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Original article

Potassium competitive acid blocker based sequential therapy in treatment of naïve and previously treated patients with *H.pylori* infection

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ABSTRACT

Background: *Helicobacter pylori* (*H. pylori*) colonize the gastric lining and cause gastrointestinal disorders. Treatment of *H. pylori* has developed lately to improve eradication rates. Our objective was to evaluate potassium competitive acid blocker based sequential therapy in treatment of naïve and previously treated patients with *H-pylori* infection. **Methodology**: Prospective cohort study included 180 patients diagnosed with *H. pylori* infection either naïve or previously treated were divided into 4 groups. Group I included naïve patients received traditional therapy (PPI 40 mg once daily,clarithromycin500mg twice daily & metronidazole 500mg twice daily)for 14days, group II included naïve patients on P-CAB based sequential(5 days of vonaprazan 20mg twice daily, moxifloxacin 400 mg once daily, nitazoxanide 500 mg twice daily, followed by 5 days of vonaprazan 20mg twice daily, levofloxacin 500mg once daily & metronidazole 500mg twice daily), group III included previously failed treatment patients received P-CAB based sequential, and group IV included previously treated patients on LOAD therapy(10 days of omeprazole 40mg once daily, levofloxacin 500mg once daily, nitazoxanide 500mg twice daily, & doxycycline 100mg twice daily). *H.pylori* stool antigen test done at the time of diagnosis and after 4- 6 weeks after end of treatment. **Results:** The cure rate among the studied groups was higher in GII (93.3%) followed by GIII (88.9%), then GIV (71.1%) and the least response is GI (62.2%). **Conclusion:** P-CAB based sequential regimen was the highest eradication rate and least side effects in comparison with traditional and LOAD therapy.

Introduction

Helicobacter pylori (*H. pylori*) infection remains a considerable world health challenge, affecting over 50% of the global inhabitants [1]. This gram-negative, spiral-shaped bacterium colonizes the human stomach lining, where it can persist for years, causing chronic inflammation that may lead to a variety of gastrointestinal disorders. *H. pylori* infection is connected to many diseases, such as chronic gastritis, peptic ulcer disease, and

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gastric adenocarcinoma, as well as mucosa-associated lymphoid tissue (MALT) lymphoma, and also linked with nongastrointestinal diseases as idiopathic thrombocytopenic purpura (ITP), and iron-deficiency anemia (IDA) [1] making it a significant contributor to global morbidity and mortality [2]. Huge worldwide prevalence and rising rate of resistance to antibiotics directed the World Health Organization to consider *H pylori* as a pathogen of high- priority in 2017. [3]

Investigating this organism is classified into nonendoscopic and endoscopic. Nonendoscopic tests as serology, *H. pylori* stool antigen& urea breathe test and endoscopic biopsy for histopathological examination, culture and rapid urease test. [3]

Choosing the treatment regimen for *H. pylori* should provide high eradication rate over 90%. During choosing the appropriate regimen for *H. pylori* treatment, some considerations should be taken, as antibiotics previously taken, regional antibiotic-resistance type, eradication rates, allergy to any antibiotic and adherence to treatment. These considerations influence the success of the treatment. [4]

Although several treatment options are available, primarily consisting of combinations of antibiotics and acid-suppressing agents, resistance is increasingly leading to treatment failures and decreasing eradication rates. [5] New treatment protocols, often referred to as "new triple therapy" (NTT), have been introduced. These approaches include various strategies, such as using higher doses or prolonged durations of PPIs, adding different antibiotics, or incorporating bismuth-based compounds in combination with triple therapy. Sequential, concomitant, and quadruple therapies are also emerging as alternatives, aiming to overcome resistance patterns and enhance treatment success. [3]

Potassium-competitive acid blockers (P-CABs) are a newer class of medications designed to suppress gastric acid secretion as they directly inhibit the H+/K+ ATPase enzyme, also known as the proton pump, in a potassium-competitive and reversible manner. One of the promising applications of P-CABs is in the treatment of *H. pylori* infections. Traditionally, *H. pylori* eradication therapy relies on a combination of PPIs with antibiotics to create an optimal pH environment that enhances antibiotic stability and activity, but PPI-based therapies can vary in effectiveness due to delayed acid suppression onset and genetic polymorphisms affecting PPI metabolism [6], while, P-CABs like vonoprazan offer more rapid and sustained acid suppression, which can improve the efficacy of *H. pylori* eradication regimens, particularly in populations with antibiotic resistance in a high rate. [7] Recent studies have shown that vonoprazan-based triple therapy, combining the P-CAB with antibiotics can achieve higher eradication rates than traditional PPI-based therapies [8]. This evidence suggests that P-CABs may serve as a valuable alternative or adjunct to PPIs in *H. pylori* treatment, potentially overcoming limitations associated with current regimens and improving treatment outcomes for affected patients globally

Nitazoxanide is primarily an antiprotozoal agent, and has shown activity against *H. pylori*, especially in resistant strains. Studies suggest that when combined with other antibiotics, it can improve eradication rates. [9] Moxifloxacin and Levofloxacin, Both are fluoroquinolones, with levofloxacin widely studied for *H. pylori* treatment as part of triple or quadruple therapy. Moxifloxacin, though less commonly used, yet it has been studied as an alternative in cases where resistance to other antibiotics is present. [10] Metronidazole is known for its broad-spectrum activity against anaerobic bacteria, and it remains a key agent in various *H. pylori* regimens. However, resistance can be an issue, leading to the exploration of combining it with other drugs to counteract this limitation. [11]

Subjects and methods

Study design and study population

Current work is multicentric prospective cross-sectional included 180 patients diagnosed with *H-pylori* infection taken from tropical medicine department, Menoufia University hospital, Liver institute, Menoufia University and internal medicine department, Alexandria University hospital during the period from July 2023 to June 2024. The study was approved by the institutional review board with an approval number (8/2024 TROP 3). Informed written consent was taken from every patient before participation in the present study.

The patients included were classified into four groups; **GI:** naïve patients (not previously treated with any specific eradication therapy for *H. pylori*) with positive H. Pylori stool Ag, received traditional treatment with (Omeprazole 40mg once daily,clarithromycin500mg twice daily and

metronidazole 500mg twice daily)for 14 days. **GII:** naïve patients with positive *H. Pylori* stool Ag, received P.CAB based sequential therapy (5 days of vonaprazan 20mg twice daily, moxifloxacin 400 mg once daily, nitazoxanide 500 mg twice daily, , followed by 5 days of vonaprazan 20mg twice daily, levofloxacin 500mg once daily and metronidazole 500mg twice daily), **GIII:** retreated patients after failed treatment with any traditional therapy for *H. pylori*, will receive P.CAB based sequential therapy with (5 days of vonaprazan 20mg twice daily, moxifloxacin 400 mg once daily, nitazoxanide 500 mg twice daily, followed by 5 days of vonaprazan 20mg twice daily, levofloxacin 500mg once daily and metronidazole 500mg twice daily), and **GIV:** retreated patients after failed treatment with any traditional therapy, received LOAD therapy with (10 days of omeprazole 40mg once daily, levofloxacin 500mg once daily and nitazoxanide 500mg twice daily, and doxycycline 100mg twice daily).

The study included naïve patients complained of gastrointestinal symptoms (abdominal pain, epigastric pain, vomiting, anorexia, dyspepsia, headache and urticaria, hematemesis and melena), those asymptomatic who were discovered on routine checkup with stool Antigen (Ag), those with *H. pylori* complications and diagnosed as infected by positive Antigen stool test and, patients previously failed treatment of *H. pylori* with traditional or LOAD therapy with *H. pylori* Ag test positive.

The study excluded non-compliant patients, recent antibiotic use within 4 weeks Pregnancy or lactation and Patients with history of allergy to any medication that included in the study. Full history taking from all patients was done including gastrointestinal symptoms e.g. epigastric pain, nausea, vomiting, hurt burn, regurgitation, hematemesis or melena and clinical examination (General and abdominal) were done.

Laboratory investigations included complete blood count (CBC), liver enzymes (ALT and AST), serum creatinine level, random blood sugar (RBS) and *H. pylori* antigen detection was done at time of diagnosis and 4 weeks after completing the full course eradication regimen by enzyme-linked immunosorbent assay (ELISA). The test was done using Premier Platinum HpSA stool Ag ELISA kits (Meridian Bioscience). The steps done by collecting the samples in clean stool container, sample preparation by weighing the sample. Diluting the sample in the stool extraction buffer then setting up the ELISA plate by adding the specific volume of the prepared stool extract to each well of the ELISA plate. Incubation at 37c for 60 minutes. Washing the wells multiple times and add the enzyme substrate solution to each well then incubate for 30 minutes. Stopping the reaction by adding the stopping solution then using an ELISA plate reader to measure the optical density (OD) and comparing it with the cut-off value (620nm). Positive results meant that OD value was above 620nm and negative results meant that the OD value was less than 620nm.

Upper endoscopy was done by (Olympus endoscope dip0230, Olympus Company, Tokyo, Japan) to selected patients with alarm symptoms (Anemia, weight loss, persistent vomiting or epigastric pain, and melena). Sedation used was midazolam. The starting dose was 1 to 2 mg. Adequate time between repeat dosing have been recommended 3-5 minutes after fasting for 6hrs.

Statistical analysis

The study data analysis was done using SPSS (Statistical Package for Social Science) version 23 (SPSS Inc., Chicago, IL, USA)**.** the quantitative data were described as mean, standard deviation (SD) and range while the qualitative type was described as frequency and percentage, regarding comparison between the studied groups, ANOVA test for comparing the quantitative normally distributed data, the qualitative data was compared by Chi square test in between the studied groups while McNemar Chi square test was the test of comparing the frequencies in pretreatment and post treatment assessment. P value was significant when equal or less than 0.05.

Results

The study evaluated 180 patients having *H. pylori* infection for their response to P.CAB treatment and (LOAD& traditional) regimens, showing the patient's age ranging from 18 to 63 with Mean ± SD 31.21±10.04 with female predominance by 55.6% to 44.4 to the males. No statistical significant difference among the studied groups according to the age and gender (P. value 0.25 & 0.91 respectively). Laboratory investigations were (CBC, ALT, AST, RBS and creatinine showing relative alterations in CBC, liver enzymes.

For the endoscopic findings in the cases that underwent upper endoscopy showed that for

gastroduodinitis percent in GI, II, III, and IV (83.3%, 100%, 42.9%&100%) respectively.

GERD was found in GI,III,IV(16.6%,28.6%,75%) respectively while hiatus hernia found in GI,II,III(16,7%,80%,28.6%) respectively. For histopathological findings, the cases with *H pylori* associated gastritis in GI,II,III,IV (83.3%,100%,71.4%,75%) respectively while adenocarcinoma in GI,III,IV(16.7%,28.6%,25%) respectively.

Stool antigen done 4 weeks after treatment for all the patients with positive stool antigen for *H pylori* before treatment showed highly significant increase in negative cases in GII than GI(P value <0.001) and, significant increase in negative cases in GIII than GIV. The percent of improvement in GI, II, III, IV was (62.2%, 93.3%, 88.9%, 71.1%) respectively.

The cure rate among the studied groups was higher in GII (93.3%) followed by GIII (88.9%), then GIV (71.1%) and the least response is GI (62.2%).

Different side effects from treatment were highest in GI (31.1%), while dropped in GIII (2.2%). Bitter taste, galactorrhea, nausea, insomnia, fatigue were absent in GIII, while galactorrhea is absent in GII&GIII.

The presenting symptoms in the studied groups (epigastric pain, abdominal pain, dyspepsia, anorexia, vomiting, headache, itching, urticaria& weight loss) were highest in GI, while they were absent in GIII&GIV. Epigastric pain was the commonest complain in GI (28.9%) and in GII (13.3%). The cases discovered by *H-pylori* stool antigen in routine checkup were in GI&GII (20%, 57.8%). Melena founded only in 1 case in GIII (2.2%) and 1 case in GIV (2.25).

Table 1. Base line demographic data and laboratory characteristics of studied groups.

	The studied groups				**P value**
	Group I	**Group II**	**Group III**	**Group IV**	
Age Mean ±SD Range	 33.64±10.64 18 – 60	 30.89±9.47 10 – 50	 29.44±10.43 18 – 63	 30.84±9.40 18 – 55	0.25
Sex Male Female	 20 (44.4) 25 (55.6)	 18 (40.0) 27 (60.0)	 21 (46.7) 24 (53.3)	 21 (46.7) 24 (53.3)	0.91
Anemia	4 (8.9)	1 (2.2)2	2 (4.4)	1 (2.2)	**0.37**
Leukocytosis	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	**0.39**
Elevated AST	2 (4.4)	3 (6.7)	1 (2.2)	0 (0.0)	**0.33**
Elevated ALT	2 (4.4)	3 (6.7)	1 (2.2)	2 (4.4)	**0.79**
High RBS	1 (2.2)	7 (15.6)	3 (6.7)	2 (4.4)	**0.08**
High Creatinine	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-------

SD (Standard Deviation) N (number) RBS (Random Blood Sugar)
AST (Aspartate Transaminase) ALT (Alanine Transaminase)

Table 2. Endoscopic findings and histopathology among the studied cases

	The studied groups			
	Group I	**Group II**	**Group III**	**Group IV**
Endoscopic findings	**N = 6 (13.3)**	**N=5(11.1)**	**N=7 (15.6)**	**N = 4 (8.9)**
Gastroduodenitis	5 (83.3)	5 (100.0)	3 (42.9)	4 (100.0)
GERD	1 (16.7)	0 (0.0)	2 (28.6)	3 (75.0)
HH	1 (16.7)	4 (80.0)	2 (28.6)	0 (0.0)
Histopathology				
H pylori associated with gastritis	5 (83.3)	5 (100)	5 (71.4)	3 (75.0)
adenocarcinoma	1 (16.7)	0 (0.0)	2 (28.6)	1 (25.0)

GERD =Gastroesophageal reflux disease
HH=Hiatus hernia

Table 3. Stool antigen results before and 4 weeks after treatment

	The studied groups				**Test**	**P value**
	Group I	**Group II**	**Group III**	**Group IV**		
Stool antigen (pretreatment)						
Positive					----	-------
Negative	45 (100)	45 (100)	45 (100)	45 (100)		
	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Stool antigen (post-treatment)						
Positive	17 (37.8)	3 (6.7)	5 (11.1)	13 (28.9)	12.60	<0.001[1]
Negative	28 (62.2)	42 (93.3)	40 (88.9)	32 (71.1)	4.44	0.035[2]
Mc Nemar Chi square	40.65	78.75	72.0	49.66		
(p value)	<0.001	<0.001	<0.001	<0.001		
Percent of improvement	62.2%	93.3%	88.9%	71.1%		

1= comparing group 1 and group 2, 2 = comparing group 3 and group 4

Table 4. Side effects detected from each treatment modality in the studied groups

	The studied groups				**Test**	**P value**
	Group I	**Group II**	**Group III**	**Group IV**		
	No (%)	**No (%)**	**No (%)**	**No (%)**		
Cure rate						
Responded to treatment	28 (62.2)	42 (93.3)	40 (88.9)	32 (71.1)	12.60	<0.001[1]
Non responsive	17 (37.8)	3 (6.7)	5 (11.1)	13 (28.9)	4.44	0.035[2]
Side effects						
Negative	31 (68.9)	39 (86.7)	44 (97.8)	36(80.0)	4.11	0.04[1]
Positive	14 (31.1)	6 (13.3)	1 (2.2)	9 (20.0)	7.20	0.007[2]
The type of side effects	N= 14	N= 6	N= 1	N= 9		
Gastric upset	3 (21.4)	1 (16.7)	1 (100)	2 (22.2)	7.30	0.20[1]
Bitter taste	1 (7.1)	1 (16.7)	0 (0.0)	0 (0.0)	2.59	0.46[2]
Galactorrhea	3 (21.4)	0 (0.0)	0 (0.0)	3 (33.3)		
Nausea	2 (14.3)	1 (16.7)	0 (0.0)	2 (22.2)		
Insomnia	1 (7.1)	3 (50.0)	0 (0.0)	0 (0.0)		
Fatigue	4 (28.6)	0 (0.0)	0 (0.0)	2 (22.2)		

1= comparing group 1 and group 2,
2 = comparing group 3 and group 4

Figure 1. The presenting symptoms between group I&II.

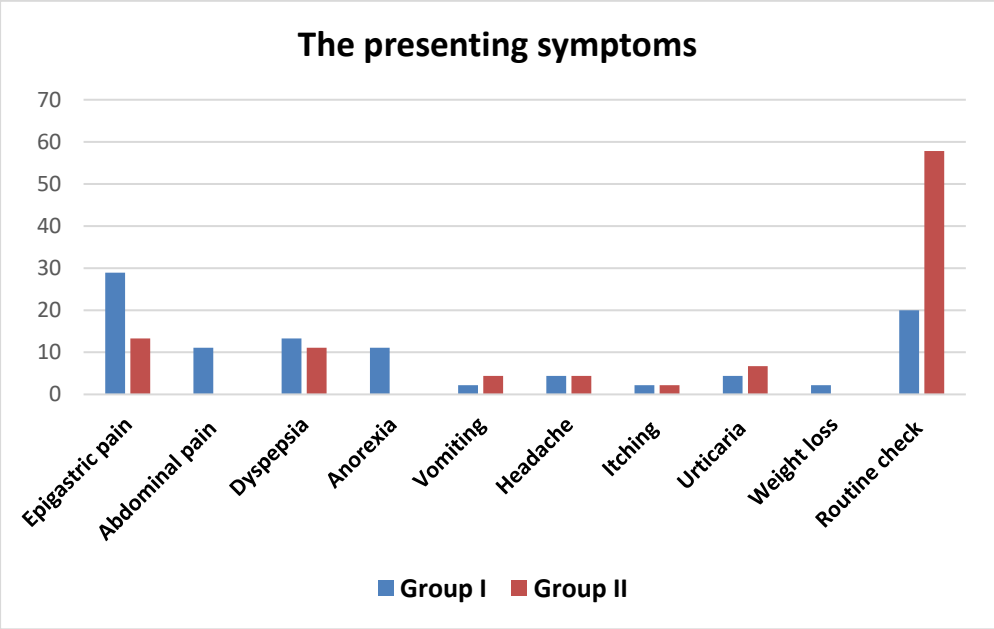


Figure 2. The cure rate among the studied groups.

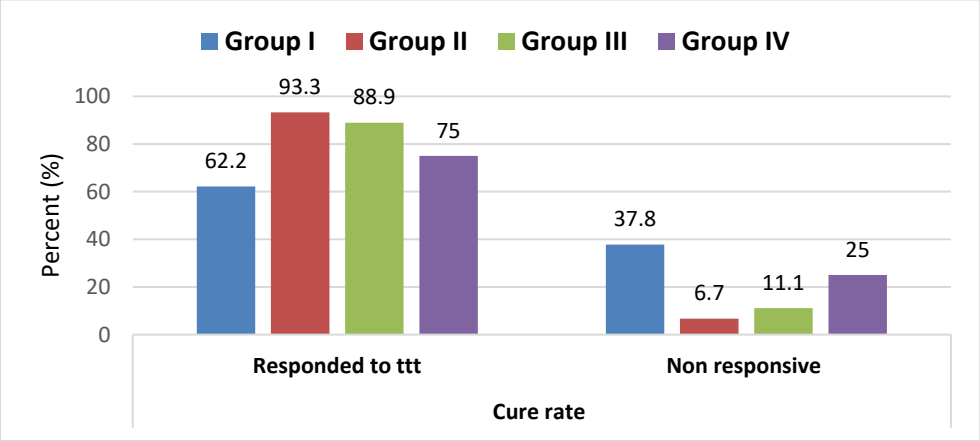
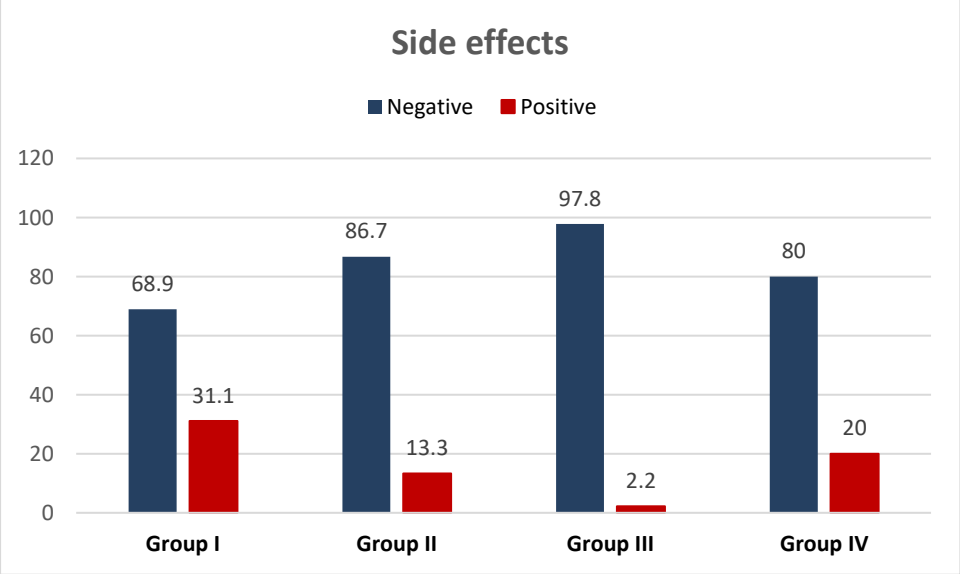


Figure 3. The side effects to the given regimens among the studied groups.



Discussion

Treatment of *H. pylori* infection has become increasingly complex as antibiotic resistance rates continue to rise worldwide, making the eradication more challenging. Due to the link of *H. pylori* to chronic gastritis, peptic ulcer, and gastric malignancies, this makes its eradication important for preventing these conditions. Treatment typically involves a combination of antibiotics and acid-suppressing medications to effectively eradicate the bacterium, but the standard approaches ended to emerging of antibiotic resistance. [12]

The current study evaluated 180 patients infected with *H. pylori* for their response to P.CAB sequential therapy and two other established regimens, showing the patient's age ranging from 18 to 63with mean± SD (31.21±10.04). **Malaty et al** reported that the new cases of *H. pylori* infections occurred before the age of 10 years and by age 18-23 years; the prevalence of the infection was 24.5% [13] and during 2014–2020, the prevalence of infection in children and adults was higher in low-income and middle-income countries. There were predominance of *H. pylori* infection in older individuals compared with children and the explanation is that most of *H. pylori* infections happened in childhood and persisting throughout life more than the risk of infection at older age. [14] Female predominance 55.6% was reported in our study, disagreeing with **Ferro et al,** who reported that there was no gender effect on the prevalence of *H. pylori* infection, [15] while **Abdulrazak et al,** demonstrated male predominance of *H. pylori*-related infection**.** [16] This may be related to methodology factors, geographical and cultural variations. [17] No statistical significant difference among the studied groups according to the age and sex (P. value 0.25 & 0.91 respectively) was found in the present study.

Laboratory investigations showed relative alterations in CBC(anemia & leukocytosis) and liver enzymes elevation in some patients of our study agreeing with **Francois et al.,** who reported changes in CBC in patients infected with *H. pylori* [18] and **Fujimoto et al.,** demonstrated metabolic disturbances, sometimes showing mild liver enzyme elevations in chronic cases. [19]

The presenting symptoms in the studied groups (epigastric pain, abdominal pain, dyspepsia, anorexia, vomiting, headache, itching, urticaria& loss of weight) were highest in GI, while they were absent in GIII&GIV. The commonest complain in GI was Epigastric pain (28.9%) and in GII (13.3%). (20%, 57.8%) of GI, GII respectively were asymptomatic and diagnosed when *H. pylori* routine checkup was done.

Gastrointestinal symptoms are obvious in naive *H. pylori* patients than in those experienced a recurrence or treatment failure. In naive patients newly infected, the bacterial load is typically high, and the immune response is often acute, leading to more intense symptoms, by contrast, patients who experience treatment failure or reinfection might have a lower bacterial load or a partially adapted immune response that reduces the acute inflammatory response thus less or absent symptoms. [20]

In the present study, the cure rate among the studied groups was higher in GII (93.3%) followed by GIII (88.9%), then GIV (71.1%) and the least response is GI (62.2%) showing high efficacy of P.CAB based sequential therapy over the LOAD therapy and confirming the low efficacy of traditional based clarithromycin therapy.

Clinical studies have demonstrated that P-CAB-based regimens achieve high rate of *H. pylori* eradication compared to PPI-based therapies; particularly in populations with high antibiotic resistance rates thus better healing of *H. pylori* induced gastritis and peptic ulcer**.** [21] Moxifloxacin has shown effectiveness against *H. pylori*, especially in patients with prior treatment failures. [22] **Marcus et al.** confirmed increasing the prevalence of resistant *H. pylori* strains to clarithromycin and treatment efficacy has significantly declined, which has led to bacterial adaptations and subsequent failure of the therapy. [23]

Clarithromycin-based triple therapy frequently fails to reach adequate eradication, so untreated or inadequately treated *H. pylori* infections are associated with major incidence of peptic ulcer disease, chronic gastritis, and gastric cancer.

Different side effects from treatment in the current study were highest in GI (31.1%), while dropped in GIII (2.2%). Bitter taste, galactorrhea, nausea, insomnia, fatigue were absent in GIII, while galactorrhea is absent in GII&GIII. Fatigue was the highest in GI (28.6%) while insomnia (50%) in GII and galatorrhea (33.3%) in GIV. **Furuta et al.,** concluded that P-CABs have been associated with fewer side effects and improved patient compliance

due to their rapid symptom relief, [24] while **Tahara & Arakawa,** showed that despite P-CAB are generally well-tolerated; they have been associated with insomnia. This effect, although relatively uncommon but is notable. [25] For fatigue which was the highest in GI; it may be related to clarithromycin. It is relatively common with it and the mechanism is related to the effect of clarithromycin on cytokine production and mitochondrial function, in addition it may cause gastrointestinal upset leading to the fatigue. Galactorrhea was high in GIV as those patients previously experienced one or more regimen of *H-pylori* treatment including proton pump inhibitors (PPIs). Galactorrhea was documented that it is one of the main side effects of PPIs. [26]

Conclusions

From our results and observations we concluded that the P-CAB based sequential regimen that we experienced in the present study had the highest eradication rate and least side effects making it more promising in *H.pylori* eradication either in naïve or previously treated patients

Limitations of the study

Noncompliant patients

Patients didn't tolerate the side effects of the drug regimens

Patients who refused upper endoscopy

Recommendations

More studies on larger numbers

Longer duration to follow up the response after treatment.

Funding statement

None

Conflict of interests

The authors declare no conflict of interest.

Data availability

All data generated or analyzed during this study are included in this puplished article.

Authors' contribution

All authors made significant contributions to the work presented, including study design, data collection, analysis, and interpretation. They also contributed to the article's writing, revising, or critical evaluation, gave final approval for the version to be published.

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