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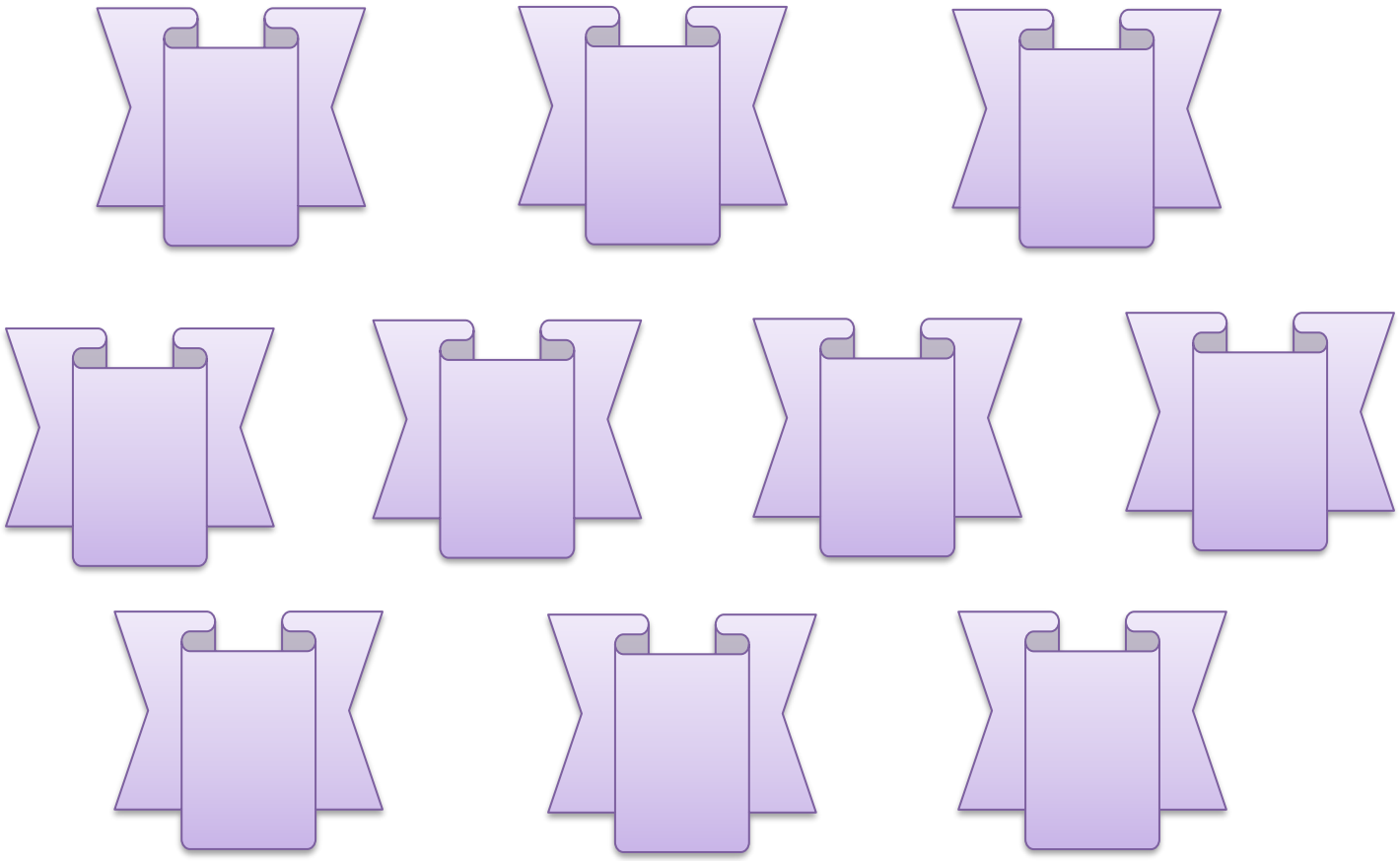

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Original Article

Vonoprazan versus Conventional Proton Pump Inhibitors Based Regimens in Helicobacter Pylori Eradication Therapy

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ABSTRACT

Background: Helicobacter pylori [H. Pylori] infection is a major risk factor for the development of gastric cancer. Gastric cancer witnessed a significant increase in recent decades. Thus, eradication of H. Pylori could reduce the incidence of gastric cancer. However, the standard treatment is not yet determined.

Aim of the Work: To evaluate the efficacy of Vonoprazan [VPZ]-based regimen compared-with proton pump inhibitors [PPI]-based regimen for H. pylori eradication therapy.

Patients and Methods: This study included 150 patients with gastro-intestinal symptoms and H. Pylori positive test. They were divided into equal three groups according to treatment regimen. The first group [I] received PPI-based regiment [triple therapy; Clarithromycin 500 mg, amoxicillin 1gm, and PPI 40 mg] twice daily for two weeks. The second group [II] received vonoprazan-based regiment [triple therapy; Clarithromycin 500 mg, amoxicillin 1 gm, and vonoprazan 20 mg] twice daily for two weeks. The third group also for vonoprazan-based regimen [dual therapy; [amoxicillin 1gm –vonoprazan 20 mg] twice daily for two weeks.

Results: The analysis indicates that the eradication rate of H. Pylori was 88% in group I, 92% in group II and 84% in group III. There was no significant difference between the three studied groups regarding eradication rate. In addition, groups were comparable regarding patient demographics except younger age of the first group than the second and third groups. Otherwise, no significant associations [differences] between groups were reported.

Conclusion: Vonoprazan triple therapy is superior to PPI- triple therapy. The dual vonoprazan-therapy is highly recommended in case of clarithromycin resistant patients. Otherwise, the triple vonoprazan therapy is recommended.

Keywords: Vonoprazan; Proton Pump Inhibitors; Helicobacter Pylori; Triple therapy; Eradication.

INTRODUCTION

Helicobacter pylori [H. Pylori] infection is a major risk factor for gastric cancer development. Gastric cancer is associated with significant morbidity and mortality. New cases of gastric cancer and cancer-related deaths worldwide in 2018 were 1,033,700 and 782,700, respectively [1]. H. Pylori is a gram negative spiral bacillus transmitted by feco-oral or through mouth to mouth. H. Pylori is responsible for about 70 % of gastric ulcers and 90% of duodenal ulcers [2]. A recent meta-analysis showed that H. pylori eradication is associated with significant reduction of the incidence of gastric cancer. Thus, effective treatment [eradication] of H. pylori is the principal worldwide strategy to prevent gastric cancer [3].

Vonoprazan [VPZ] is a new introduced potassium-competitive acid blocker. It was firstly introduced in Japan in 2015. At that time, it was used as a part of the first line, standard triple-drug regimen for eradication of H. Pylori [amoxicillin, clarithromycin, and VPZ or proton pump inhibitor [PPI] twice daily for 7 days]. Otherwise, the amoxicillin, metronidazole, and VPZ or PPI were used twice daily for 7 days as the second-line therapy. VPZ worked by direct inhibition of H+-K+ exchange, leading to significant increase of acid suppression [4].

Successful maintenance of ambient elevation of pH for at least 24 hours is a key factor for successful H. Pylori eradication. One trial showed a superior first line success of eradication of H. Pylori with the use of VPZ-based regimen over a PPI-based regimen [5]**.** Subsequent recent reviews confirmed the superiority of VPZ-based regiments as a first line treatment for H. Pylori eradication [6, 7]. Another systematic review did not show a significant higher success of a VPZ-based regimen than a PPI-based regimen in second-line eradication of H. Pylori. However, the number of patients were insufficient to produce appropriate evaluation of eradication success between the 2 regimens [7]. **Metwally *et al.*** [8] tested resistance of H. Pylori to different antibiotics and found that, the resistance rate for clarithromycin was 40% and for amoxicillin 95% and dual resistance for amoxicillin/clarithromycin was 40%. This reflected the magnitude of the problem and reflects the value of the current work.

The current study designed to evaluate the efficacy of VPZ-based regimen, and compare it with PPI-based regimen for eradication of H. pylori.

PATIENTS AND METHODS

This was a prospective, cross sectional, comparative study. It was conducted at the Department of Hepatology and Gastroenterology, Naser Institute Hospital, Cairo, Egypt. The study included 150 patients, on the duration between June 2022 and June 2023.

The inclusion criteria were clinical [gastro-intestinal] manifestations, H. Pylori positive test and no previous treatment for H. Pylori before. On the other hand, the exclusion criteria were previous surgery for the stomach [e.g., partial gastrectomy], allergy to any of drugs used in the study, pregnancy or lactation, drug addition, severe neuro-psychiatric disorder, clinical GIT manifestations with negative H. Pylori test, patient refusal or those receiving treatment for H. Pylori before the study, and intake of antibiotics, PPIs, corticosteroids, or nonsteroidal anti-inflammatory drugs [NSAIDs] within the last 4 weeks.

After full ethical justification [patient consent and ethical committee approval], the included patients were divided into three equal groups [each 50 patients]. The first group [I] included 50 naïve patients who received PPI-based regimen [Triple therapy; Clarithromycin 500 mg + Amoxicillin 1 gm + PPI 40 mg] twice daily for two weeks. The second group [II] for patients who received vonoprazan-based regimen [Triple therapy; Clarithromycin 500 mg + Amoxicillin 1 gm + Vonoprazan 20 mg] twice daily for two weeks. The third group [III] included patients who received vonoprazan-based regimen [dual therapy; Amoxicillin 1 gm + Vonoprazan 20 mg] twice daily for two weeks.

Patients eligible for inclusion in the study were subjected to clinical evaluation [achieved by history taking, detailed clinical examination, routine biochemical tests [e.g., complete blood count, coagulation profile, liver, and kidney function tests], pelvi-abdominal ultrasound, electrocardiogram, and echocardiography].

Diagnosis of H. Pylori was achieved by stool antigen test by ELISA as an initial diagnostic test and to confirm eradication [Treatment success]. It was used as a simple, non-invasive, cheap test with specificity more than 90%. We used [Fecal H. Pylori Antigen, ref KT 826, Epitope Diagnostics Inc.; San Diego, USA]. In short, 40 mg of the fecal material had been suspended in 1 ml of the buffer. Then 100 µl of this sample was added to microwell plates containing monoclonal antibody-coated material and incubated for 1 hour.

Then washed and the antibody tracer was added and incubated for half an hour. A second washing was performed and the HRP substrate was added for 10 minutes. A spectrophotometer was used to read the optical density on a 450 nm wavelength. A cutoff of 3 ng/mL was used to define positive tests as described by the Kits manufacturer [9].

Data analysis: The collected data was coded [anonymized] and fed to a personal computer through a Microsoft Excel sheet. Then, transferred to the statistical package for social science [version 26] [IBM Inc., Armonk, NY, USA. Normal distribution was examined by the Kolmogorov-Smirnov test. Continuous data was presented by their arithmetic mean and standard deviation [SD] when normally distributed or by their median and IQR [Interquartile range] when data are abnormally distributed. The categorical [qualitative] data was expressed by the relative frequency [numbers] and percentages. The qualitative data were compared by the Chi Square or Fisher Exact Tests, while quantitative data were compared by one-way analysis of variance, Kruskal-Wallis tests with post Hoc tests to compare between two groups. P value < 0.05 was considered significant.

RESULTS

In the current work, studied groups were comparable regarding patient gender, occupation and residence. However, patients in the first group were significantly younger than group III, but the difference between groups I and II or groups II and III, was statistically non-significant. The H. Pylori had a predilection to female gender, workers of rural areas [Table 1].

Regarding co-morbid conditions, the studied groups showed non-significant differences. The absences of these conditions were reported among 78%, 78% and 76% of the first, second and third groups respectively. The reported chronic medical conditions included diabetes mellitus, hypertension, ischemic heart disease, chronic kidney disease, dyslipidemia, and smoking [Table 2].

The main complaint and clinical presentation in the study group was widely diverse. The comments were epigastric pain. It was significantly higher among group I than groups II and III [94% vs 44% and 64% respectively]. On the other side, reflux symptoms were confined to group II [6.0%], while dyspepsia, nausea and vomiting were significantly higher among groups II and III than group I [12%, 18% and 10%, 28% vs 0% and 0% successively] [Table 3].

There was no statistically significant difference between the three studied groups regarding findings of abdominal US [p>0.05] [Table 4].

Before treatment, all patients had positive tests for H. Pylori antigen. The test changed to negative results in 44, 46 and 42 patients in groups I, II and III respectively. This represents eradication rate of 88%, 92% and 84% for groups I, II and III, successively. In each group, where was significant response to treatment, two weeks after initiation of therapy. However, the difference between groups after treatment was not significant [Table 5].

There was no statistically significant difference between the three studied groups regarding side effects of treatment [p>0.05] including nausea, vomiting, abdominal pain, abdominal distension, fatigue, epigastric pain, diarrhea, and constipation [Table 6]. The results of laboratory investigations after treatment showed non-significant differences between groups.

Table [1]: Patient characteristics and associated comorbid conditions among the study groups

Variables		Group I	Group II	Group III	Test	P
Gender [n, %]	Male	23[46.0%]	18[36.0%]	15[30.0%]	2.79	0.248
	Female	27[54.0%]	32[64.0%]	35[70.0%]		
Age [years]	Mean ± SD	29.12± 14.32#	32.44± 11.71	34.64± 13.83	6.758	**0.034***
	Median [IQR]	25.5 [19- 34]	32 [23- 41]	32 [24- 41]		
	Min. – Max.	12- 70	13- 57	12- 80		
Occupation [n, %]	Housewife	5[10.0%]	9[18.0%]	10 [20.0%]	8.22	0.222
	Retired	3 [6.0%]	1[2.0%]	3 [6.0%]		
	Student	19 [38.0%]	16 [32.0%]	8 [16.0%]		
	Worker	23 [46.0%]	24 [48.0%]	29 [58.0%]		
Residence [n, %]	Rural	39 [78.0%]	28 [56.0%]	33 [66.0%]	5.460	0.065
	Urban	11 [22.0%]	22 [44.0%]	17 [34.0%]		

Table [2]: Comparison between the studied groups regarding associated comorbid conditions

	Group I [n= 50]		Group II [n= 50]		Group III [n= 50]		Statistics	
	No.	%	No.	%	No.	%	Test	P-value
No	39	78.0%	39	78.0%	38	76.0%	0.076	0.963
DM	6	12.0%	5	10.0%	7	14.0%	0.379	0.827
HTN	10	20.0%	8	16.0%	6	12.0%	1.190	0.551
IHD	1	2.0%	3	6.0%	3	6.0%	1.199	0.549
CLD	0	0.0%	2	4.0%	2	4.0%	2.055	0.358
CKD	0	0.0%	1	2.0%	0	0.0%	2.013	0.365
Dyslipidemia	0	0.0%	0	0.0%	2	4.0%	4.054	0.132
Smoking	10	20.0%	12	24.0%	14	28.0%	0.877	0.645

DM: Diabetes Mellitus, HTN: Hypertension, IHD: Ischemic heart disease, CKD: chronic kidney disease, CLD: chronic lung disease

Table [3]: Comparison between the studied groups regarding clinical presentations

Main compliant	Group I [N= 50]		Group II [N= 50]		Group III [N= 50]		Chi-Square Test	
	No.	%	No.	%	No.	%	X^2	P-value
Epigastric pain	47	94.0%	22	44.0%	32	64.0%	**28.79**	**<0.001***
Heartburn	3	6.0%	11	22.0%	9	18.0%	5.341	0.069
Abdominal distention	2	4.0%	3	6.0%	0	0.0%	2.897	0.235
Reflux symptoms/ regurgitation	0	0.0%	3	6.0%	0	0.0%	**6.122**	**0.047***
Dyspepsia	0	0.0%	6	12.0%	5	10.0%	**6.082**	**0.048***
Nausea /Vomiting	0	0.0%	9	18.0%	14	28.0%	**15.508**	**<0.001***
Diarrhea	0	0.0%	1	2.0%	1	2.0%	1.014	0.602
Diarrhea alternative with constipation	0	0.0%	2	4.0%	1	2.0%	2.041	0.360
Fatigue	0	0.0%	0	0.0%	1	2.0%	2.013	0.365

Table [4]: Comparison between the studied groups regarding abdominal US

Abdominal ultrasound	Group I [N= 50]		Group II [N= 50]		Group III [N= 50]		Statistics	
	No.	%	No.	%	No.	%	Test	P
Normal	36	72.0%	25	50.0%	27	54.0%	15.197	0.365
Colonic gas distention	8	16.0%	16	32.0%	18	36.0%		
Mild hepatomegaly	3	6.0%	5	10.0%	3	6.0%		
Fatty liver	3	6.0%	5	10.0%	6	12.0%		
Renal cyst/gravels	5	10.0%	8	16.0%	3	6.0%		
Gall bladder mud/ stone	0	0.0%	1	2.0%	2	4.0%		
Ovarian cyst	0	0.0%	1	2.0%	1	2.0%		
Cirrhotic liver, splenomegaly, mild ascites	0	0.0%	2	4.0%	2	4.0%		

Table [5]: H. pylori antigen test before and after treatment in the studied groups

		H. pylori Ag				P-value
		Before treatment		After treatment		
		No.	%	No.	%	
Group I [n= 50]	Negative	0	0.0%	44	88.0%	**<0.001***
	Positive	50	100.0%	6	12.0%	
Group II [n= 50]	Negative	0	0.0%	46	92.0%	**<0.001***
	Positive	50	100.0%	4	8.0%	
Group III [n= 50]	Negative	0	0.0%	42	84.0%	**<0.001***
	Positive	50	100.0%	8	16.0%	
Test value [X^2]		-		1.515		
P-value		-		0.469		

* indicates significant difference

Table [6]: Comparison between the studied groups regarding side effects of treatment

Side effects of treatment	Group I [N= 50]		Group II [N= 50]		Group III [N= 50]		Statistics	
	No.	%	No.	%	No.	%	Test	P-value
None	34	68.0%	30	60.0%	37	74.0%	2.243	0.326
Yes	16	32.0%	20	40.0%	13	26.0%		
Nausea	12	24.0%	8	16.0%	5	10.0%	2.243	0.326
Vomiting	4	8.0%	6	12.0%	2	4.0%	3.552	0.169
Abdominal pain	5	10.0%	5	10.0%	0	0.0%	5.357	0.069
Abdominal distension	0	0.0%	2	4.0%	4	8.0%	4.167	0.125
Fatigue	3	6.0%	5	10.0%	0	0.0%	5.018	0.081
Epigastric pain	0	0.0%	0	0.0%	2	4.0%	4.054	0.132
Diarrhea	2	4.0%	3	6.0%	1	2.0%	1.042	0.594
Constipation	1	2.0%	2	4.0%	0	0.0%	2.041	0.360

DISCUSSION

This study compares the efficacy of vonoprazan [a newer PPI]-based regimens with conventional PPIs in the eradication therapy of H. pylori infection. The main advantages of Vonoprazan are the stronger suppression of acid secretion and longer duration of action, when compared to older PPI. Results revealed that all the three regimens are effective for eradication of H. pylori. The vonoprazan-based [Triple regimen] showed the highest eradication rate [92%], followed by the PPI-based [triple regimen] [88.0%] and finally the vonoprazan-based [dual-regimen] [84%].

In accordance with the results of the current work, **Chey *et al.*** [10] reported that, both triple and dual therapy with the potassium-competitive acid blockers [e.g., vonoprazan] is an effective and safe treatment with higher rates of eradication even in clarithromycin-resistant H. pylori. The eradication rate vonoprazan-based triple therapy was 84.7%, for dual therapy was 78.5% and lansoprazole triple therapy was 78.8%. However, they differ than the current work in the superior eradication rate of vonoprazan- dual therapy than conventional PPI-based triple therapy. The fact that they included a higher number of patients may explain these differences. Interestingly, and in the same study, in clarithromycin-resistant H-pylori, the vonoprazan-based dual regimen was more effective than the triple regimen. This may be added to the explanation of the higher eradication rate for dual therapy in their study when compared to the current one.

Vonoprazan exerts its action on H+, K+-ATPase in parietal cells in an acid-independent way, providing a fast antisecretory effect for over 24 h [11]. Moreover, vonoprazan exhibited a superior acid suppression effect than conventional PPI, with faster and sustained acid-inhibitory effects [12]**.** The suppression of gastric acid and maintaining intragastric pH between 6 and 8 is essential for the optimal action of antibiotics [13]**.** Thus, the efficacy of vonoprazan-based triple or dual therapy may be due to the potent acid suppression and the related effectiveness of amoxicillin, limiting the impact of clarithromycin resistance [14].

In a recent systematic review and meta-analysis, **Malfertheiner *et al.*** [15] reported that, vonoprazan-based triple therapy approaches showed the highest efficacy than PPI-based triple therapy regardless of the PPI drug. These results are confirmed in the current study.

One study from Japan, showed that vonoprazan-based therapy had significantly higher eradication rate than those treated with conventional PPI [93.6% *versus* 79.7%; $p < 0.001$]. this study agrees with the current one in the superiority of vonoprazan-based than PPI-based therapy. However, the current study did not show significant differences. This could be related to a small sample of patients included in the current work [16]. In addition, **Rokkas *et al.*** [17] conducted a network meta-analysis to compare effectiveness of different treatment protocols for H. pylori. They concluded that vonoprazan-based triple therapy was the most effective regimen than the other 7 regimens, with a significantly higher eradication rate. Most recently, **Howden *et al.*** [18] patients treated for the first-time b vonoprazan-based triple therapy had a higher eradication rate with subsequent lower rates of H. Pylori infection, lower admissions, and lower overall cost than the PPI-based therapy although vonoprazan price is higher than the PPI. **Lyu *et al.*** [19] compared vonoprazan-based triple therapy to

PPI-based triple therapy and reported that, vonoprazan-based therapy is associated with higher eradication rates than PPI-based approaches [91.4% vs 74.8%, $p < 0.05$], with lower rates of adverse events in vonoprazan-based triple therapy.

Jung *et al.* [7] also concluded that, vonoprazan-based triple therapy was superior to PPI-based triple therapy in terms of H. pylori eradication. In addition, the vonoprazan-based triple approach had comparable tolerability and incidence of adverse events.

In accordance with the current work, **Tanabe *et al.*** [20] included a total of 1355 patients and the eradication rates of proton pump inhibitor-based and the vonoprazan-based therapy were 86.3% and 97.4%, respectively.

In the current work, patients in the vonoprazan-based regimen were significantly younger in age than other groups. This could explain the higher eradication rate in this group as reported in a previous study. **Kusunoki *et al.*** [21] reported that, vonoprazan had higher success rate of first-line eradication of H. Pylori. However, the advantage was reduced with aging. However, other researchers reported no effect of patient demographics on the eradication rate of H. Pylori with different treatment approaches [22, 23]. The abnormal distribution of age in the current study also mandates the cautious treatment of obtained results.

Conclusion: The current work confirmed the superiority of vonoprazan-based triple therapy over the conventional-PPI triple regimen and vonoprazan-based dual approach, with comparable side effects. However, the differences did not reach statistical significance. The small number of included cases in the current work represents one limiting step. Thus, future large-scale studies are recommended. This limiting step did not reduce the value of the current study as it is one of the earliest clinical trials addressing this issue, especially in our country, as most of the reported literature are from Japan, and Asian countries due to the higher rate of H. pylori infection in these countries.

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