ORIGINAL ARTICLE

Therapeutic efficacy and drug safety comparison of one-week Vonoprazan triple therapy with two-weeks Esomeprazole triple therapy in *Helicobacter pylori* infection: Findings from a single-centre randomized clinical trial in population of Pakistan

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Abstract

Objective: To compare the therapeutic efficacy and drug safety of Vonoprazan and Esomeprazole triple therapies in Helicobacter pylori infection.

Method: The randomised clinical trial was conducted from December 2022 to January 2023 at the Department of Pharmacology, Army Medical College, National University of Medical Sciences, Rawalpindi, Pakistan, in collaboration with the Gastroenterology Department of Pak Emirates Military Hospital, Rawalpindi, and comprised patients found positive for Helicobacter pylori by stool antigen test. They were randomly distributed into two groups. The EAL group received two-week triple therapy with Esomeprazole 20mgand Amoxicillin 1000mg twice daily with Levofloxacin 500mg once daily. The VAL group was prescribed one-week triple therapy with Vonoprazan 20mg and Amoxicillin 1000mg twice daily with Levofloxacin 500mg once daily. Eradication success was evaluated by stool antigen test 4 weeks after starting the treatment. Safety of the therapy was assessed by noting adverse effects at days 3 and 14 of the treatment. Data was analysed using SPSS 27.

Results: Of the 122 patients, there were 61(50%) in each of the 2 groups; 30(49.2%) males and 31(50.8%) females with mean age 38.40±12.25 years in group EAL, and 35(57.4%) males and 26(42.6%) females with mean age 40.98±12.13 years in VAL group. In the EAL group, 57(93.4%) patients were found to be free of Helicobacter pylori infection compared to 58(95%) in the VAL group. Nausea 14(23%), bitter taste 41(67.2%), abdominal pain 16(26.2%) and headache 20(32.8%) were the adverse effects that were significantly more common in the EAL group compared to the VAL group B.

Conclusion: Vonoprazan-based triple therapy was found to be more effective with less reported adverse effects and potential benefits of better patient compliance due to shorter therapy duration.

Clinical Trial Number: Iranian Registry of Clinical Trials: IRCT20221207056738N1.

Keywords: Helicobacter pylori, Eradication, Vonoprazan, Esomeprazole, Levofloxacin. (JPMA 74: 432; 2024)

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Introduction

Helicobacter (H.) pylori, found predominantly in the antrum and other regions of the stomach, was originally identified in 1982.[1] This gram-negative bacteria, transmitted to humans by the orofecal route, is the underlying cause of a number of gastrointestinal (GI) disorders, such as peptic ulcer disease, gastritis and adenocarcinoma stomach cancer.[2] It is recommended that the infected patients should be given eradication treatment.[3] First-line drugs in the therapy comprises two antibiotics and one acid inhibiting drug aimed at eradicating the bacteria and prevent complications. The conventional regimen globally used was Omeprazole, Amoxicillin and Clarithromycin (OAC) for two weeks. Global literature in last decade reported lower *H. pylori* eradication rates (<80%), with Clarithromycin resistance in European and Asian countries.[4] International recommendations advise using four-medication, bismuth-based combination therapies as first-line agents in regions with significant levels of Clarithromycin resistance, but global data with quadruple regimen reported lower levels of patients compliance due to increased drug burden and side effects.[5] Antimicrobial resistance, efficacy of acid suppressors to maintain the desired potential of hydrogen (pH), virulent genes, and environmental exposure, like smoking, are the factors that influence the success of anti-*H. pylori* therapy.[6]

Worldwide prevalence of infections with *H. pylori* is between 10% and 90% of the population, and South Asian countries,[7] including Pakistan, have significant a burden of disease due to patients with less educated background, increasing age group, lower socioeconomic status (SES),

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and poor hand hygiene and sanitation practices. Local research in Pakistan reported *H. pylori* prevalence of 92%. The Pakistani population's disability adjusted life years (DALYs) for peptic ulcer was 0.1 million lower than the bordering countries of China (0.8) and India (1.9), but higher than Iran (0.03).[6]

Current treatment guiding principle for *H. pylori* eradication recommends Vonoprazan-based triple therapy for one-week duration as an alternative to proton pump inhibitor (PPI) for rapid eradication rate, patient's recovery from symptoms and quality of life (QOL) improvement.[8] The maximum efficacy in Asia was found in a 7-day Vonoprazan-based combination therapy reported in a meta-analysis. Vonoprazan, which is a potassium-competitive acid blocker (P-CAB), inhibits the binding of potassium ion to H^+-K^+ P-type adenosine triphosphatase (ATPase) pump in a reversible manner. Vonoprazan's pharmacokinetics exhibit time-dependent characteristics, resulting in sustained concentrations lasting 3-4 days, and an extended action beyond 24 hours. Therefore, it has more pronounced acid inhibition, quick onset of action, more potent effect due to its stability in acidic medium and longer duration of action in contrast with PPI.[9,10] Vonoprazan's effectiveness in eradicating *H. pylori* in comparison to PPI has not been the target of researchers in Pakistan. The current study was planned to compare the therapeutic efficacy and safety of one-week Vonoprazan with two-week Esomeprazole triple therapy in *H. pylori* infection.

Patients and Methods

The single-centre, prospective, open-labelled, randomised clinical trial, was registered with Iranian registry of clinical trials: IRCT20221207056738N1. It was conducted at the Department of Pharmacology, Army Medical College (AMC), National University of Medical Sciences (NUMS), Rawalpindi, in collaboration with the Gastroenterology Department of Pak Emirates Military Hospital (PEMH), Rawalpindi, from December 2022 to January 2023. After approval from the institutional ethics review committees, the sample size was calculated using the World Health Organisation (WHO) calculator[11] with 95% confidence interval (CI), 7% absolute precision and reported prevalence of *H. pylori* infection in line with literature.[12]

The sample was raised using non-probability purposive sampling technique. Those included were patients of either gender aged >18 years with dyspepsia symptoms and positive for *H. pylori* by stool antigen test. Those with allergy to the medicines used in triple therapies, history of previous *H. pylori* eradication therapy, pregnancy, lactation, history of serious cardiovascular, renal, liver disease, gastric malignancy or surgery, and a history of drug addiction were excluded.

After taking written informed consent from the enrolled patients, they were randomly distributed into two groups through computer-generated blocks. The EAL group received two-week triple therapy with Esomeprazole 20mg and Amoxicillin 1000mg twice daily with Levofloxacin 500mg once daily, while the VAL group was prescribed one-week triple therapy with Vonoprazan 20mg and Amoxicillin 1000mg twice daily and Levofloxacin 500mg once daily.

Demographic details, age, height and weight were recorded at baseline. At days 3 and 14, an assessment of the patient for occurrence of any of the enlisted side effects, including nausea, vomiting, bitter taste, diarrhoea, abdominal pain, headache and dizziness, was done over the telephone. Eradication success was evaluated by stool antigen test at 4 weeks after starting the treatment.

Data was analysed using SPSS 27. For quantitative statistics, mean and standard deviation were calculated, whereas frequencies and percentages were computed for qualitative data. Chi-square test was applied to assess the significance level. $P \leq 0.05$ was considered statistically significant.

Results

Of the 138 patients assessed, 122(88.4%) were included (Figure). There were 61(50%) patients in each of the 2 groups; 30(49.2%) males and 31(50.8%) females with mean age 38.40±12.25 years in EAL group, and 35(57.4%) males and 26(42.6%) females with mean age 40.98±12.13 years in VAL group. The mean body mass index (BMI) of patients was 24.19±6.69 kg/m^2 in EAL group and 23.93±4.01kg/m^2 in VAL group.

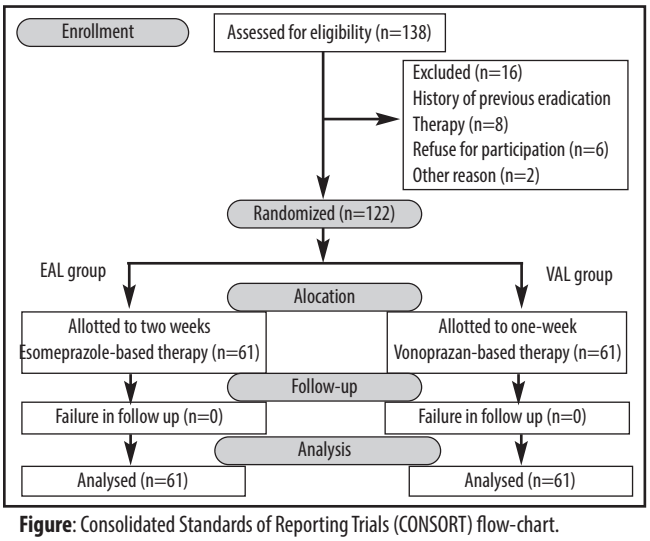

Figure: Consolidated Standards of Reporting Trials (CONSORT) flow-chart.

Table-1: Comparison of Helicobacter (H.) pylori eradication between Vonoprazan and Esomeprazole regimens.

Stool antigen test result	Vonoprazan triple therapy (n=61) [n (%)]	Esomeprazole triple therapy (n=61) [n (%)]	*p*-value
Positive	03(5.0)	04(6.6)	0.69
Negative	58(95.0)	57(93.4)	

Table-2: Comparison of Adverse Effects between Vonoprazan and Esomeprazole regimens.

Adverse effects	Vonoprazan triple therapy (n=61) [n (%)]	Esomeprazole triple therapy (n=61) [n (%)]	*p*-value
Nausea	6 (9.8)	14 (23.0)	0.05
Vomiting	01(1.6)	01 (1.6)	1.00
Bitter taste	16 (2.2)	41 (67.2)	<0.001
Diarrhoea	03 (4.9)	06 (9.8)	0.29
Abdominal pain	1 (1.6)	16 (26.2)	<0.001
Dizziness	12 (19.7)	20 (32.8)	0.10
Headache	5 (8.2)	20 (32.8)	<0.001

In EAL group, 57(93.4%) patients were found to be free of *H. pylori* infection 4 weeks since the start of the treatment compared to 58(95%) in VAL group (Table 1).

Nausea 14(23%), bitter taste 41(67.2%), abdominal pain 16(26.2%) and headache 20(32.8%) were the adverse effects that were significantly more common in EAL group compared to VAL group B ($p<0.05$), vomiting was found in 1(1.6%) patients in both groups, while all other symptoms were less frequent in VAL group compared to EAL group even if the difference was not significant (Table 2).

There were no adverse effects that required any patient in either group to stop receiving treatment or need hospitalisation. All side effects were self-cured without medical intervention.

Discussion

In the current study, Vonoprazan demonstrated better efficacy with improved eradication rate and less adverse effects in comparison with the conventional regimen, suggesting that potent acid inhibiting drug combination therapy must be prescribed to achieve the highest eradication rate.[13] The use of Levofloxacin with single dosing replacing Clarithromycin is beneficial in the selection of best treatment regimens for the cure of *H. pylori*, especially in the wake of rising antimicrobial resistance to Clarithromycin.[14] The guidelines in Japan suggested prescribing triple therapy with Vonoprazan for quick eradication.[15] The current study showed eradication rate of 95% with Vonoprazan regimen compared to 93.4% with Esomeprazole.

Ang et al. in Singapore compared one-week Vonoprazan-based triple therapy with two-week PPI-based triple therapy, using Clarithromycin and Amoxicillin two times a day. The current study replaced Clarithromycin with single-dose Levofloxacin. The earlier study had shown 96.3% eradication rate with Vonoprazan compared to 94% with the PPI-based regimen.[16] The current results are in line with the earlier findings that were based on a longer trial with double the sample size compared to the current study. Other international meta-analysis of clinical trials of the same drugs also reported better or similar eradication rates of *H. pylori* with Vonoprazan therapy.[17] Lyu et al., in their meta-analysis, found that Vonoprazan therapy was more effective. This meta-analysis included three studies performed in different locations in Japan. Total eradication rate was 91.4% in Vonoprazan-based therapies, and 74.8% in Omeprazole-based regimen.[18] In the said meta-analysis, the three studies used 750mg Amoxicillin and 200mg or 400mg Clarithromycin twice a day, with 20mg Vonoprazan. The wide varying eradication percentages of the three studies in the meta-analysis compared to the current study can be partly attributed to the difference in the duration of both the therapies and partly to changed pharmacological antibiotic agents.[18]

Li et al. reported similar efficacy of both regimens.[19] Tanabe et al. demonstrated that Vonoprazan had exceptionally better eradication rate of 91.5% compared to 79.4% for the PPI group.[20] Higher dose of Amoxicillin and replacement of Clarithromycin with Levofloxacin in the current study might be an explanation for better eradication rate.

In the current study, the adverse effects were more common in patients taking Esomeprazole triple therapy in comparison with those on Vonoprazan triple therapy, and no dropout was observed in either group. Global research has also documented therapeutic safety and low dropout rate of Vonoprazan compared to PPIs.[21] Maruyama et al. reported non-significant ($p=0.15$) difference in terms of side effects between the groups,[22] while the current study found the prevalence of nausea, headache, bitter taste and abdominal pain significantly less in Vonoprazan group.[22] Huang and Lin in a randomised trial in Chinese population assessed efficacy of Vonoprazan triple therapy and quadruple therapy in comparison with Esomeprazole quadruple therapy with two-week duration,[23] and recorded individual side effects in the three groups. Vonoprazan triple therapy proved the safest. Lyu et al. also confirmed lesser adverse effects with Vonoprazan tiple therapy compared to PPI therapy.[18]

The current study has limitations. Due to time and resource constraints, the study was conducted at a single centre with a small sample size. The study used stool antigen as the sole laboratory parameter to assess the efficacy of the therapies. The study could not involve histopathological assessment

of gastric mucosa due to limited resources and reluctance for the procedure on the part of the patients.

Multi-centre trials with relatively larger sample sizes also including histopathological tools should be conducted so that strong evidence regarding specific treatment regimen's effectiveness may be obtained for best practice interventions in clinical management of the disease.

Conclusion

Vonoprazan-based triple therapy was more effective and had less adverse effects than Esomeprazole-based therapy.

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Conflict of Interest: None.

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References

1. Muhammad JS, Zaidi SF, Sugiyama T. Epidemiological ins and outs of helicobacter pylori: a review. J Pak Med Assoc 2012;62:955-9.
2. Chey WD, Mégraud F, Laine L, López LJ, Hunt BJ, Howden CW. Vonoprazan Triple and Dual Therapy for Helicobacter pylori Infection in the United States and Europe: Randomized Clinical Trial. Gastroenterology 2022;163:608-19. doi: 10.1053/j.gastro.2022.05.055.
3. Wang D, Guo Q, Yuan Y, Gong Y. The antibiotic resistance of Helicobacter pylori to five antibiotics and influencing factors in an area of China with a high risk of gastric cancer. BMC Microbiol 2019;19:152. doi: 10.1186/s12866-019-1517-4.
4. Kuo YT, Liou JM, El-Omar EM, Wu JY, Leow AHR, Goh KL, et al. Primary antibiotic resistance in Helicobacter pylori in the Asia-Pacific region: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2017;2:707-15. doi: 10.1016/S2468-1253(17)30219-4.
5. Kim SG, Jung HK, Lee HL, Jang JY, Lee H, Kim CG, et al. Guidelines for the diagnosis and treatment of Helicobacter pylori infection in Korea, 2013 revised edition. J Gastroenterol Hepatol 2014;29:1371-86. doi: 10.1111/jgh.12607.
6. Kamani L, Ahsan M, Butt N, Luxmi S, Khan JUA, Khan E, et al. Helicobacter Pylori Management Guidelines from Pakistan. J Pak Med Assoc 2022;72(Suppl 2):s1-11.
7. Zamani M, Ebrahimtabar F, Zamani V, Miller WH, Alizadeh-Navaei R, Shokri-Shirvani J, et al. Systematic review with meta-analysis: the worldwide prevalence of Helicobacter pylori infection. Aliment Pharmacol Ther 2018;47:868-76. doi: 10.1111/apt.14561.
8. Abadi ATB, Ierardi E. Vonoprazan and Helicobacter pylori Treatment: A Lesson From Japan or a Limited Geographic Phenomenon? Front Pharmacol 2019;10:e316. doi: 10.3389/fphar.2019.00316.
9. Hu Y, Zhu Y, Lu NH. The management of Helicobacter pylori infection and prevention and control of gastric cancer in China. Front Cell Infect Microbiol 2022;12:e1049279. doi: 10.3389/fcimb.2022.1049279.
10. Shehryar M, Ahmad RU, Kareem HK, Khan L, Ashraf MF, Hassan A. et al. Efficacy, safety and cost-effectiveness of vonoprazan vs Proton Pump Inhibitors in reflux disorders and H. pylori eradication: A literature review Ann Med Surg (Lond) 2022;82:e104760.
11. World Health Organization (WHO). Sample size determination : a user's manual. Geneva, Switzerland: World Health Organization; 1986. [Online] 1986 [Cited 2024 January 18]. Available from URL: https://policycommons.net/artifacts/509820/sample-size-determination/1485782/
12. Khoder G, Muhammad JS, Mahmoud I, Soliman SSM, Burucoa C. Prevalence of Helicobacter pylori and Its Associated Factors among Healthy Asymptomatic Residents in the United Arab Emirates. Pathogens 2019;8:44. doi: 10.3390/pathogens8020044.
13. Cho JH, Jin SY. Current guidelines for Helicobacter pylori treatment in East Asia 2022: Differences among China, Japan, and South Korea. World J Clin Cases 2022;10:6349-59. doi: 10.12998/wjcc.v10.i19.6349.
14. Latif S, Akther N, Amjed S, Jafar J, Saleem B, Usman M. et al. Efficacy of standard triple therapy versus Levofloxacin based alternate therapy against Helicobacter pylori infection. J Pak Med Assoc 2018;68:1295-9.
15. Jung YS, Kim EH, Park CH. Systematic review with meta-analysis: the efficacy of vonoprazan-based triple therapy on Helicobacter pylori eradication. Aliment Pharmacol Ther 2017;46:106-14. doi: 10.1111/apt.14130.
16. Ang D, Koo SH, Chan YH, Tan TY, Soon GH, Tan CK, et al. Clinical trial: seven-day vonoprazan- versus 14-day proton pump inhibitor-based triple therapy for first-line Helicobacter pylori eradication. Aliment Pharmacol Ther 2022;56:436-49. doi: 10.1111/apt.17070.
17. Kiyotoki S, Nishikawa J, Sakaida I. Efficacy of Vonoprazan for Helicobacter pylori Eradication. Intern Med 2020;59:153-61. doi: 10.2169/internalmedicine.2521-18.
18. Lyu QJ, Pu QH, Zhong XF, Zhang J. Efficacy and Safety of Vonoprazan-Based versus Proton Pump Inhibitor-Based Triple Therapy for Helicobacter pylori Eradication: A Meta-Analysis of Randomized Clinical Trials. Biomed Res Int 2019;2019:e9781212. doi: 10.1155/2019/9781212.
19. Li M, Oshima T, Horikawa T, Tozawa K, Tomita T, Fukui H, et al. Systematic review with meta-analysis: Vonoprazan, a potent acid blocker, is superior to proton-pump inhibitors for eradication of clarithromycin-resistant strains of Helicobacter pylori. Helicobacter 2018;23:e12495. doi: 10.1111/hel.12495.
20. Tanabe H, Yoshino K, Ando K, Nomura Y, Ohta K, Satoh K, Ichiishi E, Ishizuka A, Otake T, Kohgo Y, Fujiya M, Okumura T. Vonoprazan-based triple therapy is non-inferior to susceptibility-guided proton pump inhibitor-based triple therapy for Helicobacter pylori eradication. Ann Clin Microbiol Antimicrob 2018;17:29. doi: 10.1186/s12941-018-0281-x.
21. Ang TL, Lim KW, Ang D, Wong YJ, Tan M, Yih Wong AS. Clinical audit of current Helicobacter pylori treatment outcomes in Singapore. Singapore Med J 2022;63:503-8. doi: 10.11622/smedj.2021105.
22. Maruyama M, Tanaka N, Kubota D, Miyajima M, Kimura T, Tokutake K, et al. Vonoprazan-Based Regimen Is More Useful than PPI-Based One as a First-Line Helicobacter pylori Eradication: A Randomized Controlled Trial. Can J Gastroenterol Hepatol 2017;2017:4385161. doi: 10.1155/2017/4385161.
23. Huang J, Lin Y. Vonoprazan on the Eradication of Helicobacter pylori Infection. Turk J Gastroenterol 2023;34:221-6. doi: 10.5152/tjg.2022.211041.

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FW: Principal Researcher
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KF: Study design, concept guidance and approval
SA: Literature search
SFFG: Data analysis and drafting