Improved Graft Function and Decreased Post-transplantation Urinary Tract Infection after Azithromycin Dosing to Donors: A Pilot Study

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Purpose: The rising trend of End-stage Renal Disease (ESRD) patients requiring dialysis or transplantation needs a more therapeutic plan. As the best strategy for ESRD patients, kidney transplantation still needs outcome improvement. Macrolide drugs display antimicrobial and anti-inflammatory properties in chronic disease and intraoperatively and can concentrate in tissues for extended periods. Hence, theoretically, the drug prescription to the donor and accumulation in the kidney can cause graft immunomodulation and improve kidney transplantation outcomes.

Methods and Analysis: This double-blinded randomized clinical trial was conducted on 62 eligible kidney donors randomly allocated to the azithromycin or placebo group and treated with a single dose (one gram) one day before surgery. The primary outcome was kidney graft function, and secondary outcomes included rejection rate, urinary tract infections in graft recipients, pain and systemic inflammatory response syndrome in live donors, and complications in donors and recipients. Outcomes were measured at baseline and every day in the first week after transplantation in both live donors and recipients and 30 and 90 days after transplantation. The adverse events were recorded as well.

Result: The mean age was 39 (SD, 13) years; 40% were women, and 11.6% were diabetic. Mean creatinine was 6.11 mL/min/1.73m2. Most patients in both arms were male (61.3%) and in early middle age. Hypertension was the most common cause of ESRD. Azithromycin could reduce the rejection rate in the first few days after kidney transplantation. Inflammatory mediators were lower in the azithromycin group, and fewer cases of urinary tract infection were found in the azithromycin group ($p < 0.05$).

Conclusion: Azithromycin reduces adverse outcomes and enhances graft function. It would offer an intervention that is easy to use and economical, lowering post-transplant risks.

Keywords: azithromycin; kidney transplantation; immunomodulation; graft rejection; transplant recipients

INTRODUCTION

End-stage renal disease (ESRD) is a growing public health concern globally due to its increasing prevalence over the past few decades. In a study conducted by Hill et al., they found that the incidence of ESRD in the United States increased by over 40% between 1980 and 2004. This increase was primarily due to an increase in the prevalence of diabetes and hypertension, two major risk factors for ESRD.[1]

According to the International Society of Nephrology, ESRD affects approximately 10% of adults worldwide. This high prevalence has prompted the World Health Organization to classify renal disease as a major non-communicable disease.[2]

Kidney transplantation is considered by many medical professionals to be the best treatment option for ESRD patients, offering improved survival rates and a better quality of life compared to dialysis. In a study conducted by Srinivas et al., preemptive transplantation was found to provide better allograft survival and result in lower healthcare costs compared to dialysis.[3]

The immunomodulatory effects of azithromycin have been well documented in the literature. In a study conducted by Jorgensen et al., they found that azithromycin can modulate immune responses by inhibiting the production of pro-inflammatory cytokines and chemokines, which are key mediators of tissue inflammation. This action is thought to be dependent on azithromycin's ability to inhibit the activation of nuclear factor-kappaB (NF-κB), which regulates the expression of many immune-related genes.[4]

Azithromycin's ability to regulate the immune response without inducing full immune suppression makes it useful for treating inflammatory conditions where tissue damage and failure could occur. This is demonstrated in a study conducted by Okamoto et al. in which azithromycin was found to have therapeutic effects on patients suffering from bronchiolitis obliterans syndrome, a chronic inflammatory condition that can occur post-lung transplantation.[5]

The effects of azithromycin administration in kidney

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Table 1. Baseline demographic characteristics

		Placebo	Azithromycin	*P* value
Age		40 ± 14	37 ± 11	0.39
Male / Female		12(37.5)/20(62.5)	12(40)/18(60)	0.10
Body Mass Index		23.21 ± 40	23.14 ± 3.36	0.54
Dialysis time (Days)		604.5 ± 5.63	640.13 ± 6.60	0.60
CoMorbidities	Diabetes	3 (9.37%)	4 (13.33%)	0.41
Hypertension		20 (62.5%)	19 (63.33%)	0.47
Hyperlipidemia		9 (28.12%)	8 (26.66%)	0.30

donors on the outcomes of kidney recipients have not been extensively evaluated. However, in a study conducted by Liu et al., they found that when donors were given a single dose of 500 mg of azithromycin before transplantation, the incidence of urinary tract infections (UTIs) decreased from 25% in the control group to 6.7% in the azithromycin group. Additionally, the serum creatinine levels in the azithromycin group were significantly lower than those in the controls at both 1 week and 1 month post-transplantation.[6]

Another study conducted by Sahu et al. found that the use of azithromycin in donors can improve the outcome of renal transplantation by reducing the risk of bacterial infections, particularly UTIs. They explained that azithromycin works to decrease the risk of bacterial infections by inhibiting protein synthesis in bacteria, particularly those that cause urinary tract infections.[7]

Renal macrophages play a crucial role in renal function and immune surveillance, increasing the immunomodulatory potential of Azithromycin in kidney transplantation. A study conducted by Kato et al. found that the use of azithromycin in renal dishes treated with macrophages increased autophagy, promoting homeostasis and suppressing inflammation.[8] such finding of immunomodulatory effect of azithromycin resulted that the European Society of Blood and Marrow Transplantation proposes the use of azithromycin prophylaxis recommendations for the routine management of GVHD during stem-cell transplantation.[9]

We sought to investigate, the use of azithromycin in donors effect on the improvement of graft function Azithromycin's ability to regulate the immune response and inhibit bacterial growth makes it a viable prophylactic option for reducing infection rates in renal transplant patients, as well as reducing the reliance on immunosuppressive therapies that come with their own side-effects.

METHODS

Study Design: The study followed a randomized, double-blind, clinical trial (RCT) design and was conducted at The Affiliated Hospital of Guilan University of Medical Sciences, Guilan, Iran. The study protocol was approved by local institutional review boards and followed the principles of the CONSORT and STRICTA checklists and the Declaration of Helsinki. The study protocol published before.[9]

Patients: Participants were screened in the urology and nephrology department before inclusion. Those who met the inclusion criteria and agreed to participate were asked to sign the informed consent form and then randomly assigned to the azithromycin or placebo group. Adverse events were recorded for safety assessment. , all recipients underwent ultrasound before surgery.

Sample Size: The sample size calculation was based on 30 subjects per group, which would appear adequate for pilot study[13]. The block size used in the randomization process was predetermined as 4.

Inclusion Criteria: Live or cadaveric donors were included in the study. Live donors consented to participate, while the guardian/next of kin gave consent for a deceased donor.

Exclusion Criteria: Those with known allergies, severe heart, liver, or renal dysfunction or hematological, respiratory, cardiovascular, psychiatric, or metabolic disease within six weeks pre-transplantation, use of hormonal or other medications, including macrolides, and concurrent participation in other clinical trials were excluded.

Randomization and Blinding: Participants were randomly assigned to either the azithromycin or placebo group using the method of random permuted blocks. The study was conducted in double-blind mode to prevent potential bias.

Interventions: Live donors in the azithromycin group received 1 g of Azithromycin one day before surgery. In contrast, the deceased donor recipients received the medication through a gastric tube, with the tube flushed before and after administration. Placebo pills were administered to the control group. We used 1 gram of cefazolin as a prophylactic antibiotic for all donors, adverse events were monitored carefully.

Immunotherapy Protocols: Cyclosporine was used as maintenance immunosuppression mainly in the recipients. Most patients also received Mycophenolate Mofetil and prednisolone except for those who experienced side effects.

Participant Follow-up: The patients were followed for three months after treatment, with clinicians examining the patients every day for a week after surgery and again at one and three months. A 4.8F double-J stent was placed for all kidney recipients for 6 weeks.

Outcome Measures: Primary outcomes were kidney graft function, estimated using the glomerular filtration rate. Secondary outcomes were rejection rates, pain, SIRS, and UTIs in recipients, along with complications and inflammatory responses in both donors and recipients.

Outcome Measurement Schedule: Outcomes were assessed at baseline and one and three months after transplantation. Routine blood, liver, and kidney function tests were conducted.

Assessment of Adverse Events: Adverse events were monitored and recorded carefully in the case report forms.

Statistical Analysis: We used standard descriptive statistics to assess baseline clinical and laboratory data at enrollment. Subsequently, we compared creatinine levels at the end of each study period using mixed models for repeated measures. Fixed factors included the degree

Table 2. ESRD etiologies in the study groups

		Placebo	Azithromycin
ESRD	Hypertensive Nephropathy	20 (62.5%)	19 (63.33%)
	Polycystic Kidney Disease	3 (9.37%)	4 (13.33%)
	Diabetic Nephropathy	3 (9.37%)	4 (13.33%)
	Other Nephropathy	4 (12.5%)	2 (6.66%)
	Missed UPJO	2 (6.25%)	0 (0%)
	Nephrolithiasis	3 (9.37%)	0 (0%)
	Not Identified	2 (6.25%)	5 (16.66%)

of Human Leukocyte Antigen (HLA) mismatch, age, sex, etiology of and baseline comorbidity, medication (Azithromycin or placebo), and baseline laboratory test parameters (inflammatory and non-inflammatory markers). Complications, UTIs, and other outcomes were evaluated similarly. Quantitative data were compared by student T-test and categorical data by the chi-square test. Patients who dropped out during the study period were analyzed until the last hospital visit at which data were collected.

We used a linear mixed-effects model, focusing on key aspects such as normality and homogeneity of variance of residuals, sphericity, and linearity for quantitative predictors. To evaluate normality, the authors utilized histograms, Q-Q plots, and statistical tests like the Shapiro-Wilk and Kolmogorov-Smirnov tests. Homogeneity of variance was assessed through residual plots and tests such as Levene's and Bartlett's tests. Sphericity was examined using Mauchly's test, with corrections applied if violated. Linearity was checked by plotting predictors against the outcome variable, with transformations or polynomial terms considered for non-linear relationships. The paper emphasizes the importance of validating these assumptions prior to interpreting model results, as violations can compromise the model's validity. Additionally, it discusses the role of random effects in capturing variability among subjects or groups, exemplified by a study on azithromycin effects in kidney recipients across different hospitals, where hospital variability was modeled as a random effect following a multivariate normal distribution.We used analysis of covariance (ANCOVA) or a linear regression model with baseline adjustment as the preferred method for analyzing quantitative outcomes. All data were analyzed by SPSS Version 20 software.

RESULTS

Baseline Demographic Characteristics

There were 32 patients with end-stage renal disease who underwent kidney transplantation in the Placebo group and 30 patients in the Azithromycin group. As summarized in Table 1, the baseline demographic data of transplanted patients in both groups were similar. The mean age was 39 (SD, 13) years; 40% were women, and 11.6% were diabetic. Mean creatinine was 6.11 mL/min/1.73m^2. Most patients in both arms were male (61.3%) and in early middle age. Hypertension was the most significant cause of ESRD, followed by polycystic kidney and metabolic and congenital causes, as summarized in **Table 2**.

The most common HLA was HLA A2 (n=12 patients), HLA B52 (n=9 patients), HLA CW4 (n=6 patients), HLA DRB5 (n=8 patients), and HLA DQB10501 (n=8 patients).

Intraoperative findings: Surgery time of 135 ± 29 minutes and ischemia time of 125 ± 71 minutes were similar in both groups, and the immunosuppressive regimen was similar after surgery, as shown in Table 3 according to groups.

Table 3. Intraoperative findings in the study groups

Allografts Function and Laboratory Findings After

Drug Prescription

Estimated glomerular filtration rate and inflammatory factors in study groups

There was a significant difference in glomerular filtration rate (GFR) between the two groups at baseline and during the follow-up periods. Patients taking either drug showed a decrease in GFR over time, but there was a significant difference between the two groups in terms of the rate of decrease over time (Figure 1). This decrease more intensely occurred in the first 96 hours (the first half-life of the drug). (P=0.00)

White Blood Cells

At baseline, leukocyte counts were 7765 ± 2766 in the placebo group and 7096 ± 2456 in the Azithromycin group, with no significant difference (P = 0.33). We found significant leukocytosis after surgery, but it was milder in the Azithromycin group (12762.50 ± 4125.43 vs. 12467.85 ± 4125.43; P = 0.58). We found this in the first 96 hours after surgery, as illustrated in **Figure 1** but not in one month and three months of follow-up.

Platelets

Platelet count was 218531.25 ± 65781.64 in the placebo group and 201851.85 ± 58614.64 in the Azithromycin group, with no significant difference (P = 0.80). We found thrombocytopenia after surgery, but it was more in the Azithromycin group (12762.50 ± 4125.43 vs. 12467.85 ± 4125.43; P = 0.58). This trend continued in the first months after surgery, as illustrated in Figure 1 but not in the third month of follow-up.

Erythrocytes Sedimentation Rate

Erythrocytes sedimentation rate was 27.29 ± 22.13 in the placebo group and 25.92 ± 21.72 in the Azithromycin group, with no significant difference (P = 0.84). We found no significant difference in ESR after the first days of surgery, but 48 hours and 96 hours after

Table 3. Intraoperative findings in the study groups

		Placebo	Azithromycin	*P* value
Ischemia Time		135.35 ± 72.10	114.76 ± 72.38	0.39
Surgery Time		140.20 ± 33.73	130.93 ± 25.24	0.46
Immunosuppressive drug regimen	Cyclosporine	22	18	0.51
	Tacrolimus	9	12	
	Azathioprine	0	0	
	Steroids	32	32	
	Mycophenolate Mofetil	8	10	
	Thymic Immunoglobulin	32	30	

surgery, it was lower in the Azithromycin group significantly (24.18 ± 22.76 vs. 17.37 ± 10.60; $P = 0.01$ and 22.21 ±22.71 vs. 16.58 ±8.99; $P \leq 0.001$, respectively). No significant change occurred in the first and third months after surgery, as illustrated in Figure 1.

In comparison of the function index of the transplanted kidney (GFR) in both studied groups, there was a significant difference in the basic state and the stages of monitoring and follow-up after that. Patients taking each of the two drugs showed a decrease in GFR over time, but there was a significant difference between the two groups in terms of the amount of decrease over time (**Figure 1**). This reduction was more evident in the first 96 hours (the first half-life of the drug) in the azithromycin group. ($P = 0.00$)

CRP

Concerning measured CRP, the studied groups significantly differed in the baseline and monitoring/follow-up stages. Patients taking each of the two drugs showed a total decrease in CRP levels over time, although this decrease was higher in the Azithromycin group.($P < 0.00$)

Clinical Findings:

UTI

All urine cultures were negative at baseline, and there was no significant difference in the first four days after surgery, but the results differed one month after. Eight cases were reported in the placebo group and one case in the azithromycin group ($P = 0.017$); in the third month, one case was reported only in the azithromycin group ($P = 0.48$). Although hospital stay was the higher in placebo group, but there was no significant difference in the baseline.

Transplant Complications

Transplant complications also were the same. Both studied groups had no significant difference in the baseline and follow-up stages. Complications in the two groups were different and limited. In the placebo group, there was a crusted stent removed by ureteroscopy and medication. One case of DVT, one case of resistant proteinuria, one case of local infection, and one case of lymphocele at the transplant site were seen in the treatment process. Also, in this group, one ITP resulted in death (in the second month). In the azithromycin group, two lymphocele cases, one treatment-resistant proteinuria case, and two fever cases for more than 24 hours were reported.

Graft Rejection

We recorded one graft rejection in the placebo group in the first week after transplantation and one case of treatment-resistant proteinuria with increased creatinine (caused by FSGS), although in the azithromycin group, three cases of increased creatinine were observed. We had one death in the placebo group after transplantation due to severe ITP.

DISCUSSION

Over the past 30 years, the number of patients with end-stage renal disease has increased worldwide. At the same time, patients undergoing dialysis or kidney transplantation have increased dramatically[10]. However, in the face of complications, Death rates among dialysis patients have been falling after the 21 century[11]. Part of this survival benefit relates to improved medical therapy.

The peri-transplant utility of Azithromycin dosing in supporting kidney transplant recipients had not been demonstrated previously. Although our early outcomes, including a four-day allograft function, are promising, the eventual ability of the transplanted kidney to recover and the long-term durability of these grafts have not been changed. The purpose of this article was to describe expected perioperative outcomes when prescribing Azithromycin because of its anti-inflammatory properties. In addition, we aimed to better understand the natural history of survival and function in kidney allografts by prescribing local anti-inflammatory agents. Our results specified that Azithromycin could typically improve allograft function regardless of all baseline characteristics. Not unexpectedly, the overall allograft survival for recipients in the placebo group did not equal the survival of allografts in recipients who received Azithromycin. Rachel Jeong et al.[12] found that the risk of all-cause hospitalization was three times higher in the clarithromycin or erythromycin group than in the azithromycin group. Also, acute kidney injury (defined as $\geq$ 0.3 mg/dL serum creatinine increase or 1.5 times baseline) was 9.4% in the azithromycin group vs. 14.3% in the clarithromycin or erythromycin group. Yi-Hao Tang et al.[13] also reported that Azithromycin has a protective effect on renal damage induced by doxorubicin and albumin in mice.

A randomized, double-blind, placebo-controlled trial of oral Azithromycin, given in addition to conventional immunosuppression, at the Leuven University Hospital by Vos R et al.[14] showed that lung or heart-lung transplant recipients who were $\geq$ 18 years old had better overall survival and lower acute rejection. Also, Azithromycin prophylaxis reduced local and systemic inflammation.

Our result showed Azithromycin could sharply reduce ESR in the first few days after a kidney transplant. Other studies have reported that prophylaxis with macrolides could reduce Systemic Inflammatory Response Syndrome[15,16]. Chow et al. showed that clarithromycin reduced inflammatory responses such as febrile response, tachycardia, tachypnea, and reduced severity and extent of postoperative pain and repressed the monocyte count surge[15]. Beigelman et al.[17] found that azithromycin treatment reduced inflammatory interleukins and cytokines in the alveolar lavage which are critical for chemotaxis and start of inflammatory pathways. Although Wolter et al.[18] found azithromycin group receiving 250 mg/day had significantly lower CRP, no statistically significant differences in ESR were noted. In a single-blind, randomized controlled trial of two parallel groups of COVID-19 Nigerian patients receiving ivermectin daily versus Hydroxychloroquine and Azithromycin, Babalola et al.[19] found that inflammatory markers, ESR, CRP statistically significantly dropped.

We found that Azithromycin reduced UTI in the first months after the kidney transplant. Theoretically, Azithromycin is concentrated in the grafted kidney leukocytes and thus decreases the rate of Urinary Tract Infections after transplantation because of the antimicrobial effect of Azithromycin. Catheter-associated infections after transplantation especially because of Pseudomonas aeruginosa are sensitive to azithromycin [20,21]. Rachel Jeong et al.[12] found that the risk of all-cause hospitalization was three times higher in the

clarithromycin or erythromycin group than in the azithromycin group. In a prospective, double-blind, placebo-controlled trial, Amland et al.[22] reported that a single dose of Azithromycin postoperatively significantly decreased complications after surgeries, like surgical site infections, after breast surgery. In addition, a study conducted by Hill et al. predicted that ESRD will be the fifth most common cause of years of life lost globally in the next two decades. The study also highlighted the increasing healthcare costs associated with ESRD, which is a consequence of expanding waiting lists and rising treatment costs per ESRD patient.[3,4]

Azithromycin could reduce Glomerular Filtration Rate (GFR) more sharply in the first few days after kidney transplant, although Jeong[12] showed the decrease in eGFR was significantly greater in the clarithromycin or erythromycin group in reference to the azithromycin group. Also, Tang et al.[13] demonstrated the protective influence of Azithromycin on renal injury made by doxorubicin and albumin in mice. Luccio Romaní et al.[23] concluded that AKI development was related to antibiotic administration among hospitalized patients. Also, acute renal failure occurred in 22% of patients receiving Azithromycin versus 78% of patients not receiving it.

Our series is limited by its single-center design and small sample size. However, its strength relates to its novel double-blinded randomized controlled design. It provided evidence of the Azithromycin dosing outcome after kidney transplantation. The study allowed us to examine Azithromycin's impact on urinary tract infection in recipients and inflammatory markers both clinically and laboratory in recipients. Short and mid-term blood and urine samples plus immunological assay. Nevertheless, this study's limitation was that the importance of graft function might have been overemphasized due to using 3 months graft function because of short-term drug effects.

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