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A COMPARATIVE STUDY OF EFFECTIVENESS OF ENALAPRIL, LOSARTAN AND THEIR COMBINATION IN REDUCTION OF PROTEINURIA AMONG PATIENTS OF TYPE 2 DIABETIC NEPHROPATHY

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ABSTRACT

Background

Proteinuria is a hallmark of DN (Diabetic Nephropathy), and its reduction is crucial for renal protection. ACE (Angiotensin-Converting Enzyme) inhibitors and ARBs (Angiotensin Receptor Blockers) are known to lower proteinuria and slow DN progression. However, limited data exist comparing the effectiveness and tolerability of enalapril and losartan individually and in combination in achieving anti-proteinuric effects.

Methods

This interventional study enrolled 62 newly diagnosed patients with type 2 diabetic nephropathy attending the outpatient nephrology department at Government Medical College, Kottayam. Patients were randomly assigned to receive either enalapril (n=30) or losartan (n=32), with dose titration every 2 months up to the maximum dose until achieving a 50% reduction in 24-hour urine protein (enalapril 40 mg, losartan 100 mg). Patients not achieving target proteinuria reduction were switched to combination therapy. Adverse events, including hyperkalemia, rise in creatinine, and cough, were monitored. Statistical analysis was done using SPSS version 16.

Results

Both the enalapril and losartan groups achieved a significant reduction in proteinuria during the study. At the first follow-up, Enalapril showed a greater reduction (73.3%) compared to Losartan (31.2%, $p = 0.001$). However, by the end of the study, 86.7% of Enalapril and 84.4% of Losartan patients achieved the target, showing no statistically significant difference ($p = 0.798$). Combination therapy was required in two patients (one from each group). Adverse effects were minimal and comparable, with hyperkalaemia occurring in 6.2% of losartan-treated patients and cough in 3.3% of enalapril-treated patients.

Conclusion
Enalapril and losartan are equally effective in reducing proteinuria in type 2 diabetic nephropathy with similar adverse event profiles. Either drug may be considered for initial anti-proteinuria therapy, or combination treatment may be reserved for resistant cases. Further studies with larger populations and extended follow-up are recommended to validate these findings.

Keywords: Diabetic Nephropathy, Proteinuria, Enalapril, Losartan, ACE Inhibitors, ARBs, Combination Therapy.

INTRODUCTION

With the global epidemic of type 2 diabetes mellitus, DN (Diabetic Nephropathy) has emerged as the leading cause of ESRD (End-Stage Renal Disease) worldwide.[1] Diabetic nephropathy is clinically defined by the presence of macroalbuminuria-urinary albumin excretion exceeding 300 mg in a 24-hour collection-and is characterized by a progressive increase in proteinuria, a decline in GFR (Glomerular Filtration Rate), hypertension, and heightened cardiovascular morbidity and mortality.[2,3,4,5] The most critical predictors for these adverse outcomes include hyperglycemia, proteinuria, hypertension, and hyperlipidemia.[2]

Proteinuria is a hallmark of diabetic nephropathy and plays a central role in its pathogenesis. Its progression is strongly associated with increased risk of both renal and cardiovascular events. Consequently, a reduction in proteinuria is now considered not merely a marker of therapeutic response but also a surrogate endpoint for renal protection. Evidence suggests that a 50% reduction in albuminuria within the first six months of therapy corresponds with a 36% reduction in renal endpoint risk, a 45% reduction in risk of progressing to ESRD, and an 18% lower risk of cardiovascular events during subsequent follow-up.[2]

The RAAS (Renin-Angiotensin-Aldosterone System) has been implicated in the development and progression of microalbuminuria-an early indicator of renal impairment that typically advances to macroalbuminuria in patients with type 2 diabetes.[6] Inhibiting the RAAS, either via ACE (Angiotensin-Converting Enzyme) inhibitors or angiotensin II receptor blockers, has been shown to delay the progression of chronic kidney disease and to offer significant renal protection in patients with diabetes.[2]

While optimal glycemic control remains the cornerstone of diabetic nephropathy management,[3] additional therapeutic strategies focus on blood pressure control and reduction of proteinuria using ACE inhibitors, ARBs, aldosterone antagonists, renin inhibitors, and dietary protein restriction.[3] Proteinuria should thus be recognized as both an independent renal risk factor and a critical treatment target in diabetic nephropathy.[2]

AIMS AND OBJECTIVES

The primary objective of this study is to compare the effectiveness of enalapril, losartan, and their combination in achieving a 50% reduction in proteinuria among patients with type 2 diabetic nephropathy. Additionally, the study aims to evaluate and compare the adverse reaction profiles of these treatment regimens to assess their safety and tolerability in this patient population.

MATERIALS AND METHODS

This was a prospective, randomized, open-label, comparative interventional study conducted at the Department of Nephrology, Government Medical College, Kottayam, over a period of one year from January 2013 to December 2013. The study aimed to evaluate the effectiveness of enalapril, losartan, and their combination in achieving a 50% reduction in proteinuria among patients with type 2 diabetic nephropathy, along with assessing their adverse reaction profiles. A total of 62 newly diagnosed patients meeting the eligibility criteria were randomly assigned into two treatment groups to receive either enalapril or losartan. Patients not achieving the target reduction in proteinuria with monotherapy were shifted to a combination treatment group.

Inclusion and Exclusion Criteria

Patients of either sex diagnosed with type 2 diabetic nephropathy, having proteinuria >500 mg/day and serum creatinine <3 mg/dL, were eligible for inclusion. All participants were newly diagnosed and provided written informed consent. Patients were excluded if they were unwilling to participate, had secondary causes of glomerular nephropathy, diastolic blood pressure <80 mmHg, serum potassium >5.5 mEq/L, or had a bruit over renal arteries suggestive of renovascular disease.

Sample Size Calculation

The sample size was based on a previous randomized study conducted at the Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders, which assessed the effect of enalapril and losartan on proteinuria in type 2 diabetic nephropathy patients. Using a mean difference (d) of 1.01 g/day and a SD (Standard Deviation) of 1.32, the required sample size was calculated using the formula:

$$n = \frac{2 \times (Z\alpha + Z\beta)^2 \, SD^2}{d^2}$$

$$\frac{2 \times (1.96 + 0.84)^2 \times 1.32^2}{(2.18 - 1.17)^2}$$

The calculated sample size was 27 patients per group. After accounting for a 15% dropout rate, the total sample size required was 62 patients.

Data Collection Procedure

After obtaining informed consent, all patients underwent detailed clinical evaluation, including history, physical examination, and laboratory investigations. Baseline data collected included age, blood pressure, edema, evidence of retinopathy, fasting blood sugar, 24-hour urine protein, serum creatinine, and serum potassium. Patients in the Enalapril group (n=30) started with 2.5 mg once daily, with dose titration every 2 months up to 40 mg based on proteinuria reduction and safety parameters. Similarly, the Losartan group (n=32) began with 25 mg once daily and was titrated to a maximum of 100 mg. Patients failing to achieve a 50% reduction in proteinuria with maximum monotherapy were shifted to combination therapy, with doses similarly titrated. Patients were followed up every two months to monitor 24-hour urine protein, serum creatinine, potassium levels, and adverse effects such as cough or hyperkalemia.

Statistical Analysis

The collected data were coded and entered into Microsoft Excel and subsequently analyzed using SPSS software version 16. Categorical variables were compared between the two treatment groups using the Chi-square test or Fisher's exact test, as appropriate. Continuous variables were analyzed using the Student's *t*-test for normally distributed data, and non-parametric tests were applied for data that did not follow a normal distribution. For non-normally distributed variables, results were expressed as a median with IQR (Interquartile Range).

RESULTS

Variable	Enalapril (n=30)	Losartan (n=32)	P-Value
Age (Median, IQR)	59.5 (10)	56 (12)	0.268
Sex (Male)	19 (63.3%)	16 (50%)	0.290
Systolic BP (Median, IQR)	140 (20)	150 (20)	0.057
Diastolic BP (Median, IQR)	80 (10)	80 (20)	0.589
FBS (Median, IQR)	120 (17)	140 (55)	0.065

Creatinine (Median, IQR)	1.3 (0.62)	1.2 (0.41)	0.252
Potassium (Median, IQR)	4.2 (1)	4.0 (1)	0.056
24-hour Urine Protein (Median, IQR)	925 (500)	955 (1010)	0.468
Hypertension	12 (40%)	17 (53.1%)	0.301
Diabetic Retinopathy	29 (96.7%)	29 (90.7%)	0.613
Dyslipidemia	3 (10%)	7 (21.9%)	0.304
Coronary Artery Disease	5 (16.7%)	6 (18.8%)	0.830
Table 1: Baseline Characteristics of the Study Groups			

In Table 1, there were no statistically significant differences between the enalapril and losartan groups in any of the baseline characteristics, indicating that the groups were comparable at the start of the study.

Follow-Up	**Enalapril (n=30)**	**Losartan (n=32)**	**P-Value**
First Follow-up	22 (73.3%)	10 (31.2%)	0.001
Second Follow-up	23 (76.7%)	24 (75.0%)	0.878
Third Follow-up	25 (83.3%)	27 (84.4%)	1.000
Any Time During Study	26 (86.7%)	27 (84.4%)	0.798
Table 2: Achievement of 50% Reduction in Proteinuria			

In Table 2, a significantly higher percentage of patients in the enalapril group achieved a 50% proteinuria reduction at the first follow-up (p=0.001). However, there were no significant differences between the groups in subsequent follow-ups or overall during the study period.

Time Point	**Enalapril (Median, IQR)**	**Losartan (Median, IQR)**	**P-Value**
First Follow-up	350 (390)	600 (852)	0.020
Second Follow-up	155 (180)	254.5 (401)	0.062
Third Follow-up	112.5 (44)	140 (181)	0.011
Table 3: Proteinuria at Various Follow-ups			

In Table 3, the enalapril group had significantly lower proteinuria levels than the losartan group at the first and third follow-ups. At the second follow-up, the difference was not statistically significant.

Dose (mg)	**Number of Patients**	**Percentage (%)**
2.5	22	73.3%
5	3	10.0%
10	1	3.3%
No Reduction	4	13.3%
Table 4: Dose-wise Achievement of 50% Proteinuria Reduction – Enalapril		

In Table 4, most patients (73.3%) achieved a 50% reduction in proteinuria with the lowest dose of enalapril (2.5 mg), showing high efficacy even at minimal dosing.

Dose (mg)	**Number of Patients**	**Percentage (%)**
25	10	31.2%
50	14	43.8%
100	3	9.4%
No Reduction	5	15.6%
Table 5: Dose-wise Achievement of 50% Proteinuria Reduction – Losartan		

In Table 5, losartan at 50 mg showed the highest effectiveness (43.8%) in reducing proteinuria. A stepwise dose increase resulted in greater efficacy, although a subset (15.6%) showed no response.

Parameter	Enalapril (Median, IQR)	Losartan (Median, IQR)	P-Value
Serum Creatinine (mg/dL)	1.3 (0.50)	1.165 (0.38)	0.251
Serum Potassium (mEq/L)	4.4 (0.60)	4.1 (0.40)	0.179
Systolic BP (mm Hg)	130 (20)	135 (50)	0.480
Diastolic BP (mm Hg)	80 (0)	80 (0)	0.637
Table 6: Biochemical and Clinical Parameters at Achievement of 50% Reduction			

In Table 6, there were no statistically significant differences in serum creatinine, potassium levels, or blood pressure at the time patients achieved a 50% reduction in proteinuria between the two groups.

Adverse Event	Enalapril (n=30)	Losartan (n=32)	P-Value
Rise in Creatinine	4 (13.3%)	4 (12.5%)	1.000
Hyperkalemia	0 (0%)	2 (6.2%)	0.492
Cough	1 (3.3%)	0 (0%)	0.484
Table 7: Adverse Drug Reactions			

Table 7 showed that both drugs were well tolerated. Hyperkalemia occurred only in the losartan group (6.2%), and cough was reported only in the enalapril group (3.3%). However, none of the differences were statistically significant.

DISCUSSION

Proteinuria is a hallmark feature of DN, and its progression significantly increases the risk of renal and cardiovascular morbidity and mortality. It is recognized as an independent renal risk factor and should be an essential therapeutic target in the management of DN. The RAAS (Renin-Angiotensin-Aldosterone System) plays a pivotal role in the progression from microalbuminuria to macroalbuminuria in patients with type 2 diabetes and overt nephropathy. Blocking RAAS with ACE inhibitors or ARBs has been shown to slow the progression of chronic renal insufficiency in diabetic patients, and optimizing this blockade provides more effective renal protection. Every 50% reduction in albuminuria within the first 6 months has been associated with a 36% reduction in risk for renal endpoints, a 45% reduction in the risk of ESRD (End-Stage Renal Disease), and an 18% reduction in cardiovascular events during subsequent follow-up.[2] Thus, reducing proteinuria is a crucial goal in managing diabetic nephropathy.

This study was conducted to evaluate the effectiveness of enalapril, losartan, and their combination in achieving a 50% reduction in proteinuria and to compare their adverse reaction profiles in patients with type 2 diabetic nephropathy. A total of 62 newly diagnosed patients were enrolled, ranging in age from ≥30 to >70 years. In the enalapril group, most patients were between 40–69 years, with the majority in the 60–69 age group. In the losartan group, most were aged 50–69 years. These findings align with existing literature, where the mean age in the enalapril group was 57.8 ± 10.5 years and 59.2 ± 9.2 years in the losartan group.[7]

The gender distribution showed a male predominance, with 35 males and 25 females overall, which is consistent with previous studies.[7] In the enalapril group, 63.3% were male, whereas the losartan group had an equal distribution between males and females.

Baseline characteristics, including median age, sex ratio, systolic and diastolic blood pressure, fasting blood sugar, serum creatinine, serum potassium, 24-hour urine protein, and comorbidities such as hypertension, dyslipidemia, and coronary artery disease, were compared between the two groups. No statistically significant differences were observed ($p > 0.05$ for all), indicating that the two groups were comparable at baseline.

Effectiveness of the two drugs was assessed based on the achievement of a 50% reduction in proteinuria. A statistically significant difference was observed at the first follow-up, where 73.3% of patients in the enalapril group achieved the target compared to only 31.2% in the losartan group ($p = 0.001$). However, at the second and third follow-ups, the percentages were similar between groups, with no statistically significant difference ($p = 0.878$ and $p = 1.000$, respectively). Overall, during the entire study period, 86.7% of patients in the Enalapril group and 84.4% in the losartan group achieved a 50% proteinuria reduction, which was not statistically significant ($p = 0.798$). This is consistent with the literature indicating no significant difference in the renoprotective effects of enalapril and losartan.[8]

Individually, both enalapril and losartan were effective in significantly reducing proteinuria across all follow-ups, as shown by the Wilcoxon signed-rank test ($p < 0.001$ for enalapril, $p = 0.001$ for losartan). These results align with previous studies where both drugs significantly reduced urinary albumin excretion ($p < 0.001$). A meta-analysis also supports that monotherapy with either ARBs or ACE inhibitors provides comparable reductions in proteinuria, irrespective of the underlying renal pathology.[9]

Comparing proteinuria levels between the two groups using the Mann-Whitney U test revealed that the enalapril group had significantly lower median proteinuria at the first ($p = 0.02$) and third ($p = 0.011$) follow-ups. No significant difference was observed at the second follow-up.

Dose-response analysis showed that 73.3% of patients achieved a 50% reduction in proteinuria with enalapril at 2.5 mg. An additional 10% and 3.3% of patients achieved the target with 5 mg and 10 mg doses, respectively, indicating that the majority responded to the lowest effective dose. In the losartan group, 43.8% of patients responded to the 50 mg dose, and 31.2% responded to the 25 mg dose, suggesting an effective anti-proteinuric dose range of 25–50 mg.

Biochemical parameters such as serum creatinine, potassium, and blood pressure at the time of 50% proteinuria reduction were also compared between the two groups. No statistically significant differences were observed, confirming the comparable safety profile of both drugs.

Adverse events were infrequent and comparable between groups. Cough occurred only in the enalapril group (3.3%), aligning with previous reports that this side effect is typical of ACE inhibitors and not seen with ARBs.[7] Rise in creatinine occurred in both groups at similar rates (13.3% in enalapril vs. 12.5% in losartan; $p = 1.000$), and hyperkalemia occurred in 6.2% of losartan-treated patients but was absent in the enalapril group ($p = 0.492$). These results are consistent with findings from other studies, which noted no significant differences in serum creatinine and potassium changes between the two drug groups ($p = 0.71$, $p = 0.24$).[10] Furthermore, serum potassium remained stable even at 40 mg of enalapril, consistent with literature indicating the tolerability of enalapril at higher doses.[10]

Among the 62 patients, one patient in each group failed to achieve a 50% proteinuria reduction even after the maximum doses (enalapril 40 mg and losartan 100 mg). These patients were subsequently treated with combination therapy. In both cases, the addition of the alternate drug led to the achievement of the target proteinuria reduction within two months without any adverse effects. Due to the limited number of patients in the combination group, statistical analysis was not performed.

CONCLUSION

It can be concluded that both Enalapril and Losartan are equally effective in achieving a reduction in proteinuria among patients with type 2 diabetic nephropathy, with no significant difference in their adverse reaction profiles. However, to confirm the long-term equivalence in efficacy and safety, further studies involving larger sample sizes and extended follow-up periods are warranted.

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