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Comparative Efficacy and Safety of Bismuth Quadruple and Concomitant Therapy for Empirical *Helicobacter pylori* Eradication: A Meta-Analysis of Randomized Clinical Trials

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Abstract: *Aims*: To compare the efficacy and safety of bismuth quadruple therapy with concomitant therapy in the empirical eradication of *Helicobacter pylori* (*H. pylori*) infection. *Methods*: Such databases as PubMed, Embase and the Cochrane Library and Chinese databases (China National Knowledge Infrastructure (CNKI), Wanfang Data and CBM), were searched for relevant randomized controlled trials up to February 2020. Studies were included if they assessed the efficacy and safety of bismuth quadruple therapy versus concomitant therapy in *H. pylori* eradication. Statistical analysis was performed with RevMan software 5.3. *Results*: Four studies with 616 patients were evaluated in this meta-analysis. The *H. pylori* eradication rate of bismuth quadruple therapy was similar to that of concomitant therapy (intention-to-treat analysis: pooled eradication rates, 85.5% vs 80.7%; odds ratio [OR], 1.42; 95%confidence interval (CI): [0.92–2.18]; $P>0.05$). The incidence of adverse events in bismuth quadruple therapy was lower than those in concomitant therapy (pooled incidence, 18.3% vs 25.9%; OR, 0.62, 95%CI: [0.41–0.92]; $P<0.05$). *Conclusions*: Bismuth quadruple therapy had the same efficacy to concomitant therapy in *H. pylori* eradication, and bismuth quadruple therapy was possibly better tolerated than concomitant therapy. Therefore, bismuth quadruple therapy and concomitant therapy should be equally recommended as empirical regimens in *H. pylori* eradication.

Keywords: *Helicobacter pylori*, Bismuth Quadruple Therapy, Concomitant Therapy, Meta-Analysis

1. Introduction

About 50% population in the world were estimated to be infected with *Helicobacter pylori* (*H. pylori*) [1]. *H. pylori* infection causes many gastrointestinal diseases, such as chronic gastritis, peptic ulcer, gastric cancer [2, 3]. Therefore, eradication of *H. pylori* infection would cure chronic gastritis or peptic ulcer, decrease recovery rates of chronic gastritis or peptic ulcer, and also decrease the incidences of gastric cancer.

For *H. pylori* infection, the recommended eradication regimen was triple therapy (proton pump inhibitor (PPI), amoxicillin, and clarithromycin or metronidazole) in the past guidelines. However, the eradication rates afforded by triple therapy has been declining over the past decade and has decreased to near 80% or below in 60% of countries worldwide, owing to increased *H. pylori* resistance to clarithromycin and metronidazole [4, 5]. Currently, bismuth quadruple therapy (PPI, bismuth and two antibiotics) and concomitant therapy (PPI and three antibiotics) were recommended as first-line treatments in the Maastricht V consensus and Fifth Chinese national consensus, if the prevalence of primary clarithromycin resistance is >15% [2, 3].

Many meta-analyses have investigated the efficacy and safety of bismuth quadruple therapy (BQT) or concomitant therapy (CT) versus standard triple therapy, levofloxacin-based triple therapy or sequential therapy [6-9]. However, there is currently no meta-analysis about the efficacy and safety of BQT versus CT. Therefore, we performed a meta-analysis of the available randomized

controlled trials to compare the efficacy and safety of BQT with CT in *H. pylori* eradication.

2. Methods

2.1. Criteria for Considering Studies for This Meta-Analysis

Types of Studies:

Only randomized controlled trials (RCTs) evaluating BQT versus CT for the eradication of *H. pylori* were considered. The language of the studies was restricted to Chinese and English. The following were excluded: (1) animal or non-clinical studies; (2) other study designs (letters, case reports, editorials, commentaries and reviews, etc.); (3) studies with incomplete data such as abstract-only publications; and (4) studies with duplicate data.

2.2. Types of Participants

2.2.1. Inclusion Criteria

RCTs were eligible for inclusion if enrolled participants were diagnosed as positive for *H. pylori* (with one or more confirmatory tests) on the basis of the urea breath test (UBT), histology, rapid urease test, culture, and stool *H. pylori* antigen.

2.2.2. Exclusion Criteria

RCTs were excluded if enrolled participants were diagnosed as *H. pylori*-positive solely on the basis of serology or polymerase chain reaction (PCR).

2.3. Types of Interventions

Only head-to-head RCTs were included.

Duration of treatment were similar, and proton pump inhibitors were also similar to exclude the interference of duration and proton pump inhibitors.

2.4. Types of Outcome Measures

RCTs were eligible if *H. pylori* eradication was only confirmed by UBT or stool *H. pylori* antigen, at least 4 weeks after eradication therapies. The meta-analysis assessed mainly the following outcomes. (1) Eradication rates of intention-to-treat (ITT) and per protocol (PP) analyses. (2) Incidences of adverse events (ITT): Adverse events included diarrhea, nausea, and any type of adverse events.

2.5. Search Strategy

2.5.1. Electronic Searches

Medical literatures were searched from PubMed, Embase, the Cochrane Library and Chinese databases (Wanfang Data, China National Knowledge Infrastructure (CNKI), Chinese BioMedical Literature database (CBM)) for relevant RCTs up to February 20, 2020. The following terms were used: ("concomitant" or "concurrent" or "quadruple") and ("Bismuth") and ("*Helicobacter pylori*" or "*Campylobacter pylori*") and ("randomized controlled trial") NOT ("sequential" OR "hybrid"). The language of the studies was restricted to English and Chinese.

2.5.2. Searching Other Resources

Two investigators (performed the manual searches from the reference lists of included studies and related meta-analysis about BQT or CT for identifying relevant trials.

2.6. Data Collection and Analysis

2.6.1. Selection of Studies

According to the method of previous studies [10, 11], two investigators (independently excluded the duplicate studies using Endnote software Version X8 and manual screening (author, title, journal, publication year, journal volume and issue, pages). Second, two investigators excluded the irrelevant studies through checking the title and abstract of articles. Lastly, two investigators screened the full-text of the remaining studies according to the inclusion and exclusion criteria. Disagreements were reconciled by a discussion.

2.6.2. Data Extraction

Two investigators (independently extracted data using a predesigned data extraction form: first author, publication year, country, patients, number, treatments, eradication regimens (BQT and CT), treatment duration, follow-up time, infection and eradication confirmative test, eradication rate (ITT and PP analyses), and adverse events.

2.6.3. Assessment of Risk of Bias in Included Studies

According to the method of previous studies [11, 12], the risk of bias of included RCTs was assessed using the Cochrane Risk of Bias assessment tool: (1) how the random sequence was generated; (2) how patient allocation was concealed; (3) blinding of the patients and researchers; (4) blinding of outcome assessment; (5) whether there were incomplete outcome data; (6) whether there was selective outcome reporting; and (7) other potential biases.

2.6.4. Assessment of Heterogeneity

Heterogeneity was evaluated by Cochrane's Q test, which was considered statistically significant for heterogeneity if P was <0.1, and I^2 statistics, for which <25%, 25–50% or >50% suggested low, moderate and high heterogeneity, respectively.

2.6.5. Assessment of Reporting Biases

Since less than 10 studies were included, the publication bias was not evaluated.

2.6.6. Data Synthesis and Statistical Analysis

Meta-analyses were conducted using RevMan version 5.3 (Cochrane Collaboration, Copenhagen, Denmark). Where the heterogeneity was not obvious (P<0.10, I^2>50%), the fixed-effect model was employed; otherwise, the random-effect model was used. All statistical tests were two-tailed; P<0.05 was considered statistically significant in all tests (except for the heterogeneity test), and pooled odds ratios (ORs) with 95% confidence interval (CI) were calculated.

3. Results

3.1. Studies Selection and Characteristics of Included Studies

We identified 942 studies using the defined terms. After four hundred and seventeen duplicate studies were removed, another 516 irrelevant studies were discarded because of non-relevant issue, non-head-to-head comparisons, abstract only, review articles and meta-analysis. After examination of the full text of the remaining nine articles, we finally selected four studies with sufficient data for inclusion in this meta-analysis (Figure 1). Six hundred and sixteen patients were enrolled in four studies. Of four studies, three studies were conducted in Asian region (China Mainland, Taiwan, and Korea) and only one study was done in European region (Turkey). Additionally, except one 10-day duration study, 14-day duration BQT and CT were assessed as first-line empirical treatments in three studies. In all four studies, eradication success was confirmed using the UBT at least 4 weeks after eradication therapies (Table 1).

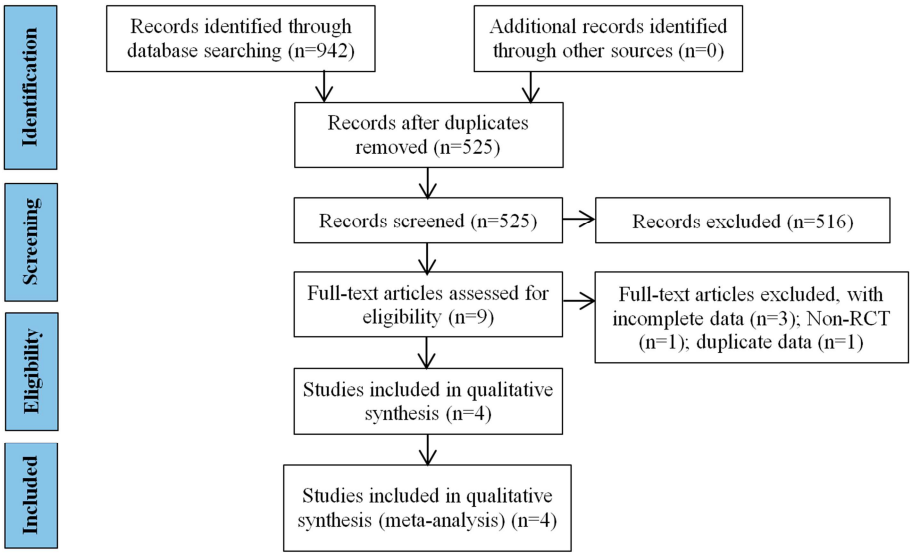

Figure 1. *Flow chart showing study selection.*

Table 1. *Characteristics of studies included in the meta-analysis.*

Study	Year	Country	Patients	Treatments	Bismuth quadruple therapy
Uygun A [13]	2012	Turkey	H. Pylori positive, non-ulcer dyspepsia	first-line eradication	esomeprazole 40 mg bid, bismuth subsalicylate 300 mg qid, amoxicillin 1 g bid, tetracycline 500 mg qid
Jheng GH [14]	2015	Taiwan	H. Pylori positive	second-line eradication (failure of standard triple therapy)	rabeprazole 20 mg bid, bismuth subcitrate 120 mg qid, tetracycline 500 mg qid, and metronidazole 250 mg qid
Li M [15]	2017	China	H. Pylori positive	first-line eradication	rabeprazole 20 mg bid, colloidal bismuth pectin 150 mg tid, amoxicillin 1 g bid, clarithromycin 500 mg bid
Kim SJ [16]	2019	Korea	H. Pylori positive and peptic ulcer disease, gastritis, gastric polyps, or early gastric cancer	first-line eradication	lansoprazole 30 mg bid, tripotassium bismuth dicitrate 600 mg bid, tetracycline 1000 mg bid, and metronidazole 500 mg bid

Table 1. *Continued.*

Study	Concomitant therapy	Treatment duration	Infection confirmative test	Follow-up	Eradication confirmative test	Number
Uygun A [13]	esomeprazole 40 mg bid, metronidazole 500 mg tid, amoxicillin 1 g bid, tetracycline 500 mg qid	14 days	histology, 14C-UBT (both positive)	6 weeks	14C-UBT	200
Jheng GH [14]	rabeprazole 20 mg bid, amoxicillin 1 g bid, tetracycline 500 mg qid, and metronidazole 250 mg qid	10 days	^{13}C-UBT, histology, culture	4 weeks	^{13}C-UBT	124
Li M [15]	rabeprazole 20 mg bid, metronidazole 400 mg bid, amoxicillin 1 g bid, clarithromycin 500 mg bid	14 days	^{14}C-UBT	4 weeks	^{14}C-UBT	156
Kim SJ [16]	lansoprazole 30 mg bid, clarithromycin 500 mg bid, amoxicillin 1000 mg bid, and metronidazole 500 mg bid	14 days	rapid urease test, histology (at least one positive)	4 weeks	^{13}C-UBT	136

UBT, urea breath test

3.2. Risk of Bias

Four RCTs showed low risk of bias according to the Cochrane Risk of Bias tool (Figure 2).

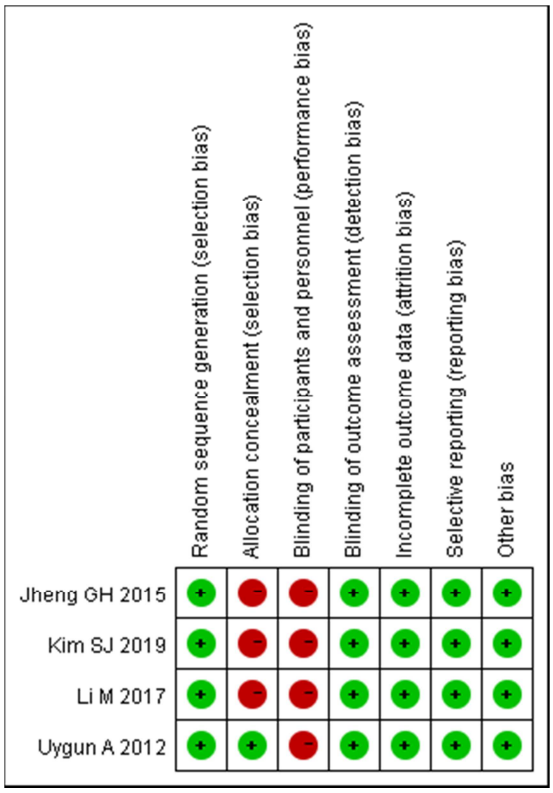

Figure 2. *Assessment of bias risk.*

3.3. Efficacy of Bismuth Quadruple Therapy (BQT) Versus Concomitant Therapy (CT)

No significant heterogeneity was identified in the ITT or PP analysis (Cochrane's Q test, df=3, P>0.1, I^2=0%). In the ITT analysis (Figure 3), *H. pylori* eradication rate of BQT was similar to CT (pooled eradication rates, 85.5% vs 80.7%; OR, 1.42; 95%CI: [0.92–2.18]; P>0.05). Interestingly, eradication rate of BQT was higher than that of CT (pooled eradication rates, 92.3% vs 86.1%; OR, 3.55; 95%CI: [1.46–8.66]; P<0.05) in the PP analysis (Figure 4). Because the non-compliant or withdrawing patients were included in the ITT analysis to minimize bias, ITT analysis was preferred to PP analysis [17]. When the data of ITT analysis were contrary to those of PP analysis, results from ITT analysis were interpreted in discussion.

3.4. Safety of Bismuth Quadruple Therapy (BQT) Versus Concomitant Therapy (CT)

All four studies provided an overall and detailed incidences of adverse events. The overall incidence of adverse events in BQT was markedly lower than that in CT (pooled incidences, 18.3% vs 25.9%; OR, 0.62; 95%CI: [0.41–0.92]; P<0.05; Cochrane's Q test, df=3, P>0.1, I^2=48%) (Figure 5). To analyze further the safety of the two regimens, we assessed the incidences of two common adverse events vomiting and diarrhea. Diarrhea incidence of BQT was markedly lower than that in CT, but vomiting incidences were similar between BQT and CT (diarrhea: 2.9% vs 6.9%, P<0.05; vomiting: 9.1% vs 10.0%, P>0.05) (Table 2).

Table 2. *Occurrence rate of common adverse events between bismuth quadruple therapy (BQT) versus concomitant therapy (CT).*

adverse events	BQT	CT	P value	heterogeneity test
diarrhea	2.9%	6.9%	0.02	P=0.23, I^2=30%
vomiting	9.1%	10.0%	0.72	P=0.40, I^2=0%

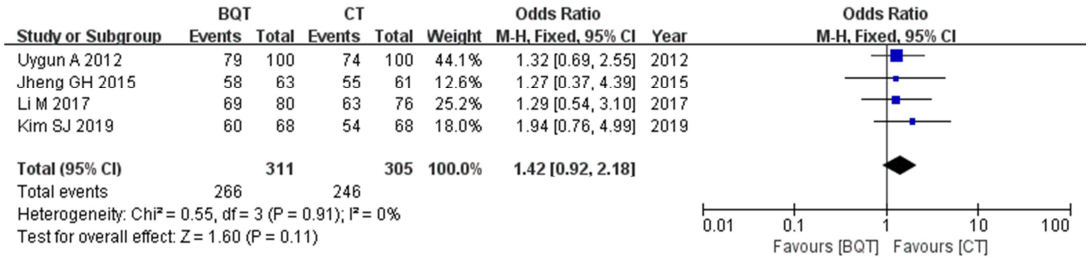

Figure 3. *Forest plot of bismuth quadruple therapy (BQT) versus concomitant therapy (CT) for H. pylori eradication in intention-to-treat analysis.*

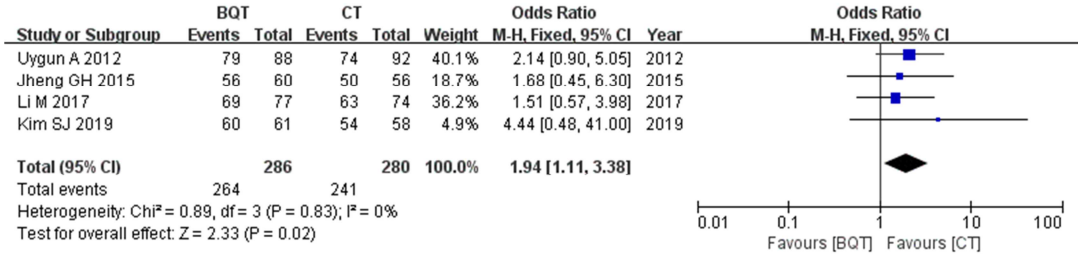

Figure 4. *Forest plot of bismuth quadruple therapy (BQT) versus concomitant therapy (CT) for H. pylori eradication in per-protocol analysis.*

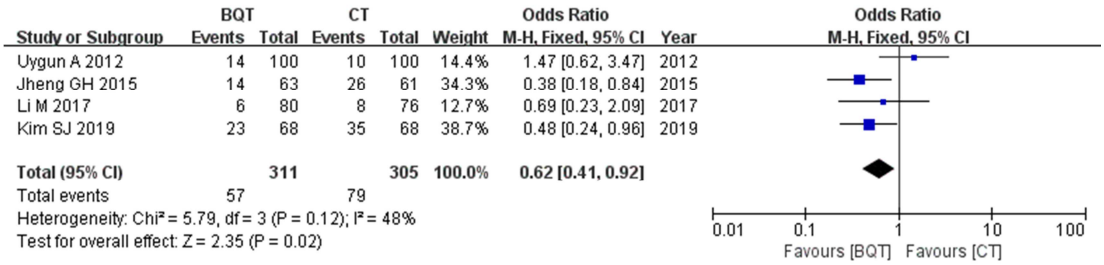

Figure 5. *Forest plot of overall adverse events between bismuth quadruple therapy (BQT) versus concomitant therapy (CT).*

4. Discussion

Owing to continuously decreasing eradication rates of standard triple therapy, other therapies were tested in many clinical trials, such as bismuth quadruple therapy (BQT), concomitant therapy (CT), sequential therapy and hybrid therapy. However, the complexity of sequential and hybrid therapies is an important disadvantage in routine practice, which reduced the patients' compliance and also the success rate of these treatments. In fact, efficacy of BQT or CT was superior to sequential therapy in same duration [8, 18, 19]. BQT and CT have been suggested as an alternatives for standard triple regimens in guidelines [2, 3].

Our meta-analysis demonstrated that BQT had the same eradication rate to CT (85.5% vs 80.7%; OR, 1.42; 95%CI: [0.92–2.18] in ITT analysis). These results were consistent with another study that reported eradication rates of BQT and CT as first-line treatment against *H. pylori* is similar in an area of high clarithromycin resistance, although the study is not a randomized controlled trial [20]. According to a report card introduced by Graham to grade *H. pylori* therapy [21], although the 85.5% eradication rate in BQT is fair (Grade C) and the 80.7% eradication rate in CT is poor (Grade D), eradication rates of BQT and CT reached to acceptable therapeutic efficacy (>80%). Of course, *H. pylori* eradication is influenced by many factors, such as therapy duration, antibiotic resistance, drug compliance. The high eradication rates of BQT and CT in the meta-analysis were possibly related to optimum duration (14-day) in the three studies, usage of low resistant antibiotics (tetracycline, amoxicillin) and good compliance (at least 82.4%) in all four studies.

Interestingly BQT was possibly safer than CT, so BQT would be well-tolerated. Most of adverse effects were mild adverse symptoms from digestive system, but serious side effects were scare. Additionally, withdrawing patients were relatively few because of adverse effects in studies. These facts indicated similar to BQT, CT was essentially well-tolerated.

Although BQT and CT was beneficial in empirical *H. pylori* eradication, several limitations in our meta-analysis was still a concern. First, the number of RCTs included was small, which precluded comparable ascertainment of the outcome. Second, because most studies was conducted in Asian regions, it may have increased selection bias. Whether the same results could be achieved in the American, European or African regions still be a question, because antibiotic resistance features of *H. pylori* varied among different regions [22]. Third, comparative BQT and CT as second-line treatments have not been extensively studied, and any conclusions made here must be cautious when BQT and CT were used as second-line treatment of standard triple therapy failure. Fourth, restricted language would lead to selection bias.

5. Conclusions

Based on the results of our meta-analysis, efficacy of bismuth quadruple therapy is similar to that of concomitant therapy in *H. pylori* eradication, and bismuth quadruple therapy is possibly better tolerated than concomitant therapy. Therefore, bismuth quadruple therapy and concomitant therapy should be equally recommended as empirical regimens in *H. pylori* eradication. However, owing to the small number and sample sizes of the included studies, the above conclusions need to be considered with caution and need to be validated in a large-scale prospective randomized trial.

Competing Interests

The authors have declared no conflicts of interest.

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