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Research Article

Vonoprazan-Based Versus Esomeprazole-Based Triple Therapy for *Helicobacter pylori*: A Randomized Trial

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ABSTRACT

Background: Vonoprazan is indeed a potassium-competitive acid blocker that exhibits acid inhibiting effects that are more powerful and longer-lasting than those produced by Proton Pump Inhibitors (PPIs).

Aim and objective: To compare between the effectiveness of two 14-day regimens; one based on vonoprazan and the other on esomeprazole, to eradicate *H. pylori*.

Patients and methods: This randomized clinical trial was performed at minia university hospital. Participants who were determined to have active *H. pylori* infection and were either untreated or had previously received therapy were randomly assigned to either the VAL group (vonoprazan 20 mg bid, amoxicillin 1000 mg bid, plus levofloxacin 500 mg once day) or the EAL group (Esomeprazole 20 mg bid., amoxicillin 1000 mg bid., and levofloxacin 500 mg once daily). After 4-6 weeks following the end of the therapy, an *H. pylori* antigen test was used to determine the degree of eradication.

Results: A total of 122 individuals were randomly assigned to either the VAL (n=61) or EAL (n=61) groups. The eradication rates of *H. pylori* were found to be 97.7 percent for the VAL group and 68.5 percent for the EAL group, respectively (P=0.031). Adverse treatment-related occurrences were minor and did not differ substantially between the two groups.

Conclusions: The VAL regimen was well tolerated and led to increased eradication rates; as a result, VAL may be thought of as a powerful regimen for treating *H. pylori*, particularly in nations with high levels of antibiotic resistance

Keywords: *H. pylori*; Therapy; Antibiotic resistance; Infection; Treatment; Gram-negative

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram-negative, microaerophilic bacterium that is found on the gastrointestinal mucosa including well over half of the world's population [1]. Infection with *H. pylori* often begins in infancy and lasts a lifetime if medication is not used to treat it [2]. Most affected individuals go for a very long time without exhibiting any symptoms [2]. Infection with *H. pylori* over an extended period of time may cause damage to the mucosa of the stomach, and that it is the primary form of persistent gastritis, gastric ulcers, duodenal ulcers, gastric adenocarcinoma, including gastric mucosa-associated lymphoid tissue lymphoma [2,3].

The most crucial element in eliminating *H. pylori* is medication adherence. It is affected by a number of variables, including the complexity and length of the therapy, any adverse effects, the willingness of the patient, the patient's educational level and socioeconomic status, and the physician's motivation [4-6].

According to current study on *H. pylori* treatment, the typical triple therapy that lasts for seven days has consistently been the treatment plan that is used most often in the Asia-Pacific region. The majority of medical professionals in Taiwan, Japan, and Korea have opted to start treatment for *H. pylori* infections with either a 7-day or 14-day course of standard triple therapy (62% and 21%, 100% and 0%, and 81% and 7%, respectively). Antibiotic resistance, on the other hand, is growing increasingly widespread around the globe, and the majority of nations now have triple therapy eradication rates

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that are lower than 80 percent [7,8]. Notwithstanding the fact that a large number of newly invented first-line treatments, including such bismuth quadruple therapy as well as non-bismuth quadruple (sequential, concomitant, as well as hybrid therapy), can increase the rate of eradication of *H. pylori* infection, eradication failure still occurs in anywhere from 3 percent to 24 percent of infected patients [9,10].

Potassium-Competitive Acid Blockers (P-CABs), such as vonoprazan, are a good alternative since they are more effective and have the advantage of fast onset of action, dose-dependent effects, and long-lasting at inhibiting the production of acid than PPIs [11]. A P-CAB for acid inhibition is called vonoprazan [12]. In comparison to PPIs, vonoprazan sustains a greater intragastric pH that lasts through 24 hours of daily dosing, this is because it acts by binding reversibly to K^+ ions and block the H^+, K^+ ATPase enzyme [13,14]. Contrary to PPIs, it is mostly metabolised by Cytochrome P450 (CYP) 3A4 and is not impacted by *CYP2C19* polymorphism [12]. Vonoprazan is anticipated to increase *H. pylori* eradication rates in comparison to traditional PPI-based treatments since substantial acid inhibition throughout therapy is essential for *H. pylori* eradication. Additionally, it has been proposed that vonoprazan's more effective acid control may enable shorter *H. pylori* treatment durations and potentially circumvent the widespread antibiotic resistance [15,16].

Levofloxacin has an excellent safety data, making it easier for doctors to utilise it in clinical settings [17]. Additionally, it is often well tolerated, and the majority of adverse reactions are mild to moderate in degree and brief [18]. Numerous studies conducted in Egypt revealed that levofloxacin-based triple treatment resulted in a greater percentage of *H. pylori* infection eradication (84.5% vs. 69.00%) in patients than clarithromycin-based triple therapy [18,19]. Due to this disparity, one may come to the realisation that the levofloxacin-based triple treatment is superior than the clarithromycin-based therapy in regards to eradicating *H. pylori* infection. The lower eradication rate of clarithromycin based triple therapy indicate much higher clarithromycin resistance in our region, and the eradication rate of standard levofloxacin based triple therapy is less satisfactory for our patients infected with *H. pylori*.

To date, no randomised trial has compared the efficacy of VAL regimen (vonoprazan 20 mg bid, amoxicillin 1000 mg bid, and levofloxacin 500 mg once day for 14 days) with that of the EAL regimen (Esomeprazole 20 mg bid., amoxicillin 1000 mg bid., and levofloxacin 500 once daily. for 14 days). It is possible that the vonoprazan-based regimen is a preferable choice for treating *H. pylori* since it has the potential to either increase or sustain the eradication rate, in addition to becoming more well-liked by patients. In order to evaluate the effectiveness and safety of the VAL and EAL regimens, we developed this randomised clinical study

MATERIALS AND METHODS

Study population

The gastrointestinal clinic in Minia, Egypt, performed this prospective, open-label, randomised controlled trial. The study protocol was approved by the local ethical committee. Individuals with *H. pylori* infection that were above the age of 18 and who had never previously received treatment or medication to eradicate the infection were eligible to participate in the study. The diagnosis of *H. pylori* infection was made after *H. pylori* infection was found in the stool using an Antigen (Ag) test as well as a histopathologic analysis of gastric samples collected during an endoscopy of the upper gastrointestinal tract. All the pateints offered to take biopsy samples from at least four distinct places (two antrum and two bodies).

In order to narrow the pool of candidates for participation in the research, the following criteria were used as exclusions: (i) History of an allergy to esomeprazole, vonoprazan, penicillin, or levofloxacin; (ii) History of substance abuse or existing alcohol abuse; (iii) Use of an antibiotic that affects *H. pylori* within the past 4 weeks; (iv) Pregnancy as well as lactation; (v) Significant cardiovascular, pulmonary, or renal, as well as active malignancy; (vi) Surgery for just a gastric or duodenal; (vii) Cirrhotic patients were excluded, since in patients with severe hepatic impairment, the metabolism of esomeprazole is decreased leading to a doubling of the AUC.

Randomization and procedures

The eligibile patients were randomised to either the VAL group (vonoprazan 20 mg bid, amoxicillin 1000 mg bid, and levofloxacin 500 mg once day for 14 days) or the EAL group (Esomeprazole 20 mg bid., amoxicillin 1000 mg bid., and levofloxacin 500 once daily. for 14 days). After giving their written informed consent, patients were instructed to follow their prescribed regimens and advised about any possible side effects. Patients provided information on their age, sex, history of smoking, history of drinking alcohol, coffee, and tea, history of using Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), and history of concurrent illnesses in addition to completing a standard questionnaire for demographic data and medical history. During treatment, follow up of the patients to study their compliance to treatment; good compliance was defined as consuming at least 80% of the advised dosage.

At the end of the two weeks, they went back to the clinic to evaluate medication compliance, adverse events, and side effects. The surveys asked about possible adverse effects, which included nausea, vomiting, bitter taste, skin rash, bloating, headaches, dizziness, and stomach discomfort. The term "treatment-related side effects" was used to describe symptoms that appeared over the course of the therapy or that became worse. Serious occurrences were defined as side effects that were severe enough to interfere with patients' regular daily activities and need hospitalisation. Patients had to have a negative *H. pylori* stool Ag test and be symptom-free six weeks after starting therapy in order to be deemed clinically cured. Failure to achieve any of these objectives was seen to constitute therapy failure.

Urine sample collection

Urine was collected from a healthy 6-year-old male neutered Great Dane using clean technique. An 8-Fr red rubber catheter was inserted transurethrally after cleaning the extruded penis with surgical scrub and sterile saline, and 60 mL of urine was obtained. The urine was stored in sterile culture tubes, and a sample was submitted to the University of Georgia (UGA) Diagnostic Laboratory to prove sterility (absence of bacterial organisms). The urine was then aliquoted into 25 cryotubes (Cryogenic vials,

Corning), containing 1.5 mL of urine each.

End points

In order to define the primary objective, this would have been the complete eradication of *H. pylori* infection. The occurrences of any and all adverse events, as well as patient compliance with the medication, have been the secondary objectives.

Statistical analysis

The estimated size of sample was determined to be consistent with past investigations. The eradication rate for Vonoprazan-Based Triple Treatment (VAL) was 97 percent, whereas the eradication rates for Esomeprazole-Based Combination Therapy (EAL) were 68.5 percent. Our anticipated sample size for each group was 50, with an 80 percent power, a 95 percent degree of confidence, and a 20 percent follow-up loss rate. A total sample size of more than 120 patients was necessary, according to the calculation. According to procedure, the data were evaluated for intention-to-treat and per protocol. The 2 test was used to assess statistical variances in eradication rates across different regimens. A P-value of 0.05 or lower was considered statistically significant when comparing the demographic information and the frequencies of adverse responses using either the 2 test or Fisher's exact test, depending on which was most applicable. SPSS statistics were used in the performance of the statistical analysis.

RESULTS AND DISCUSSION

Characteristics of the study groups

122 participants with active *H. pylori* infections were enrolled and were given a random assignment to undergo either the VAL or EAL regimen. There were a total of 122 participants in the study. All 122 patients enrolled in the study finished the study, therefore both intention-to-treat and per-protocol analyses results were similar. The starting characteristics of the two groups did not vary significantly from one another in any way (Table 1). In both of the patient groups, every patient followed their drug regimens to a higher degree than 80 percent.

Table 1: The individuals baseline characteristics for the two therapy groups.

Characteristics	VAL group (n=61)	EAL group(n=61)	P-value
Male gender, n (%)	27 (44.2%)	30 (49.1%)	0.384
Age (years), mean ± SD	55.31 ± 12.4	54.89 ± 14.25	0.367
BMI (kg/m2), mean ± SD	25.23 ± 3.76	27.35 ± 5.13	0.251
Smoking>1 pack/week, n (%)	9 (14.7%)	8 (13.1%)	0.291
Alcohol>1 day/week, n (%)	0 (0%)	0 (0%)	1
Underlying disease			
Cardiovascular disease, n (%)	2 (3.2%)	7 (11.4%)	0.062
Diabetes mellitus, n (%)	13 (21.3%)	15(24.5%)	0.352
Hypertension, n (%)	17 (27.8%)	20 (33.3%)	0.457
Dyslipidemia, n (%)	7 (11.4%)	9 (15%)	0.621
Cerebrovascular disease, n (%)	0 (4.9%)	1 (1.6%)	0.987
Connective tissue disease, n (%)	3 (4.9%)	5 (8.2%)	0.621
Other, n (%)	7 (11.4%)	5 (8.2%)	0.356
Endoscopic findings			
Non-erosive gastritis, n (%)	21 (34.4%)	17 (27.8%)	0.323
Erosive gastritis, n (%)	26 (42.6%)	27(44.2%)	0.785
Atrophic gastritis, n (%)	7 (11.4%)	5 (8.2%)	0.296
Gastric or duodenal ulcer, n (%)	11 (18.03%)	17 (27.8%)	0.076

Note: EAL group received therapy with esomeprazole, amoxicillin, and levofloxacin for 14 days; VAL group received treatment with vonoprazan, amoxicillin, and levofloxacin; Body mass index, or BMI.

Eradication of *H. pylori*

The results of the study revealed that elimination rates in the VAL group reached 97.7%, but the eradication levels in the EAL group were only 68.5%. These eradication rates tended to be greater in the VAL group as compared to the EAL group, and there was a statistically significant difference between the two groups.

Side effects of treatment

Without any statistically significant differences, both groups often complained of nausea and dizziness. The reported adverse effects are shown in Table 2. There were no significant variations inside the side effects between both the two groups. There were no significant side effects or adverse occurrences that led individuals to stop getting medication.

Table 2: Treatment side effects.

	VAL group (n=61)	EAL group (n=61)	P-value
Nausea, n (%)	8 (13.1%)	7 (11.4%)	0.417
Vomiting, n (%)	1 (1.6%)	0 (0%)	0.315
Bitter taste, n (%)	1 (1.6%)	0 (0%)	0.315
Skin rash, n (%)	2 (3.2%)	1 (1.6%)	0.418
Bloating, n (%)	5 (8.2%)	2 (3.3%)	0.243
Dizziness, n (%)	7 (11.5%)	9 (14.8%)	0.592
Headache, n (%)	1 (1.6%)	0 (0%)	0.315
Diarrhea, n (%)	7 (11.5%)	3 (4.9%)	0.187
Constipation, n (%)	3 (4.9%)	3 (4.9%)	1

Abdominal pain, n (%)	4 (6.55%)	7 (11.5%)	0.267
Dry mouth or throat, n (%)	2 (3.2%)	1 (1.6%)	0.418
Others, n (%)	3 (4.9%)	2 (3.3%)	0.648

Note: EAL group received therapy with esomeprazole, amoxicillin, and levofloxacin for 14 days; VAL group received treatment with vonoprazan, amoxicillin, and levofloxacin; Not relevant, N/A.

The efficacy of treatments aimed at eradicating *H. pylori* has already been steadily declining around the world. The key factors contributing to the failure of these treatments are noncompliance with medication regimens and the development of antibiotic resistance in *H. pylori*. The eradication rates of *H. pylori* have been the subject of study into a great number of different approaches. As a secondary treatment for *H. pylori*, the Maastricht V/Florence Consensus Report suggests amoxicillin-fluoroquinolone triple or quadruple therapy [20]. Since *H. pylori* has a low degree of in vivo antibiotic sensitivity, changing or adding antibiotics is also one of the fundamental treatments; nevertheless, doing so may increase treatment toxicity, antibiotic resistance, dysbiosis of the gut microbiota, and make the regimen more complicated. Numerous studies revealed ineffectiveness of fluoroquinolone-containing triple therapy [21,22]. In comparison to standard triple therapy involving clarithromycin; PPI levofloxacin-amoxicillin triple therapy had a cure rate of 76%, according to a meta-analysis of randomised controlled trials [23].

In the present study, we modified a 14-day PPI-based triple therapy, by replacing esomeprazole with a more potent acid inhibitor, vonoprazan, in the belief that a regime that is easy to comply with (all drugs are after meals) would significantly increase patient compliance [24]. The best time to take esomeprazole is 30 minutes before eating or drinking on an empty stomach, according to extensive research [24]. As the clarithromycin is avoided in our regimen, the treatment-related side effects are reduced, and accordingly the patient compliance is raised and thus the success rate of *H. pylori* eradication is increased.

Our VAL treatment plan was extremely successful, and the outcomes of the research demonstrate that there was a statistically significant tendency towards greater eradication rates inside the VAL group than the EAL group. Our result of a greater eradication rate with Vonoprazan (VAL) treatment as opposed to an esomeprazole therapy has a variety of pharmacological reasons. First of all, vonoprazan suppresses acid secretion more strongly and consistently than PPI [25]. In contrast to esomeprazole, it is superior because it is able to maintain the pH of the stomach at a level greater than 5 for nine out of every ten hours [26]. Most of the studies on esomeprazole revealed that it can maintain the intragastric pH more than 4, which is lower than that intragastric pH obtained by vonoprazane [27]. Therefore, vonoprazan therapy is considerably more likely than PPI therapy to improve the concentration and stability of amoxycillin and levofloxacin in the gastric mucosa because the effectiveness and duration of acid suppression are essential components of antibiotic transport into the gastric mucosa [28].

Furthermore, prior studies have demonstrated that a pH range of 6-8 may be the ideal pH for *H. pylori* eradication therapy because this range both increases the bacteria's potential for reproduction and increases the bactericidal effects of growth-dependent antibiotics [29]. To get the same level of acid-inhibiting effect as other Proton Pump Inhibitors (PPI), esomeprazole must first be taken for a minimum of five to six doses. This must be maintained throughout the duration of *H. pylori* therapy. Vonoprazan, however, has a substantially faster onset to attain its peak acid-inhibitory activity, probably after the first dosage [30]. Thirdly, unlike the drug esomeprazole, the *CYP2C19* polymorphism of vonoprazan has no effect on its pharmacokinetic characteristics [23,25]. Accordingly, the *CYP2C19* polymorphism status has no impact on vonoprazan's ability to inhibit acids [31,32].

In comparison to PPIs, vonoprazan had a higher proportion of *H. pylori* eradication, according to a study by Kiyotoki, et al. The *H. pylori* eradication rate was nearly 90% when using vonoprazan-based triple therapy (vonoprazan, amoxicillin, and clarithromycin) [33].

It was shown that vonoprazan-containing antibiotic therapy is a successful method of *H. pylori* eradication in a single-center, exploratory clinical study of patients 18 years of age or older who tested positive for the infection. It can achieve 100% success in patients receiving its first treatment and even 91% efficacy in those who have previously had eradication failure [34].

In our study, nausea was the most common side effect, and all other treatment-related adverse effects were minor and underreported for both groups, and the incidence and severity of problems were similar between the two groups, with medication compliance rates in both groups over 80%. The combination of high eradication rate for *H. pylori* (97.7%), associated by compliance rate over 80%, and minor treatment-related adverse effects is an interesting finding. This association may be explained by the use of levofloxacin instead of clarithromycin, which is associated by more adverse effects, also the extensive instructions, encouragement, and cautions regarding adverse effects that patients got from their physicians may contribute to the higher compliance rate in our study.

Our study has some limitations, firstly the urea breath yest was not used in our study because of unavailability in our locality. Secondly, we are unable to determine the exact cause of therapeutic failure of the VAL group, including whether it was caused by inadequate acid suppression, antibiotic resistance, or other factors. It's because we did not assess the prevalence of *CYP2C19* polymorphism and antimicrobial resistance within sample population. And first foremost, because of this, we are unable to determine the exact cause of treatment failure. Thirdly, despite the fact that this research was carried out in a single clinic in Egypt, it is possible that there are regional differences in the patterns of antibiotic resistance seen in *H. pylori* or other important characteristics. These regional differences may have an effect on how successfully the treatment strategy works. To compare the eradication rates, larger, multicenter trials including susceptibility testing are required. Last but not least, we tried to minimise bias in open-label trial designs by employing randomization and precise measurement of the major results.

CONCLUSION

These regional differences may have an effect on how successfully the treatment strategy works. To compare the eradication rates, larger, multicenter trials including susceptibility testing are required. Last but not least, we tried to minimise bias in open-label

trial designs by employing randomization and precise measurement of the major results. In summary, this trial demonstrated that vonoprzan-based triple treatment was well tolerated and produced much greater eradication rates for *H. pylori* infection than did triple therapy based on esomeprazole. As a result, VAL may be seen of as a powerful therapy regimen for *H. pylori*, particularlyin nations with high levels of antibiotic resistance.

CONFLICT OF INTEREST

None.

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