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Pulse Wave Analysis in Kidney Transplant Patients Using Tacrolimus

Takrolimus Kullanan Böbrek Nakli Hastalarında Nabız Dalga Analizi

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Abstract

Objective: Pulse wave velocity (PWV) allows the evaluation of arterial stiffness. Although PWV improves after transplantation, it is still higher than in healthy controls. Immunosuppressive agents may contribute to this. Our study aimed to investigate the effect of tacrolimus (TAC) blood level on PWV.

Methods: Fifty-nine kidney transplant patients using TAC with follow-up at the Organ Transplantation Clinic of University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital, were included in the study. Pulse wave analysis was measured in two measurements using the IEM ambulatory blood pressure measuring device. The relationship between arterial stiffness parameters and the patients' transplantation time, dialysis duration before transplantation, age, kidney functions, proteinuria, and TAC blood levels were examined.

Results: Between PWV and systolic (r=0.589, p<0.001), diastolic (r=0.271, p=0.038) and mean blood pressure (r=0.440, p<0.001) and age (r=0.906, p<0.001) significant correlation was detected. No correlation was detected between TAC level and PWV. When the estimated value for PWV was taken as 8.1 m/s, a significant difference was observed between PWV and age, glomerular filtration rate, Parathormone and proteinuria levels. With TAC level above 7 ng/mL, systolic (120±14 mmHg vs. 119±22 mmHg, p=0.026) and diastolic blood pressure (89±13 mmHg vs. 40±12 mmHg, p=0.023) were found to be higher. A reverse correlation was detected between TAC level and proteinuria (r=-0.316, p=0.035). There was no correlation between transplantation time, pre-transplantation dialysis duration and PWV and other arterial stiffness parameters.

Conclusion: Increase in TAC blood level may cause hypertension in kidney transplant patients. But it is not associated with PWV. PWV is affected only by age, systolic, diastolic and mean arterial pressure in kidney transplant patients using TAC.

Keywords: Tacrolimus, pulse wave velocity, hypertension

Öz

Amaç: Nabız dalga hızı (PWV), arteriyel sertliğin değerlendirilmesini sağlar. Nakil sonrası PWV iyileşmesine rağmen, sağlıklı kontrollere göre halen yüksektir. İmmünosüpresif ajanlar buna katkıda bulunuyor olabilir. Çalışmamızda takrolimus (TAC) kan düzeyinin PWV üzerine etkisini araştırmak amaçlandı.

Yöntem: Sağlık Bilimleri Üniversitesi İzmir Tepecik Eğitim ve Araştırma Hastanesi, Organ Nakli Polikliniği'nde takipli TAC kullanımı olan 59 böbrek nakli hastası çalışmaya dahil edildi. Hastalara IEM ambulatuvar kan basıncı ölçüm cihazı kullanılarak, iki ölçüm ile nabız dalga analizi ölçümü yapıldı. Arteriyel sertlik parametreleri ile hastaların nakil süresi, nakilden önceki diyaliz süreleri, yaş, böbrek fonksiyonları, proteinüri, TAC kan düzeyleri arasındaki ilişki incelendi.

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Öz

Bulgular: PWV ile sistolik (r=0,589, p<0,001), diyastolik (r=0,271, p=0,038) ve ortalama kan basıncı (r=0,440, p<0,001), yaş (r=0,906, p<0,001) arasında anlamlı korelasyon saptanmıştır. TAC düzeyi ile PWV arasında korelasyon saptanmadı. PWV için 8,1 m/s olarak kestirim değeri alındığında PWV ile yaş, glomerüler filtrasyon hızı, parathormon ve proteinüri düzeyleri arasında anlamlı farklılık görüldü. TAC düzeyi 7 ng/mL üzerinde sistolik (120±14 mmHg'ye karşı 119±22 mmHg, p=0,026) ve diyastolik tansiyon (89±13 mmHg'ye karşı 40±12 mmHg, p=0,023) daha yüksek saptandı. TAC düzeyi ile proteinüri arasında ters korelasyon tespit edildi (r=-0,316, p=0,035). Nakil süresi, nakil öncesi diyaliz süresi ile PWV ve diğer arteriyel sertlik parametreleri arasında ilişkili bulunmadı.

Sonuç: TAC kan düzeyindeki artış böbrek nakli hastalarında hipertansiyona neden olabilmektedir. Fakat PWV ile ilişkili değildir. PWV, TAC kullanımı olan böbrek nakli hastalarında sadece yaş, sistolik, diyastolik ve ortalama arteriyel basınçtan etkilenmektedir.

Anahtar Kelimeler: Takrolimus, nabız dalga analizi, hipertansiyon

Introduction

Arteriosclerosis and its complications are the leading causes of death in renal transplant recipients[1]. Pulse wave velocity (PWV) is a sensitive parameter that allows the regional assessment of arterial stiffness. PWV is an independent determinant of arterial stiffness and increased cardiovascular risk in patients with hypertension and dialysis[2,3]. Despite improvements in PWV after kidney transplantation, it is still higher than in healthy controls[4,5]. Post-transplant immunosuppressive regimens, especially cyclosporine-containing regimens, seem to diminish the beneficial vascular effects of kidney transplantation. When the effects of calcineurin inhibitors [calcineurin inhibitor (CNI) tacrolimus (TAC) and cyclosporine-A (CsA)] on arterial stiffness are compared, CsA is known to increase arterial stiffness compared to TAC[6-8]. In a previous study conducted on patients using TAC, no significant relationship was found between TAC use and PWV values, though the study did find a relationship between PWV and age[7]. However, a relationship was shown between CsA level and PWV[9]. The aim of our study was to examine the relationship between TAC level and PWV in patients who adopted the TAC regimen after transplantation. In addition, the relationship between pre-transplant dialysis duration, post-transplant duration, the renal functions, and PWV was examined.

Materials and Methods

Fifty-nine consecutive kidney transplant patients using tacrolimus who were followed up at the University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital Organ Transplantation Outpatient Clinic between 2022-2023 were included in the study. The study was approved by the Non-Interventional Ethics Committee of the University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital (decision no: 2024/09-11, date: 10.10.2024). Kidney transplant recipients with a transplant duration under one year, patients with atrial fibrillation, and patients with glomerular filtration rate (GFR) below 30 mL/min/m^2, were not included in the study. The study was designed as a retrospective case-control study. In routine outpatient clinic controls of 59 patients, pulse wave analysis was measured twice using an IEM ambulatory blood pressure measurement device. PWV and other arterial stiffness parameters [augmentation index (AIx) and pressure, pulse pressure, peripheral resistance], systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean blood pressures (MBP) were recorded with the device. Kidney transplantation dates; hemodialysis or peritoneal dialysis durations; TAC usage durations; additional diseases (diabetes, cardiovascular disease); smoking; medications used; creatinine on the day of pulse wave analysis; GFR; mean of the last 3 TAC levels of the patients; uric acid; calcium; phosphorus; parathyroid hormone (PTH); 25 (OH) vitamin D; spot urine protein creatinine ratios were recorded retrospectively from the outpatient clinic files. The relationship between the parameters measured by pulse wave analysis and tacrolimus level, transplantation time, dialysis duration before transplantation, creatinine, GFR, uric acid, PTH, vitamin D, calcium, and phosphorus levels was examined.

Statistical Analysis

SPSS version 27.0 (IBM Corp.) was used in the analysis of the data. The distribution of the data was analyzed with Kolmogorov-Smirnov and Shapiro-Wilk tests. In the comparison of means, Student's t-test was used for those showing normal distribution and Mann-Whitney U test was used for those not showing normal distribution. The chi-square test was used in the examination of categorical data. In the examination of the correlation of continuous data, Spearman and Pearson correlation tests were applied according to the distribution of the data. P<0.05 was accepted as statistically significant.

Results

The baseline demographic data of the patients are presented in Table 1. Thirty-three female and twenty-six male patients were included in the study. A significant correlation was found between PWV and age (r=0.906, p<0.001), SBP (r=0.589, p<0.001), DBP (r=0.271, p=0.038), and MBP (r=0.440, p<0.001). No correlation was found between TAC level and PWV. When the cut-off value for PWV was taken as 8.1 m/s, a significant difference was found among PWV, age, GFR, PTH, and proteinuria levels (Table 2).

When patients with TAC levels above and below 7 ng/mL were compared in terms of arterial stiffness parameters, no relationship was found between the parameters and TAC levels. SBP (120.6±14.6 mmHg vs. 119.7±22.1 mmHg, p=0.026) and DBP (89±13 mmHg vs. possibly incorrect value 40±12 mmHg, p=0.023) were higher with TAC levels above 7 ng/mL, compared to lower TAC levels. A negative correlation was found between TAC levels and proteinuria (r=-0.316, p=0.035). No relationship was found between transplantation duration, pre-transplantation dialysis duration, and PWV and other arterial stiffness parameters.

Table 1. Baseline demographic data

Variables	Mean ± SD	n
Age (years)	45.8±12.9	59
Kidney transplantation duration (months)	122.2±79.6	59
Pre-transplant dialysis duration (months)	26.2±34.1	59
Creatinine (mg/dL)	1.41±0.49	59
GFR (mL/min)	60.3±22.7	59
Calcium (mg/dL)	9.6±0.5	59
Phosphorus (mg/dL)	3.4±0.7	59
Uric acid (mg/dL)	6.7±1.5	59
PTH (pg/mL)	150±91.5	59
Vitamin D (ng/mL)	16.7±7.5	57
Hemoglobin (g/dL)	12.9±1.9	59
Spot urine protein creatinine ratio (mg/mg)	0.577±1.024	59
MBP (mmHg)	105.6±13.6	59
Systolic BP (mmHg)	120±20	59
Diastolic BP (mmHg)	78.8±24.7	59
PWV m/sec	7.01±1.49	59

MBP: Mean blood pressure, BP: Blood pressure, SD: Standard deviation, PTH: Parathyroid hormone, GFR: Glomerular filtration rate

Discussion

PWV is a valuable parameter for assessing arterial stiffness. Successful kidney transplantation leads to a decrease in PWV[4,10]. However, PWV is still higher than in healthy controls[11]. This situation seems to be related to the immunosuppressive protocol. In studies comparing arterial stiffness parameters in CsA and TAC-containing regimens, AIx and PWV were found to be higher in the CsA-containing regimen[4,7]. A significant relationship was found between TAC and age, but no data were obtained indicating that TAC increased PWV[7]. In our study, no significant correlation was found between TAC level and PWV.

There is a dose-response relationship between increasing PWV and the occurrence of major cardiovascular outcomes such as acute coronary syndrome, cerebrovascular syndromes, and death. Regardless of the threshold value, cardiovascular risk increases[12]. In a prospective study conducted in a cohort of 512 kidney transplant recipients in 2011, cardiovascular survival was found to be worse in patients with PWV ≥8.1 m/s compared to patients with PWV <8.1 m/s[13]. Therefore, the cut-off value for PWV in our study was taken as 8.1 m/s. When PWV was measured at 8.1 m/s, a significant relationship was found between PWV and GFR, PTH, proteinuria, and age. In patients with higher PWV, age was higher, GFR was lower, and PTH and proteinuria were increased. Classical risk factors influencing PWV include hypertension, age, PTH, and proteinuria[14-16]. Despite being a CNI, the lack of association between tacrolimus levels and PWV in our study may be attributed to the narrow therapeutic range of tacrolimus, as well as the prevention of sustained high levels over prolonged periods.

Age and blood pressure are the main factors affecting the PWV[17]. In our study, a significant relationship between PWV and SBP, DBP, MBP, and age was found, in line with previous studies. No relationship was found between PWV

Table 2. Patients with PWV above and below 8.1 m/sec

	Group 1 n=21	Group 2 n=38	
PWV (m/sec)	>8.1 m/sec	<8.1 m/sec	p
GFR (mL/min)	53.07±16.88	62.58±24.04	0.044[b]
Spot urine protein creatinine ratio (mg/mg)	1.171±1.304	0.408±0.880	0.036[b]
Age (years)	60.9±6.3	41.1±10.6	0.011[a]
PTH (pg/mL)	175.3±136.9	141.8±72.2	0.013[a]

[a]:Mann-Whitney U test, [b]:Student t-test, PWV: Pulse wave velocity, PTH parathyroid hormone, GFR: Glomerular filtration rate

and transplantation duration, pre-transplantation dialysis duration, and renal functions.

The cause of post-transplant hypertension is multifactorial, and one of the risk factors is CNI[14]. TAC-based regimens may be associated with a lower incidence of hypertension compared to CsA-based regimens[18,19]. In our study, no correlation was found between hypertension and TAC levels in the entire patient group, but increased systolic and diastolic blood pressure was detected in the patient group with TAC levels of 7 ng/mL. This showed us that increased TAC levels may be associated with hypertension. While it is well-established that TAC can lead to increased blood pressure (both SBP and DBP), our study did not observe an impact on PWV despite the hypertensive effects of TAC. This discrepancy could be attributed to several factors, including PWV may be influenced by other mechanisms independent of blood pressure, or that the duration of hypertension caused by TAC in our cohort was insufficient to lead to measurable changes in arterial stiffness. Arterial stiffness can be a consequence of long-term hypertension, but initially, hypertension may develop without causing significant arterial stiffening. In other words, it is possible for hypertension to develop before it leads to an increase in PWV[20]. Further investigation into the complex relationship between TAC, hypertension, and arterial stiffness is warranted to better understand these dynamics and identify other contributing factors.

Study Limitations

Our study's limitations were due to the lack of molecular markers that could predict arterial stiffness before PWV values were available. In addition, no comparison was made with other agents used in kidney transplantation, such as CsA, sirolimus, and everolimus. Only patients using TAC were included in the study.

Conclusion

In our study, the only factors affecting PWV were determined to be blood pressure and age. Although TAC levels above 7 ng/mL were found to be associated with hypertension, it was observed that they did not affect arterial stiffness parameters.

Ethics

Ethics Committee Approval: The study was approved by the Non-interventional Ethics Committee of the University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital (decision no: 2024/09-11, date: 10.10.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.Y., S.A., M.T., Concept: B.Y., Design: B.Y., Data Collection or Processing: B.Y., S.A., Analysis or Interpretation: B.Y., M.T., Literature Search: B.Y., Writing: B.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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