Original Article

Cukurova Anestezi ve Cerrahi Bilimler Dergisi

Comparative Effects of Proton Pump Inhibitors and Histamine-2 Receptor Blockers on Renal Function in Critically Ill Patients: A Retrospective Cohort Study

Uğur Serkan Çitilcioğlu[1], *Harun Özmen*[2], *Bahar Aydınlı*[2], *Didem Derici*[3]

[1] Department of Anesthesiology and Reanimation, Adana City Training and Research Hospital, Adana, Türkiye
[2] Department of Anesthesiology and Reanimation, Mersin City Training and Research Hospital, Mersin, Türkiye
[3] Department of Biostatistics, Mersin University Faculty of Medicine, Mersin, Türkiye

Correspondence: Uğur Serkan Çitilcioğlu, MD; serkancitilcioglu@gmail.com

Abstract

Aim: To compare the effects of proton pump inhibitors (PPIs) and histamine-2 receptor blockers (H_2RBs) on renal function in critically ill adults with preserved baseline kidney function. **Methods:** This retrospective cohort study included 210 intensive care unit (ICU) patients (105 PPIs, 105 H_2RBs) hospitalized for at least 15 days at Mersin City Training and Research Hospital. Serum creatinine and estimated glomerular filtration rate (eGFR) were recorded on ICU days 0, 5, 10, and 15. Acute kidney injury (AKI) was defined according to the kidney disease: Improving Global Outcomes (KDIGO) criteria. Group comparisons were performed using appropriate parametric and non-parametric tests. A sensitivity analysis was conducted after excluding patients exposed to sepsis, vasopressors, contrast, or nephrotoxic drugs. **Results:** Baseline demographics, illness severity, and potential confounders were comparable between groups. The incidence of AKI was similar in the PPI and H_2RB groups (12.4% vs 13.3%, $p = 0.81$). Serial eGFR measurements followed parallel patterns, showing an early decline and partial recovery by day 15 ($p > 0.05$ for all time points). Results remained consistent after sensitivity analysis. **Conclusion:** Short-term PPI therapy did not increase AKI risk or impair renal function compared with H_2RB use. PPI administration limited to the acute ICU phase appears safe regarding renal outcomes; however, unnecessary or prolonged administration should be avoided in accordance with current stewardship recommendations.

Keywords: Proton Pump Inhibitors; Histamine-2 Receptor Blockers; Acute Kidney Injury; Critically Ill Patients; Intensive Care Unit; Renal Function

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1. Introduction

Acid-suppressive therapy is routinely administered to critically ill patients to prevent stress-related mucosal damage and gastrointestinal bleeding[1]. Proton pump inhibitors (PPIs) and histamine-2 receptor blockers (H_2RBs) are the two primary pharmacologic options for stress ulcer prophylaxis in the intensive care unit (ICU)[2]. Although both classes effectively inhibit gastric acid secretion, concerns have emerged regarding the systemic

safety of PPIs, particularly their potential association with renal injury[3]. Population-based studies have linked long-term PPI use to acute interstitial nephritis (AIN), acute kidney injury (AKI), and chronic kidney disease (CKD)[4–6]. However, these associations are mostly derived from outpatient cohorts with chronic exposure, leaving their applicability to critically ill patients uncertain[7].

Critically ill patients are inherently susceptible to renal dysfunction due to hemodynamic instability, sepsis, exposure to nephrotoxic drugs, and fluctuations in intravascular volume[8]. Even minor elevations in serum creatinine or subtle declines in glomerular filtration rate (GFR) are independently associated with prolonged ICU stay, increased morbidity, and higher mortality[9]. In this context, any additional iatrogenic factor that may compromise renal function warrants careful evaluation. Despite the frequent preference for PPIs over H_2RBs owing to stronger acid suppression[10], their potential nephrotoxic effects during the acute phase of critical illness have not been definitively characterized.

Recent investigations have yielded conflicting results. Some studies have reported an association between prophylactic PPI use and a higher risk of new-onset AKI, while others have found no significant difference after adjusting for illness severity and concurrent risk factors[7,11]. These discrepancies may result from differences in patient populations, treatment indications, and monitoring approaches[7]. Moreover, few studies have evaluated renal function dynamically throughout the ICU stay. Assessing serial changes in estimated glomerular filtration rate (eGFR) using contemporary equations such as the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 equation may therefore provide a more accurate picture of kidney function under the complex physiological conditions of critical illness[12].

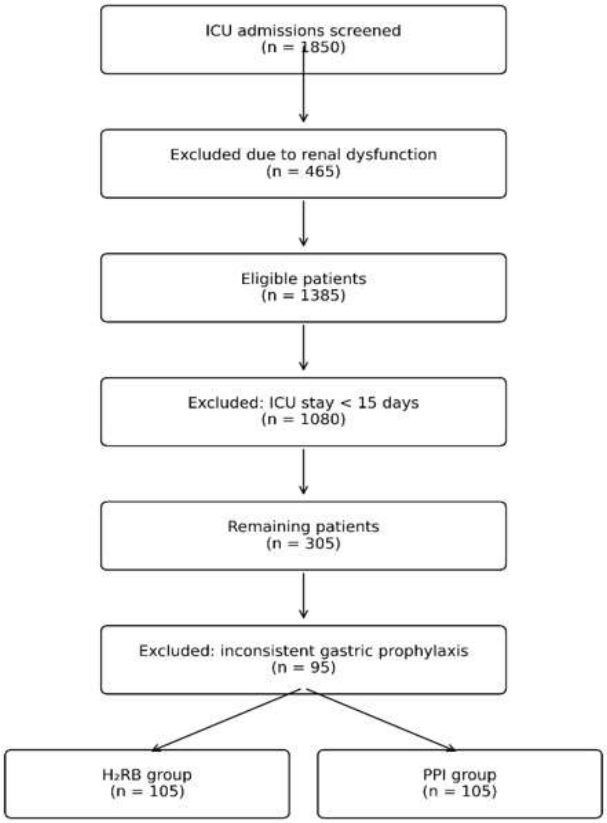

Figure 1. Study flow diagram

Given these uncertainties, the present retrospective cohort study aimed to compare the effects of PPIs and H_2RBs on renal function in critically ill adults with preserved

baseline kidney function. Serial measurements of creatinine and eGFR were analyzed together with the incidence of AKI defined by the kidney disease: Improving Global Outcomes (KDIGO) criteria[13]. By adjusting for major confounders—including sepsis, vasopressor therapy, nephrotoxic drug exposure, and contrast administration—this study sought to clarify whether short-term PPI therapy poses an additional risk for renal impairment compared with H_2RB use in the ICU setting.

2. Materials and Methods

2.1. Study design and ethical approval

This retrospective cohort study was conducted in the intensive care units (ICUs) of Mersin City Training and Research Hospital between March 1, 2017, and December 30, 2018, following approval by the Institutional Ethics Committee of Mersin University (Approval No: 2019/001, dated January 9, 2019). The study was carried out in accordance with the ethical principles of the Declaration of Helsinki. Patient data were retrieved from the hospital's electronic medical records and laboratory information system.

2.2. Patient selection

A total of 1,850 ICU admissions during the study period were screened for eligibility.

Inclusion criteria were as follows:

- Age ≥18 years
- ICU stay of at least 15 consecutive days
- Patients who received continuous monotherapy with either a PPI or H_2RB for stress ulcer prophylaxis during ICU stay
- Normal renal function at ICU admission, defined as baseline serum creatinine and eGFR within the reference range.

Exclusion criteria included:

- Known chronic kidney disease or baseline eGFR <60 mL/min/1.73 m²
- Acute kidney injury (AKI) prior to ICU admission
- Use of both PPI and H_2RB during the same ICU stay
- Missing or incomplete renal function data

After applying these criteria, 210 patients were eligible and included in the final analysis. Patients were classified into two groups according to the agent used for stress ulcer prophylaxis:

- PPI group (n = 105): received intravenous pantoprazole or omeprazole
- H_2RB group (n = 105): received intravenous ranitidine or famotidine

The choice of prophylactic agent was determined by the attending intensivist, independent of this study. A schematic summary of patient selection is presented in Figure 1.

2.3. Data collection

Demographic and clinical data—including age, sex, body weight, comorbidities, primary ICU diagnosis, and illness-severity scores [Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II), when available]—were retrieved from the electronic database. Renal function was evaluated by serum creatinine and eGFR, calculated using the CKD-EPI 2021 equation. Measurements were recorded at four predefined time points:

- Day 0 (ICU admission)
- Day 5
- Day 10
- Day 15

2.4. Endpoints

The primary endpoint was the development of acute kidney injury (AKI) during the ICU stay, defined according to the KDIGO criteria based on serum creatinine changes. Secondary endpoints included longitudinal changes in serum creatinine and eGFR between the two treatment groups over the 15-day follow-up period.

2.5. Potential confounders

Potential confounders that could influence renal function were identified a priori and systematically evaluated. These included: Presence of sepsis or septic shock, use of vasopressors or inotropes, exposure to nephrotoxic medications (e.g., aminoglycosides, vancomycin, amphotericin B, colistin), administration of intravenous contrast agents. Baseline distributions of these factors were compared between groups to ensure initial comparability.

2.6. Statistical analysis

All statistical analyses were performed using SPSS Statistics for Windows, Version 31.0 (IBM Corp., Armonk, NY, USA). Continuous variables were tested for normality using the Shapiro–Wilk test and expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]), as appropriate. Comparisons between groups were conducted using the independent-samples t-test or Mann–Whitney U test for continuous variables, and the chi-square or Fisher's exact test for categorical variables. Baseline balance between groups was additionally assessed using the standardized mean difference (SMD), with values <0.1 indicating negligible imbalance. Changes in serum creatinine and eGFR over time were analyzed using repeated-measures ANOVA or the Friedman test, depending on data distribution. The incidence of AKI between the two groups was compared using the chi-square test. A secondary sensitivity analysis was conducted by repeating all comparisons after excluding patients who were exposed to any of the identified confounding conditions during the 15-day follow-up. All tests were two-tailed, and a p-value <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

A total of 210 patients were included in the analysis, with 105 in the PPI group and 105 in the H_2RB group. Baseline demographic and clinical characteristics were similar between the two groups (Table 1). There were no significant differences in age, sex distribution, body weight, or illness severity scores (SOFA and APACHE II). Baseline renal function parameters, including serum creatinine and eGFR, were also comparable. The frequency of potential confounders—such as sepsis, vasopressor therapy, nephrotoxic drug exposure, and contrast administration—did not differ significantly between groups (all p > 0.05) (Table 1).

Table 1. Baseline characteristics and potential confounders in PPI and H_2RB groups

Variable	PPI group	H_2RB group	p-value	SMD
Age, years	65.2 ± 11.8	66.0 ± 12.3	0.62	0.07
Female sex	52 (49.5%)	50 (47.6%)	0.78	0.04
APACHE II score	19.1 ± 6.4	19.5 ± 6.2	0.68	0.06
SOFA score	7.2 ± 2.8	7.4 ± 2.9	0.71	0.07
Inotrope use	32 (30.5%)	28 (26.7%)	0.58	0.08
Nephrotoxic drug use	38 (36.2%)	41 (39.0%)	0.70	0.06
Contrast exposure	13 (12.4%)	7 (6.7%)	0.23	0.18
Sepsis/septic shock	29 (27.6%)	33 (31.4%)	0.59	0.08

Data are presented as mean ± standard deviation (SD), standardized mean difference (SMD), or number (%), as appropriate.

3.2. Incidence of acute kidney injury

The overall incidence of acute kidney injury (AKI) was comparable between the PPI and H_2RB groups (12.4% vs 13.3%, p = 0.81; Table 2). Similarly, the proportion of patients experiencing a ≥25% reduction in eGFR during ICU follow-up did not differ significantly between groups (30.5% vs 28.6%, p = 0.68).

Table 2. Incidence of renal impairment and AKI (≥25% and ≥50% decline in eGFR from baseline)

Timepoint	Outcome	PPI group	H_2RB group	p-value
Day 5	≥25% decline	34 (32.4%)	31 (29.5%)	0.68
	≥50% decline	14 (13.3%)	12 (11.4%)	0.67
Day 10	≥25% decline	29 (27.6%)	27 (25.7%)	0.77
	≥50% decline	12 (11.4%)	10 (9.5%)	0.64
Day 15	≥25% decline	22 (21.0%)	20 (19.0%)	0.74
	≥50% decline	9 (8.6%)	8 (7.6%)	0.80

Data are presented as number of patients (percentage).

3.3. Changes in renal function

Serial measurements of renal function demonstrated similar temporal patterns in both groups (Table 3). Serum creatinine showed a modest increase by day 5 followed by partial recovery by day 15, while eGFR values declined slightly during the early period and gradually improved thereafter. At none of the four time points (day 0, 5, 10, 15) were significant differences observed between the PPI and H_2RB groups in either creatinine or eGFR levels (all p > 0.05). Repeated-measures analysis confirmed no significant group-by-time interaction for eGFR (p = 0.73; Figure 2).

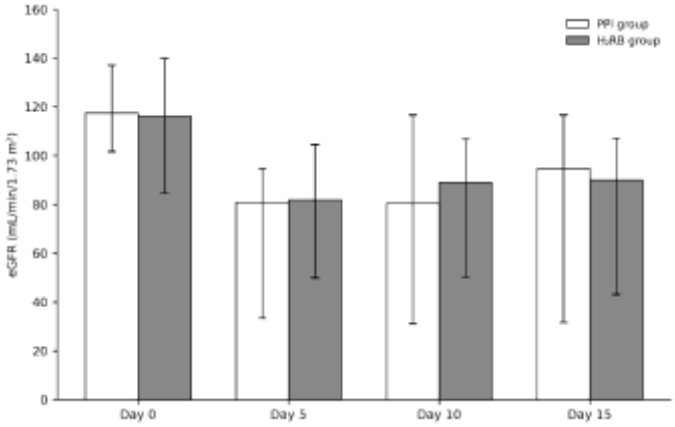

Figure 2. eGFR trends in the PPI and H_2RB groups

Values are expressed as median; error bars indicate interquartile ranges

3.4. Sensitivity analysis

After excluding patients who were exposed to potential confounding conditions during follow-up—including sepsis, vasopressor therapy, nephrotoxic drug use, or contrast administration—the results remained consistent (Table 4). No significant differences were observed in serial creatinine or eGFR values between groups at any time point (all p > 0.05).

Table 3. Estimated glomerular filtration rate (eGFR) at different time points in the PPI and H_2RB groups

Timepoint	PPI group	H_2RB group	p-value
Day 0	117.44 [101.70–137.02]	116.20 [84.70–139.92]	0.26
Day 5	80.77 [33.42–94.60]	81.86 [49.87–104.50]	0.33
Day 10	80.38 [31.02–116.71]	88.91 [50.15–106.82]	0.74
Day 15	94.60 [31.67–116.71]	89.95 [43.12–107.17]	0.39

Values are presented as median [IQR].

Table 4. eGFR values after exclusion of patients with major confounders

Timepoint	PPI group (n=68)	H_2RB group (n=72)	p-value
Day 0	118.9 [105.5–138.0]	117.8 [102.3–137.2]	0.74
Day 5	92.3 [70.2–109.1]	93.5 [72.0–110.4]	0.68
Day 10	91.0 [69.0–108.5]	92.7 [70.5–109.6]	0.71
Day 15	96.4 [75.2–113.7]	95.8 [74.3–114.1]	0.82

Values are presented as median [IQR].

4. Discussion

In this retrospective cohort study, we compared the effects of PPIs and H_2RBs on renal function in critically ill adults with preserved baseline kidney function. Throughout a 15-day observation period, no statistically significant differences were detected between the two groups regarding serum creatinine, eGFR, or the incidence of AKI. These findings remained consistent even after excluding potential confounding variables, indicating that short-term PPI exposure in the intensive care setting is not independently associated with renal impairment when compared with H_2RB therapy.

The absence of clinically measurable nephrotoxicity with PPI therapy in our cohort may be primarily attributed to the relatively short duration of drug exposure. Most studies linking PPIs to kidney injury have involved long-term use, in which mechanisms such as idiosyncratic interstitial nephritis or cumulative tubular damage are more relevant[14,15]. In critically ill patients, however, renal dysfunction is mainly driven by hemodynamic instability, systemic inflammation, and exposure to nephrotoxic agents[16]. Therefore, the lack of significant difference observed in our study likely reflects that short-term PPI exposure does not exert a clinically relevant impact on renal function in this population.

Another potential factor contributing to the lack of difference between treatment groups may be the demographic structure of our cohort. Yang et al.[17] found that PPI-related kidney injury was more frequent in younger patients, while no clear association was noted in those older than 60 years. In our study, the average age was relatively high (65.6 years), which may have reduced vulnerability to PPI-induced renal effects. Age-related physiological adaptations and diminished immune responsiveness could have provided some protection against short-term PPI-related renal stress in critically ill adults.

In contrast to our findings, Xu et al.[7] reported that prophylactic PPI use was independently associated with an increased risk of new-onset AKI in critically ill patients. This discrepancy may be better explained by residual confounding rather than a true causal relationship. In their Medical Information Mart for Intensive Care IV (MIMIC-IV) analysis, patients receiving PPIs represented a smaller and clinically more severe subgroup characterized by higher illness-severity scores, a greater prevalence of sepsis, and more frequent vasopressor use—all well-established risk factors for AKI[18]. Although propensity score matching was employed, such baseline imbalance and the influence of unmeasured confounders may have biased the observed association. Furthermore, the median time to AKI onset (~2.8 days) corresponded to the early phase of critical illness, when

hemodynamic instability and sepsis-related renal hypoperfusion are most pronounced, suggesting that early physiological deterioration rather than PPI exposure itself likely accounted for the increased AKI incidence.

A particular strength of our study lies in the serial evaluation of renal function using the CKD-EPI 2021 equation, allowing for a more accurate and dynamic assessment of glomerular filtration under fluctuating physiological conditions[12]. Both treatment groups demonstrated an initial decline in eGFR by the fifth day of ICU stay, which remained relatively unchanged through the tenth day, followed by a modest recovery by day fifteen. This temporal pattern is consistent with transient renal adaptation to the hemodynamic and inflammatory stress of critical illness rather than a drug-specific nephrotoxic effect[19]. Moreover, the stability of these findings after sensitivity analyses—excluding patients with sepsis, vasopressor requirement, contrast exposure, or nephrotoxic therapy—underscores the robustness and internal validity of our results.

The 15-day observation period was intentionally designed to represent the initial phase of critical illness, during which the majority of ICU-acquired AKI episodes emerge, paralleling the interval of greatest hemodynamic instability, systemic inflammation, and exposure to nephrotoxic insults[20]. Beyond this period, additional AKI events are uncommon, and later changes are more likely to reflect recovery dynamics or chronic renal processes[21]. Considering that previous studies have demonstrated that the average ICU length of stay in most patient populations is generally less than 15 days, the follow-up period in the present study was considered adequate to encompass the phase of greatest exposure to intensive care conditions and to evaluate the short-term renal effects of acid-suppressive therapy[22,23].

Given the ongoing debate over the renal safety of PPIs, our findings provide supportive evidence that short-term PPI use for stress ulcer prophylaxis appears safe in ICU patients with preserved baseline kidney function. H_2RBs remain an effective alternative; however, the choice of agent should be guided by the patient's individual gastrointestinal risk profile and overall clinical condition rather than concerns about acute kidney injury. Nevertheless, unnecessary or prolonged PPI use beyond the acute phase should be avoided, in accordance with current deprescribing and stewardship recommendations.

This study has some limitations that should be acknowledged. First, its retrospective design inherently limits causal inference and may have introduced residual confounding despite rigorous exclusion criteria. Second, drug exposure was determined based on electronic medication records rather than serum concentrations, thus precluding pharmacokinetic or pharmacodynamic evaluation. Third, although the 15-day observation period adequately captured the critical window for AKI development, it did not allow assessment of potential long-term renal consequences associated with extended PPI therapy.

5. Conclusion

In summary, short-term PPI therapy was not associated with an increased risk of AKI or with any significant deterioration in renal function compared with H_2RB use among critically ill adults. Serial assessment of eGFR revealed parallel trends in both groups, suggesting that short-term PPI administration limited to the acute ICU phase does not confer additional renal risk. Future prospective studies with longer follow-up are warranted to confirm these findings and to explore potential long-term renal effects of prolonged PPI exposure beyond the acute period.

genAI: No artificial intelligence-based tools or generative AI technologies were used in this study. The entire content of the manuscript was originally prepared, reviewed, and approved by all authors.

Statement of Ethics: The study was approved by the Ethics Committee of the Faculty of Medicine, Mersin University, on January 9, 2019 (Approval No: 2019/001).

Data Availability: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions: Concept, Design, Supervision (USÇ, HÖ), Data Collection and/or Processing (BA), Analysis and/or Interpretation (DD), literature review (BA), writer (USÇ), critical review (USÇ, HÖ). All authors read and approved the final manuscript.

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Conflict of Interest: The authors declare no conflict of interest.

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