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Original Article

Efficacy of Potassium-competitive Acid Blockers versus Proton Pump Inhibitors in First- and Second-line Eradication Regimens for *Helicobacter pylori* in Egyptian Patients

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Abstract

Background and objectives: The treatment of *Helicobacter pylori* (*H. pylori*) infection remains a challenge due to the increasing prevalence of drug-resistant bacteria. It is hypothesized that using more potent acid suppressants, such as potassium-competitive acid blockers (P-CABs) like Vonoprazan, may improve eradication rates. The aim of this study was to compare the effectiveness of *H. pylori* eradication regimens containing Vonoprazan with those containing proton pump inhibitors for *H. pylori* infection.

Methods: Two hundred and thirty-two patients were assigned to two groups. Group I (treatment-naïve) included: Arm 1 (intervention arm) with 58 patients who received Clarithromycin 500 mg twice daily, Amoxicillin 1 mg twice daily, and Vonoprazan 20 mg twice daily; and Arm 2 (comparator arm) with 58 patients who received Clarithromycin 500 mg twice daily, Amoxicillin 1 mg twice daily, and Esomeprazole 20 mg twice daily. Group II (treatment-experienced) included: Arm 3 (intervention arm) with 58 patients who received Levofloxacin 500 mg once daily, Vonoprazan 20 mg twice daily, Nitazoxanide 500 mg twice daily, and Doxycycline 100 mg once daily; and Arm 4 (comparator) with 58 patients who received Levofloxacin 500 mg once daily, Esomeprazole 20 mg twice daily, Nitazoxanide 500 mg twice daily, and Doxycycline 100 mg once daily. All patients received their treatment regimens for 14 days. *H. pylori* eradication was assessed four weeks after treatment.

Results: The successful eradication rate was higher in Arm 1 (58.6%) compared to Arm 2 (50%), and higher in Arm 3 (50%) compared to Arm 4 (43.1%). *H. pylori* eradication regimens including P-CABs were well-tolerated with a low incidence of adverse events.

Conclusions: The results of P-CAB-based eradication regimens are comparable to those of proton pump inhibitor-based regimens.

Introduction

Helicobacter pylori (*H. pylori*) is the most common chronic bacterial infection in humans, with conservative estimates suggesting that 50% of the world's population is affected. Infection is more frequent and acquired at an earlier age in low-resource countries compared with developed countries.[1] Once acquired, the infection persists and may or may not lead to gastro-duodenal disease. *H. pylori* infection is usually acquired during childhood.[2] Risk factors for acquiring the infection include low socioeconomic status,[3] an increasing number of siblings, and having an infected parent, especially an infected mother.[4] In low-resource countries, where the majority of children are infected before the age of 10, the prevalence in adults exceeds 80% by age 50.[5]

About one-third of adults in Northern Europe and North America are infected, whereas infection rates in Southern and Eastern Europe, South America, and Asia are often higher than 50%.[3]

Keywords: *Helicobacter pylori* (*H. pylori*); Potassium-competitive acid blocker; Proton pump inhibitor; *H. pylori* eradication; PPIs; P-CABs.

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In Egypt, a study on school children found that the prevalence of *H. pylori* infection was 72.38%. The study also reported that children living in Upper Egypt had a higher infection rate than those in Giza and Cairo (96.7% vs. 61.9%, respectively), highlighting the influence of geographical location and socioeconomic status on infection rates.[6]

A more recent study conducted on 1,120 Egyptian patients by Abdelmonem *et al*. reported an *H. pylori* infection prevalence of 52% in the Nile Delta, with a prevalence rate of 41% among children.[7]

If left untreated, *H. pylori* infection can lead to serious complications, such as peptic ulcer disease and gastric cancer.[8]

Eradication of *H. pylori* has proven challenging due to the emergence of drug-resistant bacteria, the absence of a gold standard diagnostic method, and the ineffectiveness of current vaccines.[9]

Eradication rates with classical proton pump inhibitor (PPI)-based triple therapy have decreased below 80% in Europe and the USA due to rising Clarithromycin resistance.[2,10,11] *H. pylori* susceptibility to antibiotics is impacted by intra-gastric pH, which influences antibiotic stability and activity as well as the replication status of *H. pylori*.[12] Acid-suppressive medications are essential in *H. pylori* treatment regimens, as they enhance antibiotic effectiveness.[13] Some antibiotics require active *H. pylori* replication for optimal antimicrobial activity.[14] Therefore, sustained control of intra-gastric pH may improve *H. pylori* eradication rates.[15]

It has been hypothesized that a more potent acid suppressant agent, such as vonoprazan, could increase the eradication rates of current regimens.[16] Vonoprazan is a potassium-competitive acid blocker approved in several countries for treating *H. pylori* infection and other acid-related diseases. It increases intra-gastric pH more rapidly and potently than PPIs and maintains it more consistently, which has been associated with higher *H. pylori* eradication rates.[17]

Vonoprazan has the potential to optimize *H. pylori* therapy by improving gastric acid suppression, thereby enhancing antimicrobial activity. A meta-analysis of Asian trials found that the triple combination of vonoprazan, amoxicillin, and clarithromycin produced significantly higher eradication rates compared to PPI-based triple therapy, even among patients with clarithromycin-resistant strains ($p < 0.001$).[18,19]

This study aimed to compare the effectiveness of a vonoprazan-based eradication regimen versus a PPI-based eradication regimen for the eradication of *H. pylori* infection in both treatment-naïve and treatment-experienced Egyptian patients.

Materials and methods

This prospective, non-randomized, controlled study was conducted on symptomatic patients admitted to the Tropical Medicine Department at Ain Shams University Hospitals, as well as those presenting at the outpatient clinic. The study was conducted from January 1, 2022, to June 1, 2023.

Study population

Patients with the following criteria were considered for inclusion or exclusion from the study:

Inclusion criteria

- Age above 18 years, both genders.
- Symptomatic patients diagnosed with *H. pylori* using the *H. pylori* stool antigen test.
- Patients who had not previously received *H. pylori* treatment were included in Group I (First-line eradication regimen).
- Patients who had undergone at least one eradication regimen were included in Group II (Second-line eradication regimen).
- Patients who signed an informed consent.

Exclusion criteria

- Patients who refused to sign informed consent.
- Patients who had taken PPIs, potassium-competitive acid blockers (P-CABs), and/or antibiotics within one month prior to inclusion.
- Patients with chronic debilitating or advanced systemic diseases.
- Patients on long-term treatment with low-dose aspirin and/or non-steroidal anti-inflammatory drugs.
- Pregnant or lactating females.

Sample size

Based on sample size calculations, a total of 232 participants were included in the study. Group I consisted of treatment-naïve patients (116), and Group II included treatment-experienced patients (116). Each group was divided into two arms, with 58 participants assigned to each arm.

Ethical considerations

The principal investigator obtained approval from the Faculty of Medicine Ain Shams University Research Ethics Committee (FWA 000017585) before starting the study. The approval number is FMASU MS 36/2022. All participants signed informed consent before participating in the study. The study was conducted according to the Declaration of Helsinki, which outlines ethical principles for medical research involving human subjects (https://clinicaltrials.gov/search?term=NCT06101420).

Study procedures

Patients who met the study inclusion criteria were non-randomly assigned to one of the following arms:

Group I: Treatment naïve group

Arm 1: Vonoprazan triple therapy (intervention arm): Patients received Clarithromycin 500 mg twice daily, Amoxicillin 1 mg twice daily, and Vonoprazan 20 mg twice daily.

Arm 2: PPI Triple therapy (comparator arm): Patients received the classic triple therapy: Clarithromycin 500 mg twice daily, Amoxicillin 1 mg twice daily, and Esomeprazole 20 mg twice daily.

Group II: Treatment experienced group

Arm 3: Vonoprazan quadruple therapy (intervention arm): Patients received a non-bismuth quadruple therapy: Levofloxacin 500 mg once daily, Vonoprazan 20 mg twice daily, Nitazoxanide 500 mg twice daily, and Doxycycline 100 mg once daily.

Arm 4: PPI quadruple therapy (comparator arm): Patients received a non-bismuth quadruple therapy: Levofloxacin 500 mg once daily, Esomeprazole 20 mg twice daily, Nitazoxanide 500 mg twice daily, and Doxycycline 100 mg once daily.

Patients took their treatment with water 30 m before meals under supervision. It was not possible to carry out the provided treatment.

After inclusion in the study, all participants underwent the following procedures

- History taking, including age, sex, smoking habits, any clinical comorbidities, presenting symptoms, and any laboratory tests,

especially CBC and INR, in addition to the detailed eradication regimen and duration of the treatment for the treatment-experienced patients, who were allocated to Group II.
- Complete clinical examination.
- Laboratory tests, including an initial *H. pylori* stool antigen test (Dia Sure, Azure Biotech Inc.) before inclusion in the study and four weeks after completing the eradication regimens. The intake of antibiotics and acid-suppressive therapies was prohibited two weeks prior to the test.

Principle of the procedure

- The *H. pylori* SA assay by Dia Sure, Azure Biotech Inc.[20] is a delayed one-step sandwich assay for the detection of *H. pylori* stool antigen. The assay uses a monoclonal antibody for detection and involves 200 µL of sample, which is a mixture of sample diluent and extracted *H. pylori* stool antigen. It was incubated with paramagnetic particles coated with a capture antibody. After incubation, an isoluminol-conjugated antibody was added and incubated. Following a second incubation, unbound material was removed via a wash cycle. Starter reagents were added to initiate a flash chemiluminescent reaction. The light signal, measured as relative light units, was proportional to the concentration of *H. pylori* stool antigen in the calibrators, controls, or samples.
- Medications were dispensed to each arm as follows: Medications were taken for 14 days in all four arms of the study as previously mentioned.
- Telephone contact by the principal investigator was made with each participant one week after starting the regimen to check compliance.
- Patient adherence to the prescribed treatment and adverse drug reactions were evaluated by self-report, documented by the principal investigator.
- Good compliance was defined as drug consumption of at least 75% of the total dosage.
- Two follow-up visits: The first follow-up visit was done two weeks after completing treatment to record adverse events, whether minor (e.g., nausea, gastric upset, vomiting, or diarrhea) or serious (e.g., severe, intolerable gastric upset or vomiting leading to hospitalization).The second follow-up visit was done four weeks after completing the treatment to register eradication results.
- Success rates of *H. pylori* eradication treatment were compared between treatment-naïve and treatment-experienced patients.
- Symptom relief was evaluated and compared between the equivalent groups.
- Successful *H. pylori* eradication was defined as a negative *H. pylori* stool antigen test four weeks after discontinuation of treatment.

Statistical Package

Data entry and statistical analysis of the collected data was performed using reliable genuine software statistical program.

Data management and statistical analysis

Data was collected, revised, coded, and entered into the Statistical Package for Social Science version 23. Quantitative data was presented as mean and standard deviations when normally distributed, and as median with interquartile range when not normally distributed. Qualitative variables were presented as total numbers and percentages.

Comparison between groups with qualitative data was done using the Chi-square test.

Comparison between two independent groups with normally distributed quantitative data was done using the independent t-test.

When the quantitative data was not normally distributed, the Mann-Whitney test was applied.

The confidence interval was set at 95%, and the margin of error was set at 5%. The *p*-value was considered significant as follows: *p*-value > 0.05: Non-significant, *p*-value < 0.05: Significant.

Results

Demographic data

The participants included 115 males (49.6%) and 117 females (50.4%) with ages ranging from 18 to 89 years, with a mean age of 41.50 years.

Treatment tolerance

There was no statistically significant difference between the four study groups regarding demographic data and medical history at baseline (Table 1). Table 2 shows no statistically significant difference between the groups regarding major side effects such as "severe, intolerable gastric upset or vomiting leading to hospitalization", minor side effects such as "nausea, gastric upset, vomiting, or diarrhea", and symptom relief, with *p*-values of 0.390, 0.375, and 0.515, respectively. Regarding treatment regimen adherence, the percentages were significantly higher in Arms 1 and 2 (94.8% for both) followed by Arm 4 (84.5%) and Arm 3 (77.6%), with a *p*-value of 0.008. The successful eradication rate was higher in Arm 1 (58.6%) compared to Arm 2 (50%) and higher in Arm 3 (50%) compared to Arm 4 (43.1%), though the differences did not reach statistical significance (*p*-value = 0.455).

Response to treatment

Tables 3 and 4 show no statistically significant difference between the two study groups regarding major side effects such as "severe, intolerable gastric upset or vomiting leading to hospitalization", minor side effects such as "nausea, gastric upset, vomiting, or diarrhea", and symptom relief, with *p*-values of 0.315, 0.154, and 0.142, respectively. The response to treatment based on intention-to-treat (ITT) analysis was higher in Arm 1 (58.6%) compared to Arm 2 (50%), though the difference did not reach statistical significance (*p*-value = 0.351). The per protocol (PP) analysis showed an eradication rate of 64% in Arm 1 compared to 56.9% in Arm 2, but again, no statistical significance was observed (*p*-value = 0.447).

Tables 5 and 6 show no statistically significant difference between Arms 3 and 4 regarding major side effects such as "severe, intolerable gastric upset or vomiting leading to hospitalization", minor side effects such as "nausea, gastric upset, vomiting, or diarrhea", and symptom relief, with *p*-values of NA, 1.000, and 1.000, respectively. Regarding treatment regimen adherence, the percentage was higher in Arm 4 (84.5%) compared to Arm 3 (77.6%), with a *p*-value of 0.897. The response to treatment was higher in Arm 3 (50%) compared to Arm 4 (43.1%), but the difference did not reach statistical significance (*p*-value = 0.427). In Arm 3, the ITT *H. pylori* eradication rate was 50%, while the PP analysis showed a higher eradication rate of 72.5%, though this was not statistically significant. In Arm 4, the ITT eradication rate was 43.1%, while the PP analysis showed a higher rate of 59.5%, again without statistical significance.

Table 7 shows that treatment adherence was similar in both groups, with adherence rates of 86.2% in the vonoprazan-based

Table 1. Basal demographic data and medical history of the four studied groups

		Arm 1 ()	Arm 2	Arm 3	Arm 4	Test value	*p*-value
		No. = 58	No. = 58	No. = 58	No. = 58		
Age	Mean ± SD	40.36 ± 18.49	37.79 ± 16.25	43.12 ± 16.53	44.74 ± 16.28	1.904•	0.130
	Range	19–89	18–70	20–80	18–85		
Sex	Male	25 (43.1%)	35 (60.3%)	32 (55.2%)	23 (39.7%)	6.673*	0.083
	Female	33 (56.9%)	23 (39.7%)	26 (44.8%)	35 (60.3%)		
Diabetes mellitus	Negative	53 (91.4%)	54 (93.1%)	49 (84.5%)	53 (91.4%)	2.848*	0.416
	Positive	5 (8.6%)	4 (6.9%)	9 (15.5%)	5 (8.6%)		
Hypertension	Negative	53 (91.4%)	48 (82.8%)	47 (81.0%)	45 (77.6%)	4.284*	0.232
	Positive	5 (8.6%)	10 (17.2%)	11 (19.0%)	13 (22.4%)		
Bronchial asthma	Negative	57 (98.3%)	55 (94.8%)	57 (98.3%)	54 (93.1%)	3.121*	0.373
	Positive	1 (1.7%)	3 (5.2%)	1 (1.7%)	4 (6.9%)		
Chronic liver disease	Negative	54 (93.1%)	58 (100.0%)	53 (91.4%)	52 (89.7%)	5.916*	0.116
	Positive	4 (6.9%)	0 (0.0%)	5 (8.6%)	6 (10.3%)		
Chronic Kidney disease	Negative	56 (96.6%)	57 (98.3%)	58 (100.0%)	57 (98.3%)	2.035*	0.565
	Positive	2 (3.4%)	1 (1.7%)	0 (0.0%)	1 (1.7%)		
Thyroid disease	Negative	56 (96.6%)	58 (100.0%)	57 (98.3%)	58 (100.0%)	0.565*	0.294
	Positive	2 (3.4%)	0 (0.0%)	1 (1.7%)	0 (0.0%)		
Smoking	Negative	48 (82.8%)	48 (82.8%)	49 (84.5%)	46 (79.3%)	0.563*	0.905
	Positive	10 (17.2%)	10 (17.2%)	9 (15.5%)	12 (20.7%)		
Concomitant medications	Negative	44 (75.9%)	44 (75.9%)	36 (62.1%)	39 (67.2%)	3.857*	0.277
	Positive	14 (24.1%)	14 (24.1%)	22 (37.9%)	19 (32.8%)		
Penicillin allergy	Negative	58 (100.0%)	58 (100.0%)	58 (100.0%)	56 (96.6%)	6.052*	0.109
	Positive	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.4%)		

p-value > 0.05: Non-significant (NS); *p*-value < 0.05: Significant (S); *p*-value < 0.01: highly significant (HS) •: One Way ANOVA test; *: Chi-square test.

Table 2. Examination and treatment outcomes of the studied groups

		Arm 1	Arm 2	Arm 3	Arm 4	Test value	*p*-value	Sig
		No. = 58	No. = 58	No. = 58	No. = 58			
	Positive	58 (100.0%)	58 (100.0%)	58 (100.0%)	58 (100.0%)			
Treatment regimen adherence	Negative	3 (5.2%)	3 (5.2%)	13 (22.4%)	9 (15.5%)	11.697*	0.008	HS
	Positive	55 (94.8%)	55 (94.8%)	45 (77.6%)	49 (84.5%)			
Major side effects	Negative	57 (98.3%)	58 (100.0%)	58 (100.0%)	58 (100.0%)	3.013*	0.390	NS
	Positive	1 (1.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			
Minor side effects	Negative	58 (100.0%)	56 (96.6%)	55 (94.8%)	55 (94.8%)	3.107*	0.375	NS
	Positive	0 (0.0%)	2 (3.4%)	3 (5.2%)	3 (5.2%)			
Symptoms relief	Negative	12 (20.7%)	19 (32.8%)	17 (29.3%)	17 (29.3%)	2.287*	0.515	NS
	Positive	46 (79.3%)	39 (67.2%)	41 (70.7%)	41 (70.7%)			
H. pylori stool antigen test result	Negative	34 (58.6%)	29 (50.0%)	29 (50.0%)	25 (43.1%)	2.617*	0.455	NS
	Positive	19 (32.8%)	22 (37.9%)	11 (19.0%)	17 (29.3%)			
	Dropout	5 (8.6%)	7 (12.1%)	18 (31.0%)	16 (27.6%)			

p-value > 0.05: Non-significant (NS); *p*-value < 0.05: Significant (S); *p*-value< 0.01: highly significant (HS); NA: Not applicable,*: Chi-square test.

Table 3. Comparison between Arm 1 and Arm 2 regarding examinations and treatment outcome

		Arm 1	Arm 2			
		No. = 58	No. = 58	Test value	*p*-value	Sig.
		58 (100.0%)	58 (100.0%)			
Treatment regimen adherence	Negative	3 (5.2%)	3 (5.2%)	0.000*	1.000	NS
	Positive	55 (94.8%)	55 (94.8%)			
Major Side effects	Negative	57 (98.3%)	58 (100.0%)	1.009*	0.315	NS
	Positive	1 (1.7%)	0 (0.0%)			
Minor Side effects	Negative	58 (100.0%)	56 (96.6%)	2.035*	0.154	NS
	Positive	0 (0.0%)	2 (3.4%)			
Symptoms relief	Negative	12 (20.7%)	19 (32.8%)	2.157*	0.142	NS
	Positive	46 (79.3%)	39 (67.2%)			
H. pylori stool antigen test	Negative	34 (58.6%)	29 (50.0%)	0.950	0.622	NS
	Positive	19 (32.8%)	22 (37.9%)			
	Dropout	5 (8.6%)	7 (12.1%)			

p-value > 0.05: Non-significant (NS); *p*-value < 0.05: Significant (S); *p*-value < 0.01: highly significant (HS); NA: Not applicable; *: Chi-square test.

Table 4. Intention to treat and per protocol analysis of *H. pylori* stool Ag test negative patients among treatment naïve patients

	Arm 1	Arm 2	Test value	*p*-value	Sig.
Negative *H. pylori* Ag test	ITT: 34 (58.6%)	29 (50.0%)	0.869*	0.351	NS
	PP: 34 (64.2%)	29 (56.9%)	0.578*	0.447	NS

p-value > 0.05: Non-significant (NS); *p*-value < 0.05: Significant (S); *p*-value < 0.01: highly significant (HS); NA: Not applicable,* Chi-square test.

Table 5. Comparison between Arm 3 and Arm 4 regarding examination and treatment outcome

		Arm 3	Arm 4			
		No. = 58	No. = 58	Test value	*p*-value	Sig.
	Positive	58 (100.0%)	58 (100.0%)			
Treatment regimen adherence	Negative	13 (22.4%)	9 (15.5%)	0.897*	0.343	NS
	Positive	45 (77.6%)	49 (84.5%)			
Major side effects	Negative	58 (100.0%)	58 (100.0%)	NA	NA	NA
	Positive	0 (0.0%)	0 (0.0%)			
Minor side effects	Negative	55 (94.8%)	55 (94.8%)	0.000*	1.000	NS
	Positive	3 (5.2%)	3 (5.2%)			
Symptoms relief	Negative	17 (29.3%)	17 (29.3%)	0.000*	1.000	NS
	Positive	41 (70.7%)	41 (70.7%)			
H. pylori stool Ag test	Negative	29 (50.0%)	25 (43.1%)	1.700*	0.427	NS
	Positive	11 (19.0%)	17 (29.3%)			
	Dropout	18 (31.0%)	16 (27.6%)			

p-value > 0.05: Non-significant (NS); *p*-value < 0.05: Significant (S); *p*-value < 0.01: highly significant (HS); NA: Not applicable; *: Chi-square test.

Table 6. Intention to treat and per protocol analysis of *H. pylori* stool antigen test negative patients among treatment-experienced patients

	Arm 3	Arm 4	Test value	*p*-value	Sig.
Negative *H. pylori* Ag test	ITT - 29 (50.0%)	25 (43.1%)	0.554*	0.457	NS
	PP - 29 (72.5%)	25 (59.5%)	1.534*	0.216	NS

p-value > 0.05: Non-significant (NS); *p*-value < 0.05: Significant (S); *p*-value < 0.01: highly significant (HS); NA: Not applicable; *: Chi-square test

Table 7. Comparison between vonoprazan-based treatment and PPI-based treatment regarding examinations and treatment outcome

		Vonoprazan based treatment	PPI based treatment	Test value	*p*-value	Sig.
		No. = 116	No. = 116			
Treatment regimen adherence	Negative	16 (13.8%)	12 (10.3%)	0.650	0.420	NS
	Positive	100 (86.2%)	104 (89.7%)			
Major side effects	Negative	115 (99.1%)	116 (100.0%)	1.004	0.316	NS
	Positive	1 (0.9%)	0 (0.0%)			
Minor side effect	Negative	113 (97.4%)	111 (95.7%)	0.518	0.472	NS
	Positive	3 (2.6%)	5 (4.3%)			
symptoms relief	Negative	29 (25.0%)	36 (31.0%)	1.047	0.306	NS
	Positive	87 (75.0%)	80 (69.0%)			
H. pylori stool Ag test	Negative	63 (54.3%)	54 (46.6%)	1.866	0.393	NS
	Positive	30 (25.9%)	39 (33.6%)			
	Dropout	23 (19.8%)	23 (19.8%)			

p-value > 0.05: Non-significant (NS); *p*-value < 0.05: Significant (S); *p*-value < 0.01: highly significant (HS); NA: Not applicable; *: Chi-square test.

treatment group and 89.2% in the PPI-based treatment group. Only one patient in the vonoprazan-based treatment group developed major side effects in the form of "severe, intolerable gastric upset and vomiting that led to hospitalization". Three patients in the vonoprazan-based treatment group developed minor side effects such as "nausea, gastric upset, vomiting, or diarrhea." In the PPI-based treatment group, five patients developed treatment-related minor side effects. The response to treatment was higher in the vonoprazan-based treatment group (54.3%) compared to the PPI-based treatment group (46.6%), though this difference was not statistically significant (*p*-value = 0.393).

Discussion

Vonoprazan, a newly introduced P-CAB in *H. pylori* eradication regimens, has an efficacy that is not affected by meal ingestion, as its absorption rate is independent of meals. P-CABs are rapidly absorbed, with the time to reach maximum plasma concentration being less than 2 h after oral administration. After absorption, the half-life in plasma is up to 9 h for P-CABs, compared to approximately 2 h for conventional PPIs. Therefore, P-CABs remain in the bloodstream longer and can continuously block acid secretion.[21] Consequently, the current study aimed to compare the efficacy of P-CABs versus PPIs, with identical antibiotic regimens, in the eradication of *H. pylori* infection in the Egyptian population. To our knowledge, this is the first study to address this research question in Egyptian patients.

Regarding the treatment outcomes among treatment-naïve patients in this study, in Arm 1, 34 out of 58 patients (58.6%) achieved *H. pylori* eradication according to ITT analysis, while the percentage was 64.2% according to PP analysis. In Arm 2, 29 out of 58 patients (50%) achieved *H. pylori* eradication according to ITT analysis, while the percentage was 56.9% according to PP analysis.

In comparison, a similar study on a Japanese cohort showed higher *H. pylori* eradication rates in the treatment-naïve P-CAB group (89.6%), whereas the treatment-naïve PPI group achieved 71.9% eradication according to ITT analysis.[22]

P-CABs demonstrated a higher success rate tendency among treatment-naïve *H. pylori* patients compared to the PPI-based group in the Japanese study, though the difference was not statistically significant. This result aligns with the findings of the current study, which also showed a higher tendency for eradication in treatment-naïve patients without a statistically significant difference.

Contrary to the current study's findings, Yamada *et al*. concluded that P-CABs had a statistically significant higher success rate among treatment-naïve *H. pylori* patients compared to the PPI-based group (85.7% *vs.* 73% by ITT analysis, *p*-value => 0.001).[23]

Regarding the treatment outcomes among treatment-experienced patients in this study, in Arm 3, 29 out of 58 patients (50%) achieved *H. pylori* eradication according to ITT analysis, while the percentage was 72.5% according to PP analysis. In Arm 4, 25 out of 58 patients (43.1%) achieved *H. pylori* eradication according to ITT analysis, while the percentage was 59.5% according to PP analysis.

In comparison to these findings, Matsumoto *et al*.[22] reported that in two groups of treatment-experienced patients, the introduction of P-CABs in a second-line eradication regimen resulted in 76.1% *H. pylori* eradication, while reuse of PPIs in a second-line regimen achieved eradication in 40.2% of cases.

Yamada *et al*.[23] study, which assessed the efficacy of PPIs versus P-CABs in treatment-experienced *H. pylori* patients, reported that P-CABs achieved *H. pylori* eradication in 89.4% of patients according to ITT analysis, with a rate of 96.7% according to PP analysis. In comparison, PPIs achieved eradication in 89.9% of patients according to ITT analysis, with a rate of 92.8% according to PP analysis.

In agreement with the current study's findings, Chey *et al*.[24] reported data from the first Phase

Three clinical trial conducted in the USA and Europe to compare the efficacy and safety of vonoprazan-based triple and dual therapies versus PPI-based triple therapy for the eradication of *H. pylori*. A total of 1,064 treatment-naïve adult patients with *H. pylori* infection were randomized 1:1:1 to open-label vonoprazan dual therapy (20 mg vonoprazan twice daily; 1 g amoxicillin three times daily) or double-blind triple therapy twice a day (vonoprazan 20 mg or lansoprazole 30 mg; amoxicillin 1 g; clarithromycin 500 mg) for 14 days. The primary eradication rates (for non-resistant

strains) were 84.7% for vonoprazan triple therapy, 78.5% for dual therapy, and 78.8% for lansoprazole triple therapy. In clarithromycin-resistant infections, eradication rates were 65.8% for vonoprazan triple therapy, 69.6% for dual therapy, and 31.9% for lansoprazole triple therapy.

When we consider the results of the current study alongside those from Japanese studies, we observe a trend toward higher eradication rates in the P-CAB treatment groups compared to the PPI-based groups, despite the absence of statistically significant differences between the drugs across the three studies. Contrary to the findings of the Yamada *et al*.[23] study, the current study reports a higher percentage of dropouts, particularly within the treatment-experienced group (Arms 3 and 4). In contrast, in the treatment-naïve group (Arms 1 and 2), both studies show comparable dropout rates. Furthermore, regarding treatment adherence among the four study arms, it was found that patients in Arms 1 and 2 had an adherence rate of 94.8%, whereas those in Arms 3 and 4 had adherence rates of 77.6% and 84.5%, respectively. Thus, adherence appears to be higher in the triple therapy group than in the quadruple therapy group.

Regarding treatment-related side effects experienced by the participants in the current study, among the 116 recipients of vonoprazan-based treatments (Arms 1 and 3), one patient (0.9%) experienced a major event in the form of severe, intolerable gastric upset and vomiting, which led to hospitalization. Meanwhile, three patients (2.6%) experienced minor side effects such as nausea, gastric upset, vomiting, or diarrhea.

Among the 116 recipients of PPI-based treatments (Arms 2 and 4), five patients (4.3%) experienced minor side effects, such as nausea, gastric upset, vomiting, or diarrhea.

In comparison, Chey *et al*.[24] reported that among 694 patients who received vonoprazan-based regimens, treatment-emergent adverse events were reported in 34.1% (118 of 346) and 29.9% (104 of 348) of vonoprazan triple and dual therapy groups, respectively, and in 34.5% (119 of 345) of the lansoprazole triple therapy group. Serious treatment-emergent adverse events occurred in 1.7% (6 of 346), 1.4% (5 of 348), and 0.9% (3 of 345). Treatment-related discontinuations occurred in 2.3% (8 of 346), 0.9% (3 of 348), and 1.2% (4 of 345) of patients in the vonoprazan triple, vonoprazan dual, and lansoprazole triple therapy groups, respectively. Overall, there were three deaths: two due to COVID-19 (one patient each on lansoprazole triple therapy and vonoprazan triple therapy) and one due to a fatal sudden cardiac arrest (a patient on vonoprazan triple therapy).The high dropout rates and low treatment adherence in the treatment-experienced groups in the current study could be attributed to polypharmacy, which may lead to noncompliance, in comparison to the treatment-naïve groups.

The higher success in eradication rates in the Japanese studies compared to the current study could be attributed to racial differences between Egyptian and Japanese patients. Additionally, the current study was conducted in 2023, unlike the Japanese studies, which were conducted in 2016. Over time, more aggressive, resistant *H. pylori* strains may have developed. According to Alboraie *et al*.,[25] a percentage of 50% or less of the *H. pylori* population in Egypt is believed to harbor clarithromycin-resistant *H. pylori* strains, as evidenced by culture techniques. Another explanation for the difference in eradication rates between the current study and the Japanese studies is the difference in medications used in the studies.

Limitations of the current study include the following: The small number of participants in each arm, being a single-center study, the use of a single test (*H. pylori* stool antigen test) for initial diagnosis and for confirming eradication of *H. pylori* after treatment, and being a non-controlled, non-randomized study.

H. pylori infection and the efficacy of eradication regimens were assessed using the stool antigen test because this test is more widely available, cheaper, and more accurate in Egypt compared to other non-invasive tests as the urea breath test (UBT), rapid urease test (RUT), and serology. The stool antigen test is much more affordable and accessible in Egypt, and it is non-invasive compared to RUT and histology. Kazemi *et al*.[26] conducted a study comparing the validity of five diagnostic tests for H. pylori: stool antigen test, UBT, RUT, serology, and histology. A total of 94 patients eligible for *H. pylori* testing were enrolled, and all five tests were performed for each patient. The sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and area under the Receiver Operating Curve (ROC) curve for these tests are as below, respectively. Histology: 89%, 78%, 93%, 91%, 85%, and 0.881; RUT: 93%, 75%, 95%, 94%, 86%, and 0.831; serology: 50%, 54%, 46%, 61%, 52%, and 0.563; stool antigen test: 96%, 83%, 98%, 96%, 91%, and 0.897; UBT: 89%, 73%, 92%, 90%, 82%, and 0.892. The authors concluded that the *H. pylori stool* antigen test is the most accurate diagnostic tool for *H. pylori*.

The lack of a control and placebo arm in the current study is justified as this was a comparative non-inferiority study conducted to assess the efficacy of P-CABs versus PPIs in primary and secondary eradication regimens for *H. pylori*, being the first of its kind in Egypt. Although the design of this study is considered one of its limitations, the results provide a rationale for conducting a placebo-controlled, randomized study on Egyptian patients in the future.

Conclusions

The eradication results in the P-CAB-based group are comparable to those in the PPI-based group. The treatment-experienced groups showed lower eradication rates, indicating increased *H. pylori* resistance. Adherence appeared to be higher in the triple therapy group compared to the quadruple therapy group, which was reflected in the eradication rates. *H. pylori* eradication regimens that include P-CABs are tolerable, with a low incidence of adverse events.

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Conflict of interest

There are no potential competing interests to declare.

Author contributions

Contributed to studyconcept and design (MRE, NEA), Acquisition of the data (NEA, ME, HMH) and the laboratory work was done by (YM). All authors participated in the writing and approved the manuscript.

Data sharing statement

The dataset used in this study is not available publicly, but is available from the the corresponding author at elwakilreda@gmail.com

Ethical statement

The principal investigator obtained approval from the Faculty of Medicine Ain Shams University Research Ethics Committee (FWA 000017585) before starting the study. The approval number is FMASU MS 36/2022. All participants signed informed consent before participating in the study. The study was conducted according to the Declaration of Helsinki, which outlines ethical principles for medical research involving human subjects. ClinicalTrials.gov ID: NCT06101420.

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