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COMPARISON BETWEEN HYDROCHLORTHIAZIDE AND DILTIAZEM ADDED ON TO ANGIOTENSIN RECEPTOR BLOCKER IN REDUCING PROTEINURIA IN PATIENTS WITH CHRONIC KIDNEY DISEASE

DANA A. SHARIF[a1], KAWA H. AMIN[b], BUSHRA M. ALI[c] AND KHALIL Y. KHALAF[d]

[ab]Department of General Medicine, College of Medicine, University of Sulaimani, Sulaimani City, Kurdistan Region, Iraq
[cd]Department of Family Medicine, College of Medicine, University of Sulaimani, Sulaimani City, Kurdistan Region, Iraq

ABSTRACT

Proteinuria is an early marker of chronic kidney disease. The severity of proteinuria is an indicator of progressive loss of renal function especially when it co-exits with hypertension. Therefore, many drugs are used to reduce proteinuria and halt the progression of kidney disease. The primary endpoint was to compare the additive benefit of adding either hydrochlorothiazide or diltiazemin to an angiotensin receptor blocker in reducing proteinuria in patients with chronic kidney disease. The secondary endpoint was to identify which combination is more effective in improving renal function and blood pressure control. This is a randomized open-labeled study carried out in the nephrology department in Shar hospital/ Sulaimani city in Iraq. It started from the 1st of December 2013 to the 31th of May 2014. Data from fifty-three patients were collected and then followed up for a period of six months. During this period patients were interviewed every two months and progress were documented. This study showed that patients on hydrochlorothiazide had a significant reduction in proteinuria and improvement in renal function throughout the visits compared to those on diltiazem (p=0.01). Although the diltiazem group had a lower systolic blood pressure by the end of the study but showed no significant changes in the means of all patients' measurements. In conclusion Hydrochlorothiazide may be more effective than diltiazem in reducing proteinuria and improving renal function. On the other hand diltiazem is more likely to reduce systolic blood pressure.

KEYWORDS : Proteinuria, Chronic Kidney Disease, Proteinuria, Diltiazem, Hydrochlorthiazide

Proteinuria refers to the presence oflow molecular weight protein (albumin) in the urine (USRDS, 2013). These proteins are normally present in urine in amount less than 150 mg/day. Relatively minor leakage of albumin in the urine may occur transiently after vigorous exercise, during fever or urinary tract infection, pregnancy and in orthostatic condition.

Persistent proteinuria may be an early indicator of renaldisease and increases the risk of renal impairment, hypertension and cardiovascular disease. The causes of proteinuria include either primary renal diseases such as glomerular and tubular diseases or secondary to diabetes mellitus, connective tissue diseases, vasculitis, amyloidosis, myeloma and others. Quantification of proteinuria in 24-hour urine collection is the gold standard,but urinary protein/creatinine ratio (PCR) in a single sample test makes allowance for the variable degree of urinary dilution and can allow extrapolation of 24-hour values (Goddard J, 2010).

Many drugsareused to reduce proteinuria and halt the progression of kidney diseases. Successful treatment of these patients will often require a combination of therapies, such as in type 2 diabetes and hypertension, in which this combination may offer specific cardiovascular and renoprotective advantages that go beyond BP reduction. Commonly used combinations include a renin-angiotensin system (RAS) blocker (angiotensin converting enzyme (ACE) inhibitor or an angiotensin two receptor blocker) plus a diuretic or a calcium channel blocker (CCB) (Esnault VL, 2005).

The combination of a RAS blocker with a diuretic is particularly useful, whenmono-therapy with the conventional dose of a RAS blocking agent alone is often unsuccessful or marginally successful. Additionally, high sodium intake generally blunts the anti-proteinuric effects of RAS blocker; so the use of thiazide diuretics overcomes this blunting effect.This medication is also used to treat high BP(Buter H, 1998).

On the other hand, the Non-DHPCCBs such as diltiazem and verapamil have demonstrated decreases in proteinuria, which is thought to decrease renal injury and slow the progression to ESRD in patients with CKD (Agarwal A., 2008).

MATERIALS AND METHODS

This is a randomized open labeled study started from the 1st of December 2013 to the 31st of May 2014 and took place in the nephrology department in Shar hospital/

[1]**Corresponding author**

Sulaimania city in Iraq. Initially Data from 70 patients were collected with significant proteinuria (urinary PCR of ≥ 1 or ≥ 1gm/24 hours of urine collection). After approval from the ethical comity, they were randomly assigned to either Diltiazem or Hydrochlorothiazide in adjuvant to a maximum tolerated dose of a RAS blocker and then followed up for a period of six months. Twenty-eight (52.8%) patients on Hydrochlorothiazide and twenty-five (47.2%) patients on Diltiazem finished the study and 17 patients were either declined or lost in the follow up.During this period patients were interviewed every two months and progress were documented.The primary end point was to identify which drug added on to a RAS blocker is more effective in reducing proteinuria. The secondary end point was to identify the effect of each drug on renal function and blood pressure.

Patients with urinary PCR of < 1, those whom are younger than 18 years of age and those with end stage renal failure or whom had kidney transplant were excluded from the study. Fisher exact test were used to analyse categorical variables. Independent sample t-test and ANOVA test used to analyse continuous variables (means ± SD). A p-value of<0.05 was considered as significant.

RESULTS

According to CKD classification there were a statistically significant increase inCKD stage 5(eGFR<15) in the third visit of patients,5 (83.3%) (p=0.02). However, in the second visit only one patient (16.7%) developed CKD stage 5 (Table 1).

In those patients on hydrochlorothiazide there were and increase in the number of patients with CKD stage one (two patients at first visit to six patients at third visit) as shown in table 2.

ANOVA analysis revealed that those patients on hydrochlorothiazide had a significant increase (improvement) in the means of eGFR (p=0.01) and a significant decrease(improvement) in means ofurinary PCRthroughoutthe three visits (p=0.01). However, there were no significant changes in means of systolic and diastolic pressure throughoutthe threevisits for the same group of patients.

Post hoc analysis revealed that those patients on hydrochlorothiazide had a significant increase (improvement) for means of eGFR betweenthe first andthe third visits and betweenthe second and the third visits (p= 0.03). Inaddition to this, there was a significant

Table 1: CKD Classification of Studied Patients

Variable	1st visit		2nd visit		3rd visit		Fishers exact test	P
	No.	%	No.	%	No.	%		
CKD stages (GFR)							17	0.02
≥ 90	5	31.3	2	12.5	9	56.3		
60-89	8	25.0	14	43.8	10	31.3		
30-59	13	29.5	15	34.1	16	36.4		
15-29	27	44.3	21	34.4	13	21.3		
< 15	0	-	1	16.7	5	83.3		

Table 2: CKD Classification of Studied Patients According to the Drugs

Variable		1st visit		2nd visit		3rd visit	
		Drug		Drug		Drug	
		Hydrochlorothiazide	Diltiazem	Hydrochlorothiazide	Diltiazem	Hydrochlorothiazide	Diltiazem
		No.	No.	No.	No.	No.	No.
CKD	≥90	2	3	0	2	6	3
	60-89	4	4	6	8	4	6
	30-59	8	5	9	6	8	8
	15-29	14	13	12	9	7	6
	<15	0	0	1	0	3	2

Table 3: ANOVA Analysis of Patients' Measurements Through the Three Visits According to the Drug Intake

Variable	Drug	Results of visits in Mean±SD				
		PCR	S. Cr	eGFR	Sys. BP	Dias. BP
1st visit	Hydroch.	3.6±2.1	2.2±1.05	41.01±5.4	158.5±30.7	90.6±15
	Diltiazem	2.6±1.3	2.1±1.1	45±28.9	146.6±30.3	89.5±17.4
2nd visit	Hydroch.	3±1.8	2.1±1.1	40.2±21.2	156.2±24.5	85.2±12.6
	Diltiazem	2.3±1	1.9±1.2	48.7±27.2	143±23.8	87.8±14.8
3rd visit	Hydroch.	2.1±1.7	1.8±1.2	71±68.7	155.2±25	82.5±13
	Diltiazem	2.2±2.2	1.9±1.2	51±29.5	142.5±20.4	86.9±12.5
ANOVA test (p value)	Hydroch.	**0.01**	0.4	**0.01**	0.8	0.08
	Diltiazem	0.6	0.8	0.7	0.8	0.8
Post Hoc test in between groups (p value)						
1st visit & 2nd visit	Hydroch.	0.5	0.9	0.9	0.9	0.3
	Diltiazem					
2nd visit & 3rd visit	Hydroch.	0.1	0.4	**0.03**	0.9	0.07
	Diltiazem					
1st visit & 3rd visit	Hydroch.	**0.01**	0.6	**0.03**	0.8	0.7
	Diltiazem					

Table 4: Comparison of Patient's Measurements at the First Visit According to the Drugs

Variable	Hydroch.	Diltiazem	t-test	P
	Mean±SD	Mean±SD		
PCR	3.6±2.1	2.6±1.3	1.9	0.51
S. Creatinine	2.2±1.05	2.1±1.1	0.1	0.9
eGFR	41±28.8	45±28.9	0.5	0.6
Sys. BP.	158.5±30.7	146.6±30.3	1.4	0.1
Dias. BP.	90.6±15	89.5±17.2	0.2	0.8

Table 5: Comparison of Patient's Measurements at The Third Visit According to Drugs Intake

Variable	Hydroch.	Diltiazem	t-test	P
	Mean±SD	Mean±SD		
PCR	2.1±1.7	2.2±2.2	0.1	0.8
S. Creatinine	2±1.1	1.9±1.2	0.05	0.9
eGFR	44.6±24.5	51±29.5	0.8	0.3
Sys. BP.	155.2±25	142.5±20.4	2	**0.04**
Dias. BP.	82.5±13	86.9±12.5	1.2	0.2

decrease(improvement) in the means of urinary PCRbetween the first andthethird visit(p=0.01).

ANOVA analysis also revealed no significant changes in the means of all patients' measurements for patients on Diltiazem. All these findings were shown in table 3.

Analysis of patient's measurements according to drug intake at first visit using independent t-test, revealed no significant difference in means of measurements between patients on hydrochlorothiazide and those on diltiazem as shown in table 4.

Analysis of patient's measurements according to drug intake at third visit using independent t-test, revealed a significant difference only in means of systolic blood pressure between patients on Hydrochlorothiazide and those on Diltiazem (p= 0.04). Patients on Diltiazem had

lower systolic blood pressure than those on Hydrochlorothiazide (Table 5).

DISCUSSION

In this study, there was a significant improvement in renal function by the end of the third visit.This finding was more prominent in those whom treated with Hydrochlorothiazide diuretics. This was consistent with the results of a study in France (Dussol B, 2012).

ANOVA analysis in the present study revealed that CKD patients treated with Hydrochlorothiazide had a significant improvement in eGFR and urinary PCR after three visits. This finding was consistent with results ofa study in Japan (Abe M, 2009), which concluded that a low dose of Hydrochlorothiazide had are no protective effect due to its BP lowering effect.

There are also randomized controlled trials supporting the use of the thiazide diuretic in type 2 diabetics with hypertension in reducing microalbuminuria compared with that of the ACE inhibitors, such as Enalapriland captopril. Hydrochlorothiazide or Chlorthalidone are most commonly employed to decrease the risk of cardiovascular disease(CVD) in CKD when the creatinine clearance(CrCl) level is more than 30 mL/min. These agents are not effective at CrCl levels of less than 30 mL/min because they lose their ability to excrete sodium with declining renal function.

In this study, hypertension constituted 32.1% of CKD studied sample. Hypertension is a major risk factor for cardiovascular and renal diseases. In many studies, about 60% to 90% of CKD patients with hypertension treated with either thiazide-type or loop diuretics added to either ACE inhibitors or ARBs (Brenner BM, 2001).

Other studies have shown that the combination of thiazide diuretics with agents that block the RAS is more effective than either type of treatment alone in lowering blood pressure (25,26). Most patients with CKD require more than one antihypertensive agent to reach a target BP of less than 130/80 mm Hg. Therefore, the sepatients could be treated with a diuretic in combination with a RAS blocker to reach the target BP.

In this study, we have shown that the combination of RAS blocker with Diltiazem was more effective than thiazide with a RAS blocker in reducing blood pressure in CKD patients. This finding was consistent with a study in USAthat reported a significant effect of Non-DHP CCBs on BPreduction compared to the weak effect of diuretics (Salinitri F, 2009).

On the other hand, we have revealed that Diltiazem has no significant effect on renal function of CKD patients throughout the three visits. This finding was inconsistent with a study done in Spain (Robles NR, 2013).

Although CKD is a progressive disease but reducing protein uria and controlling BP may halt or slow down this progression. We believe that further studies with larger sample size are required to support the superiority of certain drugs over the others in these patients.

CONCLUSION

In this study we have showed that Hydrochlorothiazide has a significant effect on improving renal function in CKD patients. Besides Hydrochlorothiazide may be more effective than Diltiazem in reducing proteinuria when added on to a RAS blocker in these patients. On the other hand, Diltiazem could be better in controlling blood pressure in CKD patients but probably has no significant effect on renal function or proteinuria.

REFERENCES

Abe M., Okada K., Maruyama T., Matsumoto K. Renoprotect and blood pressure lowering effect of low-dose hydrochlorothiazide added to intensive renin-angiotensin inhibition in hypertensive patients with chronic kidney disease. Int J ClinPharmacolTher. 2009; **47** (8):525-32.

Agarwal A., Haddad N., Herbert L.A., 2008. Progression of kidney disease:Diagnosis and management. In: Molony D., Craig J., eds. Evidence-Based Nephrology. Hoboken, NJ: Wiley:311-322.

Bakris G.L.: The role of combination antihypertensive therapy and the progression of renal disease hypertension: Looking toward the next millennium. Am J Hypertens 1998 (l): 11:158S-162S.

Brenner B.M., Cooper M.E., De Zeeuw D., Keane W.F., Mitch W.E., Parving H.H., et al: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001; **345**:861-869.

Buter H., Hemmelder M.H., Navis G., De Jong P.E., De Zeeuw D.,1998. The blunting of the antiproteinuric efficacy of ACE inhibition by high sodium intake can be restored by hydrochlorothiazide. NephrolDial Transplant. **13**(7): 1682–1685.

Dussol B., Moussi-Frances J., Mundler O., Morange S., Berland Y. and Von Y., et al. A Pilot Study Comparing Furosemide and Hydrochlorothiazide in Patients With Hypertension and Stage 4 or 5 Chronic Kidney Disease. The Journal of Clinical Hypertension 2012; **14** (1): 32-37.

Esnault V.L., Ekhlas A., Delcroix C., Moutel M.G., Nguyen J.M., 2005. Diuretic and enhanced sodium restriction results in improved antiproteinuric response to RAS blocking agents. Jam. Soc. Nephrol., **16**(2): 474–481.

Goddard J., Turner A.N. and Stewart L.H., 2010. Kidney and urinary tract disease. In: Niki R. Colledge, Brian R. Walker, and Stuart H. Ralston. Davidson's principles and practice of Medicine. 21st Edition. Edinburgh:CHURCHILL LIVINGSTON ELSVIER 2010, 476-486.

Melian E.B. and Jarvis B., 2002. Candesartan cilexetil plus hydrochlorothiazide combination: A review of its use in hypertension. Drugs, **62**:787-816.

Robles N.R., 2013. Blood Pressure in Renal Disease: Objectives, Surrogate Markers and Treatment. MedSurgUrols, **11**:002.

Salinitri F., Berlie H. and Desai N. Pharmacotherapeutic Blood Pressure Management in a Chronic Kidney Disease Patient. AACN Advanced Critical Care 2009; **20** (3): 205-213

United States Renal Data System. USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. National Institutes of Health.National Institute of Diabetes and Digestive and Kidney Diseases.Bethesda, MD, 2013.