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Title: Two-week bismuth-containing quadruple and concomitant therapy are effective first-line treatments for Helicobacter pylori eradication: A prospective open-labeled randomized trial

Dear Editors,

I would like to thank the editors and reviewers of the 'World journal of gastroenterology' taking their time to review my article. Reviewer's comments were very helpful for us to correct and revise our manuscript. We corrected what suggested by the reviewers and all changes we made are summarized below. We hope that our revised manuscript will be suitable for publication in World Journal of Gastroenterology.

Sincerely,

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Revision notes

The following is a point-by-point response to the reviewers' comments

Reviewer 1:

The study of Kim SJ et al has the aim of comparing two-week bismuth-containing quadruple and concomitant therapy effectiveness in first-line treatments for Helicobacter pylori eradication. The topic is not very new, since these strategies have been recommended by Italian (Zagari et al, 2015) and European (Malfertheiner et al, 2017) guidelines. However, the design is well constructed and realized. Objections are:

Comments:

1. Some linguistic corrections regarding both style and grammar need to be performed by a native speaker.

Answer:

Thanks for the comment on the language of our paper. Styles and grammar were modified throughout the manuscript.

2. It is unclear if bismuth containing quadruple regimen enclosed the use of the well-known three-in-one formulation, since antibiotic doses do not seem to agree with this pharmaceutical product, which, on the other hand, provides a package that can be used for a 10-day cycle. This aspect must be skillfully detailed.

Answer:

We appreciate your pointing out. Our bismuth containing quadruple regimen dose not contained three-in-one formulation but, each individual drugs. We have added name of product contained bismuth containing quadruple regimen and concomitant therapy in the method section as below (page 8, line 3-8). Thank you very much for your careful concern.

Eradication of H. pylori

The mBCQT regimen featured lansoprazole [Lanston LFDT® Tab] 30 mg, tripotassium bismuth dicitrate 600mg [Denol® tab.], tetracycline [Tetracycline® Cap.] 1,000 mg, and metronidazole [Flasinyl® Tab.] 500 mg twice daily for 2 weeks. CT featured lansoprazole [Lanston LFDT® Tab.] 30 mg, clarithromycin [Kloma® Tab.] 500 mg, amoxicillin [Amoxapen® Cap.] 1,000 mg, and metronidazole [Flasinyl® Tab.] 500 mg twice daily for 2 weeks.

3. Were probiotics associated to antibiotic treatments to reduce side effects? And if not, why?

Answer:

Recent researches showed that the use of probiotics with *H. pylori* eradication may be reduced adverse effects, especially antibiotic-related gastrointestinal side effects. (Shi et al. Medicine 2019; 98:15) And the Maastricht V/Florence Consensus Report also mentioned that certain probiotics reduced side-effects related to eradication therapy [Malfertheiner P *et al. Gut.* 2017; 66(1):6-30.]

In our study, the probiotics were not administered, and side effects were relatively frequent. Further studies on the eradication regimens added probiotics are needed. And we are willing to supplement this issue in the discussion and reference section as below (page11, line 20-25; page 18, line 1-3). Thank you for kindly reminding us this point.

Although neither of our regimens was associated with serious side-effects, the

overall incidence of side-effects was relatively high. Further efforts to reduce side-effects, perhaps via addition of probiotics, are essential[25]. Previous studies have found that certain probiotics, such as Lactobacillus genus and Bacillus clausii, reduce gastrointestinal problems and other side effects of eradication therapies[2,26]. It has been suggested that the increase in *H. pylori* eradication seen with use of these probiotics is not a direct effect of the probiotics, but a result of the associated reduction in side effects of therapy[2,26].

26 **Shi X**, Zhang J, Mo L, Shi J, Qin M, Huang X. Efficacy and safety of probiotics in eradicating Helicobacter pylori: A network meta-analysis. Medicine (Baltimore). 2019; 98(15): e15180 [PMID: 30985706 DOI: 10.1097/MD.0000000000015180].

4. The use of furazolidone as rescue therapy is suggested. The drug was ordered to be removed even from animals as an antibiotic by the FDA in 2002 as well as the European Medicinal Agency (EMEA; the equivalent of the FDA in the European Union) banned the drug in Europe (De Francesco et al, 2009-2012). A discussion about this problem is mandatory.

Answer:

As you mentioned, the furazolidone was removed from animal use and it is known that teratogenic and potentially carcinogenetic agent. But according to the International Agency for Research on Cancer, the drug was listed as Class III drug which is unclassifiable as to carcinogenicity in humans, even though metronidazole is classified as a Class 2B (possibly carcinogenic to humans).(Graham DY et al. *Saudi J Gastroenterol*. 2012;18(1):1–2.)

Therefore, we are willing to discuss the potential issue about carcinogenicity of furazolidone use in the discussion section and add the reference below. (page 12, line 8-17; page 18, line 12-21).

Also, furazolidone-resistant *H. pylori* is rare; the drug afforded satisfactory eradication rates (relative risk 1.17, 95% CI: 1.05–1.31)[28]. In a multivariate analysis, an

increased eradication rate when using high-dose furazolidone was noted (OR: 1.5, 95% CI: 1.3-2.7; *P*<0.001)[29]. According to a recent *in vitro* analysis, there were no strains resistant to rifabutin or furazolidone among *MDR H. pylori* (MICs <0.008; < 0.5 μg/mL). This suggests that rifabutin- and furazolidone-containing regimens have promise as rescue therapies[30]. However, there is controversy over the use of furazolidone-containing regimens because of the drug's potential carcinogenicity. Thus, furazolidone-containing regimens are recommended only in areas with high rates of resistance and for patients who have multiple prior treatment failures and have received patient counseling[29,31].

29 **Zullo A**, Ierardi E, Hassan C, De Francesco V. Furazolidone-based therapies for Helicobacter pylori infection: a pooled-data analysis. *Saudi J Gastroenterol*. 2012; 18(1): 11–17 [PMID: 22249086 DOI: 10.4103/1319-3767.91729.]

30 **Choi YI**, Jeong SH, Chung JW, Park DK, Kim KO, Kwon KA, Kim YJ, So S, Lee JH, Jeong JY, Lee SM. Rifabutin and furazolidone could be the candidates of the rescue regimen for antibiotic-resistant *H. pylori* in Korea. Can J Infect Dis Med Microbiol. 2019: 9351801. [PMID: 31360270 DOI:10.1155/2019/9351801]

31 **Graham DY**, Lu H. Furazolidone in *Helicobacter pylori* therapy: misunderstood and often unfairly maligned drug told in a story of French bread. Saudi J Gastroenterol. 2012; 18(1): 1–2 [PMID: 22249084 DOI:10.4103/1319-3767.91724]

Reviewer 2:

"Two-week bismuth-containing quadruple and concomitant therapy are effective first-line treatments for Helicobacter pylori eradication: A prospective open-labeled randomized trial" is an interesting paper. The trial is well designed and has reached a wide sample size. The paper discusses an actual topic and shows that BCQT could be considered an effective therapy for H. Pylori eradication, despite of bismuth-related side effects. References are of good quality.

Comments:

1. I suggest to update Rifabutin bibliography, as ref. 26 is quite bygone (add a more recent study such as Ribaldone et al, J Clin Med 2019, PMID: 30736338).

Answer:

Thank you for kindly reminding us this point. We reflected recent eradication rate of rifabutin on our study. We are willing to change this point in the revised paper as below (page12, line 3-7; page 18, line 4-8).

One study of rifabutin-based therapy reported an eradication rate over 70% (72.7%, 95%CI: 67.3%–77.7%, PP analysis; 71.5%, 95%CI: 66.1%–76.5%, ITT analysis)[27]. Although rifabutin-resistant *H. pylori* has been reported, rifabutin-based regimens may be useful as rescue therapies because rifabutin can be used without culture and antibiotic susceptibility testing[27].

27 **Ribaldone DG**, Fagoonee S, Astegiano M, Durazzo M, Morgando A, Sprujevnik T, Giordanino C, Baronio M, De Angelis C, Saracco GM, Pellicano R. Rifabutin-based rescue therapy for *Helicobacter pylori* eradication: a long-term prospective study in a large cohort of difficult-to-treat patients. J Clin Med. 2019; 8(2): 199 [PMID: 30736338 DOI: 10.3390/jcm8020199]

Reviewer 3:

Helicobacter pylori infection is increasingly difficult to treat mainly due to antibiotic resistance. The authors performed a prospective, randomized controlled study comparing bismuth-containing quadruple therapy (BCQT) and concomitant therapy (CT) as potential first-line treatments for H. pylori infection in Korean patients. They found the eradication rate did not statistically differ between the two groups. Most patients showed good compliance, and more CT than BCQT patients experienced adverse events. However, mBCQT was somewhat preferable, considering both side-effects and patient's compliance. The sample size of this study was not big, but it can suggest that the four-drug, 2-week first-line regimens

are worth further exploring.

Answer:

We are appriciate for for your comments on our paper.

Reviewer 4:

In this prospective randomized study, the authors reported the efficacy rates of bismuth-containing quadruple therapy (BCQT) versus concomitant therapy (CT) as first-line therapy for Helicobacter pylori eradication.

Comments:

1. The authors should specify the method (the commercial kit) used to perform urea breath test if known.

Answer:

Thanks for the careful review opinion. We specified methods used urea breath test and rapid urease test in the method section below: (page 7, line 26-28; page 8, line 16-17)

When either the Giemsa stain or rapid urease test (HP kit®; Chong Kun Dang Bio, Seoul, Korea) was positive upon upper gastrointestinal endoscopy, *H. pylori* infection was diagnosed.

The [^{13}C]-urea breath test (UBiT-IR 300®/13C-Urea breath test system; Otsuka, Tokyo, Japan) was performed no earlier than 4 weeks after treatment concluded, at which time no patient had taken proton pump inhibitors (PPIs) for at least 2 weeks. Eradication failure was defined as a positive (delta 2.5) breath test.

2. Furthermore, they should report the period between antibiotic suspension and performance of the test.

Answer:

Thank you for kindly reminding us this point. It takes 6 to 8 weeks after antibiotic suspension until performance of the test. We reported the period between antibiotic suspension and performance of the test in the method section blow: (page 7, line 18)

The [^{13}C]-urea breath test was performed at 6 to 8 weeks after antibiotic suspension.

3. In the section Conclusion when the authors report study limitations, they should also report that the strength of the study is the similarity among the two groups and the randomized design.

Answer:

Thanks for the reviewer's valuable suggestion. We reported them in the discussion section below: (page 12, line 19-21)

The limitations of this study included the small number of patients, due to the single-center design. Also, we did not culture *H. pylori*. The strengths of our study include its randomized controlled design and the acceptable therapeutic efficacy in both the BCQT and CT groups.

4. Some references should be replaced by more appropriate (or more updated) ones.

Answer:

Thanks for the comment on the references of our paper. We changed them in the revised paper

4-1. Reference 1 should be replaced with the more updated Bittencourt de Brito et al. Pathogenesis and clinical management of Helicobacter pylori gastric infection. World J Gastroenterol 2019; 25(37):5578-5589.

Answer:

We changed it in the revised and the text related reference is the same in the introduction section. Below (page 14, line 4-7)

Helicobacter pylori (*H. pylori*) infection is the principal cause of peptic ulcer disease, mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma. *H. pylori* eradication cures or prevents these diseases[1].

1 **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; 25(37): 5578–5589. [DOI:10.3748/wjg.v25.i37.5578]

4-2. Reference 4 should be replaced with another regarding other area than Korea (see for example that coordinated by Prof. Moss who participated to ACG Guidelines. This review is entitled "Pharmacological considerations and step-by-step for the treatment of Helicobacter pylori infection in the year 2018" Minerva Gastroenterol Dietol 2018; 64:310-21).

Answer:

We reflected the resistance of H. pylori eradication therapies in other countries including Europe in our study. We are willing to changed it in the discussion section and reference below (page 6, line 8-9; page 14, line 18-21)

The eradication rate afforded by legacy triple therapy (LTT) (the historical first-line treatment for *H. pylori* infection; LTT includes clarithromycin) has declined over the past decade, and has decreased to near 80% or below in some countries of Asia and Europe[2-4].

4 **Pellicano R,** Zagari RM, Zhang S, Saracco GM, Moss SF. Pharmacological considerations and step-by-step proposal for the treatment of *Helicobacter pylori*

infection in the year 2018. Minerva Gastroenterol Dietol 2018; 64(3): 310-321 [PMID: 29600697 DOI: 10.23736/S1121-421X.18.02492-3]

4-3. Reference 12 should be corrected (year and volume).

Answer: Thank you for pointing out the error. We changed them in the references section below: (page 16, line 4)

12 **Macías-García F**, Bastón-Rey I, de la Iglesia-García D, Calviño-Suárez C, Nieto-García L, Domínguez-Muñoz JE. Bismuth-containing quadruple therapy versus concomitant quadruple therapy as first-line treatment for *Helicobacter Pylori* infection in an area of high resistance to clarithromycin: A prospective, cross-sectional, comparative, open trial. *Helicobacter.* 2019; 24(1): e12546 [PMID: 30346636 DOI: 10.1111/hel.12546]

4-4. Reference 27 should be replaced with the more appropriate Pellicano et al. Rifabutin-Based Rescue Therapy for Helicobacter pylori Eradication: A Long-Term Prospective Study in a Large Cohort of Difficult-to-Treat Patients. J Clin Med. 2019 Feb 6; 8(2). pii: E199

Answer :

Thank you for kindly reminding us this point. In the updated reference, we recognized that increasing resistance of rifabutin for *H. pylori* eradication has been reported. Thus we are willing to change this point in the revised paper as below. (page 12, line 3-7; page 18, line 4-8)

One study of rifabutin-based therapy reported an eradication rate over 70% (72.7%, 95%CI: 67.3%–77.7%, PP analysis; 71.5%, 95%CI: 66.1%–76.5%, ITT analysis)[27]. Although rifabutin-resistant *H. pylori* has been reported, rifabutin-based regimens may be useful as rescue therapies because rifabutin can be used without culture and antibiotic susceptibility testing[27].

27 **Ribaldone DG**, Fagoonee S, Astegiano M, Durazzo M, Morgando A, Sprujevnik T, Giordanino C, Baronio M, De Angelis C, Saracco GM, Pellicano R. Rifabutin-based rescue therapy for *Helicobacter pylori* eradication: a long-term prospective study in a large cohort of difficult-to-treat patients. J Clin Med. 2019; 8(2): 199 [PMID: 30736338 DOI: 10.3390/jcm8020199]