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triple blockade, double blockade and single blockade of RAAS in diabetic chronic kidney disease to delay the progression towards ESKD.

METHODS

An observational prospective study was undertaken at SRN Hospital, Allahabad from July 2015 to August 2017. After detailed examination and exclusion criteria, 600 patients of DKD 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, blood sugar, 24 hour urinary protein excretion, serum urea, serum creatinine, serum potassium and glomerular filtration rate (eGFR).

All DKD 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 [10-11].

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

RESULTS

Out of 600 patients, 11 were discontinued from the study due to adverse drug reactions, 5 patients could not complete the study, leaving a total number of 584 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 of the study and Table 2 shows the comparison of eGFR between group I and III and group II and III.

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.

Group	Age	At 0 week			After 24 months		
		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)	Mean arterial pressure (mm Hg)
Group I	38.1	21.360	871.33	115.80	21.823	713.31	111.62
	\pm 12.8	\pm 3.584	\pm 246.75	\pm 6.46	\pm 3.881	\pm 156.49	\pm 7.41
Group II	45.1	24.220	846.20	115.60	21.220	751.38	112.15
	\pm 13.1	\pm 5.718	\pm 222.16	\pm 8.18	\pm 5.031	\pm 255.82	\pm 8.06
Group III	43.6	26.180	846.33	118.80	25.633	408.67	104.58
	\pm 12.2	\pm 8.512	\pm 221.99	\pm 6.17	\pm 7.584	\pm 121.60	\pm 9.50

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

Group I		Group III		t-difference	Df-t	P value
Mean	sd	Mean	sd			
21.823	3.881	25.633	7.584	1.6004	23.0	0.1232
Group II		Group III		t-difference	Df-t	P value
Mean	sd	Mean	sd			
21.220	5.031	25.633	7.584	1.5760	23.0	0.1287

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As per table no 2 eGFR was similar in all patients. It did not change significantly in all the three groups during the study. When we compared the p value between group I and group III, it was not significant (0.1232).

Similar findings were obtained while comparing group II and III (p value was 0.1287). Table 3 shows the comparison of 24 hours urinary protein excretion between group I and III and Group II and III.

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

Group I		Group III		t-difference	Df-t	P value
Mean	sd	Mean	sd			
713.31	156.49	408.67	121.60	5.4014	23.0	<0.0001
Group II		Group III		t-difference	Df-t	P value
Mean	sd	Mean	sd			
751.38	255.82	408.67	121.60	4.2170	23.0	0.0003

Table 3 revealed 24 hours urinary protein excretion after 24 months of treatment with Ramipril in group I, Ramipril + Telmisartan in group II and Ramipril + Telmisartan + Eplerenone in group . When we compared the values between

group I and III we obtained significant p value (<0.0001) suggestive of significant decline in proteinuria in group III. Similar findings were obtained while comparing group II and group III (p value 0.0003).

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

Group I		Group III		t-difference	Df-t	P value
Mean	sd	Mean	sd			
111.62	7.41	104.58	9.50	2.0727	23.0	0.0496
Group II		Group III		t-difference	Df-t	P value
Mean	sd	Mean	sd			
112.15	8.06	104.58	9.50	2.1541	23.0	0.0419

According to table 4, significant change in arterial blood pressure was recorded after 24 months. Table 5 revealed

the comparison of serum potassium values between group I and III and group II and III respectively.

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

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

In table 5, at the end of 24 months the serum potassium value of group I and group III were statistically analysed and was found insignificant. Similarly on comparing group II and group III, insignificant p value was found.

levels were normalized in the 24 month and remained normal on subsequent follow ups.

During the study, hyperkalemia was observed. Nine patients in group III had developed serum potassium levels more than 5.5 during the follow up period consequently we had to stop Eplerenone and were treated for hyperkalemia. Five of them were back to normal potassium levels in the next week and Eplerenone was again started in the lowest dose. These patients did not develop hyperkalemia on further follow ups and remaining four patient's potassium

DISCUSSION

Current treatment regimens that include an ACEI or ARB still have not been proven to halt kidney disease progression in most patients over the long term [12-15]. Indeed, a recent 5-year study found that early blockade of the RAAS with either an ACEI or ARB in patients with type 1 diabetes, while slowing the progression of retinopathy, did not protect against the progression of nephropathy on biopsy findings and measurements of urinary albumin excretion [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 [18].

Accordingly, one strategy to improve the efficacy of RAAS blockade is to combine ACEIs and ARBs. Furthermore, increased appreciation of the role of aldosterone in the pathogenesis of cardiovascular and renal disease, [19-20] suggests additional combination strategies that may offer novel ways to suppress the RAAS.

Many studies revealed that blockade of the RAAS lowers blood pressure in patients with chronic kidney disease [21-24]. In our 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 <0.0496. Similar results were obtained while comparing group II and III (p value 0.0419). Thus our 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. 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 [25-34]. In the present study, when we compared 24 hr urinary protein excretion in group I and III we obtained significant p value (<0.0001) suggestive of significant decline in proteinuria in group III. Similar findings we obtained while comparing group II and group III (p value 0.0003).

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 [35-36]. In our 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.

DKD is preventable. There is substantial evidence that early and effective therapeutic intervention in type 2 diabetes can prevent DKD, and retard progression of established DKD. Strict glycemic and blood pressure control can reduce the incidence and slow progression of DKD [37-38]. Inhibition of the renin angiotensin system decrease progression from normoalbuminuria to microalbuminuria, microalbuminuria to macroalbuminuria and the development of ESKD [39-41].

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 single blockade and 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. Given the magnitude of the problem we are facing, the exponentially rising prevalence of DKD and the consequent economic impact, "the only practical solution for eastern Uttar Pradesh, just as it would be for any other country," will be putting more effort in preventing and delaying progression of diabetic nephropathy.

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