Short Term Effects of Diltiazem on Renal Functions: A Controlled Clinical Study

Diltiazemin Böbrek İşlevleri Üzerine Kısa Dönem Etkileri: Bir Kontrollü Klinik Çalışma

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ABSTRACT

OBJECTIVE: We aimed to study acute effects of diltiazem on renal functions and its renoprotective effects in patients with chronic kidney disease (CKD).

MATERIAL AND METHODS: Among patients with CKD followed-up in our unit, fifty patients using diltiazem as a part of their treatment(the treatment group) and fifty patients not using diltiazem (the control group) were selected. Besides demographic parameters; blood pressures, creatinine, proteinuria and creatinine clearance levels at the baseline, first week, and third and sixth months were recorded.

RESULTS: The groups were matched for the mean creatinine clearance at baseline. The course of mean creatinine clearance were similar in both groups (p=0.29). There was no significant change in serum creatinine or creatinine clearance after initiation of diltiazem in the treatment group. Baseline proteinuria was higher in treatment group (p=0.012). Proteinuria at the sixth month was significantly higher in the control group compared with basal and first week levels (p<0.001 and p=0.007, respectively). But there was no change in the treatment group regarding proteinuria. Serum albumin levels were not statistically significantly different in the groups (p=0.69).

CONCLUSION: Diltiazem has no acute effect on serum creatinine and creatinine clearance in patients with CKD. It may prevent the probable increase in proteinuria.

KEY WORDS: Creatinine clearance, Diltiazem, Proteinuria, Renoprotection

ÖZ

AMAÇ: Çalışmamızda, diltiazemin böbrek işlevleri üzerine akut etkilerini ve kronik böbrek hastalığı (KBH) olan hastalarda böbrek koruyucu etkilerini çalışmayı amaçladık.

GEREÇ VE YÖNTEMLER: Ünitemizde izlenmekte olan KBH hastalarından, tedavilerinin bir parçası olarak diltiazem kullanan elli hasta (tedavi grubu) ile diltiazem kullanmayan elli hasta (kontrol grubu) çalışma için seçildi. Demografik göstergeler yanında kan basınçları, kreatinin, proteinüri ve kreatinin klirensi değerleri başlangıçta, ilk haftada ve üçüncü ile altıncı aylarda kaydedildi.

BULGULAR: Başlangıç değerlendirmesinde gruplar kreatinin klirensi açısından tam olarak benzerdi. Ortalama kreatinin klirensinin seyri her iki grupta benzerdi (p=0.29). Tedavi grubunda, diltiazen başlanmasından itibaren serum kreatinin ve kreatinin klirensi değerlerinde anlamlı değişiklik yoktu. Başlangıç proteinüri değerleri tedavi grubunda daha yüksekti (p=0.012). Kontrol grubunda altıncı aydaki proteinüri değerleri, başlangıç ve ilk hafta değerleri ile karşılaştırıldığında anlamlı olarak yüksekti (p<0.001 ve p=0.007). Fakat tedavi grubunda proteinüri açısından değişiklik yoktu. Serum albümin düzeyleri tedavi ve kontrol gruplarında istatistiksel anlamlı olarak farklı değildi (p=0.69).

SONUÇ: Diltiazemin diabetikler de dahil olmak üzere proteinürisi olan hastalarda serum kreatinin ve kreatinin klirensi değerleri üzerine akut etkisi yoktur. Proteinürideki muhtemel artmayı engelleyebilir.

ANAHTAR SÖZCÜKLER: Kreatinin klirensi, Diltiazem, Proteinüri, Renoproteksiyon

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INTRODUCTION

Chronic renal failure (CRF) is a clinical entity characterized by gradual and progressive decline in renal function due to progressive loss of renal mass and permanent reduction in the glomerular filtration rate (GFR) during the course of chronic kidney diseases. The treatment of the underlying pathology usually cannot reverse the progression in renal functional loss after a critical point of renal failure (1).

Proteinuria is one of the most valuable indicators of progression of chronic kidney disease (CKD). Renin angiotensin system (RAS) blockers that have obvious antiproteinuric effect are widely used as part of the modern treatment strategies (2-5). Non-dihydropiridine calcium channel blockers (CCB) can be added in cases where RAS blockers are not enough to reduce proteinuria to the target levels (6).

The mechanism of antiproteinuric effect of RAS blockers is the reduction in the intraglomerular pressure which may lead also to a modest reduction in creatinine clearance at the start of treatment (2-5). Although non-dihydropiridine CCB are thought to have antiproteinuric potential with similar mechanisms; their effect on creatinine clearance has not been studied yet. So, we aimed to study retrospectively the effects of diltiazem, a widely used non-dihydropiridine CCB, on proteinuria and creatinine clearance in patients with CKD.

MATERIALS and METHODS

Patients were selected among CKD patients followed-up in our outpatient's unit. Fifty patients already using diltiazem as part of their treatment were selected as the treatment group; and another 50 sequential patients not using diltiazem were selected as the control group. Those in treatment group were using sustained release form of diltiazem which is available in our country with dose of minimum 90mg/day and maximum 180 mg/day.

Patients without visits at these time periods, those who discontinued diltiazem or any other antiproteinuric agent (RAS blockers) for more than two weeks, patients who were given diltiazem in place of RAS blocker, those taking immunosuppressive treatment, patients with severe systemic diseases (malignancy, severe liver or heart disease), hypotensive patients, those having cardiac arrhythmia, and pregnant women were not included in the study.

Besides the demographic parameters like age, gender; primary kidney diseases, vital signs, laboratory data (urea, creatinine, sodium, potassium, albumin, calcium, hemoglobin, creatinine clearance, daily proteinuria), the drugs used, co-morbidities were recorded to a preformed chart at the basal evaluation, first week, third and sixth months.

The Cockroft-Gault Formula (creatinine clearance= [(140-age) X ideal body weight (kg)] / [72 X serum creatinine (mg/dl)] X 0.85 for women) was used for the estimation of creatinine clearance[7]. Urea measurement was performed with urease method using Roche P module in Abbott Architect 1600 clinical chemistry autoanalyzer. Serum albumin was measured by bromocresol green (BCG) method using Roche P module in Abbott Architect 1600 clinical chemistry autoanalyzer. Proteinuria was measured from 24-hour collected urine specimen with benzethonium chloride method using Roche P module in Abbott Architect 1600 clinical chemistry autoanalyzer. Other laboratory tests were carried on the same autoanalyzer.

Statistical analysis was with SPSS for Windows ver. 13.0 (Standard version). Numeric values were recorded as mean ± standard deviation (SD). If the numeric parameters were normally distributed, Student t-test and/or one-way ANOVA was used in the comparison of the groups. On the other hand, the Mann Whitney U test or Kruskal Wallis-H variance analysis was used when there was an abnormal distribution. For post-hoc comparisons, Tukey HSD was used. For non-numeric variables, Yates chi-square test and Fisher's exact test were used for 2X2 contingency tables. P values less than 0.05 were accepted as statistically significant.

RESULTS

A total of 100 patients (50 female, 50 male) were involved in the study. The mean age was 55±14 years. The laboratory analyses related to kidney function at baseline, 1st week, 3rd and 6th months of the study are presented in the Table I. Primary kidney disease was diabetic nephropathy in 36%, hypertensive nephrosclerosis in 20%, chronic glomerulonephritis in 19%, urologic pathologies in 13%, autosomal dominant policystic kidney disease in 4%, and secondary amyloidosis in 4% and other pathologies in 4% (Table II). The treatment group and the control group were similar regarding primary kidney diseases. The other data about age, gender, presence of diabetes and the drugs used are presented in Table II.

In the baseline evaluation, mean serum creatinine of the patients was 2.09±1.14 mg/dl (Table I). The groups were perfectly matched for the mean creatinine clearance at baseline evaluation (total group: 46.5±27.9 ml/min; treatment group: 46.5±26.59 ml/min and control group: 46.5±29.49 ml/min). The course of the mean creatinine clearance of the patients in both groups were similar throughout the study (p=0.29) (Figure 1). There was no significant change in serum creatinine or mean creatinine clearance after the initiation of diltiazem in the treatment group.

When the relationship between diltiazem use and proteinuria is examined, it is observed that diltiazem was prescribed to patients with higher levels of proteinuria and there was no increase in proteinuria (mean baseline proteinuria: 2207 ± 259mg/day) in this group (Figure II). On the other hand, the lower degree of proteinuria tended to increase throughout the study in the control group

Table I: The laboratory analyses of the patients (mean ± standard deviation).

		Treatment group (n=50)	Control group (n=50)
Baseline	Urea (mg/dl)	62 ± 30	62 ± 37
	Creatinine (mg/dl)	1.97 ± 0.75	2.21 ± 1.41
	Sodium (mmol/dl)	139 ± 2.4	139 ± 3.9
	Potassium (mmol/dl)	4.85 ± 0.73	4.80 ± 0.75
	Calcium (mg/dl)	9.05 ± 0.6	8.9 ± 1.6
	Hemoglobin (g/dl)	12.1 ± 1.8	12.1 ± 2.1
	Creatinine clearance (ml/min)	46.5 ± 26.5	46.5 ± 29.4
	*Proteinuria (mg/day)	2207 ± 259	1555 ± 302
1st Week	Urea (mg/dl)	67.16 ± 31	59 ± 33.6
	Creatinine (mg/dl)	2.04 ± 0.83	2.19 ± 1.26
	Sodium (mmol/dl)	140 ± 3	140 ± 3
	Potassium (mmol/dl)	4.8 ± 0.67	4.75 ± 0.7
	Calcium (mg/dl)	9.0 ± 0.6	9.2 ± 0.8
	Hemoglobin (g/dl)	12 ± 1.75	12 ± 2
	Creatinine clearance (ml/min)	44 ± 21.5	44 ± 29.2
	*Proteinuria (mg/day)	2195 ± 239	1504 ± 278
3rd month	Urea (mg/dl)	70 ± 45	64.5 ± 37
	Creatinine (mg/dl)	2.13 ± 0.97	2.17 ± 1.2
	Sodium (mmol/dl)	140 ± 2.9	140 ± 3.7
	Potassium (mmol/dl)	4.78 ± 0.6	4.73 ± 0.6
	Calcium (mg/dl)	9.02 ± 0.63	9.23 ± 0.65
	Hemoglobin (g/dl)	12 ± 1.75	12 ± 1.98
	Creatinine clearance (ml/min)	42.9 ± 24.7	45.8 ± 30.5
	*Proteinuria (mg/day)	2174 ± 237	1465 ±277
6th Month	Urea (mg/dl)	72.2 ± 39.8	68 ± 44.3
	Creatinine (mg/dl)	2.27 ± 1.22	2.38 ± 1.6
	Sodium (mmol/dl)	139 ± 2.9	140 ± 2.4
	Potassium (mmol/dl)	4.82 ± 0.65	4.68 ± 0.6
	Calcium (mg/dl)	9.1 ± 0.5	9.1 ± 0.8
	Hemoglobin (g/dl)	12 ± 1.76	11.9 ± 2.12
	Creatinine clearance (ml/min)	45.1 ± 26.6	44.2 ± 29
	*Proteinuria (mg/day)	2174 ± 181	2406 ± 211

***** *The data were given as mean ± standart error of mean.*

(mean baseline proteinuria 1555 ± 302mg/day). There was a statistically significant difference between the groups regarding the change in proteinuria from baseline to 6th month (p=0.041); and from first week to 6th month (p=0.018) (Figure II).

Proteinuria at the sixth month was significantly higher in the control group when compared with the levels at the basal and first week measurements (p<0.001 and p=0.007, respectively). However, there was no change in the treatment group regarding proteinuria at basal evaluation, first week and sixth month measurements. Serum albumin levels were not statistically significantly different in the treatment and control groups (p=0.69).

Although the mean systolic and diastolic blood pressures decreased about 6 mmHg in the treatment group and 3 mmHg in the control group within the six months of follow-up; it was not significant statistically both within and between the groups (Figure III).

None of the patients died or reached end stage renal disease during the study period in both of the groups.

Table II: Age, gender, primary kidney diseases, presence of diabetes mellitus and the drugs used in the treatment and control groups.

	Treatment group (n=50)	**Control group (n=50)**
Age	53 ± 15	57 ± 14
Gender (Female/male)	21 / 29	29 / 21
Primary kidney diseases		
Diabetic nephropathy	16	20
Chronic glomerulonephritis	7	12
Hypertensive nephrosclerosis	11	9
Urological pathologies	10	3
Autosomal dominant polycystic kidney disease	0	4
Secondary amyloidosis	4	0
Other	2	2
Diabetes mellitus (yes/no)	20 / 30	22 / 28
Other medications		
RAS blockers (yes/no)	31 / 19	29 / 21
Spironolactone (yes/no)	3 / 47	2 / 48
Diuretic (yes/no)	24 / 26	19 / 31
Polystyrene sulfonate (yes/no)	7 / 43	1 / 49

DISCUSSION

Besides the underlying renal disease, some hemodynamic and metabolic factors play important role in the progression of CKD. These factors, named as secondary factors include intraglomerular hypertension, glomerular hypertrophy and proteinuria (1). Proteinuria is an important indicator of renal progression in both diabetic and non-diabetic population; and decrease in proteinuria has been shown by many studies to slow down the renal progression (1, 2, 8). The renoprotective effects of angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) (named collectively as RAS blockers), which are used commonly for direct antihypertensive action and also for amelioration of these secondary factors, have also been demonstrated in many studies (3-5).

Although non-dihydropiridine CCBs (verapamil and diltiazem) are known to have anti-proteinuric effect, the proof is not so strong (6, 9, 10). There are clinical and experimental studies about the renoprotective effect of CCBs; some reporting positive, some negative and some neutral effects (8, 11, 12). There is no clinical trial which specifically studies acute effects of diltiazem on renal functions in patients with CKD.

In our study, all of the data except daily proteinuria were similar in both groups at basal evaluation (Table I). Although this is an observational study; the near perfect match of the groups in terms of basal renal function and blood pressure recordings during follow-up made it possible to examine the renoprotective effect of diltiazem more clearly (Table I, Figure III). The results of the present study showed that diltiazem has neutral effect on serum creatinine, creatinine clearance and daily proteinuria at both short and long terms. There is no acute elevation in serum creatinine or decrease in creatinine clearance in the treatment arm in 1st week analyses compared with baseline parameters. Stable levels of proteinuria during the follow-up period in the treatment group compared with the significant gradual rise in proteinuria in the control group may suggest that diltiazem may protect the patients from rising of proteinuria even in the subjects who were maintained on a RAS blocker with/without aldosterone antagonists.

A meta-analysis involving 23 studies reported that non-dihydropiridine CCBs can decrease proteinuria up to 30%; and this effect persists when added to RAS blockers or whether the patient is diabetic or not (6). In this meta-analysis, although it was found that non-dihydropiridine CCBs lowered proteinuria more than dihydropiridine CCBs with the same level of blood pressure control; the difference between the groups lost statistical significance when that analysis was repeated after adjustments for systolic blood pressure, patient number and study period.

The most important and informative study about non-dihydropiridine CCBs was conducted by Bakris et al. (13) on patients with early stage diabetic nephropathy who were followed up for five years. In this study, lisinopril and non-dihydropiridine CCBs were shown to lower blood pressure, proteinuria and creatinine clearance similarly. Additionally, systolic blood

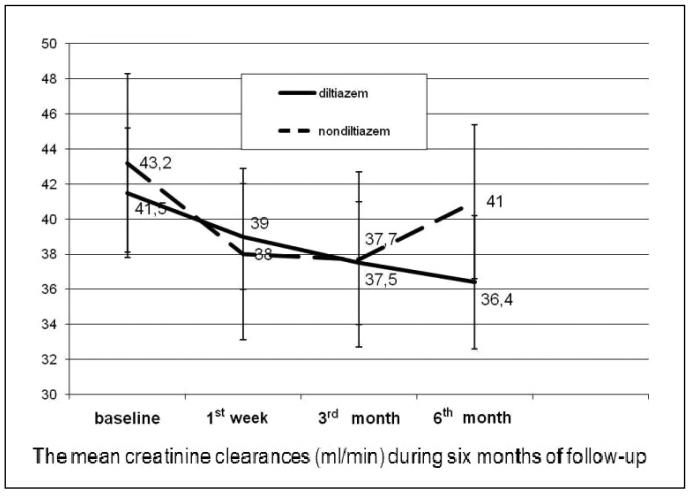

Figure 1: *The effect of diltiazem on the mean creatinine clearance.*

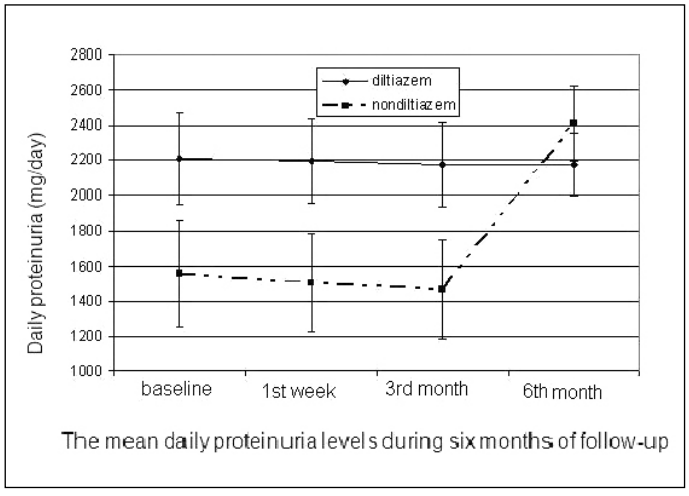

Figure 2: *The graphical presentation of changes in mean daily proteinuria of the groups.*

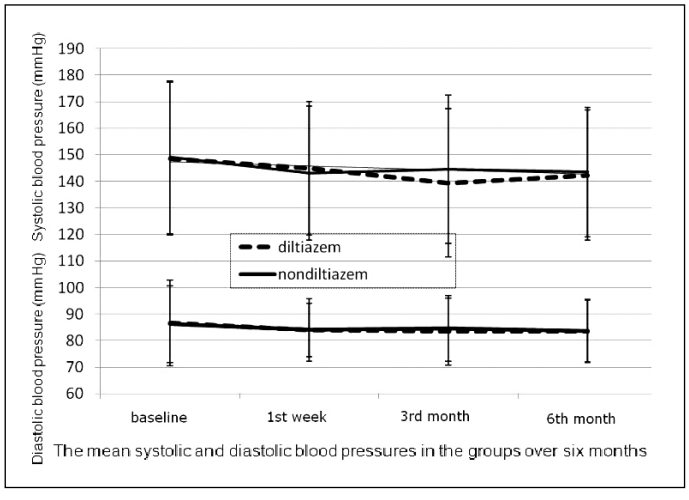

Figure 3: *Systolic and diastolic blood pressures of the groups.*

pressure was higher and the drop in creatinine clearance was more pronounced in the group taking atenolol when compared with patients using lisinopril or non-dihydropiridine CCBs. This difference in the renal functions was thought to be due to difference in blood pressure control.

A similar study was conducted with lisinopril and diltiazem; and the similar hemodynamic effects were recorded while drop in GFR was less than in patients taking beta blockers (14).

A study carried on animals showed that verapamil and diltiazem decreased the pressure in the afferent arteriole, the efferent arteriole and the intraglomerular capillaries when compared with the control group (15). The net decrease was more pronounced in renal plasma flow parallel with systemic blood pressure in this study; while filtration fraction was similar in both groups. In a similar study, diltiazem was shown to reverse vasoconstriction in afferent and efferent arterioles mediated by angiotensin-II while nifedipine had no such effect (16). Although there is no verifying information with ambulatory blood pressure monitoring in our study, there was no statistically significant difference in drop amount of both systolic and diastolic blood pressures between the treatment and control groups. Hence, this may obscure the potential antiproteinuric effect.

The disadvantage of our study is the observational nature and the inevitable changes in the drugs other than the study drug during the follow-up. To minimize this defect, we excluded patients who discontinued any drug with anti-proteinuric effect for more than two weeks.

CONCLUSION

Diltiazem, a non-dihydropirine CCB, has no acute effect on serum creatinine and creatinine clearance in patients with proteinuria including the diabetic ones. It may prevent the probable increase in proteinuria even in the patients on treatment with RAS blockers.

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