Research Article / Araştırma Makalesi

Does Diltiazem Provide Benefits on Allograft Functions in Kidney Transplant Recipients?

Diltiazem Böbrek Alıcılarında Greft Fonksiyonlarını İyileştirir mi?

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Abstract

Background: Acute and chronic calcineurin inhibitors (CNI) nephrotoxicity is a common concern in kidney transplant (KT) recipients. It is unclear whether diltiazem use can reduce CNI induced acute and chronic nephrotoxicity in (KT) recipients. In this study, we investigated the impact of diltiazem on 1 –year allograft survival and function.
Materials and Methods: This single-center retrospective study included 312 kidney transplant recipients and donors. Diltiazem receiving and diltiazem-free recipients were compared for 1-year allograft survival and functions. Available allograft biopsies were investigated for the evidence pieces of CNI induced nephrotoxicity. Factors may have a potential impact on allograft functions were evaluated (cytomegalovirus and polyoma BK viremia positivity, acute rejection episodes, donors and recipients ages and body mass indexes). A statistical package program was used for data analysis. P<0.05 was assigned significant.
Results: Seventy-three recipients in diltiazem arm and 239 in diltiazem-free arm were compared. In diltiazem and diltiazem-free arms, 1- year mortality, allograft survival rates and CNI induced nephrotoxicity incidences were 4.1% vs 3.8% (*P*=0.89), and 13.7% vs 7.1% (*P*=0.08), 18.8% vs 10.5% (*P*=0.27), respectively. However, 12-month estimated glomerular filtration rate was worse in diltiazem arm (62.75 ml/dk/1.73m^2) compared to diltiazem-free group (73.19 ml/dk/1.73m^2) (*P*=0.03). CNI toxicity had a weak impact on low eGFR in regression analysis (*P*=0.055 and 95% confidence interval).
Conclusions: Despite diltiazem use allows to CNI dose reduction, it might have undesirable impacts on long-term allograft functions, which is the main target of the allograft care.

Key Words: Allograft function, Diltiazem, Kidney transplantation

Öz.

Amaç: Akut ve kronik kalsinörin inhibitörü (KNİ) toksisitesi böbrek naklinde önemli bir sorundur. Diltiazem kullanımının KNİ toksisitesini azaltıp azaltmadığı net değildir. Bu çalışmada KNİ kullanımının 1 yıllık greft sağkalımı ve fonksiyonu üzerine etkilerini araştırdık.
Materyal ve Metod: Bu tek merkezli retrospektif çalışmada 312 böbrek alıcısı ve vericisi incelendi. Alıcılar diltiazem kullanan ve kullanmayan guruplar olarak ikiye ayrıldı. 1 yıllık alıcı ve greft sağkalımları araştırıldı. Greft biyopsilerinde KNİ toksisitesi ile 1 yıllık greft sağ kalımı arasındaki ilişki incelendi. Sitomegalovirüs ve polyoma BK virüs viremisi varlığı, akut rejeksiyon atakları, alıcı ve vericinin yaşları ve vücut kitle indekslerinin 1 yıllık greft sağ kalımı üzerine etkileri araştırıldı. Veriler bir istatistik paket programda değerlendirildi, P<0,05 anlamlı kabul edildi.
Bulgular: Alıcıların 73'ü diltiazem kullandı, 239'u diltiazem kullanmadı. 1 yıllık mortalite, greft sağ kalımı, Kalsinörin inhibitörü ilişkili nefrotoksisite diltiazem kolunda ve diltiazem kullanmayan gurupta sırasıyla; %4,1 e karşı %3,8 (*P*=0,89), %13,7'ye karşı %7,1 (*P*=0.08) ve %18,8'e karşı %10,5 (*P*=0,27) idi. 12 ay sonunda tahmini glomerüler filtrasyon hızı diltiazem kolunda daha kötü idi; 62,75 ml/dk/1.73m^2'ye karşı 73,19 ml/dk/1,73m^2 (*P*=0.03). Kalsinörin inhibitörü toksisitesinin kötü greft fonksiyonları üzerine %95 güven aralığında zayıf bir etkisi görüldü (*P*=0.055).
Sonuç: Diltiazem KNİ doz azaltımına imkân sağlasa da esasen istenen uzun dönem greft fonksiyonları üzerine olumsuz etkilere sahip olabilir.

Anahtar kelimeler: Greft fonksiyonu, Diltiazem, Böbrek nakli

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Geliş tarihi / Received:
23.10.2020

Kabul tarihi / Accepted:
24.11.2020

DOI: 10.35440/hutfd.815458

Introduction

Calcineurin inhibitors (CNIs) (tacrolimus, cyclosporine A) have a crucial importance in the kidney transplant (KT) practice due to providing better allograft survival, lower incidence of rejection, and fewer side effects compared to CNIs-free regimens (1). Immunosuppressant regimens involving CNIs are used by more than 90% of KT recipients and again more than 90% of those recipients receive tacrolimus, as a CNI (2). CNIs have a narrow therapeutic range, at lower doses cause rejection episodes, and in higher doses nephrotoxicity. It is claimed that after 10-years CNIs use, 100% of recipients would have CNIs toxicity to some degrees (3,4). Acute and chronic nephrotoxicity, hypertension, dyslipidemia, and new-onset diabetes mellitus after transplantation (NODAT) are the serious complications of CNIs that have a potential impact on allograft and recipient survival (5-7).

Diltiazem, a nondihydropyridine calcium channel blocker, is used for the treatment of high blood pressure, angina pectoris, supraventricular tachycardia. Also, in selected patients, it has some benefits in numerous off-label use as; an adjuvant option in managing migraine episodes, pulmonary hypertension (8,9). Given its unique action, it is thought diltiazem to have some unproven benefits regarding the transplantation, by reducing intestinal p-glycoprotein (p-Gp) and CYP3A activity, and subsequently increasing CNIs blood levels (10,11). In clinical practice, diltiazem is commonly used for purpose of, a) achieving quick target CNIs levels (especially immediately posttransplant), b) reducing CNIs-related costs, c) taking its antiproteinuric advantages, d) lowering blood pressure. Additionally, clinicians have a perception of lowering CNIs dosing and adding diltiazem to treatment to avoid CNI nephrotoxicity (10, 12,13).

Diltiazem use may allow approximately a 25% to 75% CNIs dose reduction in KT patients (10, 14,15). However, whether its clinical implementation in KT is only limited to cost benefits, is not clear. A few studies claimed that diltiazem use in KT recipients provides recipients survival advantages, retains kidney function, promotes graft function recovery, and decreases hepatic and renal toxicity, and the rate of acute rejection (AR) episodes. (13, 16). In contrast, previous studies demonstrated that diltiazem had no provide short-term benefits on allograft functions (17,18).

Since the cost benefit of the diltiazem is apparent but its clinical advantage is unclear, we aimed to present the impacts of diltiazem on 12-month posttransplant allograft functions, in this study.

Materials and Methods

This single-center, retrospective, and observational study is including KTs which were performed between 2016-2018 years. All deceased and living related donations were enrolled in the study. According to our immunosuppression protocol, we minimized immunosuppression afterward 3 months posttransplant. Recipients were divided into two groups; diltiazem and diltiazem-free groups. Allograft survival rates and functions at 3 and 12 months posttransplant were compared. Also, deaths and allograft losses were analyzed, for 1-year survival rates. The recipients who started to receive diltiazem afterward three months posttransplant or intolerant to diltiazem use were discarded.

Immunosuppression: All recipients were treated with induction and maintenance therapies according to individual risk grades, rather than standard protocols. In low risk patients: induction; 1.5 mg/kg rabbit anti-thymocyte globuline (rATG) (single dose), maintenance; prednisolone + a CNI (at lower range) + mycophenolate mofetil (MMF). In high risk patients: induction; 1.5 mg/kg rATG (3-5 doses); maintenance; prednisolone + a CNI (at upper range) + MMF. MMF intolerant recipients were switched to azathioprine and in patients with biopsy-proven CNI nephrotoxicity in order to reduce CNI toxicity, mTOR + low dose CNI protocols also were used. Besides, in cytomegalovirus (CMV) and polyoma B-K virus (BKV) positivity, mandatory dose changes were performed. Acute rejection (AR) episodes were treated according to the type of rejection, and responses of the treatment of the previous episodes.

Allograft functions were evaluated by using an online calculator which was based on MDRD estimated glomerular filtration rate (eGFR) formula (Modification of Diet in Renal Disease, 2009); www.mdrd.com.

The factors which have a potential to impact on allograft survival and functions; recipient and donor ages, living or related donation, CMV and BKV viremia (positivity), death censored allograft loss, AR episodes, and infections were evaluated. In order to demonstrate whether CNIs-induced nephrotoxicity was exist, recipients' available allograft biopsies were investigated.

Since that is a retrospective study, diltiazem use and dosing are not randomized and controlled. It had been given on clinical demands such as; to reduce CNIs doses, to provide cost benefits, reduce proteinuria, preventing CNI toxicity by stabilizing its intestinal influx. In our clinical protocol we commence diltiazem within 3 months posttransplant and the major approach is adding diltiazem near to the 3rd months posttransplant when minimizing CNIs is most performed.

Ethic committee approval was obtained from “Scientific Research and Ethical Committee of The Yeni Yüzyıl University”, (IRB:2020/06-475).

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 23.0, Chicago, USA. Descriptive data were expressed as mean ± SD, frequency, and percentage. Normality was tested by the Kolmogorov-

Smirnow test. An Independent T-test was used for comparison of parametric data between two groups. Categorical variables were compared using the Chi-Square test. Pearson bivariate correlation was performed to investigate the correlation between parametric variables. A linear regression model was performed to analyze the impact of categorical variables on allograft functions. P<0.05 was assigned as statistically significant at a 95% confidence interval.

Results

A total of 312 recipients (average age; 43.63 ± 13.89) and donors (average age; 50.00 ± 13.04) were evaluated. Seventy-three recipients were in diltiazem arm and 239 were in diltiazem-free arm. Age and sex distributions were similar among recipient and donors (*P*=0.29 and *P*=0.68, *P*=0.75 and *P*=0.69, respectively). In the cohort, 1-year mortality and allograft survival rate were 3.8% and 91.3%, respectively. The living related donation was 84% of all KT. The clinical and laboratory features of the two groups and their comparisons were given in Table 1 and Table 2.

Table 1. Recipients' and donors' demographical and clinical features

	N=312
Recipient age, years	43.63 ± 13.89
Donor age, years	50.00 ± 13.89
Recipient sex, male/female	188(60%)/124(40%)
Donor sex, male/female	164(52.5%)/148(47.5%)
Recipient BMI, kg/m^2	24.75 ± 5.35
Donor BMI, kg/m^2	27.76 ± 5.27
Allograft type; • Live • Deceased	 262(83.9%) 50(16.1%)
BKV, yes/no	6/60 (13.5%)
CMV, yes/no	38/260 (12.8%)
Rejection, yes/no (Bx proven)	69/191 (26.5%)
Immunological risk, • Low • High	 78.2% 21.8%
Diltiazem dose, mg	N=73 102.69 ± 39.04

BMI; body mass index, BKV; polyoma B-K virus, CMV; cytomegalovirus, Bx; biopsy.

Allograft functions at 3 months posttransplant were similar (*P*=0.42) (Figure 1). However, in the diltiazem arm, eGFR did not improve at 12 months, compared to the 3 months (*P*=0.50). In contrast, in the diltiazem-free arm after minimizing CNIs doses afterward 3 months posttransplant, eGFR was improved (67.30 ± 27.03 vs 73.19 ± 24.60, *P*= 0.02) (Figure 2). at 12 months posttransplant, in the diltiazem-free group, the better allograft functions were achieved, *P*=0.03 (Table 2).

Univariate regression analysis revealed that donor and recipient ages both had an impact on 12 months eGFR, *P*=0.03 and *P*=0.01, respectively (Table 3). Additionally, donor and recipient ages were negatively correlated to 12 months eGFR; *P*=0.07 and r^2=-0.17, *P*=0.03 and r^2=-0.16. CNIs induced toxicity had a weak impact on reduced 1-year eGFR, *P*=0.056. CMV and BKV positivity, allograft type, rejection episodes had no impact on 1-year allograft functions (Table 3). Additionally, donor and recipient BMI had no correlation to 1-year allograft function (*P*=0.88 and r^2=-0.02, *P*=0.23 and r^2=-0.17).

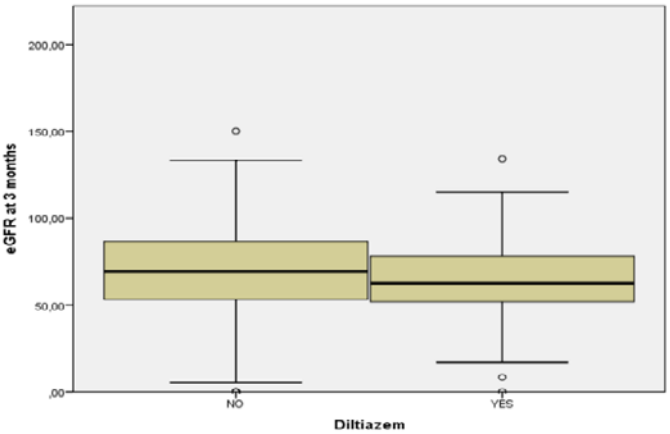

Figure 1. eGFR at 3 months posttransplant is similar among two groups (*P*=0.42).
eGFR; estimated glomerular filtration rate

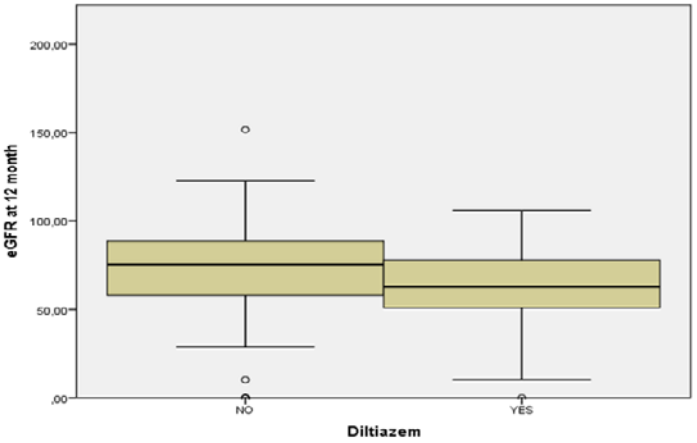

Figure 2. Diltiazem-free group has a better allograft function at 12 months posttransplant (P=0.01).

Discussion

CNIs are the hallmark of the immunosuppression treatment in KT. The major concerns regarding CNIs use are nephrotoxicity, malignancy, infections, and dysmetabolic effects. In our study, we focused on allograft survival and functions and demonstrated diltiazem has no impact on a 1-year allograft survival rate; further, in the diltiazem arm, 1-year allograft function was worse.

Table 2. Comparison of the two groups for 1-year outcomes, and for factors which might impact on survival rates.

	Diltiazem N=73	Diltiazem-free N=239	P value
Recipient age, years	42.13 ± 13.72	44.09 ± 13.94	0.29
Donor age, years	50.42 ± 49.87	49.87 ± 12.80	0.75
Recipient sex, male/female	45(61.6%)/28(38.4%)	142(59.4%)/97(40.6%)	0.68
Donor sex, male/female	40(54.7%)/33(45.3%)	124/119	0.69
Recipient BMI, kg/m^2	25.94 ± 5.69	24.25 ± 5.16	0.17
Donor BMI, kg/m^2	27.60 ± 3.68	27.84 ± 5.93	0.87
Allograft type; Living Deceased	 62 (85%) 11 (15%)	 200 (84.7%) 39 (16.3%)	 0.85
BKV positivity, yes/no	6/60 (9.1%/90.9%)	32/197 (13.9%/86.1%)	0.12
CMV positivity, yes/no	14/56 (20%/80%)	24/204 (10.5%/89.5%)	0.06
Rejection, yes/no (BPAR)	19/42 (31.1%/68.9%)	50/149 (25.1%/74.9)	0.35
Exitus, yes/no, 1-year mortality	3/70 4.1%	9/230 3.8%	0.89
Graft loss, yes/no, 1-year allograft survival	10/63 %13.7	17/222 %7.1	0.08
Immunological risk, low/high	54/19 (73.9%/26.1%)	191/48 (79.9%/20.1%)	0.60
CNI toxicity (Bx proven)	18.8%	10.5%	0.27
3 months eGFR, ml/dk/1.73m^2	64.38 ± 25.56	67.30 ± 27.03	0.42
12 months eGFR, ml/dk/1.73m^2	62.75 ± 22.24	73.19 ± 24.60	0.03

BMI; body mass index, BKV; polyoma B-K virus, CMV; cytomegalovirus, Bx; biopsy. CNI; calcineurin inhibitor, eGFR; estimated glomerular filtration rate

Table 3. Impact of factors on 12-month allograft function.

	OR	CI (95% confidence interval)	P value
Donor age, years	-0.125	(-0.778) – (-0.373)	0.03
Recipient age, years	-0.331	(-0.438) – (-0.015)	0.01
BKV positivity	-0.260	(-10.107) – (6.623)	0.68
CMV positiviy	-0.083	(-15.750) – (3.246)	0.19
Acute rejection episode	-0.060	(-10.781) – (4.130)	0.38
Allograft type (living/deceased)	+0.013	(-7.376) - (9.073)	0.83

CNIs-related nephrotoxicity occurs acutely or chronically (19). Acute toxicity may occur in anytime posttransplant, however, a serum trough tacrolimus level > 30 ng/mL is strongly associated with clinically apparent or subclinical nephrotoxicity (76%). Nevertheless, in 5.3% of patients receiving tacrolimus, the dose for drug toxicity may be lower than 10 ng/mL (20). Posttransplant early CNIs toxicity has been suggested as a cause of delayed graft function and impairs in the recovery of acute kidney injury (21,22). Liu et al, in order to avoid posttransplant early CNIs nephrotoxicity, suggested delayed initiation of tacrolimus after antilymphocyte induction therapy, and they also demonstrated there was no increased risk of AR when tacrolimus administration was delayed (23). The major concern regarding CNIs-induced chronic nephrotoxicity is the chronic allograft nephropathy. CNIs exposure results in vascular endothelial injury and renal arteriolar vasoconstriction. Eventually, chronic renal hypoperfusion and subsequently allograft ischemia causes in allograft loss (24,25). Besides, hypertension, NODAT, dyslipidemia, hyperuricemia, hypomagnesemia, metabolic acidosis, hypercalciuria, and hyperkalemia are the best-defined complication of CNIs use (4). Dr. Nankivell who is famous for his paper regarding the evolution of kidney allograft histology (3) reported a recent paper and highlighted his conclusion as; "one kidney for life" will remain largely unrealized with CNI dependent therapy-as nephrotoxicity becomes marked and histologically important a decade after transplantation and beyond, even with low-dose tacrolimus therapy (26). All considered CNI reduction strategy has become a common choice today. For this purpose, early reduction of CNIs in patients with low immunological risk and switching from standard-dose tacrolimus to low dose tacrolimus + mTORi (mammalian target of rapamycin inhibitor) are the most conventional approaches in avoiding CNI induced toxicity. Diltiazem has been used in KT patients to provide financial advantages

and to prevent CNI induced nephrotoxicity (13,16). Nevertheless, these results are arguable and long-term outcomes are not clear. Chrysostomuo et al. demonstrated that diltiazem with CsA was associated with less-severe rejection episodes, however, there was no difference in renal function or in the number of grafts lost between the diltiazem and diltiazem-free group (27). In our study, in the diltiazem arm, 1-year mortality, the rate of allograft loss, and biopsy-proven CNIs toxicity were at higher rate than the diltiazem-free group; 4.1%, 13.7%, and 18.8%, respectively. However, the differences were not significant statistically. Additionally, the 1-year allograft function was found to be reduced in the diltiazem arm, compared to the diltiazem-free group. Surprisingly, after the addition of diltiazem to treatment (within 3 months posttransplant) eGFR did not improve, in contrast, a statistically not significant reduction was observed. Considering all, higher rates of CMV, AR episodes, and CNI toxicity, which all were not significant statistically, might have an overall impact on worse outcomes. In addition, diltiazem may have increased CNI blood levels that associated with CNI nephrotoxicity. In contrast, in the diltiazem-free arm after minimizing CNIs dose according to standard protocols, eGFR at 12 months posttransplant improved compared to at the 3 months. Further, regression analysis revealed that CNIs toxicity has a weak but significant impact on 12 months allograft functions, in a 90% confidence interval.

CMV, BKV, and AR episodes are conventional risk factors regarding allograft survival, however, in our cohort, those risk factors have been found no related to worse allograft functions, at 12 months posttransplant (28-30). The impact of donors' and recipients' BMI on allograft survival is controversial. Despite existing evidence of increased risk of allograft loss in obese pediatric kidney recipients, higher BMI has not been associated with allograft loss in adults. (31,32). Also, in our study, BMI did not correlate to allograft function. Recipient age had an inverse correlation to 1-year recipients survival and donors' age was correlated to 1-year allograft survival, as expected.

In conclusion, the main targets of transplanting a renal allograft are to provide a longer recipient survival and a prolonged healthy allograft survival. In this regard, it should be given that cost-benefit has less importance, be keep in mind unproven approaches such as using diltiazem in order to prevent CNIs toxicity may be harmful rather than improving allograft functions.

Acknowledgements:

All authors declare that no conflict of interest and funding supports.

Ethical Approval: Ethic committee approval was obtained from "Scientific Research and Ethical Committee of The Yeni Yüzyıl University", (IRB:2020/06-475).

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