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Clinical Study to Compare the Efficacy of Triple Blockade with that of Double and Single Blockade of RAAS in Non-Diabetic Chronic Kidney Disease Patients

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ABSTRACT

Problem considered: *Compare The Efficacy Of Triple Blockade With That Of Double And Single Blockade Of RAAS In Non-Diabetic Chronic Kidney Disease Patients*

Objectives: *To study the effect of triple blockade of RAAS using ACE Inhibitors, ARBs and EPLERENONE in Non diabetic CKD patients, To compare it with that of single and double blockade using ACEI and ARBs and To evaluate whether the combination therapy is detrimental to renal status.*

Materials and Methods: *Patients between age of 18 to 60 years of age were taken in the study. only stable non diabetic chronic kidney disease patients were included in the study. After the washout period of two weeks 45 patients were selected, all were thoroughly interrogated, investigated and put on a planned treatment. All the patients were divided into three groups of 15 patients. All patients of Stage 1, Stage 2, Stage 3, Stage 4 whose last 3 months GFR is stable, Stage 5 whose last 6 month GFR is stable will be selected. All diabetic patients, Patient developed acute on CKD, Serum potassium value more than 5.0,Stage 4 patients whose last 3 month eGFR is unstable, Stage 5 patients whose last 6 months eGFR is unstable were excluded.*

Results: *eGFR was stable in all patients in the three groups at 0 month of study (21.33±3.95 vs 20.10±2.43 vs 20.06±2.53). It did not change significantly in all three groups during the entire duration of study. At the end of 10th month of study it was 21.14±3.81 ml/min in group 1 and 20.44±2.42 ml/min in group 2 and 20.05±2.19 in group 3 (p>0.05). When we compared mean eGFR of group I and group III, we got P value >0.05 at the end of 10th month of study which is non-significant. Similar finding we got in comparing group II and group III. The baseline urine protein level was not much different in all the three groups at the start of study at 0 months it was (1032.26±187.75 vs 1042.40±156.4 vs 1055.1±137.77).It was also seen that rate of decrease in proteinuria was more in group-3 in comparison to group-2 and it was more in group-2 in comparison to group-1 (779.23±193.18 vs 756.34±195.07 vs 618.04±77.97).The decrement in proteinuria (3> 2> 1) remained sustained throughout the duration of study (P<0.05) that is significant. When we compared mean BP of group I and group III at the end of 10 months, we got P value >0.05, which is non-significant. Similar finding we got in comparing group II and group III.Patients in group containing RAMIPRIL + TELMISARTAN + EPLERENONE were always at higher risk of developing hyperkalemia as compared to patients on RAMIPRIL+TELMISARTAN and patients on RAMIPRIL alone(group 3 > group 2 > group 1),though the differences were non-significant.*

Conclusions: *Triple blockade is effective in decreasing proteinuria in non-diabetic kidney disease patients but it does not halt the progression of disease. There is also risk of hyperkalemia, especially with triple blockade. There is no added advantage of using Triple blockade compared to a Double or a Single blockade of RAAS with regard to improvement in eGFR or decrease in Mean Arterial Pressure of the subjects during the study period of 10 months.*
Keywords: *CKD, tripleblockade, proteinuria.*

Introduction

Renin angiotensin aldosterone system[1,2] isessential for blood pressure regulation. Several pharmacological intervention have been introduced targeting renin angiotensin aldosterone axis for blood pressure regulation in chronic kidney disease patient e.g. ACE inhibitor (RAMIPRIL), AT 1 receptor blockers (TELMISARTAN), ALDOSTERONE antagonists (EPLERENONE) and direct RENIN inhibitors (ALISKIREN). Although use of ACE inhibitors and ATl receptor blockers have been associated with favorable outcome in both diabetic and non diabetic C.K.D. patients, it has been suggested that addition of an aldosterone antagonist may further slow the disease progression by decreasing proteinuria and having favorable effect on blood pressure but the risk of life threatening hyperkalemia cannot be ruled out.[3,4] To date very few studies have been conducted regarding their safety and benefit in C.K.D. Patients.[5 to 17]

Material and Methods: A prospective interventional study was initiated in the nephrology O.P.D. of Swaroop Rani Nehru Hospital, Allahabad between april 2014 to july 2015. All the patients were properly informed about the study & written consent was taken. Non diabetic chronic kidney disease patients were kept under observation for their blood pressure and renal function by laboratory assessment. Patients between age of 18 to 60 years of age were taken in the study. Only stable non diabetic chronic kidney disease patients were included in the study.

Inclusion Criteria: Before the Commencement of study, patients having chronic renal failure were kept under preliminary observation period.During this time, they were kept under surveillance for their blood pressure and renal function. Eligible subjects were non-diabetic patients of both sexes between 18 to 60 yrs of age with established CKD defined by a serum creatinine concentration ranging between 1.5 to 5.0 mg/dl. The patients were diagnosed cases of Non-diabetic CKD falling into either of the five stages of CKD according to their estimated GFR. [4]

All patients of

- Stage 1,
- Stage 2,
- Stage 3,
- Stage 4 whose last 3 months GFR is stable,
- Stage 5 whose last 6 month GFR is stable will be selected.

Exclusion Criteria

- All diabetic patients.
- Patient developed acute on CKD.
- Serum potassium value more than 5.0.
- Stage 4 patients whose last 3 month eGFR is unstable.
- Stage 5 patients whose last 6 months eGFR is unstable.

Patients who had potentially reversible and or rapidly progressing renal diseases, systemic diseases, severe cardiac or hepatic dysfunction, ankle edema or proteinuria greater than 5 gm/day were excluded.

Glomerulonephrits patients being treated with steroids, non-steroidal anti inflammatory drugs and cytotoxic drugs were excluded.

The eligible patients were instructed to follow a low protein diet containing 0.6 to 0.7 gm protein/kg Body weight and a low sodium diet 60-100 meq to sodium/day.

A caloric supply of 32-35 Kcal/kg/day was advised. Concomitant treatment consisted of calcium Carbonate during meals. No particular

phosphate restriction was prescribed.

Before being introduced in the present study (during preliminary observation) all the patients received traditional antihypertensive therapy either with a single antihypertensive drug or with various combinations of two or more agents.

Modification

After signing on informed consent form all the patients were instructed to discontinue all antihypertensive medications at least two weeks prior to initiating the studies.

After the washout period of two weeks 45 patients were selected, all were thoroughly interrogated, investigated and put on a planned treatment.

All the patients were divided into three groups of 15 patients.

Group 1 patients received ACE Inhibitor **RAMIPRIL**[18]as antihypertensive agent. Initial dose was 1.25 mg once a day.

Group 2 patients received Angiotensin receptor blocker **TELMISARTAN**[18] and ACE Inhibitor **RAMIPRIL**. Initial dose of TELMISARTAN was 20 mg once a day and Initial dose of RAMIPRIL was 1.25 mg once a day.

Furosemide (20 to 80 mg) or clonidine (0.1 mg TDS) was added if blood pressure had not been well controlled by RAMIPRIL and TELMISARTAN.

Group 3 patients received combination of Angiotensin converting enzyme inhibitor **(RAMIPRIL)** 1.25 mg, Angiotensin receptor blocker **(TELMISARTAN)** 20 mg initially and Aldosterone receptor antagonist **(EPLERENONE)**[18] 25 mg initially and dose titrated upward according to blood pressure.

The same observer examined the patients at monthly intervals (4 weekly). At each visit a complete clinical examination was done in which heart rate, blood pressure,24 hr urine protein, s. urea, s. creatinine, s. potassium were measured.

Mean BP was calculated by adding on third of Pulse Pressure to the diastolic blood pressure.

Estimated GFR was calculated using the MDRD (Modification of diet in Renal disease study) equation.

Recording of Data

Detailed history was taken and complete Physical Examination was done in all patients. It was recorded on a preplanned record sheet. All the Investigations carried out at regular intervals were recorded in the record sheet throughout the duration of the study.

Investigations

- Hb, TLC, DLC,ESR,
- Fasting Blood Sugar,
- Fasting lipid profile,
- S.Sodium, S.Potassium, S.Calcium, S.Phosphate,
- S.Urea, S.Creatinine,
- 24 Hour Urinary Protein,
- eGFR,
- USG Abdomen,
- ECG,
- 2D-Echocardiography.

FIFTY FIVE patients of chronic renal failure with hypertension formed the material for the present study. Patients were in the age range of 18 years to 60 years.26 patients were males and 19 patients were females.

At the end of washout period of two weeks all the patients were randomly divided into three groups.

- Group I : included 15 patients.
- Group II : included 15 patients.
- Group III : included 15patients.

Table no. 1- Male-Female ratio:

Groups	Male	Female	Total
Group 1	7	8	15
Group 2	9	6	15
Group 3	10	5	15

Table no. 2- Mean age(years) in three groups

	Group 1	Group 2	Group 3
Mean Age	41.40	41.73	42.13
SD	8.05	9.86	7.98

Table no. 3- Mean eGFR in three groups at 0 and 9 months:

Months	Group I	Group II	Group III
0 m	21.33±3.95	20.10±2.43	20.06±2.53
10 m	21.14±3.81	20.44±2.42	20.05±2.19

Table no. 4- Comparison of eGFR of group I and group III:

	Group I		*Group III*		
Months	**Mean**	**SD**	**Mean**	**SD**	**P value**
0 m	21.33	3.95	20.06	2.53	0.3033
10 m	21.14	3.81	20.05	2.19	0.3450

Table no. 5- Comparison of eGFR of group II and group III:

	Group II		*Group III*		
Months	**Mean**	**SD**	**Mean**	**SD**	**P value**
0 m	20.10	2.43	20.06	2.53	0.9650
10 m	20.44	2.42	20.05	2.19	0.6471

Table no.- 3,4,5 shows eGFR remained stable in all patients throughout the 10 months duration of the study.

It was similar in all patients at the 0 months of study, 21.33±3.95 ml/min in group I vs 20.10±2.43 ml/min in group II vs 20.06±2.53 ml/min in group III.

It did not change significantly in three groups during the 10 months of study (P>0.05) .

At the end of 10 months of study it was 21.14±3.81 ml/min in group I vs 20.44±2.42 ml/min in group II and 20.05±2.19 ml/min in group III.

When we compared, p value (by using unpaired t test) between group I and group III at 0 and 10 month it was >0.05(not significant). Same finding we got in comparing group II and III.(P>0.05).

Table no. 06- 24 hours urinary protein excretion in the three groups of patients at 0 and 10 months of study:

Months	Group I	Group II	Group III
0 m	1032.26±187.75	1042.40±156.42	1055.10±139.77
10 m	779.23±193.18	756.12±195.07	618.01±77.97

Table no. 07- Comparison of 24 hr urinary protein excretion of group I and groupIII

	Group I		*Group III*		
Months	**Mean**	**SD**	**Mean**	**SD**	**P value**
0 m	1032.26	187.75	1055.48	139.97	0.7083
9 m	779.23	193.18	618.04	77.97	0.0102

Table no. 08- Comparison of 24 hr urinary protein Excretion group II and group III

	Group II		*Group III*		
Months	**Mean**	**SD**	**Mean**	**SD**	**P value**
0 m	1042.40	156.42	1055.48	139.97	0.8163
10 m	756.12	195.07	618.04	77.97	0.0251

Table no.- 06,07,08 and Figure for 24 hours urinary protein: At the 0 month of study 24 hours urinary protein excretion was similar in group l patients, group II patients and group III patients (1032.26±187.75 mg/24 hours in group l, 1042.40±156.42 mg/24 hours in group II and 1055.48±139.97 mg/24 hours in group III).

After 9 months of treatment with Ramipril in group 1, with Ramipril +Telmisartan in group 2 and with Ramipril+Telmisartan+Eplerenone in group 3 it declined to 779.23±193.18, 756.12±195.07 and 618.04±77.97 mg/24 hours respectively.

So when we compared 24 hr urinary protein excretion in group I and III we got p value at end of study i.e. at 10th month of study<0.05(0.0053) suggestive of significant decline in proteinuria in group III.

Similar finding we got in comparing group II and group III (p value 0.0160).

Table no. 09- Mean Arterial Pressure of three groups at 0 and 10 months of study:

Months	Group I	Group II	Group III
0 m	116.79±5.89	115.07±7.46	111.84±7.82
10 m	102.93±5.55	104.21±6.02	101.3±5.23

Fig-1 Mean arterial pressure (mm Hg) in all three groups at 0 and at 9 months of study:

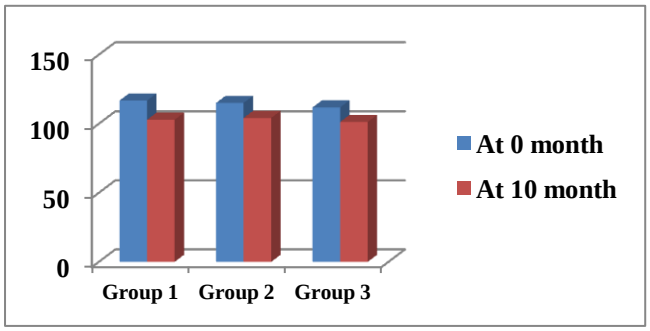

Table no. 10- Comparison of mean arterial pressure of group I and group III

	Group I		*Group III*		
Months	Mean	SD	Mean	SD	P value
0 m	116.79	5.98	111.84	7.82	0.0603
9 m	102.93	5.55	101.38	5.23	0.4710

Table no. 11- Comparison of mean arterial pressure of group II and group III

	Group II		*Group III*		
Months	Mean	SD	Mean	SD	P value
0 m	115.07	7.46	111.84	7.82	0.2570
10 m	104.21	6.02	101.38	5.23	0.2062

Table no.- 09,10,11 and Figure1 for mean arterial pressure(MAP): show MAP remained stable in all patients throughout the 10 months duration of the study.

It was similar in all patients at the 0 months of study, 116.79±5.98 mmHg in group I vs 115.07±7.46 mmHg in group II vs 111.84±7.82 mmHg in group III.

It did not change significantly in three groups during the 10 months of study.

At the end of 10 months of study it was 102.93±5.55 mmHg in group I vs 104.21±6.02mmHg in group II and 101.38±5.23 mmHg in group III.

When we compared p value (by using unpaired t test) between group I and group III at 0 and 10 months it was >0.05(non significant) (table no 16). Same finding we got in comparing group II and III. (P>0.05) .

Table no. 12- Comparison of serum potassium of three groups at 0 and 10 months of study:

Months	Group I	Group II	Group III
0 m	3.67±0.46	3.75±0.42	3.68±0.27
10 m	4.09±0.29	4.16±0.34	4.26±0.34

Table no. 13- Comparison of serum potassium levels group I and group III

	Group I		Group III		
Months	Mean	SD	Mean	SD	P value
0 m	3.67	0.46	3.68	0.27	0.9426
10 m	4.09	0.29	4.26	0.34	0.1650

Fig-2 Serum Potassium in all three groups at 0 and 10 months of study

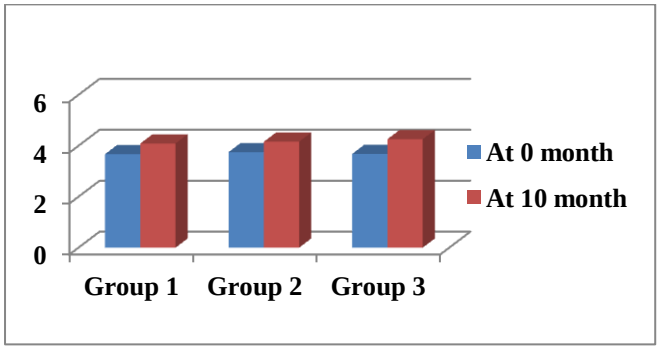

Table no. 14- Comparison of serum potassium levels of group II and group III

	Group II		Group III		
Months	**Mean**	**SD**	**Mean**	**SD**	**P value**
0 m	3.75	0.42	3.68	0.27	0.5914
10 m	4.16	0.34	4.26	0.34	0.4522

During the study adverse drug reaction, hyperkalemia was encountered.

Four patients in the third group had serum potassium >5.5 during the follow up period and we had to stop Eplerenone and followed up next week with potassium report and they were treated for hyperkalemia.

Two of them were found to have normal potassium in the next week and Eplerenone was started again in the lowest dose. These patients did not develop hyperkalemia on further follow up.

In the remaining two the potassium normalized in the 4th week and did not have hyperkalemia in the subsequent follow ups.

One patient in the second group also had serum potassium> 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.

No patient in the group-I develop any of adverse drug reaction.

So patients in group containing RAMIPRIL + TELMISARTAN + EPLERENONE were always at higher risk of developing hyperkalemia as compared to patients on RAMIPRIL+ TELMISARTAN and patients on RAMIPRIL alone.(group 3>group 2>group 1) though the differences were non significant(p value>0.05).

Discussion

Before going to discuss the outcomes, benefits and limitations of our study, lets discuss the natural history of chronic kidney disease as it will help us to know the changes/benefits/ disadvantages that we can have in patients of CKD if we start blockade of RAAS System at various levels. If we should start then at what timing to introduce drugs and what combinations of drugs?

Natural History Of Chronic Kidney Disease as per KDOQI Clinical Practice Guidelines: The level of kidney function tends to decline progressively over time in most patients with chronic kidney diseases.

The natural history of most chronic kidney diseases is that GFR declines progressively over time -

Data from the MDRD Study during an average 2-year follow-up shows that the average rate of decline in GFR was approximately 4 mL/min/year and was not related to the baseline level of GFR. Approximately 85% of patients had GFR decline during follow-up. The remaining patients experienced improvement or stabilization of GFR.

The studies reviewed for this guideline show a wide range in the rate of GFR decline among studies, as well as among individual patients. The mean rate of decline in GFR varied widely, from no decline to over 12 mL/min/1.73 m^2 per year.

The rate of decline in GFR can be used to estimate the interval until the onset of kidney failure.

Table15: Rate of GFR decline

Table 110. Years Until Kidney Failure (GFR <15 mL/min/1.73 m^2) Based on Level of GFR and Rate of GFR Decline

Level of GFR (mL/min/1.73 m^2)	Rate of GFR Decline (mL/min/1.73 m^2 per year)					
	10	8	6	4	2	1*
90	7.5	9.4	13	19	38	75
80	6.5	8.1	11	16	33	65
70	5.5	6.8	9.2	14	28	55
60	4.5	5.6	7.5	11	23	45
50	3.5	4.4	5.8	8.8	18	35
40	2.5	3.1	4.2	6.3	13	25
30	1.5	1.9	2.5	3.8	7.5	15
20	0.5	0.6	0.8	1.3	2.5	5.0

* Average age-related GFR decline after age 20–30 years

In principle, if the rate of GFR decline is constant over time, then the interval until the onset of kidney failure could be estimated from the current level of GFR and the rate of decline in GFR. An estimate of the time until kidney failure would be useful to facilitate planning for kidney replacement therapy, or may even suggest that concerns about kidney failure may be unwarranted if life expectancy is short. Table15 shows the number of years until GFR declines to 15 mL/min/1.73 m^2, calculated from the current level of GFR and the estimated rate of decline of GFR. For patients with GFR <60 mL/min/1.73 m^2, the interval until kidney failure is approximately 10 years or less if the rate of decline is ≥ 4 mL/min/1.73 m^2 per year. This rate of decline can be considered "fast".

The rate of GFR decline is related to the type of kidney disease; diabetic kidney disease, glomerular diseases, polycystic kidney disease, and kidney disease in transplant recipients are associated with a faster GFR decline than hypertensive kidney disease and tubulointerstitial kidney diseases

The rate of GFR decline is related to some non modifiable patient characteristics, irrespective of the type of kidney disease; African-American race, lower baseline level of kidney function, male gender, and older age are associated with a faster GFR decline.

The rate of GFR decline is also related to modifiable patient characteristics, irrespective of the type of kidney disease. Higher level of proteinuria, lower serum albumin concentration, higher blood *pressure* level, poor glycemic control, and smoking are associated with a faster GFR decline. The associations of dyslipidemia and anemia with faster GFR decline are inconclusive.

Angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists slow the progression of chronic kidney disease.

In our study patients on RAMIPRIL alone were in group 1, patients on RAMIPRIL+ TELMISARTAN were in group 2 and Patients in group 3 were on RAMIPRIL + TELMISARTAN + EPLERENONE. Each group was having 15 patients.

eGFR remained stable in all patients throughout the10 months duration of the study.It was similar in all patients at the 0 months of study, 21.33±3.95 ml/min in group I vs 20.10±2.43 ml/min in group II vs 20.06±2.53ml/min in group III. It did not change significantly in three groups during the 10 months of study (P>0.05) . At the end of 10 months of study it was 21.14±3.81 ml/min in group I vs 20.44±2.42 ml/min in group II and 20.05±2.19 ml/min in group III. When we compared, p value (by using unpaired t test) between group I and group III at 0 and 10 month it was >0.05(not significant). Same finding we got in comparing group II and III (P>0.05).

At the start of study 24 hours urinary protein excretion was similar in group l patients, group II patients and group III patients (1032.26±187.75 mg/24 hours in group l, 1042.40±156.42 mg/24 hours in group II and 1055.10±139.77 mg/24 hours in group III).After 10 months of treatment in group 1, in group 2 and in group 3 it declined to 779.23±193.18,756.12±195.07 and 618.01± 77.97 mg/24 hours respectively. So when we compared 24 hr urinary protein excretion in group I and III we got p value at end of study i.e. at 10th month of study<0.05(0.0053) suggestive of

significant decline in proteinuria in group III. Similar finding we got in comparing group II and group III (p value 0.0160).The decline in proteinuria was maximum with triple blockade and it differed significantly from single or double blockade.

Mean Arterial Pressure remained controlled in all patients throughout the 10 months duration of the study. It was similar in all patients at the 0 months of study, 116.79±5.89 mmHg in group I vs 115.07±7.46 mmHg in group II vs 111.84±7.82 mmHg in group III. It did not change significantly in three groups during the 10 months of study.At the end of 10 months of study it was 102.93±5.55 mmHg in group I vs 104.21±6.02mmHg in group II and 101.3±5.23 mmHg in group III. When we compared p value (by using unpaired t test) between group I and group III at 0 and 10 months it was >0.05 (non significant). Same finding we got in comparing group II and III. (P>0.05).

During the study adverse drug reaction, hyperkalemia was encountered. No patient in the group-I develop any of adverse drug reaction. patients in group containing RAMIPRIL + TELMISARTAN + EPLERENONE were always at higher risk of developing hyperkalemia as compared to patients on RAMIPRIL+ TELMISARTAN and patients on RAMIPRIL alone. (group 3>group 2>group 1) though the differences were non significant(p value>0.05).

Conclusions

Prevention of progression of chronic kidney disease is vital, especially in developing country like India, especially in Uttar Pradesh where most of the cases are diagnosed at later stage of disease because of lack of awareness, lower socio-economic status, where people cannot afford to expend their money on health . As the renin angiotensin system plays important role in progression of disease, it may be useful to block it at several levels. In our study we found that triple blockade is effective in decreasing proteinuria in non diabetic kidney disease patients. There is no added advantage of using Triple blockade compared to a Double or a Single blockade of RAAS with regard to improvement in eGFR or decrease in Mean Arterial Pressure of the subjects during the study period of 10 months. eGFR remained stable throughout study period, so we can predict that early initiation of blockade of RAAS at various levels with ACEIs, ARBs and ARAs, their combinations to delay the progression of CKD and prolong the time period till development of end stage renal disease in otherwise natural history of CKD to reach ESRD.[19,20,21]

As the study was of only 10 months duration and also there were some confounding factors like lack of randomized distribution and very small sample size, these conclusions cannot be generalized and further work is needed to prove utility of triple blockade of renin angiotensin system in comparison to double and single blockade.

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