RESEARCH PAPER | MEDICAL SCIENCE | Volume : 6 | Issue : 5 | May 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

Effectiveness and Tolerability of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in Patients With Chronic Kidney Disease

KEYWORDS: CKD, CVD, ACE inhibitors, ARB, Albuminuria.

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ABSTRACT *Chronic kidney disease (CKD) is a common clinical entity. Most common cause of End Stage Renal Disease (ESRD) worldwide is Diabetic Nephropathy. CKD is one of the independent risk factors for Cardiovascular Disease(CVD). This study was conducted to evaluate the beneficial effect of ACEi and ARB on the progression of renal failure & reduction of cardiovascular morbidity and mortality among patients suffering from chronic kidney disease. Our study demonstrates the administration of the ACEi / ARB in CKD patients was associated with lower all-cause mortality. The rate of progression to ESRD in the placebo group in our study is rapid, compared to those found in other studies conducted in similar populations.*

INTRODUCTION

Chronic kidney disease (CKD) is one of a common clinical entity. It constitutes a range of different processes of pathophysiology and associated with abnormalities in function of the kidney and a gradual decrease in GFR, which leads to end-stage renal disease (ESRD) wherein there is accumulation of body toxins, fluid and electrolytes which are normally cleared by the kidney. Most common cause of ESRD worldwide is Diabetic Nephropathy. CVD has effects on the nephrons that may initiate the CKD and is involved in the progression of disease due to reduced renal perfusion in heart failure and atherosclerosis of the renal vessels. CKD is one of the independent risk factors for CVD. ACEi and ARB in patients with CKD were resulted in reduction of proteinuria[1]. ACEi and ARB are considered standard therapies for certain Co morbid conditions such as coronary artery disease and congestive heart failure because of their favourable impact on mortality and cardiovascular outcomes. This study aims to explore the effectiveness and tolerability of both the class of drugs among CKD patients.

AIMS AND OBJECTIVES

To study the beneficial effect of ACEi and ARB on the progression of renal failure & reduction of Cardiovascular morbidity and mortality among patients suffering from chronic kidney disease.

To monitor the safety margin of the drugs and tolerability exhibited by the patients towards the adverse effects of both the classes of drugs.

MATERIALS AND METHODS

Study Design:

A Prospective, Therapeutic, Parallel Group Design, Randomized, Double Blinded, Placebo Controlled Study will be done on the patients.

Study Duration: 36 weeks

Study Participants:

The study will be conducted among outpatients as well as those admitted to the inpatient wards in the Department of Internal Medicine in KAPV Medical College & Mahatma Gandhi Memorial Government general Hospital who have been diagnosed as a case of CKD of any aetiology.

A case of CKD is assigned according to the guidelines given KDOQI. Stages of CKD are identified according to the eGFR. The eGFR is calculated by Cockraft-Gault equation with the help of plasma creatinine concentration (PCr), age, and sex and body weight of the patients.

Inclusion criteria:

Adult patients aged between 13 and 75 years diagnosed to have CKD.
Spot urine ACR ≥300 mg/g (ratio 0.3) or 24 Hrs urine protein >300mg.
The serum creatinine concentration above 1.4 mg/dl.
Written informed consent from the patients before enrolment made mandatory.

Exclusion criteria:

ACEi or ARB therapy within 3 months prior to the start of study
Treatment with corticosteroids, NSAIDs, or immunosuppressive drugs & other drugs potential to cause hyperkalemia and nephrotoxicity & drug's potential to cause hypotension
CAD or CVA patients who were already on ACEi or ARB
Known case or suspicion of B/L renal vascular disease
Serum Potassium > 5.5 meq/L
Decline in GFR >30% within 4 months without any explanation
Chronic cough, Angioedema, Allergic reactions.
Hypotension (systolic BP < 90mm Hg)

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Pregnancy
Breast feeding
Ineffective contraception

Note:
Patients who are not adherent to the treatment for more than 2weeks at any point of time was excluded from study
Patients who lost follow-up within 4months of initiation of the study, also excluded from this study.

Data Collection:
Patients who are admitted to the inpatient wards and those attending OPD of the Department of Internal Medicine at Mahatma Gandhi Memorial Government General Hospital attached to K.A.P.V.Govt.Medical college,Tiruchirapalli District, Tamil Nadu with symptoms, signs and laboratory investigations suggestive of CKD were chosen for the study. Baseline characteristics like general information of the patient, physical examination including height, weight, Blood Pressure, associated morbidity like diabetes mellitus, hypertension, cardio vascular diseases and lab investigations like Blood Sugar, Blood Urea, Serum Creatinine, Blood Hb, Complete Blood Cell Count, Total Count, Differential Count, Serum Sodium, Serum Potassium, Serum Uric Acid, Serum Phosphate, Lipid profile, Urine albumin, Urine creatinine and USG of the kidneys & Renal Doppler(Selected cases) are performed.

Interventions:
After explaining the nature of study and getting consent, the patients are divided into three groups viz; The Placebo control group, The ACEi group and ARB group. Each patient of Stage 1 & 2 given a sealed envelope containing the drug for a period of 28 days, each patient of Stage 3-5 given the drug for a period of 14 days, after which the patients are asked to come for review. One month buffer drugs also provided.

The Placebo consists of vitamin B-complex tablets 1 BD.
The ACEi consists of Tablet Enalapril 10 mg BD.
The ARB consists of Tablet Losartan 50 mg BD.
Co-interventions:
All patients were advised to reduce their sodium intake to approximately 2 g/day (corresponding to 5gms of sodium Chloride) and to consume 0.8 g protein/kg ideal body weight/day. Dietary advice regarding low potassium intake, given to all the patients. Exercise program compatible with cardiovascular health and tolerance, aiming for at least 30 minutes 5 times per week also advised. In addition to the above drugs patients were given drugs to treat etiology and control comorbidities like DM, SHT, dyslipidaemia, hyperuricemia etc. In hypertensive, BP control measures undertaken with drugs other than those employed in the trial.

Randomization method
The patients are stratified according to the severity of illness based on the eGFR as mild CKD(stage 1 and stage 2) and moderate CKD(stage 3 and stage 5). Patients in each stratum are then assigned to any of the three groups by simple randomization method using random number tables.

Allocation of the different treatment methods will be achieved by sequentially alphabetized opaque sealed envelopes containing the drugs.

Blinding
In order to avoid bias the technique of double blinding will be adopted wherein the tablets inside the envelope are prepared by the physician's friend who is not involved directly in the trial and as such the envelopes are named as A, B or C.

End points:
The primary end points:
- Doubling of the baseline serum creatinine concentration
- Serum potassium >5.5 meq/L
- The onset ESRD (as indicated by the initiation of dialysis)
- Hypotension (Systolic BP < 90mm Hg)
- >30% unexplained reduction in GFR within 4months of initiation of treatment
- Intractable dry cough, after exclusion of possible other etiologies.
- Death from any cause.

The secondary end points
Cardiovascular end point – CAD and/or HF resulting in hospitalization
Permanent neurologic deficit caused by CVA
Diagnosis of PVD

RESULTS AND ANALYSIS
Table :1
Distribution of patients from "Identified" as CKD to "Followed" in the study

Stage of CKD	*Identified*	*Excluded*	*Enrolled-For-Study*	*Lost to follow up within 4 months*	*Not adherent to the treatment*	No of Patients Followed (Studied)
1	7	1	6	0	0	6
2	15	2	13	0	1	12
3	51	4	47	2	1	44
4	70	19	51	5	3	43
5	93	57	36	9	6	21
Total	236	83	153	16	11	126

Even though 236 patients are identified as CKD, 83 (35.16%) patients met exclusion criteria, so not included, 16 (6.77%) patients lost follow up within 4months of study hence excluded from the study. 11 (4.64%) patients not adherent to the proposed treatment hence excluded from the study. Only 126 (53.38%) patients followed in this study out of 256 identified patients.

Table:2
CKD stages of the study population.

Stage	Frequency	%
1	6	4.8
2	12	9.5
3	44	34.9
4	43	34.1
5	21	16.7
Total	126	100.0

69% of CKD patients were in Stage 3&4. Stage 1 CKD contributed a minimum (4.8 %).

Table:3
Distribution of patients on the basis of treatment administered.

KIT	Frequency	%
Kit A	45	35.7
Kit B	37	29.4
Kit C	44	34.9
Total	126	100.0

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35.7 % of patients received kit A, 34.9% of patients received kit C and 29.4% of patients received kit B treatment.

Table:4
Aetiology of CKD in the study population

Etiology	Frequency	%
Diabetic Nephropathy	42	33.3
Undetermined	25	19.8
Chronic Glomerulonephritis	16	12.7
Hypertensive Nephrosclerosis	14	11.1
Chronic Interstitial Nephritis	8	6.3
Obstructive Uropathy	3	2.4
Miscellaneous	18	14.3
Total	126	100.0

Diabetes together with Hypertension being the most common etiology for nearly half of the patients. 19.8% of the other half are mainly due to undetermined etiology. A considerable proportion of CKD was due to glomerular and tubulointerstitial diseases (19%).

Table:5
Distribution of patients reached the end point.

	Frequency	Percent
Reached	62	49.21
Not reached	64	50.79
Total	126	100.0

Half of patients reached either primary or secondary end point, so treatment not continued. Only about half of the followed patients completed the study period of 36 weeks.

Table:6
Reasons for stopping treatment

Drop outs	Frequency	%
Hyperkalemia	11	8.73
Referred for renal transplant (Including one case of intractable cough)	5	3.97
Dialysis advised (Including one case of intractable cough)	9	7.14
>30% decrease in eGFR	14	11.11
Death (all-cause)	9	7.14
Cardiovascular events (Excluding death)	14	11.11
NA (Not applicable)	64	50.79
Total	126	100.0

By looking at various reasons for stopping the proposed treatment among the studied population, it is inferred that cardiovascular events and unexplained reduction in eGFR contributed the maximum of 11.11% each. Others are hyperkalemia 8.73%, indications for dialysis and death was 7.14% each. 3.97% of patients referred for renal transplantation to a higher institution.

Even though cough occurred in considerable number of patients (5/45, 11.1%) in Kit A group, it is tolerable in most of the patients and mandates termination of the treatment only in 2 (4.44%) patients among Kit A group. None of them suffered from cough in Kit B and Kit C group.

Hospitalization for CKD related illnesses
Maximum of 41 % admissions in the medical wards noted among kit B population for various CKD related illnesses. 13% among Kit A, 14% among Kit C.

Cardiovascular Events - Morbidity & Mortality
20% of cardiovascular events occurred in kit A group resulted in death**.** Maximum of 33.33% cardiovascular events resulted in death among Kit B group, none among kit C.

Cardiovascular mortality is notable in kit B. 100% death occurred in kit B group is due to cardiovascular events, when compared with all-cause mortality in the studied population. 50% of death in kit A group was due to cardiovascular events when compared to all-cause mortality, 0% in kit C group.

Mean Arterial Pressure recorded in the patients during the follow up period showed a gradual decrease in the BP from the baseline value. The MAP in the last few visits of the study period was lowest when compared to the initial period.

Table :7
Mean Distribution of eGFR of the study population measured during fixed intervals (weeks).

	Base	$_{,}^{nd}$	$_{,}$th	6th	8th	10th	12th	14th	16th	18th	20th	22nd	24th	26th	28th	30th	32nd	34th
Mean	37.1	27.3	31.0	25.6	30.5	25.2	31.8	25.8	32.2	26.6	33.6	27.6	35.7	29.6	35.4	30.2	36.3	30.1
S.D	22.5	11.2	16.9	10.3	16.6	9.8	15.7	8.8	16.0	8.2	14.4	7.2	13.3	6.8	11.9	6.4	12.3	6.0
Min	8.0	8.0	7.0	7.0	7.0	6.0	6.0	6.0	6.0	7.0	7.0	7.0	11.0	11.0	12.0	12.0	11.0	11.0
Max	103	60.0	92.0	67.0	79.0	60.0	88.0	75.0	92.0	67.0	83.0	67.0	85.0	75.0	85.0	67.0	88.0	60.0

Mean eGFR at the beginning of the study was 37.1ml/min**. Early sharp fall in mean eGFR noted during initial 2 weeks of initiation of treatment**. Then it followed an inconsistent trend throughout the study period reached mean eGFR 30.1ml/min at the end of the study.

Table :8 Mean Distribution of Serum Creatinine of the study population measured during follow up (weeks).

	Base	2	4th	6th	8th	10th	12th	14th	16th	18th	20th	22nd	24th	26th	28th	30th	32nd	34th
Mean	2.8	3.3	3.1	3.5	3.2	3.5	3.0	3.3	3.0	3.2	2.7	2.9	2.4	2.7	2.4	2.6	2.4	2.6
S.D	1.7	1.5	1.6	1.5	1.7	1.5	1.5	1.2	1.3	1.1	1.0	0.8	0.8	0.7	0.7	0.6	0.7	0.5
Min	0.6	1.0	0.6	0.9	0.7	1.0	0.7	0.8	0.6	0.9	0.7	0.9	0.8	0.8	0.8	0.9	0.8	1.0
Max	9.9	8.4	8.9	9.0	9.5	9.9	10.0	10.2	9.8	9.6	6.6	6.4	6.4	6.5	5.2	5.4	5.1	5.1

Mean creatinine at the beginning of the study was 2.8mgs %. Mean distribution of creatinine showed a rising trend up to 6weeks. Mean distribution of creatinine during 6th to 10th week is more or less in plateau**. Notable fall in mean creatinine noted after the 10th week of initiation of drugs**, reached its minimum mean value of 2.4 at the 24th week of study, followed by minor variations in its mean values.

Table :9
Mean Distribution of Spot ACR of the study population measured during fixed intervals (weeks).

	Base	$_{,}^{nd}$	$_{,}$th	6th	8th	10th	12th	14th	16th	18th	20th	22nd	24th	26th	28th	30th	32nd	34th
Mean	1.7	1.8	1.7	1.7	1.6	1.7	1.6	1.7	1.5	1.6	1.4	1.4	1.3	1.4	1.3	1.3	1.2	1.3
S.D	0.6	0.5	0.6	0.6	0.6	0.5	0.5	0.4	0.5	0.4	0.4	0.3	0.4	0.3	0.4	0.3	0.4	0.3

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Min	0.4	1.0	0.3	1.0	0.3	0.9	0.3	0.8	0.3	0.8	0.3	0.8	0.3	0.8	0.3	0.8	0.3	0.7
Max	3.6	3.7	3.8	2.01	3.5	3.5	3.6	3.7	3.8	3.9	3.2	3.1	3.2	3.3	3.1	3.2	3.3	3.4

Mean Spot urine ACR at the beginning of the study was 1.7, shown an inconsistent change with minor ups and downs with progressive decline towards the end of the study and reached mean spot ACR 1.2 at 32nd week

DISCUSSION

Our study demonstrates that treatment with either ACEi or ARB significantly reduces the rate of reduction and progression of clinical albuminuria (P value<0.05), the hallmark of CKD patients. The restoration of normo albuminuria was significantly more common in the group receiving either ACEi (Enalapril) at a dose of 20 mg daily or ARB (Losartan) at a dose of 100mg daily. These results are consistent with Parving HH, et al2 study. The rate of progression to ESRD in either diabetic or non diabetic CKD in the placebo group in our study is rapid, compared to those found in other studies conducted in similar populations. Interruption of the renin–angiotensin system with an ACEi probably induces the same degree of renoprotection as the use of an ARB. An initial drop in the glomerular filtration rate and percentage change in eGFR during the first three to four months of our study was steeper than the sustained decline during the remainder of the 34weeks period. Rate of progression of percentage change in eGFR had significant P (<0.05) value that indicates, progression towards ESRD is much faster among placebo group when compared with the ACEi / ARB group. The sustained, but slower decline in the glomerular filtration rate reflects the beneficial effect of treatment on the progression of diabetic as well as non diabetic CKD which is consistent with Mathiesen ER, Hommel E et al study3. Preventing or delaying the development of CKD is a major goal of treatment. Our findings indicate that this goal can be achieved if high-risk patients are identified early in the course of the disease and given appropriate renoprotective therapy with either ACEi or ARB. According to published guidelines for the treatment of CKD, routine screening of urine for microalbuminuria should be performed in all patients with risk factors. Unfortunately, patients at high risk for CKD are rarely identified early, which may help explain why diabetes and hypertension represents the single most important cause of ESRD in our country.

Our study demonstrates the administration of the ACEi / ARB was associated with lower all-cause mortality and lower mortality among the cardiovascular events occurring during the study compared to placebo group, which is consistent with Manjunath G et al study[4]. Dry cough due to ACEi occurs in a considerable number of patients, but intractable cough occurs rarely which mandates the termination of treatment. Cough as a side effect is not seen in any of those treated with ARB. Hypotension as a side effect of either class, did not occur in any of the subjects.

CONCLUSIONS

Treatment with ACEi or ARB in CKD (stage 1& 2) patients is associated with significant reduction in proteinuria (P<0.05), when compared with placebo.

Treatment with ACEi or ARB in CKD (stage 1& 2) patients is associated with significant reduction in percentage change in eGFR (P<0.05), when compared with placebo.

Treatment with ACEi or ARB in CKD (stage 1& 2) patients, when compared with placebo, is associated with significant reduction in high blood pressure (P<0.05).

Treatment with ACEi or ARB in CKD (stage 1& 2) patients, when compared with placebo, is associated with significant increase in the incidence of hyperkalemia(P<0.05).

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