Effects of esomeprazole and pantoprazole on renal function in stable kidney transplantation recipients: A randomized clinical trial

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ABSTRACT

Renal allograft survival requires the administration of multiple immunosuppressive drugs. This strategy may lead to gastric complications that necessitate gastro-protective medications, notably, proton pump inhibitors (PPIs). This study aimed to compare the effects of pantoprazole and esomeprazole on renal function in stable renal transplant recipients. A prospective, parallel, open-label clinical trial was performed with forty-seven adult renal transplant recipients receiving immunosuppressive therapy with cyclosporine (CSA) doses adjusted to attain trough concentrations of 100-150 μg/L, mycophenolate mofetil (MMF) at 750 mg q12 h and prednisolone at 5 mg daily at Nasser Institute, Cairo, Egypt. The enrolled participants were randomized into two groups, which received either esomeprazole or pantoprazole at the same dose (40 mg once daily). Renal function was measured at baseline and monthly for 6 months. The study was conducted between January-September 2016. Main outcome measures clinical signs of rejection reflected by renal function decline, assessed by elevated levels of serum creatinine. The mean serum creatinine level was significantly lower in the sixth month than at baseline in esomeprazole group (p 0.004); interestingly there was a continuous decrease of serum creatinine levels in esomeprazole group and nearly constant values in pantoprazole group. There was no significant difference in serum creatinine levels between the two groups. From this study, it could be concluded that esomeprazole may be preferred over pantoprazole in renal transplant recipients because it decreased serum creatinine which is one of the markers of chronic allograft rejection in stable renal transplantation recipients.

Keywords: Allograft rejection; serum creatinine; renal transplantation; proton-pump inhibitors; gastric complications.

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1. INTRODUCTION

Kidney transplantation is the treatment of choice for most patients with end-stage renal disease (ESRD). Although kidney transplantation improves the recipient’s quality of life, a chronic illness remains in which patients require medication and monitoring of graft function [1, 2]. To minimize the risk of rejection, recipients are placed on maintenance regimens of immunosuppressive medications [3].

A maintenance regimen currently consists of two classes of immunosuppressive drugs in addition to a low dose of glucocorticoids. The four classes of immunosuppressive drugs are calcineurin inhibitors (tacrolimus or cyclosporine), an antimetabolite (mycophenolate mofetil; MMF), mechanistic target of rapamycin mTOR inhibitors (sirolimus or everolimus), and co-stimulation blockers (belatacept) [4]. However, multiple adverse effects of these immunosuppressive therapies have also been reported [5, 6]. These drugs are powerful immunosuppressants, where immunosuppressant-associated long-term renal toxicity is mediated by renal arteriolar vasoconstriction; the mechanism underlying the renal toxicity of these medications is accompanied by the production of reactive oxygen species in renal tubular and glomerular cells [7]. One of the major sources of intracellular reactive oxygen species in mitochondria. Thus, these organelles are linked to cyclosporin A (CSA) renal toxicity [8].

Numerous complications of immunosuppressive treatments occur in the gastrointestinal (GI) tract. The incidence of GI complications after kidney transplantation is as high as 12% for upper GI bleeding episodes [9-11].

Proton-pump inhibitors (PPIs), such as pantoprazole and esomeprazole, are used for the treatment of symptoms of acid-related disorders and the primary prevention of gastroduodenal toxicity [12].

Long-term prophylaxis with PPIs is often utilized after kidney transplantation, regardless of the immunosuppression regimen [13]. However, concerns have been raised about adverse events, including hyponatremia, hypomagnesemia and calcineurin inhibitors (CNIs) drug interactions [14]. Exposure to PPIs may also be associated with an increased risk of incident chronic kidney disease (CKD) and CKD progression. The mechanisms by which PPIs may lead to CKD remain unknown. Reports have demonstrated an association between PPIs use and acute kidney injury (AKI) that is mainly mediated by interstitial nephritis [15].

Monitoring graft function is crucial in this population, and it is performed by measuring serum creatinine levels to evaluate kidney function [16].

This study aimed to compare the effects of pantoprazole and esomeprazole on renal function in stable renal transplant recipients on a triple immunosuppressive regimen consisting of CsA, MMF, and corticosteroids by measuring serum creatinine levels, which may reflect the rejection of the transplanted organ. To the best of our knowledge, this is the first comparative study to assess the effects of esomeprazole and pantoprazole on renal function in stable renal transplantation recipients.

2. PATIENTS AND METHODS

2.1. Study design and setting

A prospective, randomized, parallel, open-label clinical trial of renal transplant recipients with a follow-up duration of 6 months was conducted between January and September 2016; the study included an esomeprazole group and a pantoprazole group. The study was performed in
the renal transplantation unit of the Nasser Institute in Cairo, Egypt. Ethical approval was obtained from the Ain Shams University and Nasser Institute ethics committees, as well as the Egyptian Ministry of Health ethics committee (No: 7-2015/22). The Clinicaltrials.gov registration number is NCT03812419. Informed consent was obtained from all participants recruited for the study.

2.2. Patients

Eighty renal transplant recipients were screened for eligibility. The sample size was determined by a power calculation in G power software version 3.0.10, in which this sample size at $\alpha=0.05$ showed an effect size of 0.8 for the serum creatinine level. Eligible candidates for inclusion were adult stable renal transplant recipients; all participants continued the same maintenance triple immunosuppressive therapy, which had been taken for at least 3 years before the study and continued to be taken throughout the study period. All included patients had undergone transplantation 5 years before the initiation of the study. Pediatric patients, those > 65 years old, multi-organ transplant recipients, pregnant or lactating patients, those with malignancies, and those with active infections or inflammation and pre-transplant GI tract disorders were considered ineligible. Seventy candidates were eligible and recruited, out of which 47 completed the study (11 did not comply with treatment, and 12 were lost to follow-up). The study started in January 2016 and continued until September 2016.

2.3. Medications

Participants were randomly assigned to one of two groups by single randomization. Each group received 40 mg/day PPI therapy with either esomeprazole (Ezogast; Copad Pharma, Cairo, Egypt) in group I ($n=25$ at study completion) or pantoprazole (pantoprazole; Pharo Pharma, Alexandria, Egypt) in group II ($n=22$ at study completion). Besides, participants continued to receive the immunosuppressant combination of CsA (Sandimmune; Novartis, East Hanover, NJ, USA), MMF (Cellcept; Roche, Basel, Switzerland) and the corticosteroid prednisolone (Solupred; Sanofi Aventis, Tours, France).

2.4. Administration

Cyclosporine was administered in two doses adjusted to achieve a trough concentration ($C_0$) of 100-150 µg/L according to the transplantation center protocol for maintenance blood CsA levels. The morning dose was taken at least 15 minutes before or after the PPIs were taken; each patient received MMF 750 mg q12 hr and prednisolone 5 mg daily, and each group received 40 mg/day PPI therapy on an empty stomach. All medications were taken orally.

2.5. Measurements

Renal function was assessed monthly throughout the 6-month trial period. Three milliliters of blood was collected in a separator tube containing a gel that enhances coagulation and centrifuged at 147.9 g for 15 min; then, the serum was separated and used for the measurement of serum creatinine with a QuantiChrom creatinine assay kit [17]. Blood urea nitrogen was measured with a QuantiChrom urea assay kit [18], and serum uric acid was measured with a QuantiChrom uric acid assay kit [19].

2.6. Outcomes

The deterioration of renal function was defined as the doubling of the serum creatinine level, as that may indicate graft dysfunction and subsequent rejection.

2.7. Statistical analysis

SPSS version 24 (IBM, Armonk, NY, USA) was used for the data analysis. Quantitative variables are expressed as the means ± SD, and
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Qualitative variables are expressed as numbers and percentages. Chi-square ($\chi^2$) tests were used to assess the deviation of the observed distribution of qualitative variables from the expected distributions. For the quantitative variables, repeated measures analysis of variance (ANOVA) with a Bonferroni post hoc test was used for the comparison of means of related samples (within groups), and independent-sample t-tests were used for comparisons between the two groups. A $p$-value < 0.05 was considered to indicate a statistically significant test result.

### 3. RESULTS

#### 3.1. Study population

Forty-seven recipients completed the study, which was conducted between January and September 2016. They were screened, randomized and allocated according to the consort 2010 guidelines, as shown in Fig. 1. Baseline demographics (age, sex, and weight) were not different between the two groups, as shown in Table 1.

Table 1. Demographic data comparison at the baseline between the esomeprazole and pantoprazole groups of renal transplant recipients on triple immunosuppressive maintenance regimen.

| Demographic variables | Group (I) Esomeprazole 40 mg/day | Group (II) Pantoprazole 40 mg/day |
|-----------------------|----------------------------------|-----------------------------------|
| Age (years)           | Mean ± SD (range)                | Mean ± SD (range)                |
|                       | 39.9 ± 13.2 (20-65)              | 38.3 ± 10.1 (20-60)              |
|                       | Female                           | Female                           |
|                       | 32%                              | 36.4%                            |
|                       | Male                             | Male                             |
|                       | 68%                              | 63.6%                            |
| Weight (kg)           | Mean ± SD (range)                | Mean ± SD (range)                |
|                       | 74.0 ± 20.2 (37-117)             | 84.0 ± 19.1 (55-125)             |

Group (I) n= 25

Group (II) n= 22

Age and weight are represented as the mean ± SD, while sex is presented as the percentage. The Chi-square ($\chi^2$) test was used to assess the deviation of the observed distribution of qualitative variables from the expected distribution.
3.2. Renal function test

we compared renal function tests in the two study groups as a continuous monitoring parameter for the effect of the two studied PPIs (esomeprazole or pantoprazole) on the transplanted kidney where we found that serum creatinine was the only renal function test that showed a decrease in esomeprazole group ($p=0.004$) at month 6 (1.1 ± 0.4 mg/dL) than at baseline (1.4 ± 1.5 mg/dL) as shown in Fig. 2. And no statistically detected change in esomeprazole group through the whole period of the study 6 months for (BUN and uric acid), pantoprazole group showed no statistical difference in all the assessed parameters for the study duration. Upon comparing the 3 assessed renal function test (Serum creatinine, BUN and serum uric acid) between the two groups no statistically significant difference was detected at any time point for any of the assessed parameter data illustrated in Tables 2 and 3.
Fig. 2. Serum creatinine level (mg/dl) comparisons between group I and group II throughout the study period (6 months) in renal transplant recipients on a triple immunosuppressive maintenance regimen (cyclosporine adjusted to attain a C₀ of 100-150 µg/L, mycophenolate mofetil 750 mg q12 hr and prednisolone 5 mg daily). Group (I) n= 25 Group (II) n= 22

* Determination of serum creatinine levels occurred at the baseline and monthly for 6 months in renal transplant recipients in both the esomeprazole and pantoprazole groups (40 mg/day) who were receiving maintenance triple immunosuppressant therapy, using repeated measures ANOVA with the Bonferroni post hoc test. Independent-samples t-tests were used to assess the serum creatinine changes in group I and group II at different time points.

Table 2. Blood urea nitrogen (BUN) comparison in the two study groups for 6 months in stable renal transplant recipients on triple immunosuppressive maintenance regimen.

| Parameter                  | Group I | Group II |
|----------------------------|---------|----------|
| Blood urea nitrogen        |         |          |
| Mean ±SD                   |         |          |
| Baseline                   |         |          |
| 32.6 ±10.8                 | 33.3    |
| 9 ±1.1                     | 33.1    |
| 3 ±0.5                     | 31.3    |
| 7 ±0.5                     | 32.4    |
| 4 ±0.4                     | 31.2    |
| 4 ±0.4                     | 30.3    |
| 6 ±0.5                     | 29.1    |
| 5 ±0.5                     | 28.2    |
| 4 ±0.4                     | 27.3    |
| 7 ±0.5                     | 26.4    |

| Group I | Group II |
|---------|----------|
| Renal function | Months | Months |
| Baseline | 1 | 2 | 3 | 4 | 5 | 6 | 1 | 2 | 3 | 4 | 5 | 6 | P Value |
| 32.6 ±10.8 | 33.3 | 33.3 | 31.3 | 32.4 | 31.2 | 30.3 | 29.1 | 28.2 | 27.3 | 26.4 | 25.5 | 24.6 | 0.95 |

| Mean ±SD | Group I | Group II |
|----------|---------|----------|
| Baseline | 1 | 2 | 3 | 4 | 5 | 6 | 1 | 2 | 3 | 4 | 5 | 6 | P Value |
| 32.6 ±10.8 | 33.3 | 33.3 | 31.3 | 32.4 | 31.2 | 30.3 | 29.1 | 28.2 | 27.3 | 26.4 | 25.5 | 24.6 | 0.95 |

| Mean ±SD | Group I | Group II |
|----------|---------|----------|
| Baseline | 1 | 2 | 3 | 4 | 5 | 6 | 1 | 2 | 3 | 4 | 5 | 6 | P Value |
| 32.6 ±10.8 | 33.3 | 33.3 | 31.3 | 32.4 | 31.2 | 30.3 | 29.1 | 28.2 | 27.3 | 26.4 | 25.5 | 24.6 | 0.95 |

| Mean ±SD | Group I | Group II |
|----------|---------|----------|
| Baseline | 1 | 2 | 3 | 4 | 5 | 6 | 1 | 2 | 3 | 4 | 5 | 6 | P Value |
| 32.6 ±10.8 | 33.3 | 33.3 | 31.3 | 32.4 | 31.2 | 30.3 | 29.1 | 28.2 | 27.3 | 26.4 | 25.5 | 24.6 | 0.95 |

| Mean ±SD | Group I | Group II |
|----------|---------|----------|
| Baseline | 1 | 2 | 3 | 4 | 5 | 6 | 1 | 2 | 3 | 4 | 5 | 6 | P Value |
| 32.6 ±10.8 | 33.3 | 33.3 | 31.3 | 32.4 | 31.2 | 30.3 | 29.1 | 28.2 | 27.3 | 26.4 | 25.5 | 24.6 | 0.95 |

| Mean ±SD | Group I | Group II |
|----------|---------|----------|
| Baseline | 1 | 2 | 3 | 4 | 5 | 6 | 1 | 2 | 3 | 4 | 5 | 6 | P Value |
| 32.6 ±10.8 | 33.3 | 33.3 | 31.3 | 32.4 | 31.2 | 30.3 | 29.1 | 28.2 | 27.3 | 26.4 | 25.5 | 24.6 | 0.95 |

| Mean ±SD | Group I | Group II |
|----------|---------|----------|
| Baseline | 1 | 2 | 3 | 4 | 5 | 6 | 1 | 2 | 3 | 4 | 5 | 6 | P Value |
| 32.6 ±10.8 | 33.3 | 33.3 | 31.3 | 32.4 | 31.2 | 30.3 | 29.1 | 28.2 | 27.3 | 26.4 | 25.5 | 24.6 | 0.95 |
Table 3. Serum uric acid comparison in the two study groups for 6 months in stable renal transplant recipients on triple immunosuppressive maintenance regimen.

| Parameter | Group I | Group II |
|-----------|---------|----------|
|           | Esomeprazole group (40 mg/day) | Pantoprazole group (40 mg/day) |
|           | Months | Months | Renal function |
| Serum uric acid Mean ± SD | Baseline | 1 | 2 | 3 | 4 | 5 | 6 | Baseline | 1 | 2 | 3 | 4 | 5 | 6 | P- Value |
| 6.8 ± 1.6 | 6.7 ± 1.0 | 6.6 ± 0.9 | 6.5 ± 1.0 | 6.5 ± 1.0 | 6.4 ± 1.0 | 6.5 ± 1.5 | 6.5 ± 1.0 | 6.3 ± 1.0 | 6.4 ± 1.0 | 6.5 ± 1.5 | 6.4 ± 1.0 | 6.6 ± 1.5 | 0.57 | 0.36 | 0.65 | 0.67 |

Comparison of serum uric acid monthly for the study duration of 6 months both within group using repeated measures ANOVA and the Bonferroni post hoc test and between groups using an independent-samples t-test.

4. DISCUSSION

The current study is of practical clinical importance because it compared the nephrotoxic effects of the two studied PPIs used in renal transplantation recipients by assessing renal function at monthly intervals for 6 months. The present study showed a continuous decrease in serum creatinine levels in the esomeprazole group over the 6 months and near-constant levels of serum creatinine in the pantoprazole group. There were no differences between the two groups regarding serum creatinine levels or any other renal function test.

Different immunosuppressive drugs, CNI such as CsA, the anti-proliferative agent MMF and steroids are used as maintenance immunosuppressive regimens in renal transplant recipients [20]. PPIs are commonly prescribed for kidney transplant recipients [21]. CSA and PPIs are metabolized by CYP3A4 in the liver, and an increase in CsA concentration has been recognized as being linked to PPI co-administration [22].

Chronic graft dysfunction is characterized by a progressive impairment in kidney function associated with the occurrence or worsening of arterial hypertension and proteinuria [23]. Graft failure is defined as either returning to dialysis or death with a functioning graft [24].

The long-term use of CNIs is a major contributing factor to the development of CKD. The nephrotoxic mechanism is thought to be related to alterations in the vascular tone at the level of the afferent arteriole [25].

The CsA dose in our study was adjusted according to the study centre protocols to avoid any elevation of CsA serum levels leading to
nephrotoxicity or any decreases below the effective concentration leading to allograft rejection, which is in line with the findings in relevant studies stating that nephrotoxicity due to CsA is dose-dependent, and it is reversible with a decrease in the dose or drug withdrawal [26]. Another supporting report stated that the nephrotoxic potential of CsA is clinically, histologically, and molecularly indistinct at all levels of detection [27].

Despite its well-known limitations, the serum creatinine concentration remains the most commonly used marker of the glomerular filtration rate (GFR) following kidney transplantation because of the convenience and low cost of its measurement. The nadir value of serum creatinine during the first weeks after transplantation is used as the benchmark for identifying subsequent graft dysfunction [28]. There is agreement among nephrology studies about the role of serum creatinine levels in indicating graft failure after renal transplantation [29].

As several PPIs are now available, it is important to compare their effectiveness and side effects, especially concerning the kidney. A very surprising finding showed a gradual decrease in serum creatinine levels in the esomeprazole group throughout the entire study period. There was no other significant finding in other renal function tests either within each of the study groups or in comparisons between the two groups. Xie et al. recently reported that AKI does not mediate the association between PPIs and the occurrence of CKD, which may explain the current study findings [30]. An alternative hypothesis suggests that PPIs may increase the CKD risk by promoting hypomagnesemia, which conflicts with our findings [31]. Another speculation is that enteric infections are known adverse effects of PPIs that are attributed to changes in the gut microbiome [32]. An altered gut microbiome, as well as endotoxins entering circulation, may contribute to uremic toxicity and CKD progression [33].

In chronic graft dysfunction, a phenomenon known as creeping creatinine occurs, which is a gradual increase in creatinine levels over time [34]. Its diagnosis requires the demonstration of the existence of a negative slope in the creatinine level with a minimum of 6 measurements performed during the last months of follow-up (from 3 to 18 months) [35].

Furthermore, treatment with PPIs is associated with a significantly elevated risk of doubling serum creatinine levels and progression to ESRD, which contradicts the present findings [36].

This contradiction between the present study findings and those in previously published studies may stem from the fact that the exact nephrotoxic mechanisms of PPIs are not well established and currently remain merely speculations; in addition, previous studies focused on the group effect either in AKI or CKD patients, with no in-depth research into different members of the PPIs family, while the current study compared the effects of two members of the PPIs family (esomeprazole and pantoprazole) commonly used in renal transplantation recipients.

**Limitations**

As the study was performed in a single-center outpatient clinic, the sample size was relatively small, and the duration of follow-up was limited to 6 months.

**Conclusion**

In stable renal transplant recipients receiving immunosuppressive maintenance therapy, esomeprazole may be preferable to pantoprazole because it resulted in continuously decreasing serum creatinine levels, while the use of pantoprazole resulted in constant serum creatinine levels.
**Recommendations**

The effect of esomeprazole on renal function should be further investigated in a larger number of recipients, for longer duration and in multiple centers to detect its potential beneficial effect in this population.

**Conflict of interest**

The authors declare that they have no conflicts of interest.

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Not applicable

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