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Randomized Controlled Trial of Treatment of Chronic Kidney Disease of Uncertain Aetiolgy with Enalapril

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Abstract

Introduction: A double blind placebo controlled randomized trial was conducted to investigate the effect of angiotensin-converting-enzyme (ACE) inhibitor enalapril on the progression of Chronic Kidney Disease (CKD) caused by chronic exposure to nephrotoxins.

Methods: 263 people aged 18-70 years diagnosed with CKD stages I, II or III who were not taking ACE inhibitors, who had no other chronic disease or contraindication for treatment with ACE inhibitors, were randomly assigned to enalapril or placebo. The main outcomes were albumin to creatinine ratio (ACR) and estimated glomerular filtration rate (eGFR).

Results: The mean systolic and diastolic blood pressure levels declined significantly in both enalapril and placebo groups with no significant difference in the two groups. There was a significant improvement in the albumin to creatinine ratio in the enalapril group compared to the placebo group ($p<0.005$). In the enalapril group, the mean albumin to creatinine ratio declined from 162.0 mg/g (SD 321.7) at baseline, to 55.4 mg/g (SD 122.4) at one year follow up; while in the placebo group, the mean albumin to creatinine ratio increased from 197.9 mg/g (SD 461.6) at baseline to 253.2 mg/g (SD 558.7), at one year follow up. In both groups, the eGFR declined significantly, during the 12 month follow-up, lower in the enalapril group, although with no significant difference. In the enalapril group the mean (eGFR) declined from 71.7 ml/min (SD 22.2) to 57.1 ml/min (SD16.1), while in the placebo group the mean eGFR declined from 73.8 ml/min (SD 24.2) to 54.7 ml/min (SD 20.3).

Conclusion: Enalapril is beneficial in reducing albuminuria in patients with chronic kidney disease of uncertain aetiology.

Keywords: Enalapril; Nephrotoxins; Chronic kidney disease of uncertain aetiology; Randomized control trial; Proteinuria

Introduction

Chronic Kidney Disease of uncertain aetiology, which cannot be attributed to diabetes mellitus, hypertension, glomerulonephritis, chronic pyelonephritis or other known etiologies, emerged in the North Central Region of Sri Lanka about two decades ago. Research upto date suggest that the most probable aetiology of this condition is long term exposure to nephrotoxic heavy metals and pesticides, together with deficiency of selenium and genetic susceptibility [1-3]. Chronic Kidney Disease due to longterm exspoure to environmental Nephrotoxins (CKDn) is slowly progressive, probably starting in the second decade of life, and asymptomatic until very advanced. Interstitial fibrosis and tubular atrophy with or without nonspecific interstitial mononuclear cell infiltrate is the dominant histopathological observation [2,4,5]. It has become a major public health problem causing serious economic and health consequences particularly in the lower socioeconomic communities in the North Central Region region in Sri Lanka. The health care costs for the management of these patients are considerable as those in end stage kidney disease require haemodialysis or transplantation. Further, these high technology interventions are not readily accessible to the majority with CKDn due to economic constraints. This highlights the need to find prevention strategies and treatment modalities for slowing and reversing the progression of CKDn in those with early stages of the disease [6,7].

Main treatment modalities to slow down the progression to chronic renal disease are likely to be through control of blood pressure and proteinuria. The importance of proteinuria as a significant risk factor for end stage kidney disease is well recognized [8]. Proteinuria reduction is considered as a surrogate marker of renoprotection in proteinuric renal disease [9]. Angiotensin II mediates hemodynamic effects as well as inflammation and fibrosis in the kidney, heart, and vasculature [10]. ACE inhibitors can boost renal repair by promoting

survival and repair of podocytes, preventing mesangial cell hyperplasia, and inducing glomerular endothelial cell remodeling. Other mechanisms include reduction of the expression of plasminogen activator inhibitor 1, an inhibitor of matrix degradation, decreased expression of collagen I and IV and TGF-b, and increased metalloproteinase activity [11]. Treatment that is targeted at reducing proteinuria has been shown to reduce progression of diabetic and non-diabetic kidney disease [12-18]. In most forms of proteinuric chronic renal disease, glomerular filtration rate continues to decline even when the initial insult has been removed [12]. Angiotensin converting enzyme inhibitors have been shown to be effective in retarding the progress of some forms of proteinuric kidney disease [12-34].

Currently there are no known treatment modalities to retard the progression of tubule-interstitial damage caused by nephrotoxins. If ACE inhibitors are found to be effective in retarding the progress of CKDn it will be a cost effective intervention for controlling this major public health problem in Sri Lanka.

The objective of this prospective double blind controlled study was to investigate the efficacy of enalapril, on the progression of CKDn by comparing and evaluating the effect of enalapril to a placebo on estimated glomerular filtration rate and albuminuria. We hypothesised that treatment with enalapril for 12 months in subjects with CKDn, would blunt decline in glomerular filtration rate and albuminuria compared with placebo.

Methods

Subjects living in two districts (Anuradhapura and Polonnaruwa) in the North Central Region of Sri Lanka, diagnosed as having CKDn in a population prevalence study (1), who satisfied inclusion criteria of the trial were invited to participate. The trial was registered in the Sri Lanka Clinical Trials Registry. Ethical clearance for the study was obtained from the Ethical Review Committee, Medical Research Institute, Ministry of Health, Sri Lanka. All participants gave written informed consent. Patients were potentially eligible if they were between 18 and 70 years and had albumin to creatinine ratio > 30mg/g and estimated glomerular filtration rate >15 ml/min. The response rate was 70.87% (n=427). Patients who were already on treatment with either an ACE inhibitor or an angiotensin receptor blocker were excluded (n=41). Another 54 patients were excluded based on other exclusion criteria (pregnancy-4, breast feeding-16, renal calculus with urinary tract dilatation-4, diabetes mellitus-7, malignancy-2, eGFR <15 ml/min^{-8}, recent history of acute kidney injury following snake bite-2, rheumatoid arthritis-2, glomerulonephritis-2, not willing to take western medicine-7). Repeat urine albumin to creatinine ratio was <30 mg/g in 69 patients. They were excluded from the study.

The patients with CKDn were graded as follows: (using the Chronic Kidney Disease Epidemiology collaboration (CKD- EPI) equation) (1)

Stage 1: persistent albuminuria (i.e. ACR ≥ 30 mg/g in initial and repeat urine sample) and eGFR >90 ml/min/1.73 m2

Stage 2: persistent albuminuria and eGFR 60-89 ml/ min/1.73 m2

Stage 3: persistent albuminuria and eGFR 30-59 ml/ min/1.73 m2

Stage 4: persistent albuminuria and eGFR 15-30 ml/ min/1.73 m2.

Patients who had no exclusion criteria (n=263) were randomized to treatment and placebo groups (Figure 1), and followed up at the Teaching Hospital Anuradhapura and Base Hospitals Padaviya and Medirigriya.

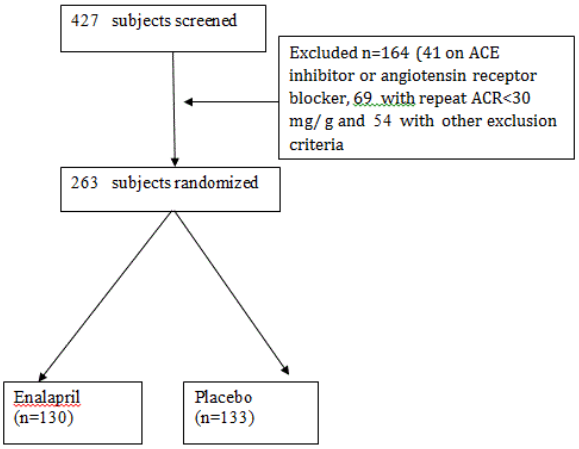

Figure 1: Recruitment and randomization of study subjects.

Following informed consent and completion of the baseline assessments, participants were randomized into the trial in a 11 ratio to placebo and enalapril arms. Randomization was provided by the World Health Organization using a computer-generated programme. Patients, investigators, monitoring members and outcome assessors were blinded to group assignment and intervention. The randomization list and blinding codes remained confidential, and only the study statistician had access to the randomization list.

At the baseline visit, laboratory tests were done for urine sediment analysis, urine albumin creatinine ratio, hemoglobin, white cell count and differential count, glucose, urea, HbA1C, uric acid, cholesterol, triglycerides, liver enzymes, bilirubin and 24 hour urine analysis. All analyses were performed according to standard procedures using automatic analyzers. Allocation concealment was extended to the laboratory personnel.

Participants were seen at two pre-randomization visits, and every month after randomization for 12 months. Those who were randomized were commenced on enalapril or placebo. Enalapril or placebo were started at low dose and titrated up based on blood pressure, proteinuria and serum potassium level. All treatments other than enalapril were continued at the discretion of the responsible physician. Blood pressure was measured as the mean of two measurements made in the seated position using a mercury sphygmomanometer. Measurement of urinary albumin creatinine ratio was performed on spot urine samples. During each visit and at the end of follow-up, it was assessed: compliance, symptoms, blood pressure, serum creatinine, and serum potassium and urine albumin to creatinine levels. The abbreviated Modification of Diet in Renal Disease (MDRD) equation was used to estimate eGFR.

Nine patients underwent renal biopsy on clinician direction (not as part of study protocol).

During the course of the study, 5 cases in the enalapril group and one case in the placebo group were switched over to losartan due to persistent dry cough. Five cases were withdrawn due to other reasons (Figure 1). Loss of appetite and hyperkalaemia necessitated the discontinuation of treatment in 2 patients in the enalapril group. One patient in the placebo group was withdrawn from the study due to

pregnancy. In the enalapril group, one patient (68 years) suffered a myocardial infarction and one patient (64 years) suffered a stroke.

Confidentiality of participants' data was protected by identifying patients on all study forms by a unique patient identification number. No study forms or other documents collected for the purpose of this study revealed the participant's name. No subject identifiers were presented on any files transmitted to any committee or any institution.

Statistical Analysis

In order to calculate the sample size and the power estimates two indices of improvement were selected; Estimated Glomerular Filtration rate (eGFR) and urine Albumin Creatinine Ratio (ACR). To ensure a power of at least 80%, at α=5% and to detect up to 14.04 ml/min discrepancies in eGFR rate and up to 20.77 mg/gr discrepancies in ACR rate, 51 cases and 51 controls were required. Assuming that eGRF rate and ACR rate follow a normal distribution with standard deviations of σ=30.84 ml/min and σ=50.52 mg/gr respectively, a sample size of 100 in each arm was required to ensure a statistical power of the test at least 80% at α=5% and account for 25% loss of cases and controls during follow up.

Data collected during the baseline visit and the 12 follow up visits were analyzed to test the change in albuminuria and estimated glomerular filtration rate in participants receiving enalapril and compared to participants receiving the placebo. Intention to treat analysis was used where the baseline allocation to active treatment or control treatment was used over all of the study period. Due to non-symmetric distributions the Wilcoxon rank-sum (Mann-Whitney) test was used for continuous data. Proportions were tested using Fischer´s exact test.

Results

As shown in table 1, there was no significant difference in the baseline characteristics (age, sex distribution, systolic and diastolic blood pressure, albumin to creatinine ratio and eGFR) in the enalapril and placebo groups.

Characteristics	Enalapril group (n=130)	Placebo group (n=133)	P value
Age (years) (mean, SD*)	47.7 (13.3)	48.3 (13.6)	0.18
Male sex (number, %)	61 (46.92)	51 (38.35)	0.17
Blood pressure (mmHg) Systolic mean, (SD)	124.5 (17.9)	125.2 (18.9)	0.76
Diastolic mean, (SD)	78.3 (10.6)	80.4 (11-6)	0.14
Albumin creatinine ratio (ACR)	162.0 (321.7)	197.9 (461.6)	0.47

Table 1: Baseline characteristics of patients in enalapril group and placebo group. *SD: Standard deviation.

The mean systolic and diastolic blood pressure levels declined significantly in both enalapril and placebo groups. The mean reduction in systolic blood pressure was 11.6 and 9.9 mm Hg (p=0.005, 0.031), respectively. The mean reduction in diastolic blood pressure was 9.7 and 8.3 mmHg (p ≤ 0.001), respectively. There was no significant difference between the enalapril and placebo groups in the reduction in systolic blood pressure and diastolic blood pressure.

There was a significant improvement in the albumin to creatinine ratio (ACR) in the enalapril group compared to the placebo group (p<0.005). In the enalapril group, the mean albumin to creatinine ratio declined from 162.0 mg/g (SD 321.7) at baseline, to 55.4 mg/g (SD 122.4) at one year follow up; while in the placebo group, the mean albumin to creatinine ratio increased from 197.9 mg/g (SD 461.6) at baseline to 253.2 mg/g (SD 558.7), at one year follow up (Table 2). The trend of ACR by month until the end of study in the placebo group and enalapril group is shown in figure 2 and 3 respectively, enalapril group demonstrating a decline throughout the study period.

Variable	Enalapril group (n=56)	Placebo group (n=48)	P
Systolic blood pressure (mmHg) mean, (SD*)	112.9 (15.5)	115.3 (12.2)	0.58
Diastolic blood pressure (mmHg) mean, (SD)	68.6 (12.4)	72.1 (7.1)	0.14
Albumin creatinine ratio (mg/g) mean, (SD)	55.4 (122.4)	253.2 (558.7)	0.005
Estimated glomerular filtration rate (eGFR) mean, (SD)	57.1 (16.1)	54.7 (20.3)	0.63

Table 2: Outcomes of enalapril group and placebo group. * SD: Standard deviation.

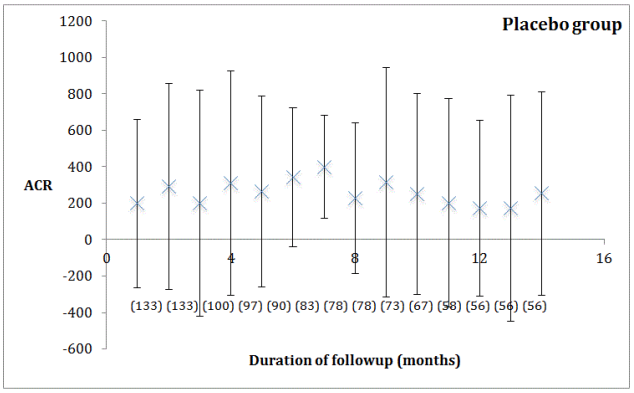

Figure 2: Effect of placebo on albumin to creatinine ratio (ACR) during follow up. Number of subjects at each follow up visit is shown in parentheses.

In both groups, the eGFR declined significantly (p<0.001) during the 12 month follow up. In the enalapril group the mean eGFR declined from 71.7 ml/min (SD 22.2) to 57.1 ml/min (SD16.1). In the placebo group the mean eGFR declined from 73.8 ml/min (SD 24.2) to 54.7 ml/min (SD 20.3). The decline in eGFR was less marked in the enalapril group, although there was no significant difference in the rate of decline between the two groups (Table 2). The trend of eGFR in the

placebo group and enalapril group during the 12 months is shown in figures 4 and 5 respectively.

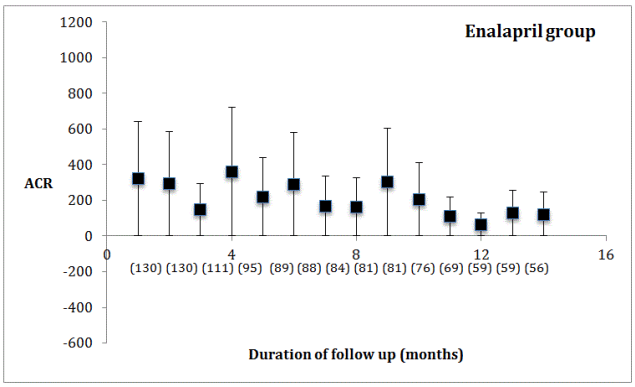

Figure 3: Effect of enalapril on albumin to creatinine ratio (ACR) during follow up. Number of subjects at each follow up visit is shown in parentheses. (Difference in ACR between placebo and enalapril groups was significant at all follow up visits after the first 3 months)

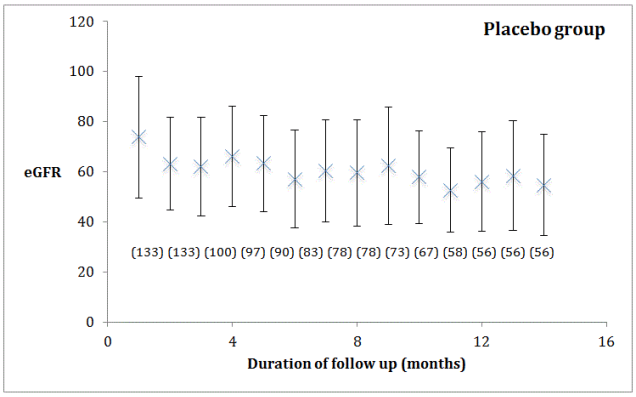

Figure 4: Effect of placebo on the estimated glomerular filtration rate (eGFR) during follow up. Number of subjects at each follow up visit is shown in parentheses.

All nine biopsy reports were reported as interstitial fibrosis and tubular atrophy with or without nonspecific interstitial mononuclear cell infiltrate as the dominant histopathological lesion.

Discussion

This is the first study which has investigated the efficacy of enalapril in the treatment of chronic kidney disease due to nephrotoxins. Our results demonstrate the beneficial effect of enalapril in decreasing ACR, with a significant reduction at the end and throughout the study period. We interpret these results as demonstrating that enalapril was effective in reducing albuminuria in these patients with nephropathy due to longterm exposure to environmental toxins (CKDn).

ACE inhibitors are proven to have beneficial effect on proteinuric chronic kidney disease [12-34]. Proteinuria plays an important role in the progression of both non diabetic and diabetic kidney disease and the pathological process implicated in this regard [16,35,36]. Ramipril efficacy in Nephrology Study showed that in proteinuric nephropathy of various aetiologies higher proteinuria at inclusion was associated with faster GFR decline. Ramipril therapy slowed glomerular filtration rate decline and end stage kidney disease development effectively [12,34]. The benefit of enalapril on slowing progression of renal disease has also been demonstrated in children with chronic disease [37] and patients on automated peritoneal dialysis [38].

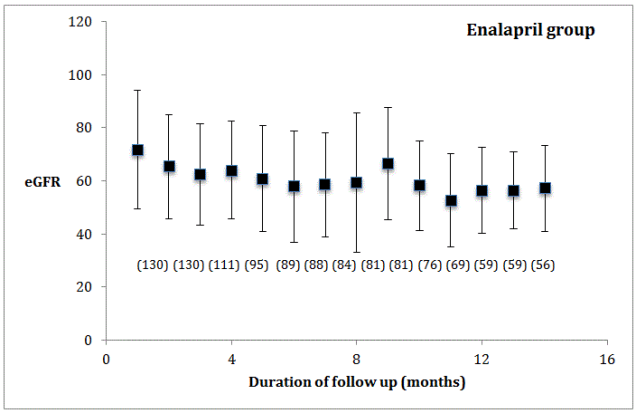

Figure 5: Effect of Enalapril on the estimated glomerular filtration rate (eGFR) during follow up. Number of subjects at each follow up visit is shown in parentheses.

In diabetic nephropathy, a 50% reduction in albuminuria was associated with a relative risk reduction for end stage renal disease of approximately 50% (8). Other studies have also shown a renoprotective effect of ACE inhibitors on progression of nondiabetic kidney disease [18,19,25,27,29]. A Cochrane review of 49 studies containing 12 067 diabetic patients at all stages of CKD found that ACEi and angiotensin receptor blockers improved end-stage renal disease and other outcomes (39).

In our study, there was no slowing of the rate of progression of nephropathy in the enalapril group or the placebo group, as reflected in the eGFR during the 12 month follow up. However, eGFR declined less in the enalapril group, although statistically the difference was not significant. A longer follow up period might demonstrate a beneficial effect, as reported in other studies with ACE inhibitors [12].

Blood pressure reduction itself lowers urinary protein reduction rate and retards the rate of GFR deterioration in chronic kidney disease [21,23,30,40]. Blood pressure reduction throughout the study was similar in both enalapril group and the control group. Hence, the beneficial effect of enalapril on proteinuria reduction appear to be independent of the antihypertensive effect and may be attributed to other pleiotropic effects [9,12].

No subjects in the trial were prematurely withdrawn due to acute deterioration of renal function. In the enalapril group 5 patients were switched over to losartan due to persistent dry cough. A meta-analysis of 17 randomized control trials has reported that there is a higher risk of dry cough in patients taking enalapril compared to losartan although the effects of enalapril and losartan on blood pressure and renal function are comparable [41]. Almost 30% of patients in the ACE inhibitor arm developed hyperkalemia higher than 5 mmol/l. However, hyperkalaemia necessitated the discontinuation of treatment only in 2

patients in the enalapril group. ACE inhibitors as well as angiotensin II receptor blockers are known to increase serum potassium concentrations in patients with chronic kidney disease. In a randomized, double-blind study treating stage 3 CKD with olmesartan and enalapril, 37% on olmesartan and 40% on enalapril developed hyperkalemia higher than 5 mmol/L [42].

Despite current available treatments, most patients with chronic kidney disease still continue to have residual proteinuria and progression of disease [13,15,16,18]. For example, in controlled trials, about one fifth of patients with severe diabetic nephropathy who have been intensively treated still progress to end stage renal disease in about 3 years [13,15].

CKDn has a major negative impact on a range of clinical outcomes including quality of life and often result in catastrophic spending due to the high cost of longterm care including renal dialysis. There is therefore a need for the development of new strategies to reduce exposure to nephrotoxins and to arrest the rate of loss of renal function to lessen the need for dialysis. Presence of varying degrees of mononuclear inflammatory cells in different stages of CKDn suggests activation of immune competent cells by the primary nephrotoxic injury. Use of immunosuppression to control the immune activation in selected cases will be a hypothesis to test [43,44].

Limitations: Attrition of subjects at different stages was the main limitation of the study. However the effect of enalapril on reduction of proteinuria could be demonstrated at all stages of follow up and was significant after the first 3 months (Figure 3).

At present chronic kidney disease attributed to environmental toxins has been reported from many parts of the world [3]. This study is limited to a sample of individuals from Sri Lanka, diagnosed as having chronic kidney disease attributed to environmental nephrotoxins. However, these results may have implications for treatment of people living in other parts of the world, who have chronic kidney disease due to longterm exposure to environmental toxins such as heavy metals and pesticides. Further studies are needed in different settings to investigate the efficacy of ACE inhibitors in delaying the progress of CKDn.

Conclusions

Enalapril reduces the mean albumin to creatinine ratio at the end and throughout the study period. The blood pressure reduction was similar in groups, the enalapril and the placebo group; the beneficial effect of enalapril on proteinuria reduction is independent of its antihypertensive effects. Further longterm studies are needed to investigate the beneficial effect of ACE inhibitors on CKDn.

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Conflict of interest

None of the authors have any conflict of interest.

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