ISSN 2228-9860 eISSN 1906-9642 CODEN: ITJEA8

International Transaction Journal of Engineering, Management, & Applied Sciences & Technologies

http://TuEngr.com

Evaluation of the Effectiveness and Safety of the Hybrid Scheme of Eradication Therapy of Helicobacter Pylori Infection

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Paper ID: 13A11L

Volume 13 Issue 11

Received 29 March 2022
Received in revised form 14 July 2022
Accepted 19 July 2022
Available online 22 July 2022

Keywords:
Helicobacter pylori; Helicobacteriosis; Eradication therapy; Hybrid therapy; Four-component therapy; Standard triple therapy; H. pylori.

Abstract

The purpose of this work is to conduct a comprehensive comparative study of the efficacy and safety of a hybrid scheme of eradication therapy in patients with confirmed Helicobacter pylori infection. We conducted a randomized comparative study of 180 people with clinically confirmed helicobacteriosis. Upon completion of drug therapy, patients underwent control instrumental diagnostic studies to analyze the effectiveness and safety of the prescribed treatment. The results of our study showed high efficiency and optimal safety of the hybrid scheme of eradication therapy in the treatment of Helicobacter pylori, in comparison with the standard triple scheme and the four-component bismuth-containing scheme. The effectiveness of this method directly depends on the individual characteristics of the patient, the severity of clinical manifestations of helicobacteriosis, the level of resistance to antibacterial therapy. Important for the optimization of eradication therapy is the study of the acid-forming function of the stomach for the selection of a proton pump inhibitor in the optimal dosage and a pronounced antisecretory effect.

Discipline: Medicine, therapy

Cite This Article:

Magomedova, A.Sh., Isaeva, Z.M., Magomedova, Z.Sh., Ausheva, L.B., Drozdenko, V.R., Gabachev, R.L., ... Babatkhanov, A.S. (2022). Evaluation of the effectiveness and safety of the hybrid scheme of eradication therapy of Helicobacter Pylori infection. *International Transaction Journal of Engineering, Management, & Applied Sciences & Technologies, 13*(11), 13A11L, 1-9. http://TUENGR.COM/V13/13A11L.pdf DOI: 10.14456/ITJEMAST.2022.222

1 Introduction

One of the most common modern infectious diseases is Helicobacter pylori infection (helicobacteriosis). The prevalence of infection varies depending on the geographical region, the age of the patient, his ethnicity and socio-economic status. Helicobacteriosis is a term that was introduced by Russian scientists to denote all processes in the human body after the pathogen enters it. Helicobacteriosis occurs as a result of ingestion of the spiral gram-negative bacterium Helicobacter pylori and damage to the mucous membrane of the stomach and duodenum [1-3].

Helicobacter pylori can cause diseases of the digestive system (atrophic gastritis, peptic ulcer of the stomach and duodenum, cancer), worsen the course of many chronic diseases, due to the negative effect on the organs and systems of the body [4-6].

The main ways of transmission of the pathogenic microorganism are fecal-oral, contact-household [7-9].

2 Literary Review

Invasive (endoscopic) and non-invasive (non-endoscopic) methods of examination are used to diagnose Helicobacter pylori. As an invasive method of investigation, gastroscopy is performed with a biopsy of the gastric mucosa and duodenum for subsequent histological analysis [10]. Such a study is the most informative.

Non-invasive methods of investigation include: urease breath test and determination of antigen in feces. Urease breath test is absolutely harmless, its reliability is 80-85%. Determining the concentration of ammonia in the exhaled air allows to determine the presence of bacteria in the body, because it is known that Helicobacter pylori decomposes urea into ammonia and carbon dioxide [11]. This method is used for primary diagnosis, as well as for monitoring the course of anti-helicobacter therapy and checking the effectiveness of treatment already carried out.

For the prevention and treatment of Helicobacter pylori-associated diseases, eradication therapy is used aimed at the complete destruction of the pathogenic microorganism in the mucous membrane of the stomach and duodenum, thus creating favorable conditions for the healing of ulcers and other mucosal damage [12].

In 2011, the so-called hybrid scheme of eradication therapy became widely known among the gastroenterological community. Numerous clinical trials have confirmed the high efficacy and optimal safety of the drugs used [13-16]. In the study, the hybrid scheme of eradication therapy is represented by a complex two-stage ten-day four-component protocol of antihelicobacteric treatment in a standard single dosage [17]. In the first 5 days, a proton pump inhibitor (PPIs) is taken in combination with amoxicillin, in the next 5 days, PPIs are taken (lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg, rabeprazole 20 mg, esomeprazole 20 mg), amoxicillin 1000 mg, clarithromycin 500 mg and metronidazole (tinidazole) 500 mg. All medications are taken 2 times a day.

The mechanism of action of these drugs has a complex antihelicobacteric efficacy, by reducing the bacterial load and reducing the formation of transmembrane channels in the bacterial cell for the excretion of antibiotics, thereby increasing the effectiveness of subsequent use of clarithromycin and metronidazole (tinidazole) [18]. Amoxicillin slows down the synthesis processes in the bacterial cell membrane of penicillin-binding proteins - enzymes that carry out the final stages of biosynthesis of the main component of the cell wall of the microorganism - peptidoglycan, which leads to impaired growth and death of the bacterium [19]. Clarithromycin inhibits bacterial ribosome protein synthesis, which leads to the formation of defective protein molecules and the death of the microorganism [20]. Metronidazole (tinidazole) damages the DNA of a bacterial cell, penetrates into the cell and causes the death of a microorganism [21].

Thus, at the first stage of application of the protocol, clarithromycin-resistant strains of Helicobacter pylori and most bacteria on the surface of the mucous membrane are destroyed. At the second stage, the remaining bacteria are destroyed, including those in the depth of the gastric pits, and those adhered to the epithelium (taking into account the effect of clarithromycin on biofilms and the high ability to penetrate into tissues) [22].

Evaluation of the effectiveness of the hybrid scheme of eradication therapy is carried out 4-6 weeks after the end of therapy. To avoid false negative results, antibacterial drugs and bismuth-containing drugs are discontinued 4 weeks before testing, and PPIs 1-2 weeks before testing [23].

Eradication therapy is considered successful with a negative result of a respiratory urease test, the absence of the pathogenic microorganism Helicobacter pylori in the examined biopsy during histology. Serological examination to assess the result is not effective, since antibody levels often persist for many years after therapy. Other combinations of tests are possible, but they are expensive methods [24-27].

The decrease in the effectiveness of eradication therapy regimens in the treatment of Helicobacter pylori contributes to the further search, study and development of alternative treatment options for infection. This review systematizes the literature data on the hybrid scheme of eradication therapy, considers the effectiveness and safety of this method in the prevention and treatment of helicobacteriosis.

3 Method

Three groups of 60 people participated in a randomized controlled clinical trial to evaluate the efficacy and safety of a hybrid scheme of eradication therapy for helicobacteriosis. The course of treatment with antihelicobacteric drugs lasted 10 days. All patients kept self-monitoring diaries in which they recorded side effects of therapy.

Upon admission to the medical institution, all patients underwent examinations: physical examination, clinical and biochemical blood tests, ultrasound examination of abdominal organs. Special tests were used for the primary diagnosis of Helicobacter pylori. If esophagogastroduodenoscopy (EGDS) was performed at the hospital stage, then a rapid urease test

with biopsy sampling for morphological examination was used. In cases of EGDS at the prehospital stage, a urease breath test was used.

Omeprazole was the drug of choice in order to unify the results obtained.

The first group consisted of patients who received standard triple eradication therapy: omeprazole (20 mg 2 times a day), clarithromycin (500 mg 2 times a day) and amoxicillin (1000 mg 2 times a day) (Table 1).

Table 1: Scheme of standard triple eradication therapy for Helicobacter pylori

Treatment days	The first component	The second component	The third component
1-10 days	Omeprazole 20 mg 2 times a day	Clarithromycin 500 mg 2 times a day	Amoxicillin 1000 mg 2 times a day

The second group consisted of patients who received standard four-component bismuth-containing eradication therapy: omeprazole (20 mg 2 times a day), tetracycline (500 mg 4 times a day), metronidazole (500 mg 3 times a day), bismuth tricalium dicitrate (120 mg 4 times a day) (Table 2).

Table 2: Scheme of four-component bismuth-containing eradication therapy in Helicobacter pylori

Treatment days	The first component	The second component	The third component	The fourth component
1-10 days	Omeprazole 20 mg 2 times a day	Tetracycline 500 mg 4 times a day	Metronidazole 500 mg 3 times a day	Bismuth tricalium dicitrate 120 mg 4 times a day

The third group consisted of patients who received a hybrid scheme of eradication therapy: omeprazole (20 mg 2 times a day) and amoxicillin (1000 mg 2 times a day) were taken for the first 5 days, followed by omeprazole (20 mg 2 times a day), amoxicillin (1000 mg 2 times a day), clarithromycin (500 mg mg 2 times a day) and metronidazole (500 mg 2 times a day) for the next 5 days (Table 3).

Table 3: Scheme of hybrid eradication therapy in Helicobacter pylori

Treatment days	The first component	The second component	The third component	The fourth component
1-5 days	Omeprazole 20 mg 2 times a day	Amoxicillin 1000 mg 2 times a day	-	-
6-10 days	Omeprazole 20 mg 2 times a day	Amoxicillin 1000 mg 2 times a day	Clarithromycin 500 mg 2 times a day	Metronidazole 500 mg 3 times a day

In the presented work, research methods were used: statistical, descriptive, comparative, analytical. Statistical data analysis was carried out using special software MedCalc (Belgium).

4 Results and discussion

After completing the course of treatment, an analysis of the efficacy and safety of Helicobacter pylori eradication therapy was carried out.

The analysis of efficacy in the studied groups of patients was carried out by the methods of intention-to-treat (ITT) and per-protocol (PP). The final sample of PP consisted of: 58 patients in

the first group, 57 patients in the second group, 56 patients in the third group. 9 people were excluded from the sample due to absence from the control examination or self-cancellation of the course of treatment due to pronounced side effects.

As a result of this study, the hybrid scheme of eradication therapy turned out to be the most effective: ITT 85%, PP 91.1%. In second place is bismuth containing a four-component scheme of eradication therapy: ITT 78.3%, p= 0.3587; PP 82.4%, p=0.2674. This is followed by the classical triple scheme of eradication therapy: AT 73.3%, p = 0.1237; PP 75.9%, p=0.043. Comparative data are given in Table 4.

Table 4: Comparative efficacy of eradication therapy in Helicobacter pylori

Eradication therapy	Effectiveness, ITT	Effectiveness, PP
Triple therapy	73,3%	75,9%
Four - component therapy	78,3%	82,4%
Hybrid therapy	85%	91,1%

The data obtained correspond to the results of a number of works by foreign authors. Studies from various countries of the world have confirmed the effectiveness of the hybrid scheme of eradication therapy: ITT 77.6–97.4% and PP 82.6–99.1%.

In 29 patients (18 men, 11 women), eradication was not achieved: of them in the first group - 14 people, in the second - 10 people, in the third - 5 people.

Within the framework of this work, the analysis of possible reasons for the decrease in the effectiveness of the hybrid scheme of eradication therapy revealed the following features in the studied group of patients:

1) The presence of risk factors: age over 60 years, smoking, obesity, diseases of the respiratory system, diseases of the cardiovascular system, diabetes mellitus. The lowest odds ratio (0.41) and at the same time the p value closest to the target level (p = 0.059692) was found for a BMI of > 30 kg/m2, which indicates a possible trend of the negative impact of obesity on the success of eradication. As for the criterion $\chi 2$, which characterizes the probability of a non-random nature of the revealed patterns, $\chi 2 = 2.49$ was determined with respect to smoking, but with a value of p-level = 0.114572, which does not allow considering this factor as influencing the result. And the largest value of $\chi 2 = 4.47$, with a reliable value of p-level = 0.034495, was again set for a BMI of > 30 kg/m2.

2) Insufficient antisecretory activity of the prescribed PPI. This criterion is detected by 48-hour pH-metry, with the performance of a pharmacological test with omeprazole in a standard dosage. The analyzed data of 48-hour pH-metry before and after taking the drug showed: complete resistance to omeprazole was not recorded, in some patients a period of time with a pH > 4 lasting less than 16 hours per day was recorded, which indicates insufficient suppression of acid formation in the stomach due to insufficient antisecretory activity of the prescribed PPIs, which may be due to the pharmacokinetic features of omeprazole.

3) High level of antibiotic resistance. According to the consensus of Maastricht-V (2015), double resistance to clarithromycin and metronidazole reduces the effectiveness of standard triple

and hybrid eradication therapy regimens. The effectiveness of therapy in the absence of resistance to clarithromycin and metronidazole is 98.5%, in the presence of isolated resistance to metronidazole or clarithromycin - 92.9–97.6%, and with double resistance to clarithromycin and metronidazole - 80.0%.

4) Duration of the treatment protocol. In Iran, a study showed that reducing the course of therapy to 10 days reduces the effectiveness by about 10%. Studies conducted in Taiwan and China, which evaluated the effectiveness of ten-day, twelve-day and fourteen-day courses of treatment, showed approximately the same 90% effectiveness. Similarly, studies conducted in South Korea and Spain showed acceptable levels of eradication when using a ten-day hybrid scheme exceeding 85%. Thus, the identified regional differences may be related to the difference in antibiotic resistance in the studied regions.

When assessing the safety of the hybrid scheme of eradication therapy, special attention was paid to the side effects of drugs and subjective complaints of patients. The main complaints were nausea, dizziness, general weakness, decreased appetite, dysgeusia, abdominal pain, diarrhea. Side effects had varying degrees of severity, and did not have a significant impact on daily activities. The frequency of side effects when using the hybrid scheme was 28.3%. Most of the patients received a full course of drug therapy. Therefore, we can conclude about the optimal safety of the hybrid scheme of eradication therapy, which is due to the use of three antibacterial drugs.

5 Conclusion

The results of our study showed high efficiency and optimal safety of the hybrid scheme of eradication therapy in the treatment of Helicobacter pylori, in comparison with the standard triple scheme and the four-component bismuth-containing scheme. The effectiveness of this method directly depends on the individual characteristics of the patient, the severity of clinical manifestations of helicobacteriosis, the level of resistance to antibacterial therapy. Important for the optimization of eradication therapy is the study of the acid-forming function of the stomach for the selection of a proton pump inhibitor in the optimal dosage and a pronounced antisecretory effect. In general, the effectiveness of the hybrid scheme requires further study and clinical trials on a larger number of patients.

6 Availability of Data and Material

Data can be made available by contacting the corresponding author.

7 References

[1] Ivashkin VT, Trukhmanov AS, Gonik MI. Rebamipide using in gastroesophageal reflux disease treatment. Ter Arkh. 2020 May 19;92(4):98-104. Russian. doi:10.26442/00403660.2020.04.000568.

[2] Ivashkin VT, Lapina TL, Bondarenko OY, Sklanskaya OA, Grigoriev PY, Vasiliev YV, Yakovenko EP, Gulyaev PV, Fedchenko VI. Azithromycin in a triple therapy for H.pylori eradication in active duodenal ulcer. World J Gastroenterol. 2002 Oct;8(5):879-82. DOI: 10.3748/wjg.v8.i5.879.

[3] Boraeva, T. T., Vadaeva, M. A., Matveeva, U. V., Revazova, A. B., Albegova, B. Z., Kanukoeva, D. T., Mishvelov, A. E. and Povetkin, S. N. Dynamics of Diseases of the Upper Digestive Tract in Children, *Journal*

of Pharmaceutical Research International, 2021; 33(38B), 48-57. DOI: 10.9734/jpri/2021/v33i38B32098

[4] de Brito BB, da Silva FAF, Soares AS, Pereira VA, Santos MLC, Sampaio MM, Neves PHM, de Melo FF. Pathogenesis and clinical management of Helicobacter pylori gastric infection. World J Gastroenterol. 2019 Oct 7;25(37):5578-5589. DOI: 10.3748/wjg.v25.i37.5578.

[5] Rauf A, Abu-Izneid T, Olatunde A, Ahmed Khalil A, Alhumaydhi FA, Tufail T, Shariati MA, Rebezov M, Almarhoon ZM, Mabkhot YN, Alsayari A, Rengasamy KRR. COVID-19 Pandemic: Epidemiology, Etiology, Conventional and Non-Conventional Therapies. International Journal of Environmental Research and Public Health. 2020; 17(21):8155. DOI: 10.3390/ijerph17218155

[6] Ayivi R, Ibrahim S, Colleran H, Silva R, Williams L, Galanakis C, Fidan H, Tomovska J and Siddiqui SA. COVID-19: human immune response and the influence of food ingredients and active compounds. Bioactive Compounds in Health and Disease. 2021;4(6):100

[7] Fischbach W, Malfertheiner P. Helicobacter Pylori Infection. Dtsch Arztebl Int. 2018 Jun 22;115(25):429-436. DOI: 10.3238/arztebl.2018.0429.

[8] Ranjha MMAN, Shafique B, Rehman A, Mehmood A, Ali A, Zahra SM, Roobab U, Singh A, Ibrahim SA and Siddiqui SA (2022) Biocompatible Nanomaterials in Food Science, Technology, and Nutrient Drug Delivery: Recent Developments and Applications. *Front. Nutr.* 8:778155. DOI: 10.3389/fnut.2021.778155

[9] Gneush, A. N., Luneva, A. V., Machneva, N. L., Lysenko, Y. A., Aniskina, M. V., Verevkina, M. N., Kilyashanov, M. H., &Povetkin, S. N. (2021). Biotechnology of Microorganisms Growing– Fundamentals for the Development of a Litter Biodestructor. Journal of Pharmaceutical Research International, 33(36B), 1-11. DOI:10.9734/jpri/2021/v33i36B31946

[10] Rzhepakovsky I, Anusha Siddiqui S, Avanesyan S, Benlidayi M, Dhingra K, Dolgalev A, Enukashvily N, Fritsch T, Heinz V, Kochergin S, Nagdalian A, Sizonenko M, Timchenko L, Vukovic M, Piskov S, Grimm WD. Anti-arthritic effect of chicken embryo tissue hydrolyzate against adjuvant arthritis in rats (X-ray microtomographic and histopathological analysis). Food Sci Nutr. 2021 Aug 18;9(10):5648-5669. DOI: 10.1002/fsn3.2529

[11] Ilyasov KK, Demchenkov EL, Chernyshkov AS, Rodin IA, Pushkin SV, Povetkin SN, et al. Features of the phytopharmacological preparations in the metaphylaxis of urolithiasis. Pharmacophore. 2020;11(5):66-71

[12] Wang YK, Kuo FC, Liu CJ, Wu MC, Shih HY, Wang SS, Wu JY, Kuo CH, Huang YK, Wu DC. Diagnosis of Helicobacter pylori infection: Current options and developments. World J Gastroenterol. 2015 Oct 28;21(40):11221-35. DOI: 10.3748/wjg.v21.i40.11221.

[13] Shahida Anusha Siddiqui, Nur Alim Bahmid, Ahmed Taha, Ibrahim Khalifa, Sipper Khan, Hadis Rostamabadi & Seid Mahdi Jafari (2022) Recent advances in food applications of phenolic-loaded micro/nanodelivery systems, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2022.2056870

[14] Siddiqui SA, Ali Redha A, Snoeck ER, Singh S, Simal-Gandara J, Ibrahim SA, Jafari SM. Anti-Depressant Properties of Crocin Molecules in Saffron. Molecules. 2022; 27(7):2076. DOI: 10.3390/molecules27072076

[15] Maslova, A. Y., Tskaeva, A. A., Ashurova, Z. A., Abazova, A., Ismailov, M. M., Ismailova, M. M., Baklanov, I. S., Mishvelov, A. E., Povetkin, S. N. and Baklanova, O. A. Study of the effect of Baricitinib on the Course of COVID-19, *Journal of Pharmaceutical Research International*, 2021; 33(35A), pp. 204-213. DOI: 10.9734/jpri/2021/v33i35A31890

[16] Ranjha MMAN, Shafique B, Rehman A, Mehmood A, Ali A, Zahra SM, Roobab U, Singh A, Ibrahim SA and Siddiqui SA (2022) Biocompatible Nanomaterials in Food Science, Technology, and Nutrient Drug Delivery: Recent Developments and Applications. *Front. Nutr.* 8:778155. DOI: 10.3389/fnut.2021.778155

[17] Andreev DN, Maev IV, Dicheva DT, Samsonov AA, Partzvania-Vinogradova EV. Efficacy and safety of

the use of rebamipide in the scheme of triple eradication therapy of Helicobacter pylori infection: a prospective randomized comparative study. Ter Arkh. 2018;90(8):27-32. DOI: 10.26442/terarkh201890827-32.

[18] Maev IV, Samsonov AA, Golubev NN. [Helicobacter pylori: what schemes of eradication are essential today?]. Ter Arkh. 2011;83(8):41-4. Russian.

[19] Rzhepakovsky IV, Areshidze DA, Avanesyan SS, Grimm WD, Filatova NV, Kalinin AV, Kochergin SG, Kozlova MA, Kurchenko VP, Sizonenko MN, Terentiev AA, Timchenko LD, Trigub MM, Nagdalian AA, Piskov SI. Phytochemical Characterization, Antioxidant Activity, and Cytotoxicity of Methanolic Leaf Extract of *Chlorophytum Comosum* (Green Type) (Thunb.) Jacq. Molecules. 2022; 27(3):762. DOI: 10.3390/molecules27030762

[20] Yun J, Wu Z, Qi G, Han T, Zhang D. The high-dose amoxicillin-proton pump inhibitor dual therapy in eradication of Helicobacter pylori infection. Expert Rev Gastroenterol Hepatol. 2021 Feb;15(2):149-157. DOI: 10.1080/17474124.2021.1826306.

[21] O'Connor A, Vaira D, Gisbert JP, O'Morain C. Treatment of Helicobacter pylori infection 2014. Helicobacter. 2014 Sep;19 Suppl 1:38-45. DOI: 10.1111/hel.12163.

[22] Blinov AV, Nagdalian AA, Povetkin SN, Gvozdenko AA, Verevkina MN, Rzhepakovsky IV, Lopteva MS, Maglakelidze DG, Kataeva TS, Blinova AA, Golik AB, Osipchuk GV, Shariati MA. Surface-Oxidized Polymer-Stabilized Silver Nanoparticles as a Covering Component of Suture Materials. Micromachines. 2022; 13(7):1105. DOI: 10.3390/mi13071105

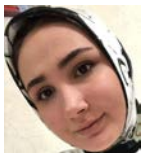
[23] Wermeille J, Zelger G, Cunningham M. The eradication treatments of Helicobacter pylori. Pharm World Sci. 1998 Feb;20(1):1-17. DOI: 10.1023/a:1008638102503.

[24] Tovlahanova TJH et al. Study of the Effect of the Image Scanning Speed and the Type of Conductive Coating on the Quality of Sem-Micrographs of Oxide Nano Materials for Medical Use. Ann Med Health Sci Res. 2021;11:S3:60-64

[25] Orsaeva AT, Tamrieva LA, Mischvelov AE, Osadchiy SS, Osipchuk GV, Povetkin SN, Simonov AN. Digital clinic “smart ward. Pharmacophore. 2020;11(1):142-146

[26] Zimmerman T, Siddiqui SA, Bischoff W, Ibrahim SA. Tackling airborne virus threats in the food industry: A proactive approach. Int. J. Environ. Res. Public Health. 2021;18:4335.

[27] Rauf A, et al. Therapeutic Potential of Herbal Medicine for the Management of Hyperlipidemia: Latest updates. Environmental Science and Pollution Research. 2022;29. DOI: 10.1007/s11356-022-19733-7



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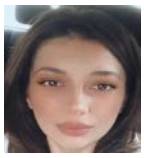

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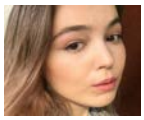

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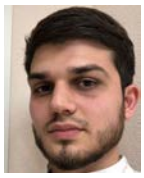

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