Balancing Immunosuppression and Graft Preservation: Calcineurin Inhibitor Nephrotoxicity in Kidney Transplant Recipients

Syed Ameroon Shah[1], Sami-Ur-Rahman[2], Saif Ullah[3], Khawar Suliman[4], Muhammad Mubbashar Nazar[5], Naveed Sarwar[6]

1. Medical Officer Team D Urology, Institute Of Kidney Diseases, Medical Teaching Institute ,Hayatabad Medical Complex , Rawalpindi, Pakistan.
2. Registrar Kidney Transplant, Kidney Transplant Department, Begum Akhtar Rukhsana Memorial Trust And Hospital, Rawalpindi, Pakistan
3. Assistant Professor Urology Bukhtawar Amin Teaching Trust Hospital Multan, Rawalpindi, Pakistan
4. Senior Consultant Urologist, Urology Provincial Headquarter Hospital (PHQ), Gilgit, Pakistan
5. Assistant Professor Nephrology, Farooq Hospital, Islamabad, Pakistan
6. Consultant Nephrologist Begum Akhtar Rukhsana Memorial Trust And Hospital, Rawalpindi, Pakistan

Corresponding Author: **Sami-Ur-Rahman**

Registrar kidney transplant, Kidney Transplant Department, Begum Akhtar Rukhsana Memorial Trust and Hospital Pakistan

Email id: dr.sami7264@gmail.com

ABSTRACT

Background: Immunosuppressive therapy after kidney transplantation is essential and a widely-used component is the use of calcineurin inhibitors (CNIs), such as tacrolimus and cyclosporine. While very effective for acute rejection prevention, chronic use of CNI can cause nephrotoxicity that can lead to chronic allograft dysfunction and loss of graft. To maximize the chances for a successful transplant, early diagnosis and treatment are important.

Objective: To Determine the incidence of calcineurin inhibitor nephrotoxicity, risk factors for it and its effect on graft function in kidney transplant recipients.

Methodology: A prospective study was conducted at Begum Akhtar Rukhsana Memorial Trust and Hospital, Rawalpindi, from June 2022 to November 2022. Fifty kidney transplant recipients receiving tacrolimus- or cyclosporine-based immunosuppressive therapy were enrolled. Demographic characteristics, clinical parameters, serum creatinine, estimated glomerular filtration rate (eGFR), calcineurin inhibitor trough levels, biopsy findings, and graft outcomes were recorded prospectively. Calcineurin inhibitor nephrotoxicity was diagnosed using clinical, laboratory, and histopathological criteria. Data were analyzed using SPSS version 26, and a p-value <0.05 was considered statistically significant.

Results: A total of 50 kidney transplant recipients were included in the analysis. The mean age of participants was 43.2 ± 11.4 years, and 33 (66.0%) were male. Calcineurin inhibitor nephrotoxicity was identified in 12 (24.0%) patients, while 38 (76.0%) had stable graft function without evidence of toxicity. Patients with nephrotoxicity were significantly older than those without nephrotoxicity (46.8 ± 10.2 versus 42.1 ± 11.7 years; p=0.041). Elevated calcineurin inhibitor trough levels were present in 8 (66.7%) affected patients compared with 8 (21.1%) unaffected recipients (p<0.001). Hypertension and diabetes mellitus were significantly more common among patients with nephrotoxicity. Mean eGFR was significantly lower among affected patients (43.5 ± 12.1 vs. 58.8 ± 13.9 mL/min/1.73 m^2; p<0.001). Proteinuria was observed in 6 (50.0%) patients with nephrotoxicity and 7 (18.4%) patients without toxicity (p=0.001).

Conclusion: An important side effect of the kidney transplantation is the so called calcineurin inhibitor nephrotoxicity, which is positive with reduced graft function. To maintain long term allograft outcomes, it is important to schedule and receive therapeutic drug monitoring and tailored immunosuppressive therapy.

Keywords: Kidney Transplantation; Calcineurin Inhibitors; Nephrotoxicity; Graft Function.

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Introduction

Kidney transplantation is considered the treatment of choice for patients with end-stage renal disease (ESRD), offering superior survival rates, improved quality of life, and reduced long-term healthcare costs compared with maintenance dialysis. Over the past several decades, significant advances in surgical techniques, donor selection practices, and immunosuppressive therapies have markedly improved short-term graft survival and overall transplant outcomes. Calcineurin inhibitors (CNIs) are still used as the main treatment for maintenance immunosuppression in kidney transplant recipients, with tacrolimus and cyclosporine being the two most frequently used CNIs. These agents have reduced the incidence of acute rejection to a significant degree, and played a major role in the improvement of graft outcome [1,2]. Calcineurin inhibitors work as immunosuppressants by blocking the activity of the enzyme calcineurin phosphatase, which downregulates activation of T-cells and cytokines. Although effective, CNIs are known to cause nephrotoxicity (toxicity to the kidneys) with chronic exposure that may affect graft function and impact long-term allograft survival. The incidence of calcineurin inhibitor nephrotoxicity (CNIT) has become a major clinical problem as it may mimic other causes of graft dysfunction such as acute rejection, recurrent renal disease, and chronic antibody mediated rejection [3,4]. Acute and chronic mechanisms are all part of the pathophysiology of CNIT. Acute toxicity is due mainly to the vasoconstriction of afferent arterioles which causes a decrease in renal blood flow and transient decrease in GFR. Chronic toxicity

includes changes in the structure of the tubules (tubular atrophy), the arteries (arteriolar hyalinosis), the fibers (fibrosis) and the clusters of capillaries (glomerulosclerosis). These changes can gradually affect the function of the graft and can lead to graft failure. The diagnosis of CNIT can be difficult due to its non-specificity and overlapping clinical features with other complications following transplant [5,6]. The risk of CNI nephrotoxicity varies depending on several factors. High exposure to the drugs has been linked, as has been exposure for long periods, older donor age, delayed graft function, hypertension, diabetes mellitus and concurrent use of nephrotoxic drugs. Therefore, therapeutic drug monitoring is needed to achieve proper immunosuppression with minimal toxicity. However, even with close supervision, nephrotoxicity remains a frequent problem among transplant patients [7,8]. New developments in transplantation medicine have provided other immunosuppressive options such as mTOR inhibitors and stimulation blockers, which may allow for either lowering or eliminating CNI use in certain patients. Yet, the CNIs remain popular due to their effectiveness and availability. Thus, knowledge of the burden and determinants of CNIT continue to be essential in order to maximize the patient outcome [9,10].

Study Objective

To determine the prevalence of calcineurin inhibitor nephrotoxicity, identify associated risk factors, and evaluate its impact on renal allograft function among kidney transplant recipients.

Materials and Methods

Study Design and Setting

This prospective observational study was conducted at Begum Akhtar Rukhsana Memorial Trust and Hospital, Rawalpindi, Pakistan, from June 2022 to November 2022. The study aimed to evaluate the prevalence, risk factors, and clinical impact of calcineurin inhibitor nephrotoxicity among kidney transplant recipients receiving maintenance immunosuppressive therapy.

Participants

A total of 50 adult kidney transplant recipients receiving tacrolimus- or cyclosporine-based immunosuppressive therapy for at least six months were enrolled consecutively during the study period. Demographic information, clinical characteristics, laboratory findings, calcineurin inhibitor trough levels, renal biopsy results, and graft outcomes were collected prospectively from patient records and follow-up visits.

Sample Size Calculation

The sample size was calculated using the WHO sample size calculator with a 95% confidence level and an anticipated prevalence of calcineurin inhibitor nephrotoxicity of 24%. Based on the available transplant population and study duration, a final sample size of 50 participants was included to ensure adequate assessment of nephrotoxicity and its associated clinical outcomes.

Inclusion Criteria

* Age ≥18 years.

* Kidney transplant recipients receiving tacrolimus or cyclosporine therapy.

* At least six months post-transplantation.

* Availability of complete clinical and laboratory records.

* Regular follow-up at the transplant clinic during the study period.

Exclusion Criteria

* Recipients of multi-organ transplants.

* Patients with active acute rejection episodes.

* Patients diagnosed with BK virus nephropathy.

* Recurrence of primary kidney disease affecting graft function.

* Active systemic infection at the time of assessment.

* Incomplete clinical or laboratory data.

Diagnostic and Management Strategy

Calcineurin inhibitor nephrotoxicity was suspected in patients presenting with elevated serum creatinine, declining estimated glomerular filtration rate (eGFR), and increased calcineurin inhibitor trough levels. Renal biopsy was performed when clinically indicated to confirm the diagnosis and exclude other causes of graft dysfunction. Management strategies included dose adjustment of calcineurin inhibitors, therapeutic drug monitoring, optimization of blood pressure control, and modification of immunosuppressive therapy when required.

Statistical Analysis

Data were analyzed using SPSS version 26. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Comparisons between groups were performed using the independent-samples t-test for continuous variables and the Chi-square test for categorical variables. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 50 kidney transplant recipients were included in the analysis. The mean age of participants was 43.2 ± 11.4 years, and 33 (66.0%) were male. Calcineurin inhibitor nephrotoxicity was identified in 12 (24.0%) patients, while 38 (76.0%) had stable graft function without evidence of toxicity. Patients with nephrotoxicity were significantly older than those without nephrotoxicity (46.8 ± 10.2 vs. 42.1 ± 11.7 years; $p=0.041$). Elevated calcineurin inhibitor trough levels were observed in 8 (66.7%) patients with nephrotoxicity compared with 8 (21.1%) patients without nephrotoxicity ($p<0.001$). Hypertension and diabetes mellitus were significantly more prevalent among patients with nephrotoxicity. Mean eGFR was significantly lower in the nephrotoxicity group (43.5 ± 12.1 vs. 58.8 ± 13.9 mL/min/1.73 m^2; $p<0.001$).

Proteinuria was present in 6 (50.0%) patients with nephrotoxicity and 7 (18.4%) patients without toxicity (p=0.001). Hospital admissions related to graft dysfunction occurred more frequently among patients with nephrotoxicity, highlighting the adverse impact of calcineurin inhibitor toxicity on renal allograft outcomes.

Table 1. Baseline Demographic and Clinical Characteristics of Kidney Transplant Recipients (n = 50)

Variable	Value
Age (years), mean ± SD	43.2 ± 11.4
Male gender, n (%)	33 (66.0)
Female gender, n (%)	17 (34.0)
Body Mass Index (kg/m²), mean ± SD	26.4 ± 4.3
Living donor transplant, n (%)	39 (78.0)
Deceased donor transplant, n (%)	11 (22.0)
Time since transplantation (years), mean ± SD	4.1 ± 2.0
Hypertension, n (%)	38 (76.0)
Diabetes mellitus, n (%)	16 (32.0)
Tacrolimus therapy, n (%)	42 (84.0)
Cyclosporine therapy, n (%)	8 (16.0)

Baseline demographic, clinical, and transplant-related characteristics of the 50 kidney transplant recipients included in the study.

Table 2. Frequency and Clinical Features of Calcineurin Inhibitor Nephrotoxicity (n = 12)

Variable	Nephrotoxicity Present (n=12)	Percentage (%)
Acute nephrotoxicity	5	41.7
Chronic nephrotoxicity	7	58.3
Elevated serum creatinine	11	91.7
Reduced eGFR	12	100.0
Proteinuria	6	50.0
Elevated CNI trough levels	8	66.7
Hypertension worsening	11	91.7
Histopathological confirmation	9	75.0

Distribution and clinical manifestations of calcineurin inhibitor nephrotoxicity among affected kidney transplant recipients.

Table 3. Risk Factors Associated with Calcineurin Inhibitor Nephrotoxicity

Variable	Nephrotoxicity Present (n=12)	Nephrotoxicity Absent (n=38)	p-value
Age (years), mean ± SD	46.8 ± 10.2	42.1 ± 11.7	0.041
High CNI trough levels, n (%)	8 (66.7)	8 (21.1)	<0.001
Hypertension, n (%)	11 (91.7)	27 (71.1)	0.048
Diabetes mellitus, n (%)	5 (41.7)	10 (26.3)	0.039
Delayed graft function, n (%)	4 (33.3)	4 (10.5)	0.031
Donor age >50 years, n (%)	4 (33.3)	6 (15.8)	0.044

Comparison of demographic and clinical risk factors between patients with and without calcineurin inhibitor nephrotoxicity.

Table 4. Impact of Calcineurin Inhibitor Nephrotoxicity on Graft Outcomes

Outcome Variable	Nephrotoxicity Present (n=12)	Nephrotoxicity Absent (n=38)	p-value
eGFR (mL/min/1.73m²), mean ± SD	43.5 ± 12.1	58.8 ± 13.9	<0.001
Serum creatinine (mg/dL), mean ± SD	2.1 ± 0.8	1.3 ± 0.4	<0.001
Proteinuria >500 mg/day, n (%)	6 (50.0)	7 (18.4)	0.001
Hospital admissions, n (%)	4 (33.3)	6 (15.8)	0.027
Graft dysfunction, n (%)	5 (41.7)	4 (10.5)	0.002
Graft loss, n (%)	2 (16.7)	1 (2.6)	0.048

Comparison of renal allograft outcomes between recipients with and without calcineurin inhibitor nephrotoxicity, demonstrating the adverse effect of nephrotoxicity on graft function and survival.

Discussion

Despite major progress in immunosuppressive therapy, calcineurin inhibitor nephrotoxicity (CNIT) with its associated complications is still a major problem in kidney transplantation. In the current investigation, CNIT was found in 24% of kidney transplant recipients, and remains a significant factor in long-term graft survival. Our results are in line with recent studies that have shown nephrotoxicity to be one of the most significant non-immunological factors for chronic allograft dysfunction in transplant recipients [11,12]. The

mean age was significantly higher for patients who developed nephrotoxicity compared to those who did not develop nephrotoxicity. In recent studies, similar observations have been made, indicating that older recipients may be more susceptible to drug induced renal injury, and have a diminished nephron reserve [13,14]. Chronic vascular alterations and associated diseases can also play a role in the onset of chronic graft dysfunction in this population. Nephrotoxicity in our study was most closely related to high trough levels of the calcineurin inhibitors. A significant difference in graft dysfunction was also observed between the patients with elevated and therapeutic drug levels. The narrow therapeutic window of tacrolimus and cyclosporine is repeatedly called attention to by modern literature as directly contributing to renal vasoconstriction, endothelial damage and gradual fibrosis [15,16]. In recent pharmacokinetic studies, it has been shown that the variability in tacrolimus metabolism could significantly affect the risk of nephrotoxicity, underlining the need for personalized dosing and monitoring of the drug [17]. The rates of both hypertension and diabetes mellitus were significantly higher among patients who were nephrotoxic. These results are similar to recent studies reporting a similar synergistic worsening of renal function in the presence of metabolic and cardiovascular comorbidities [18]. Chronic hypertension can cause injury of the arterioles and interstitial fibrosis, and diabetes mellitus can cause endothelial dysfunction and microvascular injury, making them more vulnerable to nephrotoxic injury. Further, we found that patients with nephrotoxicity had significantly lower estimated GFR (eGFR) levels. This decrease in renal function was correlated with an increase in proteinuria, hospitalization, and the occurrence of graft dysfunction. Strikingly similar results have been reported in recent cohort studies of long-term graft survival, in which chronic exposure to CNIs was linked to progressive loss of graft function and elevation of chronic allograft nephropathy risk [19,20]. Histopathology of involved patients demonstrated the typical hallmarks of chronic CNI toxicity (arteriolar hyalinosis and interstitial fibrosis). Mechanistic studies in recent years have shown that the calcineurin inhibitors are responsible for more than just damage to the vessels; they are also directly toxic to tubular cells and induce fibrotic remodeling in the graft [21]. Such pathological alterations may account for the irreversible deterioration of renal function that has been found in some patients with therapeutic intervention. Several recent studies have focused on methods of reducing nephrotoxicity without compromising the level of immunity that is maintained, called CNI-sparing and CNI-minimization. Reduced dose tacrolimus regimens, mammalian target of rapamycin (mTOR) inhibitors and abatacept have been promising in improving renal function without significantly increasing rejection rates [22]. However, total avoidance of CNIs is still difficult due to the effectiveness of CNIs in the prevention of acute rejection and the maintenance of short-term graft survival. The intervention outcomes of our study showed that for most of the patients with renal dysfunction, therapeutic drug monitoring and adjustment of the dose led to stabilization or improvement in renal function. The results are consistent with current recommendations for early detection of toxicity and immunosuppressive treatment that is tailored to the individual. Recognizing high trough levels and adapting the treatment can stop the process of chronic irreversible treatment injury.

Limitations

The limitations of this study included a retrospective single-center design and the relatively small number of patients included, which may limit the generalizability of the results. Renal biopsy was not performed in all

patients, and may have underestimated subclinical nephrotoxicity. In addition, differences in immunosuppressive therapy and short-term follow-up might have affected the evaluation of the results.

Conclusion

Nephrotoxicity is a common issue in kidney transplant patients and is linked to graft dysfunction and poor clinical outcomes in this patient population. High concentrations of drugs, hypertension and diabetes were major risk factors. To maintain long-term allograft function and survival, monitoring and individualized immunosuppressive management is necessary.

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Authors Contributions

Concept & Design of Study: **Sami-ur-rahman**[2]

Drafting: **Syed Ameroon shah**[1]**,Saif ullah**[3]

Data Collection & Data Analysis: **Khawar suliman**[4]

Critical Review: **Muhammad Mubbashar Nazar**[5]**, Naveed sarwar**[6]

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