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Original Research Article

Effect of spironolactone with angiotensin receptor blocker on albuminuria in type 2 diabetic patients with nephropathy

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ABSTRACT

Background: Diabetic nephropathy is the most important cause of the end-stage renal disease (ESRD). The aim of the study is to evaluate the effect of spironolactone 25 mg once daily in addition to losartan 50 mg once daily for 12 weeks for proteinuria reduction in diabetic nephropathy.
Methods: This is a prospective clinical trial was carried out in the department of nephrology, national institute of kidney diseases and urology (NIKDU), Dhaka, Bangladesh from March 2015 to April 2016. A total of 60 patients attended the study considering inclusion and exclusion criteria. Proper ethical consent was taken from the relevant. Collected data were classified, edited, and analyzed into the computer for statistical analysis using SPSS version 22.
Results: The mean serum creatinine baseline, end of 1st, 4th, 8^{th,} and 12th weeks were significantly low ($p<0.05$) in the control group and significantly decline ($p<0.05$) in subsequent follow-up in both Intervention and control groups. The mean serum potassium- baseline, end of 1st, 4th, 8^{th,} and 12 weeks were not statistically significant ($p>0.05$) and significantly increased ($p<0.05$) in both groups. Improvement of urine albumin creatinine ratio was found 96.7% and 83.3% at end of 12th weeks in both groups respectively. It was observed that mean eGFR-baseline, end of 4th and 12th weeks were statistically significantly higher ($p<0.05$) in both groups with baseline.
Conclusions: The addition of spironolactone 25 mg once daily with losartan potassium 50 mg daily for a 12-week period did not show a significant role in the reduction of proteinuria in diabetic nephropathy patients.

Keywords: Diabetic nephropathy, Type 2 diabetes mellitus, Albuminuria; Spironolactone

INTRODUCTION

Diabetes mellitus is defined as a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.[1] Diabetes mellitus is considered as an all organ affecting disease. Although the metabolic derangement of diabetes is related primarily to the failure of efficient glucose uptake by insulin-dependent cells it also produces an altered scenario of protein and fat metabolism of the whole body. According to WHO 2000, diabetes mellitus is defined by fasting plasma glucose ≥7 mmol/l and 2-hours after 75 gm glucose drink ≥11.1 mmol/l. There are two prediabetic stages; impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG). IGT is defined by fasting plasma glucose <7 mmol/l and 2-hours after 75 gm glucose drink ≥7.8-<11.1 mmol/l. IFG is defined by fasting plasma glucose 6.1 to 6.9 mmol/l and 2-h plasma glucose <7.8 mmol/l.[2]

Etiologically there are three types of diabetes. These are- a) type 1, b) type 2 and c) gestational diabetes.[3] But the incidence of diabetes mellitus is continuously increasing and about 90.0% of patients with diabetes mellitus have

type 2 diabetes mellitus.[4] Usually onset of type 2 DM occurs after the late thirties whereas type 1 manifests earlier.[5] Showed the incidence rate of the onset of type 2 diabetes was 1.6, 4.3, and 3.9 per 1,000 person-years for age-groups 18-29, 30-39, and 40-50 respectively.[5] Diabetes mellitus is one of the systemic diseases affecting the kidneys. It is believed that the total number of people with diabetes will be more than double between the years 2000 and 2030.[6] For developing countries, adult diabetes numbers are likely to increase by 69% from 2010 to 2030.[7] Magnitude of diabetes mellitus in Bangladesh is increasing. Though the number of DM patients is unknown due to the lack of countrywide surveys, an increasing trend of diabetes registration in all the referral centers in Bangladesh has been noticed in recent years. Only in BIRDEM (Bangladesh institute of research and rehabilitation in diabetes, endocrine, and metabolic disorders), Dhaka, a total of about 20603 new interventions of diabetes are diagnosed every year and at present, about 5.6 million are registered diabetic patients in Bangladesh.[8] So, it could be realized that the actual number is much higher than this registered number. A study shows the short-term effect of adding spironolactone to conventional antihypertensive treatment including diuretics and maximally recommended doses of an ACE inhibitor or an angiotensin 2 receptor blocker (ARB) on albuminuria and blood pressure in type 2 diabetic patients with nephropathy.[9] This study is designed to reveal the effect of spironolactone with angiotensin receptor blockers (losartan) on albuminuria reduction in type 2 diabetes mellitus with diabetic nephropathy.

Objectives

The main objective of the study is to evaluate the effect of spironolactone 25 mg once daily in addition to losartan for 12 weeks for proteinuria reduction in diabetic nephropathy and the specific objectives are 1. To compare the effect of combined losartan potassium 50 mg and spironolactone 25 mg once daily with only losartan potassium 50 mg once daily in reduction of proteinuria 2. To compare the effect of spironolactone 25 mg/day on serum potassium, serum creatinine, and e-GFR.

METHODS

This study was a prospective clinical trial. It was carried out in the department of nephrology, NIKDU, Dhaka during the period of March 2015 to April 2016. This study was used the purposive sampling technique. A total of 60 patients attended the study in two groups where 30 were the intervention group and 30 were the control group. This study was carried out on patients with diabetic nephropathy who were attending the outpatient department of the nephrology unit in the above-mentioned hospital from March 2015 to April 2016. Proper ethical consent was taken from the respective. Collected data were classified, edited, coded, and entered into the computer for statistical analysis using SPSS version 22. Inclusion criteria were patients with diabetic nephropathy who were attending the outpatient department and exclusion criteria were patient/attendant unwilling to give informed consent to take part in the study and patients with economic constraints to be the necessary investigations. The patients were interviewed face to face by the researcher of this study for the purpose of data collection. Then the patient was examined by the researcher for certain signs and those were recorded in the checklist.

RESULTS

It was observed that half (50.0%) patients belonged to age 41-50 years in the intervention group and 13 (43.3%) in the control group. The mean age was found 51.0±19.6 years in the Intervention group and 50.7±9.7 years in the control group. Eighteen (60.0%) patients were male in intervention and 16 (53.3%) in the control group. The difference was not statistically significant ($p>0.05$) between the two groups (Table 1). Study shows urine albumin creatinine ratio at baseline and different follow up. The difference of mean urine albumin creatinine ratio-baseline, end of 4th weeks, end of 8th weeks, and end of 12th weeks were not statistically significant ($p>0.05$) between the two groups. Mean urine albumin creatinine ratio-end of 4th weeks, end of 8th weeks, and end of 12th weeks were statistically significantly lower ($p<0.05$) within the intervention group compared with baseline. Mean urine albumin creatinine ratio-end of 12th weeks was statistically significantly lower ($p<0.05$) within the control group compared with baseline. Reduction of urine albumin creatinine ratio was found 96.7% in the intervention group and 83.3% in the control group when compared with baseline vs end of 12 weeks. Which was higher in the intervention group but not statistically significant ($p>0.05$) between the two groups due to the small sample size (Table 2). We found diastolic blood pressure at baseline and different follow up. The difference of mean diastolic blood pressure- baseline, end of 1st week, end of 4th weeks, end of 8th weeks, and end of 12th weeks were not statistically significant ($p>0.05$) between the two groups. Mean diastolic blood pressure- end of 1st week, end of 4th weeks, end of 8th weeks, and end of 12th weeks were statistically significantly lower ($p<0.05$) within the intervention group compared with baseline. It was found that End of the 12th-week intervention group mean 7.9±1.5 and the control group mean 7.6±1.0. Mean HbAlc-baseline, and end of 12th weeks was almost similar between the two groups. Mean HbAlc- end of 12th weeks was statistically significant ($p<0.05$) within the intervention and control groups compared with baseline. (Table 3). Mean diastolic blood pressure-end of 1st week, end of 4th weeks, end of 8th weeks, and end of 12th weeks were statistically significantly lower ($p<0.05$) within the control group compared with baseline. Improvement of diastolic blood pressure was found 73.3% in the intervention group and 70% in the control group when compared with baseline vs end of 12 weeks. The difference was not statistically significant ($p>0.05$) between the two groups (Figure 1). It was observed e-GFR at baseline and different follow up. The difference of mean eGFR

baseline, end of 4th weeks, and end of 12th weeks were statistically significant (p<0.05) between the two groups. Mean eGFR-end of 4th weeks, end of 8th weeks, and end of the 12th weeks were statistically significantly higher (p<0.05) within the intervention group compared with baseline. Mean e-GFR- end of 4th weeks, end of 8th weeks, and end of 12th weeks were statistically significantly higher (p<0.05) within the control group compared with baseline. Improvement of e-GFR was found at 86.7% in the intervention group and 90.0% in the control group when compared with baseline vs end of 12 weeks. The difference was not statistically significant (p>0.05) between the two groups (Figure 2).

Table 1: Distribution of the study patients by particulars of the patients, (n=60).

Particulars of the patients	Intervention group, (n=30)		Control group, (n=30)		P value
	N	%	N	%	
Age (Year)					
≤40	3	10	4	13.33	
41-50	15	50	13	43.33	
51-60	7	23.33	8	26.67	
>60	5	16.67	5	16.67	
Mean±SD	51.0±9.6		50.7±9.7		[a]0.779[ns]
Range (min, max)	30.70		30,72		
Sex					
Male	18	60	16	53.33	[b]0.602[ns]
Female	12	40	14	46.67	

ns=not significant, [a]p value reached from unpaired t test, [b]p value reached from chi square test.

Table 2: Distribution of the study patients by urine albumin creatinine ratio, (n=60).

Urine albumin creatinine ratio	Intervention group, (n=30)	Control group, (n=30)	P value
	Mean±SD	Mean±SD	
Baseline	2.35	2.15	[a]0.053[ns]
Range (min, max)	1.8, 3.2	1.6, 3.1	
End of 4th week	2.16	2.08	[a]0.176[ns]
Range (min, max)	1.23, 3.19	1.08, 2.77	
P value (Baseline vs 4th weeks)	[b]0.001[s]	[b]0.001[s]	
End of 8th weeks	2.07	2.07	[a]0.701[ns]
Range (min, max)	1.20, 3.13	1.02, 2.76	
P value (Baseline vs 8th weeks)	[b]0.001[s]	[b]0.001[s]	
End of 12th week	1.97	2.01	[a]0.953[ns]
Range (min, max)	1.25, 3.09	1.01, 2.75	
P value (Baseline vs 12th weeks)	[b]0.001[s]	[b]0.001[s]	
Percentage of improvement	96.70%	83.30%	[c]0.097[ns]
(Baseline vs end of 12th weeks)	(n=30)	(n=30)	

*Log transformation was done, s=significant, ns=not significant, [a]P value reached from Mann-Whitney U-test, [b]P value reached from Wilcoxon signed ranks test.

Table 3: Distribution of the study patients by HbA1c, (n=60).

HbA1c (%)	Intervention group, (n=30)	Control group, (n=30)	P value
	Mean±SD	Mean±SD	
Baseline	8.7±2.1	8.3±1.7	[a]0.421[ns]
Range (min, max)	5.9, 14.0	5.7, 12.4	
End of 12th week	7.9±1.5	7.6±1.0	[a]0.366[ns]
Range (min, max)	6.1, 12.2	6.1, 10.2	
P value (Baseline vs 12th weeks)	[b]0.001[s]	[b]0.002[s]	

s=significant, ns=not significant, [a]P value reached from unpaired t-test, [b]P value reached from paired t test.

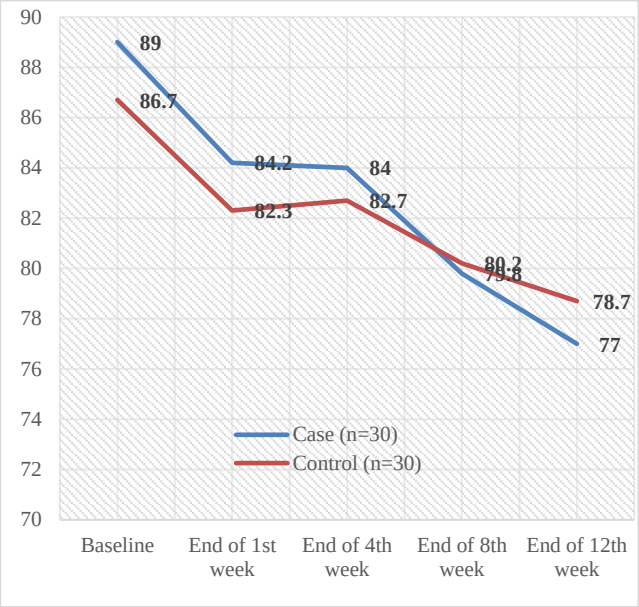

Figure 1: Line diagram shows mean diastolic blood pressure of the study patients, (n=60).

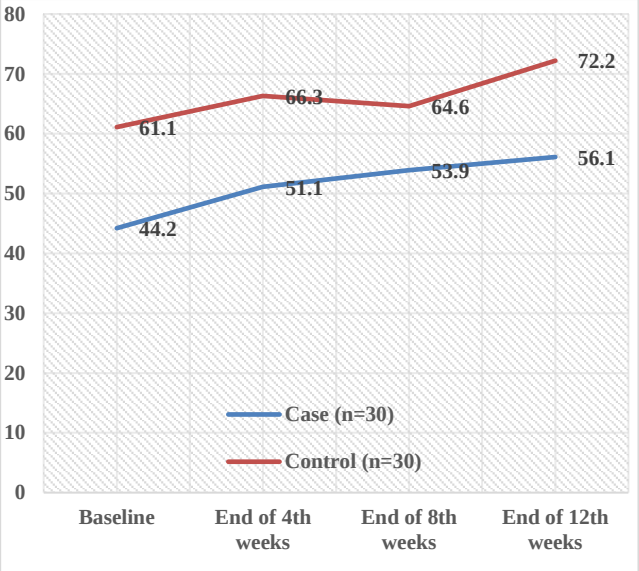

Figure 2: Line diagram shows mean e-GFR of the study patients, (n=60).

DISCUSSION

This prospective clinical trial was carried out with an aim to compare the combined effect of losartan potassium 50 mg and spironolactone 25 mg once daily with losartan potassium 50 mg once daily alone and to compare the effect of spironolactone 25 mg/day on proteinuria and on serum creatinine, serum potassium, e-GFR and on blood pressure. A total of 60 patients with diabetic nephropathy attended the outpatient department of the nephrology unit of the national institute of kidney diseases and urology, Dhaka, from March 2015-April 2016. Among them, 30 patients received both losartan potassium 50 mg and Spironolactone 25 mg daily. The patient who cannot tolerate losartan 50 mg-once daily, serum creatinine>2 mg/dl, serum potassium k+>5.5 mmol/l, patient with congestive cardiac failure, urinary tract infection, obstructive nephropathy, pregnant and lactating mother and patients who had an allergy to losartan or spironolactone were excluded from the study. The present study findings were discussed and compared with previously published relevant studies. In this present study, the mean age was found 51.0±9.6 years (30-70 years) in the intervention group and 50.7±9.7 years (30-72 years) in the control group. The difference was not statistically significant (p>0.05) between the two groups (Table 1). Similarly, Ma et al the difference was not statistically significant (p>0.05) between the two groups.[10,11] Zi et al it was observed that the mean eGFR was found 44.2±14.0 ml/min/1.73 m² in the intervention group and 61.1±18.5 ml/min/1.73 m² in the control group. The serum creatinine and e-GFR were statistically significant (p<0.05) between the groups. Moreover, this is in contrast with the study of Da et al and Sh et al who have found a significant drop in systolic blood pressure during their studies.[9,13,16] Ro et al and Va et al have reported the same results.[15] The suggested drug combination has not also a considerable adverse effect on diastolic blood pressure. This agrees with the studies of Sa et al and Ro et al and Va et al has found a minor drop in diastolic blood pressure in his patients too.[9,12,15,17] Ch et al reported that no evidence of differences was seen within the groups or between the groups in change in DBP at 3 and 6 MO; however, at 6 MO, there was a difference between the groups with the DBP being higher in the ramipril only group (p<0.05). Target DBP of <90 mmHg was achieved in all but one participant in the ramipril group. In this study, it was observed that Improvement of diastolic blood pressure was found 73.3% in the intervention group and 70% in the control group when compared with baseline vs end of 12 weeks. The difference was not statistically significant (p>0.05) between the two groups (Figure 1).[13] Sh et al found median (range) number of antihypertensive drugs was 3 (2-5). Mean urine albumin creatinine ratio-end of 12th weeks was statistically significantly lower (p<0.05) within the control group compared with baseline. Improvement of urine albumin creatinine ratio was found 96.7% in the intervention group and 83.3% in the control group when compared with baseline vs end of 12 weeks. Which was higher in the intervention group but not statistically significant (p>0.05) between the two groups due to the small sample size (Table 2).[11] Zi et al the difference was not statistically significant (p>0.05) between the two groups. In this current study, it was observed that mean e-GFR- baseline, end of 4th weeks, and end of 12th weeks was statistically significantly higher in both groups (p<0.05). Mean e-GFR- end of 4th weeks, end of 8th weeks and end of 12th weeks were statistically significantly higher (p<0.05) within the intervention group compared with baseline, mean e-GFR- end of 4th weeks, end of 8th weeks, and end of 12th weeks were statistically significantly higher (p<0.05) within the control group compared with baseline. Improvement of e-GFR was

found at 86.7% in the intervention group and 90.0% in the control group when compared with baseline vs end of 12 weeks. The difference was not statistically significant (p>0.05) between the two groups (Figure 2).[10] Ma et al found the mean GFR was 115.6±23.5 mL/min in spironolacton+losartan group and 112.5±25.6 mL/min in the spironolacton+placebo group. The difference was not statistically significant (p>0.05) between the two groups.[11] Zi et al found the mean GFR was 79.84±18.05 mL/min in the intervention group and 82.55±19.18 mL/min in the control group. The difference was not statistically significant (p>0.05) between the two groups. Glomerular filtration rate (GFR) dropped a little in both groups.[11] Zi et al study, though there was no significant difference between the groups. It opposes the studies of Sa et al and Va et al who have reported significant fall in GFR in the control group, whereas, it is comparable to the study of.[12,14,15,16] Bi et al and Da et al have reported that GFR decreased more prominently in the intervention group compared to the control group after 1 month of treatment, but the reverse occurred after 1-year treatment. All of the above-mentioned studies showed a decline in e-GFR. But the current study showed an increase eGFR in subsequent follow-up in both groups, which may be due to strict control of blood pressure, blood sugar, and reduction of proteinuria, a decrease of serum creatinine. Mean HbAic level at baseline and end of 12th weeks follow-up was almost similar between the two groups. Mean HbA1c level at end of 12th weeks was significantly (p<0.05) decline from baseline in both groups (Table 3).[10] Ma et al the difference was not statistically significant (p>0.05) between the two groups, which are comparable with the current study.

Limitations

The study population was selected from one selected hospital in Dhaka city, so that the results of the study may not reflect the exact picture of the country. The time period of study was too short to comment about the effect of a drug. Its study population was pretty small and the level of proteinuria was different between the two groups before the intervention. Although it was not statistically significant. Therefore, in the future, further study may be undertaken with large sample size and prolonged period.

CONCLUSION

There was a reduction of proteinuria, blood pressure, serum creatinine, and improvement of e-GFR in patients receiving ARB and spironolactone together and also in patients who received ARB alone, but the difference was not significant between the two groups. So, spironolactone 25 mg once daily for 12 weeks did not show a significant role in the reduction of proteinuria at this duration.

Recommendations

More studies with higher doses may need to be done to establish the long-term beneficial clinical effects of spironolactone alone in different stages of diabetic nephropathy. Further studies can be undertaken by including large number of patients. Both groups of patients should be matched for age, sex, serum creatinine, e-GFR, HbAlc.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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