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Long-term Effects of Gastric Acid Prophylaxis in Kidney Transplant Recipients

Efectos a largo plazo de la profilaxis del ácido gástrico en receptores de trasplante renal

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RESUMEN

Objetivos: La supresión profiláctica de la secreción de ácido gástrico con inhibidores de la bomba de protones o antagonistas de los receptores H2 se administra a menudo después del trasplante renal. La asociación de los inhibidores de la bomba de protones o los antagonistas de los receptores H2 con el rechazo agudo, la hipomagnesemia y la pérdida del injerto en los receptores de trasplante renal no está bien establecida. **Materiales y Métodos:** Realizamos un estudio de cohorte retrospectivo de 302 receptores de trasplante renal en un centro (57% varones; edad media 35,5±11,2 años) con más de seis meses de seguimiento postrasplante. Los receptores se agruparon según la profilaxis del ácido gástrico: solo inhibidores de la bomba de protones (n=179), solo antagonistas de los receptores H2 (n=42), inhibidores de la bomba de protones y antagonistas de los receptores H2 (n=55) y no usuarios (n=26). El resultado primario fue el rechazo agudo comprobado por biopsia. La pérdida del injerto y la hipomagnesemia se definieron como resultados secundarios. **Resultados:** Los no usuarios eran más jóvenes y en su mayoría bajo inmunosupresión libre de esteroides en comparación con otros grupos de estudio (p = 0,030 y p = 0,009, respectivamente). El resultado primario fue similar entre los grupos de estudio (p = 0,266). Los análisis de Kaplan-Meier también demostraron tasas similares de supervivencia del injerto a 10 años: 95,5 % para los inhibidores de la bomba de protones, 97,6 % para los antagonistas de los receptores H2, 100 % para los inhibidores de la bomba de protones/antagonistas de los receptores H2 y 96,2 % para los no usuarios (p = 0,275). **Conclusiones:** El uso de inhibidores de la bomba de protones no se asocia con rechazo agudo o pérdida del injerto, pero puede causar hipomagnesemia leve en receptores de trasplante renal.

PALABRAS CLAVE: rechazo agudo; antagonistas de los receptores H2; hipomagnesemia; trasplante

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ABSTRACT

Objectives: Prophylactic acid suppression with proton pump inhibitors or H2 receptor antagonists is often administered after kidney transplantation. The association of proton pump inhibitors or H2 receptor antagonists with acute rejection, hypomagnesemia, and graft loss in kidney transplant recipients is not well established. **Materials and Methods:** We performed a retrospective cohort study of 302 kidney transplant recipients at one center (57% male; mean age 35.5±11.2 years) with more than six months post-transplant follow-up. Recipients were grouped according to gastric acid prophylaxis: only proton pump inhibitors (n=179), only H2 receptor antagonists (n=42), proton pump inhibitors and H2 receptor antagonists (n=55), and nonusers (n=26). The primary outcome was biopsy-proven acute rejection. Graft loss and hypomagnesemia were defined as secondary outcomes. **Results:** Nonusers were younger and mostly under steroid-free immunosuppression compared to other study groups (p = 0.030 and p = 0.009, respectively). The primary outcome was similar across study groups (p = 0.266). Kaplan-Meier analyses also demonstrated similar 10-year graft survival rates: 95.5% for proton pump inhibitors, 97.6% for H2 receptor antagonists, 100% for proton pump inhibitors/H2 receptor antagonists, and 96.2% for nonusers (p = 0.275). **Conclusions:** Using proton pump inhibitors is not associated with acute rejection or graft loss but may cause mild hypomagnesemia in kidney transplant recipients.

KEYWORDS: acute rejection; H2 receptor antagonists; hypomagnesemia; kidney transplantation; proton pump inhibitors

INTRODUCTION

The use of Proton pump inhibitors (PPIs) and H2-receptor antagonists (H2RAs) is frequent after kidney transplantation for prophylaxis or treatment of gastroesophageal reflux disease, dyspepsia, or peptic ulcer disease. Although the favorable safety profile of these agents led them to become some of the most frequently used drugs, prolonged exposure has been associated with impaired kidney function [1], hypomagnesemia [2], and other complications, including dementia in the general population. Kidney transplant recipients often have reduced glomerular filtration rates (GFR) compared to the general population and are particularly vulnerable to the nephrotoxic adverse effects of medications.

The mechanism of PPI-induced hypomagnesemia is still uncertain. However, low urine magnesium (Mg) and fractional Mg excretion show intestinal absorption defects or increased losses in the gut [3,4]. The loss of function in TRPM6 due to high intestinal pH may be responsible for PPI-related hypomagnesemia [5]. One study found that the long-term use of H2RAs was also associated with hypomagnesemia [6]. Kidney transplant recipients are particularly vulnerable to co-medications that increase the risk of hypomagnesemia because calcineurin inhibitors (CNIs), a mainstay of transplant immunosuppression, are associated with lower serum magnesium levels [3]. Hypomagnesemia is, in turn, associated with adverse clinical outcomes, including an increased risk of cardiovascular morbidity and mortality [7] in the general population, as well as associated with new-onset diabetes after transplantation (NODAT) [8].

Kidney transplant recipients receive drugs with narrow therapeutic indices, such as CNIs, mammalian target of rapamycin inhibitors (mTORi), and mycophenolic acid (MPA) derivates. Interactions of PPI and H2RA with these drugs can lead to significant clinical consequences. For example, in some pharmacokinetic studies, PPIs have reduced mycophenolate mofetil (MMF) absorption by suppressing gastric acidification [9]. In randomized controlled [10] and observational studies [11], low serum MPA levels were associated with an increased risk of acute rejection and overall poor allograft outcome. It is also uncertain whether poor allograft survival in kidney transplant recipients receiving PPI is caused by PPI-associated acute interstitial nephritis (AIN) [12].

We conducted a retrospective cohort study at one center to advance our understanding of the clinical outcomes of using PPI and/or H2RA in kidney transplantation. We compared outcomes,

including biopsy-proven acute rejection (BPAR), hypomagnesemia, and allograft loss in kidney transplant recipients who receive PPI and/or H2RA, compared with no gastric acid prophylaxis.

MATERIALS AND METHODS

Patients and Study Design

This research was approved by the ethical committee of the Istanbul University School of Medicine Clinical Studies Board (IRB approval number 2011/483-480), complied with the Declaration of Helsinki and registered with ClinicalTrials.gov (NCT03123796). All patients enrolled in the study provided written informed consent to extract their medical data into the center's research database.

Patients who underwent kidney transplantation at a tertiary care center between 2000 and 2012 were included in this retrospective, single-center cohort study. Kidney transplant recipients at least 18 years of age who were followed up for longer than six months were initially enrolled. We excluded patients who used any form of gastric acid prophylaxis (PPI and/or H2RA) for less than six months or needed adequate information regarding the use of these agents. Also, the study did not include patients with multi-organ transplantation and systemic severe illnesses (i.e., cancer, overt congestive heart failure, active opportunistic infections).

In total, 302 kidney transplant recipients [171 (57%) men; 154 (51%) from deceased donors, mean age 35.5±11.2 years] were enrolled. PPI and H2RA for gastric acid prophylaxis were defined as using lansoprazole 30 mg daily or equivalent doses of other PPIs, famotidine 40 mg daily, or equivalent doses of other H2RAs, respectively. Kidney transplant recipients were grouped based on their PPI and/or H2RA intake: Only PPI (n=179), only H2RA (n=42), used PPI and H2RA (PPI/H2RA) (n=55), and nonuser groups (n=26). Recipient and donor data (demographic, clinical, and immunologic) were retrieved from medical records, and the last follow-up was in January 2017.

Definition of Immunosuppressive Regimens

Induction therapy (ATG Fresenius, 2 mg/kg/day, for 3 to 7 days) was used in all kidney transplant recipients from deceased donors. Patients were categorized based on induction immunosuppressive regimens into three groups: Antithymocyte globulin (ATG), interleukin-2 receptor blocking antibodies (IL2rAb), and no induction treatment. Induction use in the data is recorded as a binary indication (given or not), but the dose and duration of treatment information are unavailable.

All patients received intraoperative methylprednisolone bolus injection at a dosage of 500 mg and afterward were treated by triple maintenance immunosuppressive regimen including a CNI (cyclosporine or tacrolimus), an antiproliferative drug [azathioprine (AZA) or MPA derivates] and prednisolone. Calcineurin inhibitors were initiated two days and antiproliferatives one day before living-related and unrelated donor transplantations. Target blood levels of cyclosporine (C0) and tacrolimus after transplantation were 200-300 ng/mL and 8-12 ng/mL for the first three months and 50-150 ng/mL and 4-8 ng/mL for subsequent months, respectively. MMF and AZA were administered at 2 g/day (1440 mg/day for mycophenolate sodium) and 1.5 mg/kg/day, respectively. On postoperative day 1, patients received methylprednisolone beginning with a dose of 120 mg daily, with a rapid taper, and reaching the maintenance dose of 10 mg daily within the first month and 5 mg daily within the first year. Alterations were made in treatment strategies per immunologic risk and post-transplant complications, if necessary.

A maintenance immunosuppressive regimen was defined at three months after kidney transplantation. If the maintenance treatment was altered during the follow-up after the first three months, the immunosuppressive treatment regimen at the last follow-up was recorded as maintenance treatment. There were no HLA identical transplantations. For some patients, CNIs were decreased, stopped, or switched to mTOR inhibitors because of the side effects of CNIs and infections in the long term.

Follow-up Principles

Patients were initially followed at the transplantation clinic at weekly intervals after surgery, and follow-up intervals were increased to one month and then three months.

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Laboratory data from patients' charts included serum creatinine, albumin, Mg, tacrolimus, cyclosporine trough levels, urinalysis, and complete blood count. Estimated GFR (eGFR) was calculated using the serum creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [13]. Proteinuria was measured with protein to creatinine ratio (UPCR) in spot urine specimens. Serum Mg levels were determined using standard laboratory methods in our center. Mg levels considered after at least a 6-month of any form of gastric acid prophylaxis. For analytic purposes, the mean value of three consecutive measurements of serum Mg between posttransplant 6-24 months was calculated, and hypomagnesemia was defined as a mean Mg level of <0.70 mmol/L. The follow-up period was considered as the time interval between kidney transplantation and the last outpatient visit, graft failure, or death.

Study Outcomes

The primary outcome was the incidence of BPAR. The standard indication for graft biopsy in our center is a ≥25% rise in serum creatinine and/or new onset ≥1 g/g proteinuria with no apparent cause. Secondary outcomes were graft loss and hypomagnesemia. Graft loss was defined as the return to dialysis, re-transplantation, or allograft removal. During the last visit, eGFR was also analyzed as an exploratory outcome.

Statistical Analyses

Results are reported as the mean±SD when normally distributed or as the median (interquartile range [IQR]) otherwise. Comparisons of continuous variables between the groups were evaluated by using analysis of variance (ANOVA) or Kruskal-Wallis tests, where appropriate. Differences in the proportions of different patient groups were compared by the chi-squared or Fisher's exact test. Logistic regression analyses were performed to delineate predictors of BPAR and hypomagnesemia, which were reported as odds ratio (ORs) and 95% confidence intervals (CIs). Multivariate Cox regression analysis was carried out to determine predictors of graft loss, and results were described as hazard ratios (HRs) and 95% CIs. In regression, variables found to affect the outcomes (p-value of 0.2 or less) were included in multivariable analyses. Statistical analyses were performed using SPSS statistical software (SPSS version 21.0, IBM Corp., Armonk, NY, USA). Kaplan-Meier curves were generated using MedCalc for Windows (MedCalc version 19.0, MedCalc Software, Ostend, Belgium). A p-value of 0.05 or less was considered to be statistically significant.

RESULTS

Overall Characteristics of Patients

Over the study period, 302 kidney transplant recipients (131 women, 171 men) were followed up for a median of 109 (IQR 82-155) months. Median follow-up durations were different among study groups: 91.0 (73-112) months for PPI group, 163.5 (133.7-192) months for H2RA group, 168 (132-233) months for PPI/H2RA group, and 118 (70.5-252.2) months for nonuser group (p<0.001). The mean age of the cohort was 35.5±11.2 years.

Among the cohort, users of PPIs, H2RAs, PPI/H2RAs, and nonusers were identified in 179 (59.3%), 42 (13.9%), 55 (18.2%), and 26 (8.6%) patients, respectively. Patients who received PPIs were younger than those who received H2RAs and combined therapy but similar in age to those with nonusers: 44.4±10.9 in the PPI group, 49.5±10.5 in the H2RA group, 50.9±9.9 in the PPI/H2RA group and 42.9±11.7 in the nonuser group (p=0.030). The deceased donor kidney transplantation rate was lower in the nonuser group [(5), 19.2%] than the PPI, H2RA, and PPI/H2RA groups [90 (50.3%), 22 (52.4%) and 37 (67.3%), respectively; p=0.001]. All groups showed similar donor age, donor sex, primary kidney disease, HLA mismatches, panel reactive antibody (PRA) levels, CNI, and diuretic use. MMF use was less common in PPI/H2RA group as compared to other groups (p=0.001), while corticosteroids were lower in the nonuser group (p=0.009). The baseline demographic, clinical, and laboratory characteristics of patients are shown in **Table 1**.

Table 1: Baseline demographic, clinical, and laboratory characteristics of patients

Characteristics	All patients (n=302)	PPI (n=179)	H2RA (n=42)	PPI/H2RA (n=55)	Nonusers (n= 26)	P value
General characteristics						
Female sex, n (%)	131 (43.4)	80 (44.7)	15 (35.7)	25 (45.5)	11 (42.3)	0.74
Age, years, mean±SD	46.2±11.1	44.4± 10.9	49.5±10.5	50.9±9.9	42.9±11.7	**0.030**
Deceased donor, n (%)	153 (50.7)	90 (50.3)	22 (52.4)	37 (67.3)	5 (19.2)	**0.001**
Donor age, mean±SD	40.76±13.5	42.52± 13.8	37.71±11.9	35.24±12.8	45.2±11.2	0.30
Female donor sex, n (%)	104 (34.4)	61 (34.1)	15 (35.7)	16 (29.1)	12 (46.2)	0.51
Follow-up period (months), median (IQR)	109 (82-155)	91 (73-112)	163.5 (133.7-192)	168.0 (132-233)	118 (70.5-252.2)	**<0.001**
Primary kidney disease n (%)						
Diabetic nephropathy	11 (3.6)	6 (3.4)	3 (7.1)	0 (0.0)	2 (7.7)	0.50
Hypertensive nephropathy	15 (5.0)	7 (3.9%)	2 (4.8%)	5 (9.1)	1 (3.8)	
Chronic glomerulonephritis	61 (20.1)	53 (29.6)	9 (21.4)	11 (20.0)	8 (30.8)	
Chronic pyelonephritis	22 (7.3)	15 (8.4)	4 (9.5)	1 (1.8)	2 (7.7)	
Polycystic kidney disease	5 (1.7)	3 (1.7)	1 (2.4)	1 (1.8)	0 (0)	
Amyloidosis	6 (3.4)	6 (3.4)	0 (0)	5 (9.1)	2 (7.7)	
Unknown	99 (32.8)	56 (31.3)	16 (38.1)	19 (34.6)	8 (30.8)	
Others	56 (18.5)	33 (18.4)	7 (16.7)	13 (23.6)	3 (11.5)	
Number of HLA mismatches n (%)						
0	14 (4.6)	9 (5)	2 (4.8)	2 (3.6)	1 (3.8)	0.85
0-5	281 (93.0)	167 (93.3)	38 (90.5)	51 (92.7)	25 (96.2)	
6	7 (2.3)	3 (1.7)	2 (4.8)	2 (3.6)	0 (0)	
Pre-transplant PRA ≥10%, n (%)	9 (3)	7 (3.9)	1 (2.4)	0 (0)	1 (3.8)	0.50
Immunosuppressive medications n (%)						
CNIs	260 (86.1)	159 (88.8)	33 (78.6)	46 (83.6)	22 (84.6)	0.33
Mycophenolic acid derivatives	233 (77.2)	148 (82.7)	33 (78.6)	31 (56.4)	21 (80.8)	**0.001**
Steroids	286 (94.7)	172 (96)	41 (97.6)	52 (94.5)	21 (80.8)	**0.009**
Diuretic use	13 (4.3)	7 (3.9)	2 (4.8)	3 (5.5)	1 (3.8)	0.96

Abbreviations: CNIs, calcineurin inhibitors; **HLA**, human leukocyte antigen; **H2RA**, H2-receptor antagonists; **IQR**, interquartile range; **PPIs**, proton pump inhibitors; **PRA**, panel reactive antibodies; **SD**, standard deviation

Study Outcomes

The primary outcome (incidence of BPAR) was similar across study groups (16.2% in PPI, 4.8% in H2RA, 12.7% in PPI/H2RA, and 11.5% in nonuser groups; p=0.266). Overall, 13 patients experienced graft loss over 54 (49.5-155) months.

Graft loss rates were similar across study groups (6.1% in PPI, 2.4% in H2RA, 0% in PPI/H2RA, and 3.8% in nonuser groups; p=0.227). Kaplan-Meier analyses revealed that 10-year graft survival rates were 95.5% in PPI, 97.6% in H2RA, 100% in PPI/H2RA, and 96.2% in nonuser groups (p=0.275 with log-rank test) (**Figure 1**).

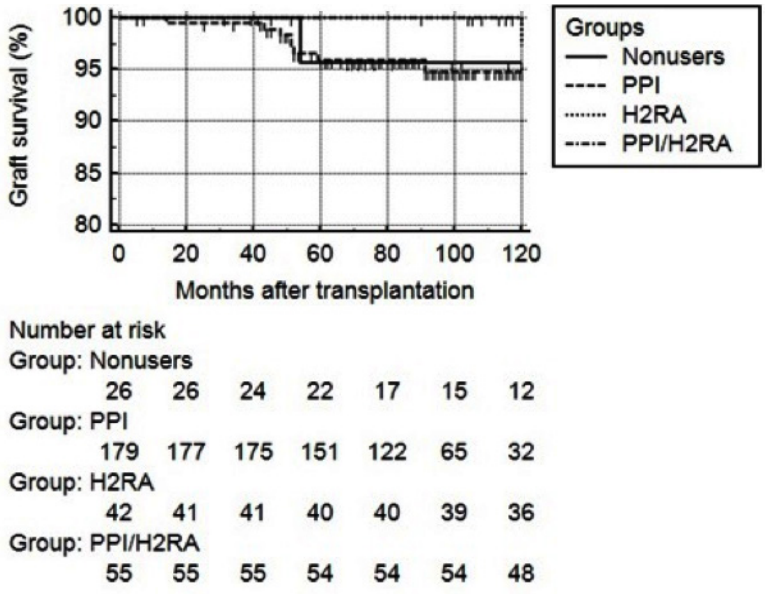

Figure 1: Ten-year graft survival rates.

Ten-year graft survival rates were 95.5% in PPI, 97.6% in H2RA, 100% in PPI/H2RA, and 96.2% in nonuser groups (p=0.275 with log-rank test) (H2RA: H2 receptor antagonist, PPI: proton pump inhibitor)

Hypomagnesemia was more common in the PPI group (38.5%) as compared to H2RA (19%), PPI/H2RA (25.5%), and nonuser (30.8%) groups; however, this was not statistically significant (p=0.053). Mean serum Mg levels were similar between groups (p=0.135) (**Table 2**).

Table 2: Laboratory parameters and study outcomes in various groups

Outcomes	**PPI (n=179)**	**H2RA (n=42)**	**PPI/H2RA (n=55)**	**Nonusers (n=26)**	**P value**
BPAR, n (%)	29 (16.2)	2 (4.8)	7 (12.7)	3 (11.5)	0.266
Graft loss, n (%)	11 (6.1)	1 (2.4)	0 (0)	1 (3.8)	0.227
Hypomagnesemia*, n (%)	69 (38.5)	8 (19.0)	14 (25.5)	8 (30.8)	0.053
Mg (mmol/l), mean±SD	0.72±0.11	0.76±0.09	0.73±0.06	0.72±0.073	0.135
Last eGFR (ml/min/1.73m^2), median (IQR)	66.9 (45.5-83.2)	62.5 (55.4-77.9)	57.4 (40.9-71.5)	59.9 (40.8-77.5)	0.051

**Hypomagnesemia was defined as a mean Mg level of <0.70 mmol/L*
Abbreviations: BPAR, biopsy-proven acute rejection; **eGFR**, estimated glomerular filtration rate; **H2RA**, H2-receptor antagonists; **IQR**, interquartile range; **Mg**, magnesium; **PPIs**, proton pump inhibitors; **SD**, standard deviation

Last visit eGFR was 66.9 (45.5-83.2) ml/min/1.73m2 in the PPI group, 62.5 (55.4-77.9) ml/min/1.73m2 in the H2RA group, 57.4 (40.9-71.5) ml/min/1.73m2 in the PPI/H2RA group, and 59.9 (40.8-77.5) ml/min/1.73m2 in the nonuser group (p=0.051).

Predictors of Primary and Secondary Outcomes

Logistic regression analyses of all patients revealed that only CNI-based immunosuppressive treatment predicted BPAR (OR: 0.347, 95% CI 0.148-0.811, p=0.015) (**Table 3**), whereas no variable predicted hypomagnesemia (**Table 4**).

Table 3: Univariate logistic regression analyses regarding biopsy-proven acute rejection in all patients

Predictors	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CIs)	P value	Odds Ratio (95% CIs)	P value
Recipient age	1.014 (0.984-1.044)	0.366		
Donor age	1.017 (0.902-1.042)	0.182	1.013 (0.984-1.042)	0.380
Recipient sex (female)	0.638 (0.320-1.272)	0.202		
Donor sex (female)	0.867 (0.428-1.756)	0.693		
Number of HLA mismatches	1.210 (0.909-1.609)	0.191	1.215 (0.910-1.620)	0.186
Donor type (living)	0.603 (0.306-1.188)	0.144	0.633 (0.302-1.325)	0.225
PPI use	2.339 (0.881-6.214)	0.088	2.381 (0.825-6.866)	0.108
H2RA use	0.547 (0.250-1.196)	0.130	0.696 (0.288-1.683)	0.421
Primary kidney disease				
Diabetic nephropathy	0.628 (0.078-5.036)	0.661		
Hypertensive nephropathy	2.457 (0.744-8.119)	0.140	2.768 (0.795-9.640)	0.110
Chronic glomerulonephritis	1.151 (0.557-2.382)	0.704		
Chronic pyelonephritis	0.618 (0.139-2.748)	0.527		
Amyloidosis	1.166 (0.249-5.458)	0.846		
CNI-based immunosuppression	0.368 (0.167-0.807)	0.013	0.347 (0.148-0.811)	**0.015**
Steroid-free immunosuppression	2.439 (0.313-18.977)	0.394		

***Abbreviations: CI**, confidence interval; **CNI**, calcineurin inhibitor; **H2RA**, H2 receptor antagonists; **HLA**, human leukocyte antigen; **PPI**, proton pump inhibitor.*

Table 4: Univariate and multivariate logistic regression analyses regarding hypomagnesemia in all patients

Predictors	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CIs)	P value	Odds Ratio (95% CIs)	P value
Recipient age	0.944 (0.581-1.534)	0.815		
Donor age	1.005 (0.987-1.023)	0.583		
Recipient sex	0.944 (0.581-1.534)	0.815		
Donor sex	1.211 (0.734-2.000)	0.454		
Number of HLA mismatches	1.092 (0.893-1.336)	0.393		
PPI use	1.833 (0.986-3.407)	0.055	0.701 (0.362- 1.359)	0.293
H2RA use	0.490 (0.282- 0.853)	0.012	1.772 (0.984- 3.190)	0.057
Diuretic use	1.806 (0.591-5.525	0.300		
Primary kidney disease				

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Predictors	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CIs)	P value	Odds Ratio (95% CIs)	P value
Diabetic nephropathy	0.444 (0.094- 2.097)	0.306		
Hypertensive nephropathy	1.027 (0.341- 3.089)	0.963		
Chronic glomerulonephritis	0.887 (0.513- 1.534)	0.668		
Chronic pyelonephritis	0.754 (0.286-1.990)	0.569		
Amyloidosis	1.297 (0.413-4.071)	0.656		
CNI-based immunosuppression	2.288 (1.017-5.151)	0.045	2.102 (0.925-4.777)	0.076
Steroid free immunosuppression	0.610 (0.220- 1.688)	0.341		

***Abbreviations: CI**, confidence interval; **CNI**, calcineurin inhibitor; **H2RA**, H2 receptor antagonists; **HLA**, human leukocyte antigen; **PPI**, proton pump inhibitor.*

Table 5: Univariate and multivariate Cox regression analyses regarding graft loss in all patients

Predictors	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CIs)	P value	Hazard Ratio (95% CIs)	P value
Recipient age	0.982 (0.931-1.036)	0.517		
Donor age	1.043 (1.000-1.089)	0.049	1.024 (0.979-1.072)	0.293
Recipient sex	1.321 (0.439-3.980)	0.620		
Donor sex	1.252 (0.408-3.836)	0.694		
Number of HLA mismatches	1.682 (1.002-2.823)	0.049	1.475 (0.870-2.503)	0.149
Donor type	1.311 (0.416-4.136)	0.644		
PPI use	2.425 (0.524-11.220)	0.257		
H2RA use	0.166 (0.021-1.294)	0.087	0.219 (0.027-1.768)	0.154
Chronic glomerulonephritis as primary kidney disease	2.446 (0.797-7.508)	0.118	2.310 (0.735-7.262)	0.152

***Abbreviations: CI**, confidence interval; **H2RA**, H2 receptor antagonist; **HLA**, human leukocyte antigen; **PPI**, proton pump inhibitor*

DISCUSSION

In this retrospective cohort study, we found that the risks of BPAR and graft loss were similar across patients with and without gastric acid prophylaxis, and hypomagnesemia was slightly increased in kidney transplant recipients who received PPIs. This work adds to the existing literature, in which some prior studies (14,15) have found a possible increased risk of acute rejection with PPI use while others have not (16,17).

A plausible biological mechanism exists for an association between PPIs and kidney allograft rejection. PPIs may reduce exposure to MPAs through decreased MMF dissolution at higher gastric pH levels. Reduced serum MPA levels can increase rejection rates (10,18,19). In vitro, studies have shown that MMF tablets completely dissolve at pH 4.0, but only 47% and 13% of the tablet

dissolve at pH 5 and 7, respectively (20). Although their potencies and duration of action differ, all PPIs have been shown to increase gastric pH levels to above 4.0 (20,21). Therefore, this drug-drug interaction is considered a class effect (15). Nevertheless, we found no relationship between PPI use and rejection.

We also did not demonstrate any association between the use of H2RA and rejection. Several studies show that even after five days of treatment, tolerance to the effects of H2RAs develops, and the pharmacological ability to inhibit gastrin secretion reduces (22,23). This tolerance may explain why H2RA use was not associated with acute rejection. Our center does not routinely perform MPA therapeutic drug monitoring and gastric pH. Therefore, we could not confirm the reduction of MPA exposure due to the co-administration of our patients with PPI.

A few publications have examined associations between PPI use and outcomes among kidney transplant recipients. A study comparing 125 patients taking pantoprazole with 77 patients using ranitidine found no significant difference between the two groups regarding BPAR frequency (16). In a comparison of 213 kidney transplant recipients receiving PPIs versus 390 kidney transplant recipients on ranitidine by Knorr et al., BPAR in the first-year post-transplant was similar in both groups (15). However, PPI intake and rejection rates were associated with African American patients. In another study, BPAR was similar among 183 patients using PPI and 339 using H2Ras (16). A recently published single-center retrospective analysis of 455 kidney transplant recipients found no significant relationship between PPI use and BPAR over 3.3 years of follow-up (24), and a recently published meta-analysis of 6786 kidney transplant recipients revealed similar findings (12). Our study differs from these previous reports with well-established control groups such as H2RA, PPI/H2RA, and nonuser groups, and follow-up time is relatively longer than these studies.

Studies have reported conflicting results examining the relationship between PPI use and hypomagnesemia in kidney transplant recipients. A cohort study of 512 patients found no significant association between PPI use and hypomagnesemia (5). On the other hand, in a recent study with 686 stable outpatient kidney transplant recipients, PPI use was associated with lower Mg values and lower 24-hour urinary Mg excretion. More patients with hypomagnesemia were found using PPI (25). A meta-analysis showed a similar relationship between the risk of hypomagnesemia and the use of PPI in kidney transplant recipients (12). Our study did not find any relationship between PPI use and hypomagnesemia in the multivariate analysis, even though there was a trend of hypomagnesemia in patients using PPI. These results are inconsistent with studies in the general population and kidney transplant recipients that reported hypomagnesemia related to PPI use (26); however, our finding may have been an underestimation considering the number of enrolled patients.

Polypharmacy is an increasing problem in kidney transplant recipients. Although PPIs have been used extensively to prevent gastrointestinal complaints and complications of immunosuppressive drugs, particularly corticosteroid therapy, Food and Drug Administration (FDA) guidelines do not recommend PPI use with this indication (27). Furthermore, almost two-thirds of these drugs are unnecessarily prescribed (28). A precise decision should be made considering the risk-benefit ratio for each patient planning to start gastric acid prophylaxis.

Our study has several limitations:

1. It has a single-centered retrospective design with an imbalance of patient characteristics across the study groups. A cause-effect relationship cannot be established.
2. Donor-specific antibodies, known to be closely related to rejections, have not been regularly monitored after transplantation.
3. Graft survival rates could have been overestimated due to selection bias.

However, the main strength of our study is the long follow-up period. In addition, the study included different groups according to gastric acid prophylaxis.

In conclusion, using PPI in kidney transplant recipients is not associated with BPAR and graft loss but may be associated with mild hypomagnesemia. Further prospective multicenter studies are needed to reveal the outcomes of PPI use in kidney transplant recipients.

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