ORIGINAL ARTICLE

THE COMPARISON OF EFFICACY BETWEEN LOSARTAN AND DILTIAZEM AS ANTIPROTEINURIC AGENT IN NON-DIABETIC RENAL DISEASES

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Background: Multiple options have been tried to counter the proteinuria secondary to renal diseases. Clinicians and researchers are trying to find the best option for this purpose. **Objective:** To compare efficacy of Losartan and Diltiazem in management of proteinuria in non-diabetic renal diseases at a tertiary care hospital of Pakistan. It was a Quasi-experimental study, conducted at the Department of nephrology Pak Emirates Military Hospital Rawalpindi**.** Five months, November 2020 to March 2021. **Methods:** A total of 122 patients of non-diabetic renal diseases with significant proteinuria were included in the study. They were randomly divided into two groups via lottery method. Group I received losartan while group II received Diltiazem in standard dose for three months. After three months they underwent 24 hours' urinary protein levels and divided into complete, partial and non-responders to treatment. Age, gender, duration of illness and type of antiproteinuric treatment was correlated with response to treatment among the study population. **Results:** Out of 122 patients, 80 (65.6%) were males while 42 (34.4%) were females. Membranous nephropathy 20 (16.4%) was the commonest non-diabetic renal disease seen in our study participants. Thirty (24.5%) had complete remission after three months of treatment, 60 (49.2%) had partial response while 32 (26.3%) had no response to treatment. Chi-square test revealed that use of losartan had statistically significant relationship (p-value<0.001) with good response among the study participants. **Conclusion**: Membranous nephropathy leading to proteinuria was the commonest non-diabetic renal disease encountered in our setup. Around 2/3rd of our patients showed either complete or partial response to treatment and Losartan was superior to Diltiazem in achieving response in our study participants.

Keywords: Diltiazem; Losartan; Proteinuria; Non-diabetic renal disease

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INTRODUCTION

Renal diseases have been an area of interest for clinicians and researchers because effects of malfunctioning of this organ does not confine to one system but overall wellbeing of the human body is challenged especially when this dysfunction becomes chronic.[1] Epidemiological data from across the globe suggests that renal diseases are highly prevalent in all parts of the world with pattern clearly showing increased incidence in the last decade.[2,3] Treatment of renal diseases involve a multidisciplinary and multimodality approach ranging from dietary modifications to kidney transplant.[4]

Various metabolic pathways get affected in chronic renal failure leading to multiple biochemical and haematological abnormalities.[5]Various diabetic and non-diabetic renal conditions may lead to proteinuria which if prolonged may lead to severe health related consequences. In addition to treatment of underlying cause, various treatment options have been tried to counter the proteinuria among patients suffering from renal diseases due to any cause.[6]

Various studies have been done in past to look for various options for managing the patients with renal disease presenting with proteinuria. Praga *et al*. in 2003 conducted a double-blind randomized trial with an intention to compare the efficacy of losartan and amlodipine for proteinuria found in non-diabetic renal disease. They concluded that Losartan was more effective as compared to amlodipine in decreasing the proteinuria in patients with non-diabetic protein-uric renal diseases.[7] Lee *et al*. in 2011 studied the effect of losartan on proteinuria and urinary angiotensinogen excretion in non-diabetic renal disease patients. They revealed that after two years of treatment with Losartan, proteinuria in non-diabetic renal disease patients decreased significantly as compared to age and gender matched controls. GFR also remained more stable in group having Losartan as compared to controls.[8] An interesting

network meta-analysis was published by Ye *et al*. in 2020 comparing the proteinuria management with different angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for normotensive patients with chronic kidney disease. It was concluded that combination therapy of Olmesartan plus temocapril appeared to be the most efficacious option for reducing proteinuria in patients with CRF without evidence of hypertension. They suggested that treatment of proteinuria should be tailored according to each patient evaluating the risks and benefits for available options.[9]

Renal diseases are common in our part of the world and huge number of patients remain undiagnosed and hidden. Sometimes proteinuria is the accidental finding on routine investigations. Shams *et al*. published a study from Mardan looking for the effect of atorvastatin on proteinuria among patients of CKD and concluded that 40 mg of atorvastatin is effective and optimal dose for reducing proteinuria in CKD patients.[10] Limited local data has been available regarding use of antihypertensive agents to control proteinuria among non-diabetic renal disease patients. We therefore planned this study with the aim to compare the efficacy of Losartan and Diltiazem in management of proteinuria in non-diabetic renal diseases at a tertiary care hospital of Pakistan.

MATERIAL AND METHODS

This quasi-experimental study was conducted at the department of nephrology in Pak Emirates Military Hospital Rawalpindi from November 2020 to March 2021. Sample size was calculated by WHO Sample Size Calculator with population prevalence proportion of proteinuria as 8.6%.[11] Non probabilities Consecutive sampling technique was used to gather the sample. All patients of non-diabetic kidney disease between the age of 18 and 65 were included in the study. Diagnosis of kidney disease was done as per National Kidney Foundation/Kidney Disease Outcome Quality Initiative (NKF/KDOQI) 2002.[12] Exclusion criteria were the patients who were diabetic or dependent on dialysis already or had few sessions of any kind of renal replacement therapy. Patients who were candidates for renal transplant were also not included in the study. Patients with any renal or extra renal malignancies or those who were not compliant to low protein diet were excluded as well. Pregnant females were also part of the exclusion criteria. Patients with evidence of any extra-renal cause of proteinuria were also excluded from the study.

Ethical review board committee of the hospital granted ethical approval for this study via letter number (A/28/EC/213/2020). Written informed consent was taken from all the potential participants of this study before the start of study after complete description of the study. Non-diabetic renal disease patients fulfilling the above-mentioned inclusion and exclusion criteria presenting at nephrology OPD were included in the study. Group I received losartan while group II received Diltiazem in standard dose for three months in addition to routine treatment of kidney disease and underlying illness. 24 hours urinary protein was carried out on all the study participants at baseline, before the start of medications and then after three months of treatment. Patients were classed into complete, partial and non-responders to treatment on the basis of 24 hours urinary protein levels. Age, gender, duration of illness and type of antiproteinuric treatment was correlated with response to treatment among the study population.

Proteinuria at the start of study was defined as proteins in urine >3gm/day[13]
Response was defined as:[14]
Complete responders- proteins in urine <500 mg/day
Partial responders- proteins in urine 500–3000 mg/day
Non-responders- proteins in urine >3 gm/day

Descriptive statistics were used in this study. Mean and standard deviation was calculated for age and duration of illness in patients in both the groups. Frequency and percentage were calculated for gender of the patients, types of non-diabetic renal diseases and response to treatment. Chi-square was applied to look for the relationship of age, gender, duration of illness and type of antiproteinuric treatment with response to antiproteinuric treatment. All statistical analysis was performed using Statistics Package for Social Sciences version 24.0 (SPSS-24.0). Differences between groups were considered significant if *p*-values were less than or equal to 0.05.

RESULTS

One hundred and twenty-two patients were finally recruited in the study from which data could be collected and analysed. Out of 122 patients, 80 (65.6%) were male while 42 (34.4%) were female. Table-1 summarizes the general characteristics of study participants. Mean age of patients in group I was 34.944±7.75 years while mean age of patients in group II was 35.721±7.59 years. Table-2 shows the distribution of types of non-diabetic renal diseases seen in study participants. Membranous nephropathy 20 (16.4%) was the commonest non-diabetic renal disease seen in our study participants.

Thirty (24.5%) had complete remission after three months of treatment, 60 (49.2%) had partial response while 32 (26.3%) had no response to treatment. Chi-square test revealed that use of losartan had statistically significant relationship (*p*-value<0.001) with good response among the study participants (Table-3).

Table-1: Characteristics of patients with chronic kidney disease included in the study (n=122)

Parameters	
Age	
Mean Age in group I (years)	34.944±7.75 years
Mean age in group II	35.721±7.59 years
Type of treatment	
Group I (Losartan)	68 (55.7%)
Group II (Diltiaezm)	54 (44.3%)
Duration of illness	
Mean duration of disease in group I	3.1±4.125 years
Mean duration of disease in group II	3.8±3.766 years
Gender	
Male	80 (65.6%)
Female	42 (34.4%)
Overall response to treatment	
Complete responders	30 (24.5%)
Partial responders	60 (49.2%)
Non-responders	32 (26.3%)

Table-2: Types of non-diabetic renal diseases found in study participants (n=122)

Disease	Frequency (%)
Membranous nephropathy	20 (16.4)
Focal segmental glomerulo-sclerosis	18 (14.7)
Hypertensive nephro-sclerosis	14 (11.5)
Lupus nephritis	13 (10.6)
Interstitial nephritis	17 (13.9)
Minimal change disease	11 (9.1)
Membranoproliferative Glomerulonephritis	11 (9.1)
Multiple Myeloma	10 (8.2)
Rhabdomyolysis	05 (4.1)
Amyloidosis	03 (2.4)

Table-3: Relationship of type of antiproteinuric treatment and other variables with response to treatment

Socio demographic factors	Complete responders	Partial responders	Non -responders	*p*-value
Age				
50 year or less	17 (56.7%)	32 (53.3%)	19 (59.4%)	0.851
>50	13 (43.3%)	28 (46.7%)	13 (40.6%)	
Gender				
Male	20 (66.7%)	41 (68.3%)	19 (59.4%)	0.687
female	10 (33.3%)	19 (31.7%)	13 (40.6%)	
Duration of Illness				
< 2 years	16 (53.3%)	43 (71.7%)	20 (62.5%)	0.221
>2 years	14 (46.7%)	17 (28.3%)	12 (37.5%)	
Type of treatment				
Losartan	23 (76.7%)	38 (63.3%)	7 (21.9%)	<0.001
Diltiazem	07 (23.3%)	22 (26.7%)	25 (78.1%)	

DISCUSSION

Multiple options have been tried to counter the proteinuria secondary to renal diseases and still clinicians and researchers are trying to find the best option for this purpose. Disease burden is not less regarding non diabetic renal ailments and it's like an iceberg with minimum patients getting the right management. Liu *et al*.[15] published an interesting meta-analysis in 2017 and included eleven randomized controlled trials with over 700 patients to investigate the efficacy and safety of pentoxifylline plus angiotensin-converting enzyme inhibitors /angiotensin receptor blockers for proteinuria and kidney function in patients with CKD. It was concluded that combination of these medications had reno-protective effect and vital role in managing proteinuria among the patients suffering from renal diseases. We compared angiotensin receptor blocker with calcium channel blocker and concluded that angiotensin receptor blocker is a better option to manage proteinuria among patients with non-diabetic renal diseases.

A similar paper was published by Tan *et al.*[16] in 2015 with objective to assess the efficacy and safety of combining pentoxifylline with angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker in diabetic nephropathy. They concluded that Pentoxifyllin had a significant role in reducing proteinuria among patients with diabetic nephropathy regardless of hypertensive and glycaemic control. Our target population was different from that of Tan *et al*. and we included only non-diabetic patients but our findings were similar and losartan was found having good antiproteinuric properties.

Steuber *et al*.[17] in 2019 studied the role of non-dihydropyridine Calcium Channel Blockers for the treatment of Proteinuria among patients suffering from renal diseases. They evaluated non-dihydropyridine Calcium Channel Blockers alone or in combination with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and concluded that calcium channel blockers significantly reduced proteinuria among these patients. Our results were slightly different in this regard and calcium channel blocker was found inferior to Losartan in reducing proteinuria among our study participants.

A double-blind trial was conducted by Janssen *et al*. to compare the effects of amlodipine and lisinopril on proteinuria in nondiabetic renal failure.[18] They revealed that ACE-inhibitor lisinopril resulted in a decrease in proteinuria significantly and more than amlodipine. Our choice of medications was slightly different as compared to Janssen et al. but results were similar in the context that calcium channel blocker emerged as inferior option to reduce proteinuria as compared to Losartan.

There were few limitations in our study. Patients were followed up for three months only therefore long-term effect of these agents on proteinuria could not be determined. Sample size was also small and patients were recruited from nephrology unit of one hospital only which limits the generalization of our results.

CONCLUSION

Membranous nephropathy leading to proteinuria was the commonest non-diabetic renal disease encountered in our setup. Around 2/3rd of our patients showed either complete or partial response to treatment and Losartan was superior to Diltiazem in achieving response in our study participants.

Conflict of interest
None
Acknowledgement
None

AUTHORS'S CONTRIBUTION

Salahuddin: Data collection, literature search, write up, proof reading. MNA: Study design, literature search, proof reading. KMR: Data analysis, proof reading. ARA: Study design, data interpretation, proof reading. FRK: Literature search, data collection, write up. AWM, TT, BB, Wahaj, AK: Data collection, data interpretation, proof reading.

REFERNCES

1. Fraser SD, Blakeman T. Chronic kidney disease: identification and management in primary care. Pragmat Obs Res 2016;7:21–32.
2. O'Callaghan-Gordo C, Shivashankar R, Anand S, Ghosh S, Glaser J, Gupta R, *et al*. Prevalence of and risk factors for chronic kidney disease of unknown aetiology in India: secondary data analysis of three population-based cross-sectional studies. BMJ Open 2019;9(3):e023353.
3. Ruwanpathirana T, Senanayake S, Gunawardana N, Munasinghe A, Ginige S, Gamage D, *et al*. Prevalence and risk factors for impaired kidney function in the district of Anuradhapura, Sri Lanka: a cross-sectional population-representative survey in those at risk of chronic kidney disease of unknown aetiology. BMC Public Health 2019;19(1):763.
4. Grill AK, Brimble S. Approach to the detection and management of chronic kidney disease: What primary care providers need to know. Can Fam Physician 2018;64(10):728–35.
5. Aoun M, Karam R, Sleilaty G, Antoun L, Ammar W. Iron deficiency across chronic kidney disease stages: Is there a reverse gender pattern? PLoS One 2018;13(1):e0191541.
6. Haider MZ, Aslam A. Proteinuria. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 [cited 2021 Jan]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK564390/
7. Praga M, Andrade CF, Luño J, Arias M, Poveda R, Mora J, *et al*. Antiproteinuric efficacy of losartan in comparison with amlodipine in non-diabetic proteinuric renal diseases: a double-blind, randomized clinical trial. Nephrol Dial Transplant 2003;18(9):1806–13.
8. Teplan V, Schück O, Votruba M, Poledne R, Kazdová L, Skibová J, *et al*. Metabolic effects of keto acid--amino acid supplementation in patients with chronic renal insufficiency receiving a low-protein diet and recombinant human erythropoietin--a randomized controlled trial. Wien Klin Wochenschr 2001;113(17-18):661–9.
9. Ye H, Huo Z, Ye P, Xiao G, Zhang Z, Xie C, *et al*. Comparative proteinuria management of different angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for normotensive patients with CKD: a Bayesian network meta-analysis. PeerJ 2020;8:e8575.
10. Shams S, Khan MA, Ayaz M, Afridi SG. Efficacy of Atorvastatin on Proteinuria in Chronic Kidney Disease Patients of District Mardan, Pakistan. J Appl Environ Biol Sci 2018;8(3):81–7.
11. Bezinque A, Noyes SL, Kirmiz S, Parker J, Dey S, Kahnoski RJ, *et al*. Prevalence of Proteinuria and Other Abnormalities in Urinalysis Performed in the Urology Clinic. Urology 2017;103:34–8.
12. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39(2 Suppl 1):S1–266.
13. Wahbeh AM, Ewais MH, Elsharif ME. Comparison of 24-hour urinary protein and protein-to-creatinine ratio in the assessment of proteinuria. Saudi J Kidney Dis Transpl 2009;20(3):443–7.
14. Bökenkamp A. Proteinuria-take a closer look!. Pediatr Nephrol 2020;35(4):533–41.
15. Liu D, Wang LN, Li HX, Huang P, Qu LB, Chen FY. Pentoxifylline plus ACEIs/ARBs for proteinuria and kidney function in chronic kidney disease: a meta-analysis. J Int Med Res 2017;45(2):383–98.
16. Tian ML, Shen Y, Sun ZL, Zha Y. Efficacy and safety of combining pentoxifylline with angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker in diabetic nephropathy: a meta-analysis. Int Urol Nephrol 2015;47(5):815–22.
17. Steuber TD, Lee J, Holloway A, Andrus MR. Nondihydropyridine Calcium Channel Blockers for the Treatment of Proteinuria: A Review of the Literature. Ann Pharmacother 2019;53(10):1050–9.
18. Janssen JJMW, Gans ROB, Meulen JVD, Pijpers R, Wee PMT. Comparison between the effects of amlodipine and lisinopril on proteinuria in nondiabetic renal failure: A Double-Blind, Randomized Prospective Study. Am J Hypertens 1998;11(9):1074–9.

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