

Comparison of tacrolimus levels in saliva and blood serum of patients after heart transplantation

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ABSTRACT

Introduction: Considering that the lack of correct understanding of tacrolimus serum levels leads to irreversible complications such as kidney failure, convulsions, etc. in heart transplant patients, it is very important to understand the factors affecting the metabolism and serum levels of this drug. In addition, saliva can be used as a more accessible source to measure tacrolimus levels.

Methods: In our study, 7 patients including 4 men and 3 women were included in the study, 3 patients due to DCM, 1 patient due to myocarditis, 1 patient due to ICM, 1 patient due to ARVC and 1 patient due to RHD underwent heart transplant surgery. In this study, we aim to compare the levels of tacrolimus in the saliva and serum of patients after heart transplantation. We hypothesize that there may be a correlation between the levels of tacrolimus in saliva and serum, as both are potential sources for drug monitoring in heart transplant patients.

Results: Our study highlights the importance of accurately monitoring tacrolimus levels in heart transplant patients. While saliva-based monitoring of tacrolimus levels may be a convenient alternative to blood draw, our findings suggest that it may not provide accurate.

Conclusion: These findings indicate that caution should be exercised when using salivary tacrolimus levels as a sole indicator of drug concentration and further research is necessary to better understand and interpret salivary tacrolimus levels in clinical practice and to optimize post-transplant care for heart transplant patients.

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Introduction

About 8,000 heart and lung transplants are successfully performed in the world every

year (1). However, mortality after heart and lung transplantation is also very significant. Kidney failure is one of the causes of death in transplant recipients, which usually occurs in

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the early hours after transplantation. During these hours, the kidneys are exposed to many stimulating and toxic factors. Meanwhile, tacrolimus poisoning is very common, and during this critical period, the pharmacokinetics of this drug may have significant changes through fluctuations in drug absorption, changes in protein metabolism, anemia, and organ failure. Little information and findings are available on the pharmacokinetics of tacrolimus in the early hours after heart and lung transplantation (2). Tacrolimus is one of the drugs that suppress and weaken the immune system. Since the immune system may reject the transplanted organ in the recipient's body, it is necessary to prescribe immunosuppressive drugs such as tacrolimus along with some other drugs to prevent the immune system from rejecting the transplanted organ in these people (3).

In this study, we aim to compare the levels of tacrolimus in the saliva and serum of patients after heart transplantation. We hypothesize that there may be a correlation between the levels of tacrolimus in saliva and serum, as both are potential sources for drug monitoring in heart transplant patients. By comparing the levels of tacrolimus in both saliva and serum samples, we can assess whether saliva can serve as a reliable alternative to blood for monitoring drug levels in heart transplant patients. Furthermore, understanding the correlation between tacrolimus levels in saliva and serum can lead to the development of non-invasive methods for monitoring drug levels in heart transplant patients.

Tacrolimus is an immunosuppressive drug commonly used in heart transplantation to prevent organ rejection. It works by inhibiting the activity of T-lymphocytes, a type of white blood cell that plays a key role in immune responses. Tacrolimus, like all drugs, may cause unwanted side effects in the body in addition to the necessary effects. The most common complications include diabetes mellitus (sweet), infection, hyperglycemia (increased blood sugar), hyperkalemia (increased potassium), kidney toxicity, changes in mental status, increased blood urea nitrogen, increased blood creatinine, sensory impairment, headache, and They are shaking (4,5). For this reason,

measuring and controlling the amount of tacrolimus in the serum and saliva of patients after heart transplantation is of particular importance. Determining the dose of this drug depends on its minimum amount in the whole blood, which is very variable and unpredictable in the early hours after heart and lung transplantation, and can be toxic even within the therapeutic range (6). Factors affecting the amount of tacrolimus include food and drug interactions, inflammation, ischemia, reperfusion injuries, unstable hemodynamic status of the patient, age, etc. (7, 8). Currently, the usual method of measuring tacrolimus is from blood samples of patients. It is possible that the amount of tacrolimus in the saliva of patients can also represent the total level of tacrolimus in the body. However, not many studies have been done on comparing and investigating the relationship between the amount of this substance in blood and saliva. If the studies show that the amount of tacrolimus in blood and saliva have a strong and significant relationship with each other, it is possible to replace blood sampling with a much easier, painless and low-cost method of sampling patients' saliva. The present study focuses on comparing the amount of tacrolimus in the saliva and blood of heart transplant recipients and investigating the factors affecting its amount.

Patients and Method

To further investigate the clinical implications of tacrolimus levels in saliva and serum, we enrolled a cohort of post-heart transplant patients in a longitudinal study. The patients provided both saliva and blood serum samples at regular intervals for analysis of tacrolimus levels. This suggests that monitoring tacrolimus levels in saliva can accurately reflect the drug concentration in the blood, providing a non-invasive and convenient option for therapeutic drug monitoring in heart transplant patients

In our study, 7 patients from montaserieh Hospital including 4 men and 3 women were included in the study, 3 patients due to Dilated cardiomyopathy DCM, 1 patient due to myocarditis, 1 patient due to Ischemic cardiomyopathy ICM, 1 patient due to Arrhythmogenic right ventricular dysplasia

ARVC and 1 patient due to Rheumatic heart disease RHD underwent heart transplant surgery.

Due to the difference in the metabolism of people, in the use of tacrolimus and drug interactions, the serum and saliva levels of the mentioned drug are different in different people with a fixed dose (7).

In this study, the serum level of tacrolimus in the blood and saliva of all heart transplant patients with a fixed dose after the transplant (0.5-1 mg) is examined. All transplant patients take 0.5-1 mg of the drug every 12 hours on the second day after transplantation.

Dose adjustment is determined based on serum levels checked every 5 to 7 days. In this study, in addition to the serum level, the tacrolimus salivary level is also measured.

In this study, we used a validated method to measure tacrolimus levels in both saliva and blood serum samples. This method used high performance liquid chromatography coupled with mass spectrometry to accurately quantify the tacrolimus concentration in each sample.

Statistical analyses

Data related to demographic and clinical observations (age, weight, gender) of patients were analyzed using SPSS 24 software. Descriptive statistical methods, including central indices, dispersion and frequency distribution, were used to describe the data, and the Pearson correlation test or its non-parametric equivalent, the Spearman correlation test, will be used to check the correlation between salivary and serum tacrolimus levels. The scatter plot was used to check the linear correlation between salivary and serum tacrolimus levels. In the tests, $p < 0.05$ will be considered as a significant level. This study is based on the census method and includes 7 heart transplant patients in 2023.

Results and Findings

In our study the average dose of tacrolimus in patients was 0.75 mg. It is done with the range of (0.5-1) mg daily and the amount of tacrolimus based on time and body surface.

The average blood tacrolimus in patients is 25.6 $\mu\text{g/Lit}$ and the average saliva tacrolimus

is 6.8 $\mu\text{g/Lit}$. In terms of statistical analysis, no significant relationship was found between tacrolimus blood and saliva levels and genotypic levels in blood.

Our analysis revealed that the tacrolimus levels in saliva were consistently lower than those in blood serum, indicating that saliva may not accurately reflect the drug concentration in heart transplant patients. Further research is necessary to determine the factors contributing to this discrepancy and to establish guidelines for interpreting salivary tacrolimus levels in clinical practice.

Discussion

MacDonald C and colleagues have shown in a 2015 study that the level of tacrolimus is an important factor for predicting the occurrence of acute kidney injury after heart transplantation in children (9).

Belostotsky V and colleagues in 2011 compared tacrolimus levels in blood and saliva of kidney recipient children and did not find any significant relationship between the two (10).

Staatz CE and colleagues concluded in a review study that accurate measurement and prescription dosage and formulation of tacrolimus in solid organ transplant patients are very important because exceeding the permissible level of tacrolimus in the body of these patients can seriously harm them (11).

Sikma MA and his colleagues have focused on the amount of tacrolimus immediately after heart and lung transplantation in recipient patients, and have also examined the factors affecting its serum level and its toxic effects on the kidneys, and have concluded that Measuring the level of this drug immediately after heart and lung transplantation is very important and has a direct relationship with the incidence of side effects of this drug, including transplant rejection or kidney damage due to its high level (1).

Storset E and his colleagues in a study in 2016, pointing out that the optimal amount of tacrolimus in transplanted patients is not well known, stated the results of their study on 406 patients and tacrolimus measurement in them as follows: suppressors Low-target immunity with tacrolimus base is safe and effective (12).

Dasari and colleagues, considering the importance of determining the amount of tacrolimus to determine the therapeutic dose in transplant patients, in their study in 2016, designed a protocol to estimate the amount of tacrolimus in liver transplant patients, one of the advantages of which is predicting the appropriate dose to achieve the therapeutic concentration. They have expressed and considered this method cost-effective (4).

These findings have significant implications for post-transplant care, as accurate monitoring of tacrolimus levels is crucial for optimizing patient outcomes and preventing rejection. Saliva-based monitoring has been proposed as a non-invasive and convenient method for measuring tacrolimus levels. However, our study suggests that caution should be exercised when relying solely on salivary tacrolimus levels, as they may not accurately reflect the drug concentration in heart transplant patients. Further research is needed to fully understand the factors influencing the difference in tacrolimus levels between saliva and serum, and to determine the reliability of saliva-based monitoring in this patient population. Overall Conclusion on Tacrolimus Levels in Heart Transplant Patients: In conclusion, our study demonstrated a significant difference in tacrolimus levels between saliva and serum samples in heart transplant patients. This suggests that saliva may not be a reliable alternative to blood draw for assessing tacrolimus concentration in these patients.

Conclusion

Our study highlights the importance of accurately monitoring tacrolimus levels in heart transplant patients. While saliva-based monitoring of tacrolimus levels may be a convenient alternative to blood draw, our findings suggest that it may not provide accurate measurements of drug concentration in this patient population. Further research is needed to better understand the factors influencing the difference in tacrolimus levels between saliva and serum, and to establish guidelines for interpreting salivary tacrolimus levels in clinical practice. In conclusion, the analysis of tacrolimus levels in the saliva and blood serum of heart transplant patients revealed

consistent differences between the two samples. These findings indicate that caution should be exercised when using salivary tacrolimus levels as a sole indicator of drug concentration and further research is necessary to better understand and interpret salivary tacrolimus levels in clinical practice and to optimize post-transplant care for heart transplant patients.

Future Research Directions in Tacrolimus Studies

In light of our findings, future research should focus on investigating the factors contributing to the disparity in tacrolimus levels between saliva and serum. Additionally, further studies are needed to determine the correlation between tacrolimus concentrations in saliva and clinical outcomes in heart transplant patients.

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