International Journal of Medical Science and Clinical Inventions 4(6): 3030-3033, 2017
DOI:10.18535/ijmsci/v4i6.13 **ICV 2015: 52.82**
e-ISSN:2348-991X, p-ISSN: 2454-9576

Original Research paper

A Comparative study of effectiveness of Spironolactone and Telmisartan in reducing microalbuminuria in normotensive patients of Diabetic nephropathy

Dr. Mohd.Faisal[1], Dr. A.K Khare[1],Dr.Ankit Srivatava[1],Dr.R.R.Singh[2], Dr.Farrukh kidwai[1]

[1]Department of Pharmacology , Hind Institute of Medical Sciences, Barabanki, U.P
[2]Department of Medicine, Hind Institute of Medical Sciences, Barabanki, U.P
Corresponding Author -Dr. Mohd.Faisal

Abstract:
Objective: To compare the effect of Spironolactone with Telmisartan in reducing microalbuminuria in normotensive patients of diabetic nephropathy.
Methods: This was an open labelled ,prospective and randomized control study. Diabetic patients of either sex, age 25 to 75 years, Hb1Ac≤8% and Random urinary albumin to creatinine ratio of 30-300mg/gr Cr were included in the study. Consenting patients were screened for eligibility. A total number of 110 patients were included after taking informed consent in the study. The patients were divided into two groups using computer generated random table. Group 1 received Spironolactone(25 mg once a day); Group 2 received Telmisartan (40 mg once a day). A detailed history and thorough clinical examination was done for each case. Specific emphasis was given on the treatment and family history as well as life style modifications followed by the patients as instructed by the doctor.
Results: There was insignificant decrease in SBP and DBP in Group 1 and significant decrease in Group 2. There was no significant ($p>0.05$) difference in urinary albumin to creatinine ratio at all the time intervals between the groups.There was significant decrease in urinary albumin creatinine ratio in both groups during six month treatment.($p=0.0001$). The sodium was found to be significantly ($p=0.001$) different at 4 week between the groups. No significant effect of time X group interaction in the change in urinary albumin to creatinine ratio and HbA1C.
Conclusion
The study concludes that Spironolactone can be recommended as an alternative treatment for patients with diabetes and early nephropathy when the risk of hyperkalemia with spironolactone is minimal. The reduction in urinary albumin creatinine ratio in Spironolactone was independent of reduction in systolic blood pressure and Diastolic blood pressure.

Key words: Diabetic Nephropathy, Microalbuminuria, Normotensive, Spironolactone, Telmisartan

INTRODUCTION

Diabetic nephropathy is characterized by persistent albuminuria, a relentless decline in glomerular filtration rate (GFR), raised arterial pressure and increased relative mortality for cardiovascular diseases (Parving et al, 1996). Diabetic nephropathy (DN) is one of those complications which has a prevalence of 7% to 21% reported in different studies conducted in Asia (Amos et al, 1997).

Microalbuminuria predicts the development of diabetic nephropathy and increase blood pressure contributes to the progression of nephropathy in type 1 diabetes. Also in type 2 diabetes it is predictive of clinical proteinuria and increase mortality (Rahman et al, 2016).

Clinical and experimental evidences show that aldosterone can cause nephrosclerosis progression and renal fibrosis in patients with diabetes and hypertension.ACEIs and ARBs failure in long term suppression of aldosterone is the main cause of their defeat in proteinuria management (Schjoedt et al, 2004). So, the blockage of mineralocorticoid receptors with spironolactone can prevent kidney and heart damages.

Telmisartan is a non-peptide angiotensin II type 1 receptor (AT1) antagonist with high lipophilicity and the longest half-life compared with other ARBs.10 Available in oral preparation, it is highly bound to plasma proteins (99.5%), mainly albumin. It is metabolized by conjugation, is not metabolized by the cytochrome P450 system, and is eliminated in feces. Of the available ARBs, telmisartan has the greatest stimulating effect on PPAR and this effect decreases insulin resistance, increases insulin sensitivity, and reduces dyslipidemia, thereby providing greater target-organ protection (Benson et al, 2004).

This study was therefore designed to compare the effect of Spironolactone with an ARB Telmisartan in reducing microalbuminuria in normotensive patients of diabetic nephropathy.

MATERIAL AND METHODS

The study was conducted at Hind Institute of Medical Sciences, Barabanki, a tertiary care teaching hospital in

Barabanki, Uttar Pradesh. A proper protocol approval was taken by the Institutional Ethical Committee. This was an open labelled ,prospective and randomized control study. Expected duration for participation of each subject enrolled in the study was six months and the total duration of the study was one year.

Diabetic patients of either sex, age 25 to 75 years, Hb1Ac≤8% and Random urinary albumin to creatinine ratio of 30-300mg/gr Cr were included in the study.

Patients with diastolic & systolic blood pressures more than 80 and 130 mmHg respectively, serum potassium level > 5 meq/L, prior acute MI or stroke during the preceding six-month period, taking proteinuria-affecting medications (corticosteroids, NSAIDs, immunosuppressant drug), collagen vascular disease, obstructive uropathy, alcohol & substance abuse and pregnancy & lactation were excluded from the study.

Treatment Protocol

Consenting patients were screened for eligibility. A total number of 110 patients were included after taking informed consent in the study. The patients were divided into two groups using computer generated random table.

Group 1 received Spironolactone(25 mg once a day)

Group 2 received Telmisartan (40 mg once a day).

A detailed history and thorough clinical examination was done for each case. Specific emphasis was given on the treatment and family history as well as life style modifications followed by the patients as instructed by the doctor.

The patients were called for follow up every 4 weeks for a period of 24 weeks and random Urinary albumin/creatinine ratio, serum sodium/ potassium, ,systolic and diastolic blood pressure were measured at every 4 weeks and at the end of 24 weeks. HbA1c was measured at the end of 12 weeks and at the end of 24 weeks.

Methods

Blood Pressure was measured by Sphygmomanometer. The patients were allowed to relax for 15 minutes before measuring the blood pressure.

Blood was drawn from cubital vein of arm of each patient by a 3cc disposable syringe and transferred into plain and EDTA vial. About 2ml blood was placed into EDTA tube to perform HbA1c .Then serum sample was obtained by centrifugation at room temperature. Random urine samples were collected from patients for determination of microalbuminuria and creatinine. The urine samples were centrifuged by the same way as serum to precipitate all the debrises.

Statistical analysis

The results are presented in mean±SD and percentages. The Chi-square test was used to compare the categorical variables. The Unpaired t-test was used to compare the continuous variables between the groups. The repeated measures of analysis of variance (ANOVA) was used to test the effect of time and time X group interaction in the change in continuous variables. The Paired t-test was used to compare the changes in the continuous variables within the group from 0 week to subsequent time periods. The p-value<0.05 was considered significant. All the analysis was carried out on SPSS 16.0 version (Chicago, Inc., USA).

RESULTS

There was no significant difference in the age and gender between the groups showing comparability of the two groups (Table-1)

Table-1: Demographic profile between the groups

Demographic profile	Group 1 (n=50)		Group 2 (n=47)		p-value[1]
	No.	%	No.	%	
Age in years					
40-50	7	14.0	7	14.9	0.90
51-60	20	40.0	17	36.2	
>60	23	46.0	23	48.9	
Mean±SD	57.26±7.17		56.90±7.14		
Gender					
Male	28	56.0	22	46.8	0.31
Female	22	44.0	25	53.2	

[1]Chi-square test

There was no significant (p>0.05) difference in SBP and DBP at 0 week showing comparability of the groups in terms of SBP & DBP. There was significant (p=0.001) difference in the SBP at all the time intervals except at 24 week between the groups. There was significant (p=0.001) difference in the DBP at 4 week and no significant (p>0.05) difference at other time periods between the groups. The repeated measures of analysis of variance showed that there was no significant (p>0.05) effect of time and time X group interaction in the change in SBP and DBP. However, the reduction was insignificant in Group 1 and significant in Group 2 (Fig.1).

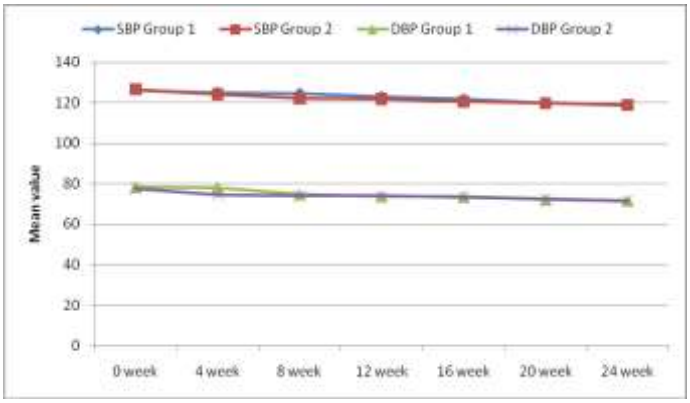

Fig.1: Comparison of SBP (mmHg) and DBP (mmHg)

between the groups across the time periods

There was no significant (p>0.05) difference in urinary albumin to creatinine ratio at all the time intervals between the groups. The repeated measures of analysis of variance showed that there was no significant effect of time (F=2.21, p=0.31) and no significant effect of time X group interaction (F=1.13, p=0.45) in the change in urinary albumin to creatinine ratio (Table-2). There was significant decrease in urinary albumin creatinine ratio in both groups during six month treatment.(p=0.0001).

Table-2: Comparison of urinary albumin to creatinine ratio (mg/g) between the groups across the time periods

Time periods	Group 1 (n=50)	Group 2 (n=47)	p-value[1]
0 week	172.24±55.34	172.48±58.87	0.98
4 week	162.62±54.39	165.52±55.80	0.77
8 week	152.08±54.78	154.70±55.12	0.81
12 week	141.24±53.70	141.62±52.77	0.97
16 week	130.72±52.40	128.80±49.70	0.85
20 week	120.90±51.86	113.18±46.57	0.43
24 week	113.74±61.85	97.80±43.30	0.09

[1]Unpaired t-test

There was no significant (p>0.05) difference in sodium and potassium between the groups at 0 week. The sodium was found to be significantly (p=0.001) different at 4 week between the groups. The repeated measures of analysis of variance showed that there was no significant effect of time (F=1.11, p=0.55) and no significant effect of time X group interaction (F=2.10, p=0.33) in the change in sodium. The potassium was found to be significantly (p<0.05) different at 4 week and subsequent time periods between the groups. The repeated measures of analysis of variance showed that there was significant effect of time (F=112.12, p=0.0001) and significant effect of time X group interaction (F=32.14, p=0.0001) in the change in potassium (Fig.2).

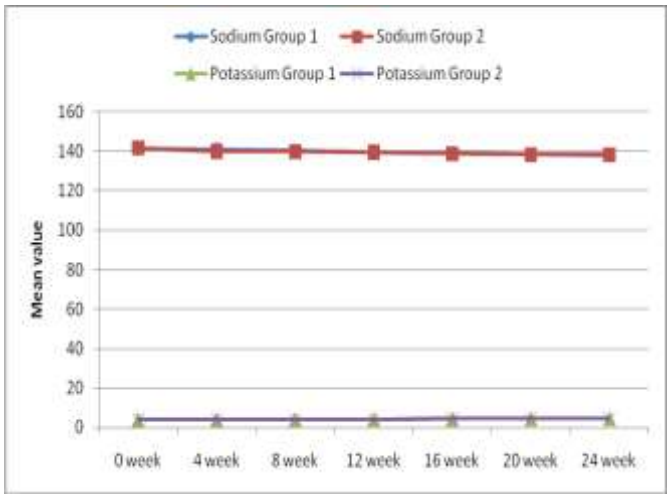

Fig. 2: Comparison of Sodium (mEq/L) and serum potassium (mEq/L) between the groups across the time periods

There was no significant (p>0.05) difference in HbA1c between the groups at all the time periods. The repeated measures of analysis of variance showed that there was no significant effect of time (F=2.20, p=0.23) and no significant effect of time X group interaction (F=1.12, p=0.48) in the change in HbA1c (Table-3).

Table-3: Comparison of HbA1c (%) between the groups across the time periods

Time periods	Group 1 (n=50)	Group 2 (n=47)	p-value[1]
0 week	7.72±0.22	7.70±0.20	0.57
12 week	7.64±0.22	7.59±0.23	0.26
24 week	7.61±0.32	7.57±0.28	0.47

[1]Unpaired t-test, *Significant

DISCUSSION

Diabetic patients with microalbuminuria have increased risk of progression to overt proteinuria, and after some time, renal failure. Studies have shown that microalbuminuria may spontaneously resolve to normoalbuminuria in a substantial proportion of patients, mainly in type 1 diabetics, or may progress to macroalbuminuria referred to as overt nephropathy (Koulouridis and Speaker, 2009).

Aldosterone, the end product of the renin-angiotensin-aldosterone system (RAAS), has attracted renewed attention as an important mediator of both cardiovascular and renal disease (Epstein, 2001). Telmisartan is an angiotensin II receptor blocker that shows high affinity for the angiotensin II receptor type 1 (AT_1), with a binding affinity 3000 times greater for AT_1 than AT_2.

In the present study, There was significant (p=0.001) difference in the SBP at all the time intervals except at 24 week between the groups. There was significant (p=0.001) difference in the DBP at 4 week and no significant (p>0.05) difference at other time periods between the groups. The repeated measures of analysis of variance showed that there was no significant (p>0.05) effect of time and time X group interaction in the change in SBP and DBP. However, the reduction in SBP and DBP was significant in Group 2 and insignificant in Group 1. The findings of this studty is similar to the study Kato et al (2015) .

In the present study, there was no significant effect of time as well as effect of time X group interaction in the change in urinary albumin to creatinine ratio. There was significant decrease in urinary albumin creatinine ratio in both groups during six month treatment. Makino et al (2008) reported that the patients treated with either dose of telmisartan showed lower transition rates from microalbuminuria to overt nephropathy compared to the placebo group. Kato et al (2015) also showed similar findings with the treatment by spironolactone as in the present study.

The present study showed that the sodium was found to be significantly different at 4 week between the groups. It was also found in this study that there was no significant effect of time as well as time X group interaction in the change in sodium. The potassium was also found to be significantly different at 4 week and subsequent time periods between the groups in this study. No effect of time was found in the change in potassium. However, Atieh et al (2014) reported significant change in the sodium. In the present study, there was no significant ($p>0.05$) difference in HbA1c between the groups at all the time periods. The repeated measures of analysis of variance showed that there was no significant effect of time and no significant effect of time X group interaction in the change in HbA1c.

One of the limitations of the present study was small sample size and less study duration. Thus, the studies with larger sample size and long duration are recommended to have robust results.

CONCLUSION

The study concludes that Spironolactone can be recommended as an alternative treatment for patients with diabetes and early nephropathy when the risk of hyperkalemia with spironolactone is minimal. The reduction in urinary albumin creatinine ratio in Spironolactone group was independent of reduction in Sytsolic blood pressure and Diastolic blood pressure suggesting this anti-proteinuric action of Spironolactone independent of its hemodyanamic action.

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