REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

Title:
Modified quadruple therapy or bismuth-containing quadruple therapy in the first-line treatment of Helicobacter Pylori in Turkey

Authors:
Ahmet Yozgat, Benan Kasapoglu, Selim Demirci, Fevzi Coskun Sokmen

DOI: 10.17235/reed.2020.7261/2020
Link: PubMed (Epub ahead of print)

Please cite this article as:
Yozgat Ahmet, Kasapoglu Benan, Demirci Selim, Coskun Sokmen Fevzi. Modified quadruple therapy or bismuth-containing quadruple therapy in the first-line treatment of Helicobacter Pylori in Turkey. Rev Esp Enferm Dig 2020. doi: 10.17235/reed.2020.7261/2020.

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

OR 7261

Modified quadruple therapy versus bismuth-containing quadruple therapy in first-line treatment of Helicobacter Pylori in Turkey

Ahmet Yozgat[1], Benan Kasapoğlu[2], Selim Demirci[3], Fevzi Coşkun Sökmen[4]

1. Internal medicine. Gastroenterology Department. Ufuk University Hospital. Ankara.
Orcid: 0000-0002-4414-9929

2. Gastroenterology Department. Lokman Hekim University. Lokman Hekim Akay Hospital.
Orcid: 0000-0003-3858-0103

3. Gastroenterology Department. Abdurrahman Yurtaslan Oncology Training And Research Hospital. Ankara.
Orcid: 0000-0003-3482-7957

4. Internal Medicine Department. Abdurrahman Yurtaslan Oncology Training And Research Hospital. Ankara.
Orcid: 0000-0002-5621-8274

Correspondence: Ahmet Yozgat
Baskent Bulvari 224/B Atlantis City Sİtesi
Yosun Blok No:78 Batıkent, Ankara, Turkey
e-mail: a_yozgat@yahoo.com

ABSTRACT

Aim

Helicobacter pylori (H.pylori) eradication is still an important issue in countries with high antibiotic resistance. In this study we aimed to compare the efficacy and safety of two bismuth-containing treatment modalities in *H pylori* treatment, in Turkey.

Material and Method

Subjects with *H pylori* infection who were treated with either bismuth-containing quadruple therapy (pantoprazole 40 mg bid, tetracycline 500 mg qid, metronidazole 500 mg tid, bismuth subcitrate 262 mg qid daily) (BQT group) or modified quadruple therapy

(pantoprazole 40 mg bid, amoxicillin 1 g bid, metronidazole 500 mg tid, bismuth subcitrate 262 mg qid daily) (MBQT group) for 14 days were compared retrospectively. The eradication success rate, adverse events related to the medications and compliance were investigated.

Results: Totally 128 patients in BQT group and 102 patients in MBQT group completed the treatment. The overall rate of adverse events was significantly more common in BQT group compared with the MBQT group (39.4 % vs. 18.6 %; p:0.001). Among the adverse events, nausea-vomiting and abdominal discomfort was significantly more common in BQT group than MBQT group (p:0.001). The adverse events were mild-moderate in both groups and any life threatening adverse event was not determined in any of the patients.

Conclusion

Although both regimens were highly effective and safe in H.pylori eradication; both ITT and PP eradication rates were higher and adverse events were lower in modified quadruple therapy group. Modified quadruple therapy should be kept in mind in first-line treatment of H.pylori in regions with high clarithromycin and metronidazole resistance.

Keywords

H. Pylori, Quadruple therapy, First-line treatment.

Abbreviations

BQT:Bismuth quadruple therapy

MBQT: Bismuth quadruple therapy

H.Pylori: Helicobacter pylori

MALT: Mucosa-associated lymphoid tissue

Intention-to-treat:ITT

Per-protocol:PP

INTRODUCTION

Helicobacter pylori (H.pylori) is a gram negative bacterium. The world's population were effected by this pathogen more than 50 % and causes a public health problem worldwide. The International Agency for Research on Cancer classified H. *Pylori* as carcinogen because it

is associated with peptic ulcer, mucosa-associated lymphoid tissue (MALT) lymphoma and gastric adenocarcinoma (1, 2). Due to the increased prevalence of antimicrobial resistance of *H.pylori,* eradication success rates with standard treatment regimens has fallen down in worldwide (3-5).

In Maastrich V Consensus Conference report, Bismuth-containing quadruple treatments suggested as the best alternative first-line treatments in populations having a dual clarithromycin and metronidazole resistance higher than 15 % (6). In recent studies, bismuth add-on regimens were defined as the highest effective in first line treatment of *H.pylori* infection (7).

Clarithromycin and metronidazole resistance are defined as the main factors in H.pylori eradication failure (8). In Turkey, high Clarithromycin resistance rates reaching more than 40 % have been reported in previous studies (9, 10). Metronidazole resistance is another important problem in H.pylori eradication in all over the world, reaching more than 20 % in many countries; and in Turkey metronidazole resistance was determined as more than 30 % (11, 12). However, for the eradication of H. *pylori*, the effects of high metronidazole drug resistance were shown to be highly overcome by extending the treatment duration and escalating the administered dose (13). In a recent meta-analysis, Sezgin et al investigated the mean eradication rates of the standard triple therapy (STT) consisting of standard doses of a proton pump inhibitor along with amoxicillin 1 g BID and clarithromycin 500 mg BID for 7 to 14 days in first-line H. pylori eradication in adults in Turkey. In a total of 45 studies and 3715 patients were investigated in this analysis. The eradication rates reported according to the intention-to-treat (ITT) and per-protocol (PP) analyses were 60 % and 57 %, respectively (14). Regarding all these data, H.pylori eradication is still an important issue in countries with high Clarithromycin and metronidazole resistance. We aimed to compare two bismuth-containing treatment modalities safety and effectivity in *H pylori* treatment, in Turkey.

MATERIAL AND METHODS

The study was performed in Gastroenterology Department of Dr Abdurrahman Yurtaslan Oncology Hospital, Ankara, Turkey. In this study, subjects with *H pylori* infection who were treated with either bismuth-containing quadruple therapy or modified quadruple therapy for 14 days between March and October 2018 were compared retrospectively. Bismuth-

containing quadruple therapy including pantoprazole, bismuth subcitrate, metronidazole, tetracycline, (262 mg qid, 40 mg bid, 500 mg tid, 500 mg qid daily, respectively) and modified quadruple therapy included pantoprazole, amoxicillin, metronidazole and bismuth subcitrate (40 mg bid, 1 g bid, 500 mg tid and 262 mg qid daily, respectively). We investigated eradication rate, side effects related to the medications and adherence.

The *H pylori* infection is diagnosed by histological examination of biopsies taken from patients in endoscopy. In our gastroenterology outpatient clinic, there is a routine protocol for the H.pylori eradications. Patients diagnosed with the active H.pylori infection are all asked for the antibiotic resistance and informed about the treatment regimens and their adverse effects. All patients who are prescribed antibiotic treatment are asked to visit at the end of the treatment regimen (2 weeks after enrollment) to check for adverse events and for drug adherence and to adjust eradication success and to check for side effects after 6 weeks of therapy. Data were obtained from patient records and the patients with incomplete records were excluded from the study. The study was performed according to the guidelines for Good Clinical Practice and the Declaration of Helsinki (1996 version, amended October 2000). Abdurrahman Yurtaslan Oncology Training And Research Hospital Local Ethics Committe approved the study with the number of 2019/447. Since the study was retrospective informed consents could not be obtained, so the patients privacy information was removed from the data analysis.

Patient previously treated with H. pylori; with an allergy to the started medications; pregnant or breast-feeding women, patients with gastric cancer, history of gastric surgery were excluded from the study.

Statistical analysis

Data analyzed using SPSS software for windows (IBM SPSS 20, IBM Corp,NY). Demographic features of two groups are compared with chi square test. All patients taken at least the first dose of started medications included and assessed for the ITT analysis. Only those who continue and complete the treatment without violating the regulations (violation is <80 % treatment compliance) included and assessed for the PP analysis. $p<0.05$ was considered statistically significant.

Results

In a total of 278 patients were investigated. Among those, 34 patients were excluded due to missing data in their records. In that aspect totally 244 patients (142 in BQT group and 102 in MBQT group) were included in the analyses. Demographic features of the study participants are summarized in Table 1.

Totally 128 patients in BQT group and 102 patients in MBQT group completed the treatment (Table 2). Intention to treat analysis revealed 81.69 % and 88.23 % in BQT group and MBQT group, respectively. Per protocol analysis revealed 90.62 % and 95.74 % in BQT group and MBQT group, respectively.

The incidence of adverse events is summarized in Table 3. Compared with the MBQT group, all side effects were more common in the BQT group. The overall rate of adverse events was significantly more common in BQT group compared with the MBQT group (*p*:0.001). Among the adverse events, nausea-vomiting and abdominal discomfort was significantly more common in BQT group than MBQT group (*p*:0.001). The adverse events were mild and moderate in both groups and any life threatening adverse event was not determined in any of the patients.

DISCUSSION

In this study we determined that; the eradication rates of bismuth-containing quadruple therapy and modified bismuth-containing quadruple therapy were all high enough to be defined as effective. Eradication rates of ITT and PP were higher in MBQT group than the BQT group, but the differences were not statistically significant. The adverse events associated with these treatment modalities were generally more common in BQT group.

In Turkey, due to the resistance of clarithromycin and metronidazole, bismuth containing regimens generally recommended eradication of H. *Pylori* infection. The mostly preferred and recommended treatment modality is the BQT. In previous literature there are many studies reporting the efficiency of this treatment. Gao et al reported that, in 120 patients with known penicillin allergies, the eradication rates were 86.7 % for ITT and 94.5 % for PP (15). Salmanroghani et al (16) compared the efficacy and tolerability of tetracycline with high-dose amoxicillin (1000 mg three times a day) in bismuth-based quadruple therapy and reported that eradication rate was higher with the amoxicillin-containing regimen than the tetracycline-containing regimen: 95.51 % vs. 83.8 % by per-protocol analysis and 92.9 % vs.

76.5 % by intention-to-treat analysis.Castro Fernández et al (17) reported that with three-in-one capsule formulation containing bismuth subcitrate, metronidazole and tetracycline, treatment compliance was 96 % and in 28.5 % of the patients adverse effects were determined. The effectiveness of this treatment based on intention to treat was 91.5 % and per protocol was 95.2 %. Very recently Alsamman et al (18) compared different treatment modalities in H. pylori eradication including quadruple, triple and doxycycline quadruple regimens and reported that Quadruple therapy for 14 days was the best.

Modified quadruple therapy was defined as an alternative for this treatment with high cure rates. Zhang et al (19) compared the efficacy and tolerability of 14-ay modified bismuth quadruple therapy: lansoprazole, amoxicillin, bismuth potassium citrate, with metronidazole or clarithromycin and both regimens were highly effective. Cure rates of ITT and PP were 96.9 % and 88.9 % in metronidazole administered group, respectively. Choe et al (20) reported the cure rates with 14-day bismuth containing quadruple therapy as 88.1 % by ITT and 96.6 % by PP analysis and defined this treatment as an alternative to triple therapy for the first-line eradication. Chen et al (21) reported that both ampiric modified bismuth quadruple therapy and susceptibility-guided therapy were highly effective with ITT rates of 85.4 % and 91.6 % , respectively and with per-protocol eradication rates of 97.6 % and 97.7 % without any significant differences.

The data comparing these two regimens is limited in previous literature. Chen et al (22) compared bismuth-containing quadruple therapies with tetracycline or amoxicillin for rescue treatment of H.pylori and reported that the ITT and PP rates were 88.5 % and 93.7 % for amoxicillin and 87.2 % and 95.3 % for tetracycline groups, respectively. They also reported that compliance was higher and adverse events were less common in amoxicillin group than tetracycline group. Our findings are also supporting these data. Lim et al (23) started a multicenter, randomized and open-label trial comparing quadruple therapy with modified bismuth therapy in Korea and still not reported the results.

In this study we determined that, the overall adverse effects were significantly more common in BQT group compared with the MBQT group (39.4 % vs. 18.6 %). Gao et al (15) r eported mild to moderate adverse effects in 46.7 % of the patients and Jheng et al (24) reported the adverse events in 22.2 % of the patients treated with BQT. Choe et al (17) reported the rate of adverse events as 23 % in patients treated with MBQT. Our results were

also compatible with the previous literature regarding the rates of adverse events.

There are some limitations of this study that should be mentioned. First, this is a retrospective study performed in a single tertiary hospital. Phenotypic or genotypic antibiotic resistance testing was not performed which was the main limitation of this study. Different time periods of treatments were not analyzed which may be the topic of another study.

CONCLUSION

We compared the efficiency and safety profiles of bismuth containing treatment regimens, quadruple therapy and modified quadruple therapy, in Turkey. Although both regimens were highly effective and safe in H. pylori eradication; both ITT and PP eradication rates were higher and adverse events were lower in modified quadruple therapy group. Modified quadruple therapy should be kept in mind in H. Pylori first line therapy in regions with high resistance of metronidazole and clarithromycin treatment.

AUTHOR CONTRIBUTIONS

Study design: A.Y, B.K; Data collection: S.D, F.C.S; Data analysis: S.D, F.C.S; Manuscript preparation: A.Y, B.K.

Acknowledgements:

The authors declare that there are no conflicts of interest in this study. In the process of research and writing of this manuscript we declare that we do not receive any financial support.

REFERENCES

1 Schistosomes, liver flukes and Helicobacter pylori. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7-14 June 1994. IARC monographs on the evaluation of carcinogenic risks to humans. 1994;61:1-241.

2 Fischbach W, Malfertheiner P. Helicobacter Pylori Infection. Deutsches Arzteblatt international. 2018 Jun 22;115(25):429-36.

3 Cagdas U, Otag F, Tezcan S, Sezgin O, Aslan G, Emekdas G. [Detection of Helicobacter pylori and antimicrobial resistance in gastric biopsy specimens]. Mikrobiyoloji bulteni. 2012 Jul;46(3):398-409.

4 Megraud F. H pylori antibiotic resistance: prevalence, importance, and advances in testing. Gut. 2004 Sep;53(9):1374-84.

5 Houben MH, van de Beek D, Hensen EF, de Craen AJ, Rauws EA, Tytgat GN. A systematic review of Helicobacter pylori eradication therapy--the impact of antimicrobial resistance on eradication rates. Alimentary pharmacology & therapeutics. 1999 Aug;13(8):1047-55.

6 Malfertheiner P, Megraud F, O'Morain CA, et al. Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report. Gut. 2017 Jan;66(1):6-30.

7 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 Apr;24(2):e12565.

8 Dore MP, Leandro G, Realdi G, Sepulveda AR, Graham DY. Effect of pretreatment antibiotic resistance to metronidazole and clarithromycin on outcome of Helicobacter pylori therapy: a meta-analytical approach. Digestive diseases and sciences. 2000 Jan;45(1):68-76.

9 Özden A BG, Bağlan P. Helicobacter pylori'nin klaritromisine karşı direncinin sıklığı. Turkish Journal of Gastroenterology. 2004;15 (Suppl 1):40.

10 Onder G, Aydin A, Akarca U, Tekin F, Ozutemiz O, Ilter T. High Helicobacter pylori resistance rate to clarithromycin in Turkey. Journal of clinical gastroenterology. 2007 Sep;41(8):747-50.

11 De Francesco V, Giorgio F, Hassan C, et al. Worldwide H. pylori antibiotic resistance: a systematic review. Journal of gastrointestinal and liver diseases : JGLD. 2010 Dec;19(4):409-14.

12 Kocazeybek B, Tokman HB. Prevalence of Primary Antimicrobial Resistance of H. pylori in Turkey: A Systematic Review. Helicobacter. 2016 Aug;21(4):251-60.

13 Papastergiou V, Georgopoulos SD, Karatapanis S. Treatment of Helicobacter pylori infection: meeting the challenge of antimicrobial resistance. World journal of gastroenterology. 2014 Aug 7;20(29):9898-911.

14 Sezgin O, Aydin MK, Ozdemir AA, Kanik AE. Standard triple therapy in Helicobacter pylori eradication in Turkey: Systematic evaluation and meta-analysis of 10-year studies. The Turkish journal of gastroenterology : the official journal of Turkish Society of Gastroenterology. 2019 May;30(5):420-35.

15 Gao W, Zheng SH, Cheng H, et al. [Tetracycline and metronidazole based quadruple regimen as first line treatment for penicillin allergic patients with Helicobacter pylori infection]. Zhonghua yi xue za zhi. 2019 May 28;99(20):1536-40.

16 Salmanroghani H, Mirvakili M, Baghbanian M, Salmanroghani R, Sanati G, Yazdian P. Efficacy and Tolerability of Two Quadruple Regimens: Bismuth, Omeprazole, Metronidazole with Amoxicillin or Tetracycline as First-Line Treatment for Eradication of Helicobacter Pylori in Patients with Duodenal Ulcer: A Randomized Clinical Trial. PloS one. 2018;13(6):e0197096.

17 Castro Fernandez M, Romero Garcia T, Keco Huerga A, et al. Compliance, adverse effects and effectiveness of first line bismuth-containing quadruple treatment (Pylera(R)) to eradicate Helicobacter pylori infection in 200 patients. Revista espanola de enfermedades digestivas : organo oficial de la Sociedad Espanola de Patologia Digestiva. 2019 Jun;111(6):467-70.

18 Alsamman MA, Vecchio EC, Shawwa K, Acosta-Gonzales G, Resnick MB, Moss SF. Retrospective Analysis Confirms Tetracycline Quadruple as Best Helicobacter pylori Regimen in the USA. Digestive diseases and sciences. 2019 Oct;64(10):2893-8.

19 Zhang W, Chen Q, Liang X, et al. Bismuth, lansoprazole, amoxicillin and metronidazole or clarithromycin as first-line Helicobacter pylori therapy. Gut. 2015 Nov;64(11):1715-20.

20 Choe JW, Jung SW, Kim SY, 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 Apr;23(2):e12466.

21 Chen Q, Long X, Ji Y, et al. Randomised controlled trial: susceptibility-guided therapy versus empiric bismuth quadruple therapy for first-line Helicobacter pylori treatment. Alimentary pharmacology & therapeutics. 2019 Jun;49(11):1385-94.

22 Chen Q, Zhang W, Fu Q, et al. Rescue Therapy for Helicobacter pylori Eradication: A Randomized Non-Inferiority Trial of Amoxicillin or Tetracycline in Bismuth Quadruple Therapy. The American journal of gastroenterology. 2016 Dec;111(12):1736-42.

23 Lim H, Bang CS, Shin WG, et al. Modified quadruple therapy versus bismuth-containing quadruple therapy in first-line treatment of Helicobacter pylori infection in Korea; rationale and design of an open-label, multicenter, randomized controlled trial. Medicine. 2018 Nov;97(46):e13245.

24 Jheng GH, Wu IC, Shih HY, et al. Comparison of Second-Line Quadruple Therapies with or without Bismuth for Helicobacter pylori Infection. BioMed research international. 2015;2015:163960.

Table 1. Demographic and clinical characteristics of patients

	BQT group (n:142)	MBQT group (n:102)	p
Gender (M/F)	56/86	42/60	0.714
Age (years)	49.21±7.42	48.62±8.64	0.821
Smoking habit (%)	98 (69.01)	69 (67.67)	0.854

M: Male; F: Female; Age data are presented as mean ± SD (Student T Test); Gender, smoking habit (Chi square test); P< 0.05

Table 2. Treatment compliance, H. Pylori eradication rates, and drug adverse effects

	BQT group (n:142)	MBQT group (n:102)	p
Completion of treatment (%)	128 (90.14)	94 (92.15)	0. 151
Rate of eradication	116	90	0.121
ITT (95 % CI)	81.69 (75.9-88.1 %)	88.23 (80.8-93.9 %)	0.210
PP (95 % CI)	90.62 (85.5-95.7 %)	95.74 (91.5-99.8 %)	0.121

Chi square test

Table 3. Drug adverse effects

	BQT group (n:142)	MBQT group (n:102)	p
Skin rash	8 (5.6)	4 (3.9)	0.561
Nausea ± vomiting	26 (18.3)	9 (8.8)	0.001
Metallic taste	21 (14.7)	15 (11.7)	0.681
Abdominal discomfort	24 (16.9)	6 (5.8)	0.001
Dizziness	16 (11.2)	9 (8.8)	0.232
Headache	14 (9.8)	8 (7.8)	0.412
Total	56 (39.4)	19 (18.6)	0.001

Chi square test

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology