60 ANOS ARQUIVOS DE GASTROENTEROLOGIA

ORIGINAL ARTICLE

doi.org/10.1590/S0004-2803.230302-23-51

Efficacy and safety of gemifloxacin containing treatment regimen in first-line treatment of *Helicobacter Pylori*

Recep **ALANLI**[1], Murat Bulent **KUCUKAY**[1], Muhammet Fatih **AYDIN**[2], Bilal **ERGÜL**[3] and Fahri **YAKARYILMAZ**[3]

[1] Lokman Hekim University, Faculty of Medicine, Ankara Hospital, Department of Internal Diseases, Ankara, Turkey. [2] Altınbas University, Faculty of Medicine, Medical Park Bahcelievler Hospital, Department of Gastroenterology, Istanbul, Turkey. [3] Lokman Hekim University, Faculty of Medicine, Ankara Hospital, Department of Gastroenteology, Ankara, Turkey.

HIGLIGHTS

- In eradication treatment of *H. pylori* gemifloxacin containing triple treatment regimen was as effective as bismuth containing quadruple treatment.
- Drug adverse effects were fewer and milder in the gemifloxacin group.
- Since treatment period was shorter and pills to be taken were fewer compared to quadruple treatment, patient compliance was significantly higher in the gemifloxacin group.

ABSTRACT – Background – After eradication of *Helicobacter pylori (H. pylori)* chronic gastritis will resolve, complications due to *H. pylori* infection and recurrence of infection will be prevented. **Objective –** To determine efficacy and safety of gemifloxacin containing treatment regimen in first line treatment of *H. pylori* with comparison to bismuth containing quadruple therapy. **Methods –** This retrospective study was conducted in a tertiary care university hospital between January 2018 and January 2021 with 410 participants who were diagnosed to have *H. pylori* infection with biopsies obtained during upper gastrointestinal system endoscopy. Patients were distributed into two groups according to their first-line treatment regimens. First group patients were treated with amoxicillin, gemifloxacin and pantoprazole and second group patients were treated with amoxicillin, metronidazole, bismuth subcitrate and pantoprazole for seven days. **Results –** Intention to treat and per protocol ratios for gemifloxacin containing regimen were 90.0% and 91.2%, while quadruple treatment has these ratios as 91.7% and 93.8% respectively. Treatment success rate in both regimens were similar. But adverse effects were lower and patient compliance were better in patients who had gemifloxacin containing treatment (P<0.001). **Conclusion –** Gemifloxacin containing treatment regimen is as effective as bismuth containing quadruple treatment regimen for *H. pylori* infection and patient compliance is better in this group. Gemifloxacin containing treatment regimens may be novel and effective alternatives for eradication of *H. pylori* infection.

Keywords – Bismuth; Gemifloxacin; fluoroquinolones; *Helicobacter pylori*; treatment efficacy.

Received: 30 March 2023
Accepted: 29 May 2023

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
Corresponding author:
Recep Alanli. E-mail:
recepalanli@gmail.com

INTRODUCTION

Helicobacter pylori (*H. pylori*) infection affect more than a half of whole world population. Person to person transmission is possible through gastrointestinal system and infection generally results in chronic gastritis. *H. pylori* infection is known to cause mucosa associated lymphoid tissue lymphoma (MALT) and gastric adenocarcinoma[1].

After eradication of *H. pylori* chronic gastritis will resolve, complications due to *H. pylori* infection and recurrence of infection will be prevented[2]. Many antibiotics have been used in eradication of *H. pylori* but antimicrobial resistance is a serious problem worldwide[3,4]. Resistance to clarithromycin has increased up to 40% in Turkiye and 50% in China[4]. For this reason, bismuth containing treatment regimens are recommended the first opinion in countries where clarithromycin resistance exceeds 15%, in Maastrich VI consensus report[1]. Treatment failure for *H. pylori* is increasing worldwide due to increases in resistance to antibiotics and low patient compliance because of drug adverse effects. For this reason more convenient and more effective treatments are being sought for eradication of *H. pylori*[5,6].

Fluoroquinolones like, levofloxacin and moxifloxacin are used in eradication of *H. pylori* and they were found to be effective[7-10]. In addition, patients who used fluoroquinolones had milder adverse effects compared to other antibiotics used in eradication of *H. pylori*[11]. Antibiotic resistance against levofloxacin in treatment of *H. pylori* is increasing[12]. Gemifloxacin, on the other hand, is a novel and promising treatment choice in eradication of *H. pylori*. In a study effectiveness of gemifloxacin, levofloxacin, moxifloxacin, ciprofloxacin and gatifloxacin were inspected for *H. pylori,* in vitro. Gemifloxacin was found to be most effective fluoroquinolone against *H. pylori,* amongst these[13]. There are few studies evaluating in vivo effectiveness of gemifloxacin against *H. pylori*. In these studies gemifloxacin was found to be effective in eradication of *H. pylori*[14,15].

The aim of the presented study is to evaluate efficacy and safety of gemifloxacin, amoxicillin and pantoprazole containing treatment regimen and its comparison to amoxicillin, metronidazole, bismuth subcitrate and pantoprazole containing quadruple treatment regimen in first-line treatment of *H. pylori*.

METHODS

This retrospective study was conducted in a tertiary care university hospital between January 2018 and January 2021 with 410 participants who were diagnosed to have *H. pylori* infection with biopsies obtained during upper gastrointestinal system endoscopy. Patients who received following eradication treatments for *H. pylori* were included; first group was constituted with patients who were treated with amoxicillin, gemifloxacin and pantoprazole (AGP) and second group was constituted with patients who were treated with amoxicillin, metronidazole, bismuth subcitrate and pantoprazole (AMBP). Patients who were under 18 years of age, pregnant, lactating, who had prior gastric surgery history and who were previously treated for *H. pylori* were excluded. Patients in whom necessary medical records for the study could not be obtained were also excluded. This study was approved by Lokman Hekim University Ethics Committee for Observational Studies with a decision number 2022/104, by local Ethics Committee and it was conducted in compliance with Declaration of Helsinki and good clinical practices directives.

Upper gastrointestinal tract endoscopies were performed by same gastroenterologist with Olympus GIF Type Q150 videoendoscope (Olympus Medical Systems Corp., Tokyo, Japan). To detect *H. Pylori* infection, two biopsies were obtained from both gastric antrum and corpus regions. Biopsy specimens were stained by hematoxylin and eosin and modified Giemsa methods, and were inspected under light microscopy.

The eradication treatment regimens for *H. pylori* were inspected in two groups. In first group (AGP group) the patients who had gemifloxacin 1×320 mg, amoxicillin 2×1 g for 7 days with a proton pump inhibitor pantoprazole 2×40 mg per oral. Second group (AMBP group) had amoxicillin 2×1 g, metronidazole 3×500 mg, bismuth subcitrate 4×262 mg and pantoprazole 2×40 mg for 7 days. 8 weeks after eradication treatment, all participants were confirmed

with stool *H. pylori* antigen test (OnSite *H. pylori* Ag Rapid Test, MDSS GmbH, Hannover, Germany). Proton pump inhibitor usage has been stopped 2 weeks before stool antigen test in all participants. Drug adverse effects, if occurred, were obtained in control visits. Eradication rates were calculated according to completion of treatment regimens; all patients were evaluated by intention-to-treat analysis (ITT) and the patients who completed the treatment were evaluated by per-protocol analysis (PP).

All data were evaluated using the statistical software SPSS for Windows (version 25, SPSS, Armonk, NY, USA). Quantitative data were presented as mean ± standard deviation for normally distributed variables. Categorical data were presented as frequency and percentage. Chi-square and student's *t*-tests were used to evaluate difference between study groups. Significance was determined by detection of a *P* value below 0.05.

RESULTS

A total of 410 patients; 128 males (31.2%) and 282 females (68.8%) were inspected. Mean age was 46.6±12.48 (males 45.16±12.87, females 47.26±12.27, *P*=0.116). Of total 410 patients, 289 (70.5%) had gemifloxacin containing triple treatment and 121 (29.5%) had bismuth containing quadruple treatment. After eradication treatments in both groups, 29 (10.0%) patients in AGP group and 10 (8.3%) patients in AMBP group had still positive results for *H. pylori* stool antigen test (treatment failure). Eradication rate in both groups were similar in means of ITT and PP and they were over 90.0% (TABLE 1).

In 33 (11.4%) of AGP group and in 41 (33.9%) of AMBP group at least one adverse drug effects were observed. Most frequent adverse drug effects were abdominal discomfort and nausea. When compared to AMBP group, drug adverse effects were fewer and milder in AGP group (TABLE 2). Patient compliance was higher in AGP group. 4 (1.3%) patients in AGP group and 9 (7.4%) patients in AMBP group could not tolerate treatment and quited (*P*=0.001).

Antral gastritis and pangastritis were the most frequent endoscopy findings. Endoscopic findings of patients were shown in TABLE 3.

TABLE 1. Comparison of demographic characteristics and efficacy of treatment between study groups.

	AGP treatment (n=289)	AMBP treatment (n=121)	*P* value
Age (years)	46.92±11.85	45.83±13.91	0.421*
Male/female ratio	88/201	40/81	0.603†
ITT (95%CI)	90.0% (88.0–92.0)	91.7% (90.1–93.6)	0.577†
PP (95%CI)	91.2% (89.2–92.8)	93.8% (90.9–94.8)	0.406†

AGP: amoxicillin gemifloxacin, pantoprazole; AMBP: amoxicillin, metronidazole, bismuth subcitrate, pantoprazole; ITT: intention to treat; CI: confidence interval; PP: per protocol. *Student's *t*-test, †Chi-square test.

TABLE 2. Comparison of frequency of drug adverse effects observed between study groups.

Complaint	AGP treatment (n=289)	AMBP treatment (n=121)	*P* value*
Diarrhea	14 (4.8%)	12 (9.9%)	0.055
Nausea	18 (6.2%)	20 (16.5%)	0.001
Vomiting	10 (3.5%)	9 (7.4%)	0.081
Abdominal discomfort	18 (6.2%)	25 (20.6%)	<0.001
Headache	9 (3.1%)	9 (7.4%)	0.051
Vertigo	7 (2.4%)	8 (6.6%)	0.039
Metallic bitter taste	11 (3.8%)	14 (11.5%)	0.003
Frequency of observance of at least one drug side effect	33 (11.4%)	41 (33.9%)	<0.001

AGP: amoxicillin, gemifloxacin, pantoprazole; AMBP: amoxicillin, metronidazole, bismuth subcitrate, pantoprazole. *Chi-square test.

TABLE 3. Comparison of endoscopic findings of study groups.

Pathologic finding	AGP treatment (n=289)	AMBP treatment (n=121)	*P* value*
Antral gastritis	155 (53.6%)	70 (57.8%)	0.434
Gastric ulcer	1 (0.3%)	1 (0.1%)	0.524
Esophagitis	32 (11.1%)	12 (9.9%)	0.730
Pangastritis	117 (40.5%)	54 (44.6%)	0.438
Atrophic gastritis	49 (17.0%)	20 (16.5%)	0.916
Duodenal ulcer	27 (9.3%)	5 (4.1%)	0.073
Duodenitis	22 (7.6%)	12 (9.9%)	0.440

AGP: amoxicillin, gemifloxacin, pantoprazole; AMBP: amoxicillin, metronidazole, bismuth subcitrate, pantoprazole. *Chi-square test.

DISCUSSION

This present study has documented that gemifloxacin containing triple treatment for eradication of *H. pylori* was as effective as bismuth containing quadruple treatment. In addition drug adverse effects were significantly lower and patient compliance was significantly higher in gemifloxacin containing triple treatment.

Despite many different treatment regiments experienced over three decades in eradication of *H. pylori*, treatment success is still a remarkable problem worldwide[16]. In addition, resistance to metronidazole and levofloxacin increase in time and this will eventually result in inevitable treatment failure in future[12].

Gemifloxacin is an antibiotic affecting both gram negative and gram positive bacteria[17]. Amongst others, gemifloxacin has been reported to be more effective fluoroquinolone against *H. pylori,* in vitro[13,18,19]. There are two studies documenting in vivo effectiveness of gemifloxacin against *H. pylori*. In the first study, 60 patients had gemifloxacin, amoxicillin, bismuth and omeprazole and another 60 patients had clarithromycin, amoxicillin, bismuth and omeprazole for 10 day as first line treatment of *H. pylori*. Gemifloxacin containing treatment regimen was found to be as effective as clarithromycin containing treatment regimen[15]. The second study inspected 120 patients who had prior eradication treatment against *H. pylori* with clarithromycin, amoxicillin, bismuth and proton pump inhibitor but failed. These patients were treated with gemifloxacin, amoxicillin, bismuth and omeprazole for 14 days as second line eradication treatment. Eradication rate was found to be high as 91.4% for PP and 88.3% for ITT[14]. In present study, despite gemifloxacin containing eradication treatment were given for a shorter time as seven days and the regimen did not contain bismuth, eradication rates for PP and ITT were found to be higher than aforementioned studies. For this reason, gemifloxacin containing triple treatment regimes may be a good alternative in eradication of *H. pylori*.

Because of increasing risk for antibiotic resistance, bismuth containing eradication regimens are recommended in *H. pylori* infections[20]. Studies report high effectiveness of amoxicillin, metronidazole, bismuth and pantoprazole containing quadruple treatments against *H. pylori*[21,22]. But gemifloxacin containing triple treatment regimens that do not contain bismuth were not compared to AMBP regimen before. In this presented study, both AGP and AMBP groups had similar effectiveness in eradication of *H. pylori*, in addition patient compliance was higher in AGP group. Patients who discontinued treatment regimen because of adverse effects were lower in AGP group. From patients' aspect, amount of pills to be taken daily is as low as five tablets in AGP group compared to 11 tablets in AMBP group, which will increase patient compliance in eradication treatment.

In a study from Nepal, most frequent adverse drug affects related to antibiotics were abdominal discomfort, constipation, diarrhea and metallic taste[23]. Different rates of adverse drug effects were reported in eradication treatment for *H. pylori* in clinical studies. A study reported high frequency of 37.0% as adverse drug affects, in patients who got levofloxacin, amoxicillin and PPI treatment[24]. Frequency of observation of at least one drug adverse effect for AMBP treatment regimen is reported as 18.6% in a study[21], where another reports it as 28.5%[25]. Fluoro-

quinolones cause less frequent drug adverse effects compared to other antibiotics used in eradication treatment for *H. pylori*[11]. Gemifloxacin is a fourth line fluoroquinolone. A study from Iran reported that patients who got gemifloxacin containing eradication regimen experienced less frequent and intense drug adverse effects when compared to bismuth containing quadruple eradication regimens[15]. In concordance with aforementioned studies, present study documents that patients in group with gemifloxacin treatment experienced less adverse drug effects. Almost 89.0% of participants in this group had no adverse drug effect. Based upon this finding, it may be proposed that gemifloxacin is a safe and well tolerable drug in treatment of *H. pylori* infection.

This study has some limitations. It's retrospective design and study setting in single center are limitations. In addition, genotypical and phenotypical profiles for resistance to antibiotics for *H. pylori* were not evaluated.

In conclusion; gemifloxacin, amoxicillin and PPI containing triple eradication regimen for *H. pylori* is as effective as bismuth containing quadruple treatment with higher patient compliance and lower drug adverse effects. Short treatment period, low number of pills to be taken for treatment are advantages, which increases patient compliance and lowers probability of patients to discontinue treatment. Triple treatment regimen containing gemifloxacin may be an appropriate treatment choice in eradication of *H. pylori*. Prospective, randomised clinical studies inspecting the effectiveness and safety of gemifloxacin in eradication treatment for *H. pylori* will bring more precise results.

ACKNOWLEDGMENTS

Authors thank to Fatih Acikgoz for statistical analysis and advices, Mustafa Metin Yildirimkaya for laboratory tests and Emre Akarsu for pathologic examinations.

Authors' contribution

Alanli R: research design and concept, data collection and/or processing, analysis and interpretation, literature search, writing of manuscript, final approval. Kucukay MB and Yakaryilmaz F: data collection and/or processing, analysis and interpretation, literature search, writing of manuscript, final approval. Aydin MF: data collection and/or processing, analysis and interpretation, writing of manuscript, final approval. Ergül B: data collection and/or processing, analysis and interpretation, writing of manuscript, final approval.

Orcid

Recep Alanli: 0000-0003-4663-1898.
Murat Bulent Kucukay: 0000-0003-3657-6565.
Muhammet Fatih Aydin: 0000-0001-6056-9360.
Bilal Ergül: 0000-0001-9286-7119.
Fahri Yakaryilmaz: 0000-0002-4328-474X.

Alanli R, Kucukay MB, Aydin MF, Ergül B, Yakaryilmaz F. Efetividade e segurança do regime de tratamento contendo gemifloxacino no tratamento de primeira linha para *Helicobacter pylori*. Arq Gastroenterol. 2023;60(3):350-5.

RESUMO – **Contexto** – Após a erradicação do *Helicobacter pylori* (HP), a gastrite crônica será resolvida, as complicações devido à infecção por HP e a recorrência da infecção serão prevenidas. **Objetivo** – Determinar a eficácia e segurança do regime de tratamento contendo gemifloxacino no tratamento de primeira linha do HP, em comparação com a terapia quádrupla contendo bismuto. **Métodos** – Este estudo prospectivo foi conduzido em um hospital universitário de atendimento terciário entre janeiro de 2018 e janeiro de 2021, com 410 participantes diagnosticados com infecção por HP, obtidos por meio de biópsias durante a endoscopia do sistema gastrointestinal superior. Os pacientes foram divididos em dois grupos de acordo com seus regimes de tratamento de primeira linha. Os pacientes do primeiro grupo foram tratados com amoxicilina, gemifloxacino e pantoprazol, e os pacientes do segundo grupo foram tratados com amoxicilina, metronidazol, subcitrato de bismuto e pantoprazol por 7 dias. **Resultados** – As taxas de intenção de tratar e por protocolo para o regime contendo gemifloxacino foram de 90,0% e 91,2%, enquanto o tratamento quádruplo apresentou essas taxas como 91,7% e 93,8%, respectivamente. A taxa de sucesso do tratamento em ambos os regimes foi similar. No entanto, os efeitos adversos foram menores e a adesão dos pacientes foi melhor nos que receberam o tratamento contendo gemifloxacino (P<0,001). **Conclusão** – O regime de tratamento contendo gemifloxacino é tão eficaz quanto o regime de tratamento quádruplo contendo bismuto para a infecção por HP, e a adesão dos pacientes é melhor neste grupo. Os regimes de tratamento contendo gemifloxacino podem ser alternativas novas e eficazes para a erradicação da infecção por HP.

Palavras-chave – Bismuto; gemifloxacino; fluoroquinolonas; *Helicobacter pylori*; eficácia de tratamento.

REFERENCES

1. Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F et al. European Helicobacter and Microbiota Study Group and Consensus panel. Management of Helicobacter pylori infection-the Maastricht VI/Florence Consensus Report. Gut. 2022;61:646-64. doi: 10.1136/gutjnl-2012-302084.
2. Sugano K, Tack J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, et al. Kyoto global consensus report on Helicobacter pylori gastritis. Gut. 2015;64:1353-67. doi: 10.1136/gutjnl-2015-309252.
3. Khademi F, Poursina F, Hosseini E, Akbari M, Safaei HG. Helicobacter pylori in Iran: A systematic review on the antibiotic resistance. Iran J Basic Med Sci.2015;18:2-7.
4. Thung I, Aramin H, Vavinskaya V, Gupta S, Park JY, Crowe SE, et al. Review article: the global emergence of Helicobacter pylori antibiotic resistance. Aliment Pharmacol Ther. 2016;43:514-33. doi: 10.1111/apt.13497.
5. Graham DY, Fischbach L. Helicobacter pylori treatment in the era of increasing antibiotic resistance. Gut. 2010;59:1143-53. doi: 10.1136/gut.2009.192757.
6. Graham DY, Shiotani A. New concepts of resistance in the treatment of Helicobacter pylori infections. Nat Clin Pract Gastroenterol Hepatol. 2008;5:321-31. doi: 10.1038/ncpgasthep1138.
7. Kang KK, Lee DH, Oh DH, Yoon H, Shin CM, Park YS, et al. Helicobacter pylori eradication with moxifloxacin-containing therapy following failed first-line therapies in South Korea. World J Gastroenterol. 2014;20:6932-8. doi: 10.3748/wjg.v20.i22.6932.
8. Saad RJ, Schoenfeld P, Kim HM, Chey WD. Levofloxacin-based triple therapy versus bismuth-based quadruple therapy for persistent Helicobacter pylori infection: a meta-analysis. Am J Gastroenterol. 2006;101:488-96. doi: 10.1111/j.1572-0241.2006.00637.x.
9. Rokkas T, Sechopoulos P, Robotis I, Margantinis G, Pistiolas D. Cumulative H. pylori eradication rates in clinical practice by adopting first and second-line regimens proposed by the Maastricht III consensus and a third-line empirical regimen. Am J Gastroenterol. 2009;104:21-5. doi: 10.1038/ajg.2008.87.
10. Ergül B, Koçak E, Taş A, Filik L, Köklü S. Bismuth, moxifloxacin, tetracycline, lansoprazole quadruple first line therapy for eradication of H. pylori: A prospective study. Clin Res Hepatol Gastroenterol. 2013;37:527-9. doi: 10.1016/j.clinre.2012.10.014.
11. Di Caro S, Fini L, Daoud Y, Grizzi F, Gasbarrini A, De Lorenzo A, et al. Levofloxacin/amoxicillin-based schemes vs quadruple therapy for Helicobacter pylori eradication in second-line. World J Gastroenterol. 2012;18:5669-78. doi: 10.3748/wjg.v18.i40.5669.
12. Savoldi A, Carrara E, Graham DY, Conti M, Tacconelli E. Prevalence of Antibiotic Resistance in Helicobacter pylori: A Systematic Review and Meta-analysis in World Health Organization Regions. Gastroenterology. 2018;155:1372-82. doi: 10.1053/j.gastro.2018.07.007.
13. Minehart HW, Chalker AF. In vitro activity of gemifloxacin against Helicobacter pylori. J Antimicrob Chemother. 2001;47:360-1. doi: 10.1093/jac/47.3.360.
14. Mahmoudi L, Farshad S, Seddigh M, Mahmoudi P, Ejtehadi F, Niknam R. High efficacy of gemifloxacin-containing therapy in Helicobacter Pylori eradication: A pilot empirical second-line rescue therapy. Medicine. 2016;95:e4410. doi: 10.1097/MD.0000000000004410.
15. Masoodi M, Talebi-Taher M, Tabatabaie K, Khaleghi S, Faghihi AH, Agah S, et al. Clarithromycin vs. Gemifloxacin in Quadruple Therapy Regimens for Empiric Primary Treatment of Helicobacter pylori Infection: A Randomized Clinical Trial. Middle East J Dig Dis. 2015;7:88-93.
16. Rokkas T, Gisbert JP, Malfertheiner P, Niv Y, Gasbarrini A, Leja M, et al. Comparative Effectiveness of Multiple Different First-Line Treatment Regimens for Helicobacter pylori Infection: A Network Meta-analysis. Gastroenterology. 2021;161:495-507. doi: 10.1053/j.gastro.2021.04.012.
17. Le TP, Xiong YQ. Gemifloxacin. Drugs Today. 2001;37:401-410. doi: 10.1358/dot.2001.37.6.627959.
18. Cheng A, Sheng WH, Liou JM, Wang HP, Wu MS, Lin JT, et al. Comparative in vitro antimicrobial susceptibility and synergistic activity of antimicrobial combinations against Helicobacter pylori isolates in Taiwan. J Microbiol Immunol Infect. 2015;48:72-9. doi: 10.1016/j.jmii.2012.08.021.
19. Chang WL, Kao CY, Wu CT, Huang AH, Wu JJ, Yang HB, et al. Gemifloxacin can partially overcome quinolone resistance of H. pylori with gyrA mutation in Taiwan. Helicobacter. 2012;17:210-5. doi: 10.1111/j.1523-5378.2012.00935.x.
20. Ko SW, Kim YJ, Chung WC, Lee SJ. Bismuth supplements as the first-line regimen for Helicobacter pylori eradication therapy: Systemic review and meta-analysis. Helicobacter. 2019;24:e12565. doi: 10.1111/hel.12565.
21. Yozgat A, Kasapoglu B, Demirci S, Coskun Sokmen F. Modified quadruple therapy or bismuth-containing quadruple therapy in the first-line treatment of Helicobacter pylori in Turkey. Rev Esp Enferm Dig. 2021;113:490-3. doi: 10.17235/reed.2020.7261/2020.
22. Choe JW, Jung SW, Kim SY, Hyun JJ, Jung YK, Koo JS, et al. Comparative study of Helicobacter pylori eradication rates of concomitant therapy vs modified quadruple therapy comprising proton-pump inhibitor, bismuth, amoxicillin, and metronidazole in Korea. Helicobacter. 2018;23:e12466. doi: 10.1111/hel.12466.
23. Shakya Shrestha S, Bhandari M, Thapa SR, Shrestha R, Poudyal R, Purbey B, et al. Medication Adherence Pattern and Factors affecting Adherence in Helicobacter Pylori Eradication Therapy. Kathmandu Univ Med J. 2016;14:58-64.
24. Hafeez M, Qureshi ZA, Khattak AL, Saeed F, Asghar A, Azam K, et al. Helicobacter Pylori Eradication Therapy: Still a Challenge. Cureus. 2021;13:e14872. doi: 10.7759/cureus.14872.
25. Castro Fernández M, Romero García T, Keco Huerga A, Pabón Jaén M, Lamas Rojas E, Llorca Fernández R, et al. Compliance, adverse effects and effectiveness of first line bismuth-containing quadruple treatment (Pylera®) to eradicate Helicobacter pylori infection in 200 patients. Rev Esp Enferm Dig. 2019;111:467-470. doi: 10.17235/reed.2019.5950/2018.