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Efficacy and Safety of Hybrid Therapy for *Helicobacter pylori* Eradication: A Meta-Analysis of Head-to-Head Randomized Clinical Trials

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Abstract: *Background*: The efficacy and safety of hybrid therapy as the empirical first-line therapy was still unclear in *Helicobacter pylori* (*H. pylori*) infection, so the efficacy and safety of hybrid therapy was evaluated which was compared to the other eradication therapies in guidelines. *Methods*: PubMed, Embase, Cochrane Central Register of Controlled Trials, Wanfang and Chinese BioMedical Literature database (CBM) were searched up to February 2020. Head-to-head randomized controlled trials were included that assessed efficacy and safety of hybrid therapy compared with other therapies (standard triple therapy, concomitant therapy, bismuth quadruple therapy or sequential therapy). Statistical analysis was performed with RevMan software 5.3. *Results*: Ten studies (2941 participants) as first-line treatment for *H. pylori* were identified. In the same proton pump inhibitors and duration, *H. pylori* eradication rate of hybrid therapy was higher than that of standard triple therapy (pooled eradication rates, 94.2% vs 85.4%; OR, 2.68; 95%CI: [1.42–5.06], $P<0.05$). However, there were no significant differences of eradication rates between hybrid therapy and sequential therapy (pooled eradication rates, 82.7% vs 84.9%; OR, 0.97; 95%CI: [0.85–1.11], $P>0.05$), concomitant therapy (pooled eradication rates, 83.5% vs 84.1%; OR, 0.96; 95%CI: [0.66–1.40], $P>0.05$), or bismuth quadruple therapy (pooled eradication rates, 95.2% vs 94.0%; OR, 1.28; 95%CI: [0.70–2.34], $P>0.05$). No significant differences in overall adverse events were found among hybrid therapy and standard triple therapy, sequential therapy, concomitant therapy or bismuth quadruple therapy. *Conclusions*: Hybrid therapy could be a suitable alternative to sequential therapy, concomitant therapy and bismuth quadruple therapy in first-line regimens. Hybrid therapy should be then recommended as empirical first-line regimen in *H. pylori* eradication.

Keywords: *Helicobacter pylori*, Hybrid Therapy, Bismuth Quadruple Therapy, Concomitant Therapy, Standard Triple Therapy, Sequential Therapy, Meta-Analysis

1. Introduction

Helicobacter pylori (*H. pylori*) infection affect approximately 50% of the global population. [1] *H. pylori* infection causally contributed to many gastrointestinal diseases, such as chronic gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue (MALT) lymphoma and gastric adenocarcinoma. [2, 3] *H. pylori* eradication would produce long-term relief of dyspepsia symptom, and even cure gastritis, peptic ulcer and MALT lymphoma, and reduce the development risk of gastric adenocarcinoma.

In the past decades, standard triple therapy (STT, proton pump inhibitor (PPI) and two antibiotics: amoxicillin, and clarithromycin or metronidazole) were recommended as first-line eradication regimen in many regions, because it afforded satisfactory eradication rate initially. In recent years, numerous evidences indicated the eradication rates afforded by standard triple therapy progressively declined to an unacceptable level (<80%). [4-7] Increasing resistance of *H. pylori* strains to clarithromycin and metronidazole is the major cause of eradication failure. Alternative eradication regimens have been proposed in the presence of clarithromycin

resistance, such as bismuth quadruple therapy (BQT), concomitant therapy (CT), sequential therapy (ST), hybrid therapy (HT). In fact, several trials demonstrated above therapies produced acceptable cure rates. However, the optimal therapy remains elusive in *H. pylori* eradication.

Hybrid therapy consisted of a PPI and amoxicillin for 10-14 d with the addition of other two antibiotics (e.g. metronidazole, clarithromycin) for 5-7 d. Limited meta-analyses investigated efficacy and safety of hybrid therapy compared with sequential therapy, concomitant therapy or standard triple therapy. [8-11] However, some non-head-to-head or different duration randomized controlled trials (RCTs) were included in these meta-analyses. Additionally, incomplete inclusion of trials were not included such as comparative studies of hybrid therapy and bismuth quadruple therapy or newly published studies in recent year. These meta-analyses were likely to have reported less accurate or robust results. In the present study, we conducted a meta-analysis of the similar-duration and head-to-head randomized controlled trials to compare the efficacy and safety of hybrid therapy with other therapies in the eradication of *H. pylori*.

2. Methods

2.1. Criteria for Considering Studies for This Meta-Analysis

2.1.1. Types of Studies

Only head-to-head randomized controlled trials (RCTs) evaluating hybrid therapy (HT) versus other therapies (e.g. STT, ST, CT or BQT) in the eradication of *H. pylori* were considered. The language of the studies was restricted to Chinese and English.

The following studies were excluded: (1) non-clinical studies; (2) eradication data cannot be determined; (3) non-RCT studies; (4) conference abstract; and (5) studies with duplicate data.

2.1.2. Types of Participants

RCTs were eligible for inclusion if enrolled participants were documented by at least one positive results of the urea breath test (UBT), histology, rapid urease test, culture, and stool *H. pylori* antigen. The enrolled participants were naive to therapy.

2.1.3. Types of Interventions

Only head-to-head RCTs were included. Proton pump inhibitors and duration were similar in two treatment arms to exclude the interference of different duration and proton pump inhibitors.

2.1.4. Types of Outcome Measures

Successful *H. pylori* eradication was defined as (1) a negative result of UBT or stool *H. pylori* antigen, (2) at least two negative results of histology, rapid urease test and culture, at least 4 weeks after completion of treatments. The primary outcome of the meta-analysis was the eradication rates (namely efficacy) of HT compared with other therapies (data from intention-to-treat (ITT) and per protocol (PP) analyses). The secondary outcome was the incidences of overall adverse events (namely safety) of HT compared with other therapies (data from ITT analysis).

2.2. Search Strategy

2.2.1. Electronic Searches

RCTs were identified by searches of PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and two Chinese databases (Wanfang and Chinese BioMedical Literature database (CBM)) up to February 25, 2020. The search terms (title/abstract or MeSH) were used: ("sequential" or "concomitant" or "triple" or "bismuth" and "hybrid") and ("*Helicobacter pylori*" or "*Campylobacter pylori*") and ("randomized controlled trial"). The language of the articles was restricted to English and Chinese.

2.2.2. Searching Other Resources

Two researchers identified relevant trials through the manual searches from the reference lists of the selected articles and related meta-analyses about hybrid therapy.

2.3. Data Collection and Analysis

2.3.1. Selection of Studies

According to the method of previous studies [12, 13], 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.

2.3.2. Data Extraction and Quality Assessment

Two investigators independently extracted data using a standard data extraction sheets: first author, publication year, country, patients, number, comparative treatments, eradication regimens (HT and other therapies (STT, ST, CT or BQT), treatment duration, follow-up time, infection and eradication confirmative test, eradication rate (ITT and PP analyses), and adverse events (ITT analyses). According to the method of previous studies [13, 14], the risk of bias of included RCTs was assessed using the Cochrane Risk of Bias assessment tool, any disagreements were resolved through a discussion.

2.3.3. Assessment of Heterogeneity

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

2.3.4. Assessment of Reporting Biases

Since < 10 studies were analyzed in each comparison, the publication bias was not evaluated.

2.3.5. Data Synthesis and Statistical Analysis

We conducted meta-analysis 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; conversely, 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

Two hundred and fourteen studies were identified using the defined terms. Of these, 203 studies were discarded because of duplication, non-RCT, non-clinical studies and conference abstract. After examination of the full text of the remaining 11 articles, we finally selected 10 studies with sufficient data for inclusion in this meta-analysis (Figure 1). Twenty-nine hundred and forty-one patients were enrolled in all ten studies. Of ten studies, two studies compared HT and STT, threes studies compared HT and ST, two studies compared HT and CT, and three studies compared HT and BQT. Of ten studies, eight studies were conducted in Asian region (China Mainland, Taiwan, Iran and Korea) and only two studies was done in European region (Turkey, Spain and Italy). Additionally, except one 10-day and one 12-day duration study, duration of the other 8 studies was 14-day. In all ten studies, HT as first-line treatment were investigated and successful eradication was confirmed at least 4 weeks after completion of eradication therapies (Table 1).

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

Study	Year	Country	Patients	Comparative regimens	Hybrid therapy	Other therapies
Hsu PI [15]	2015	Taiwan	naive H. pylori-positive and peptic ulcer disease or gastritis	HT versus STT	pantoprazole 40 mg bid, amoxicillin 1 g bid, 12 days; metronidazole 500 mg, clarithromycin 500 mg bid, initial 7 days	pantoprazole 40 mg bid, amoxicillin 1 g bid, and clarithromycin 500 mg bid, 12 days
Makhlough A [16]	2016	Iran	naive H. pylori-positive and uremia	HT versus STT	pantoprazole 40 mg bid, amoxicillin 500 mg bid, 14 days; tinidazole 500 mg, clarithromycin 500 mg bid, final 7 days	pantoprazole 40 mg bid, amoxicillin 500 mg bid, and clarithromycin 500 mg bid, 14 days
Oh DH [17]	2014	Korea	naive H. pylori-positive and peptic ulcer disease or gastritis	HT versus ST	rabeprazole 20 mg bid, amoxicillin 1 g bid, 14 days; clarithromycin 500 mg bid, metronidazole 500 mg bid, final 7 days	rabeprazole 20 mg bid, amoxicillin 1 g bid, initial 7 days; rabeprazole 20 mg bid, clarithromycin 500 mg bid, metronidazole 500 mg bid, final 7 days
Hwang JJ [18]	2015	Korea	naive H. pylori-positive and peptic ulcer disease or gastritis	HT versus ST	rabeprazole 20 mg bid, amoxicillin 1 g bid, 14 days; clarithromycin 500 mg bid, metronidazole 500 mg bid, final 7 days	rabeprazole 20 mg bid, amoxicillin 1 g bid, initial 7 days; rabeprazole 20 mg bid, moxifloxacin 400 mg qd, metronidazole 500 mg bid, final 7 days
Kefeli A [19]	2018	Turkey	naive H. pylori-positive and gastritis	HT versus ST	rabeprazole 40 mg bid, amoxicillin 1 g bid, 14 days; clarithromycin 500 mg bid, metronidazole 500 mg bid, final 7 days	rabeprazole 40 mg bid, amoxicillin 1 g bid, initial 7 days; rabeprazole 40 mg bid, clarithromycin 500 mg bid, metronidazole 500 mg bid, final 7 days
Molina - Infante J [20]	2013	Spain Italy	naive H. pylori-positive and dyspepsia, peptic ulcer disease, or familiar history of gastric cancer	HT versus CT	omeprazole 40 mg bid, amoxicillin 1 g bid, 14 days; metronidazole 500 mg bid, metronidazole/tinidazole 500 mg bid, final 7 days	omeprazole 40 mg bid, amoxicillin 1 g bid, clarithromycin 500 mg bid, metronidazole/tinidazole 500 mg bid, 14 days
Heo J [21]	2015	Korea	naive H. pylori-positive and peptic ulcer disease, gastritis, gastric adenoma, or early gastric cancer	HT versus CT	esomeprazole 20 mg bid, amoxicillin 1 g bid, 10 days; clarithromycin 500 mg bid, metronidazole 500 mg bid, final 5 days	esomeprazole 20 mg bid, amoxicillin 1 g bid, clarithromycin 500 mg bid, metronidazole 500 mg bid, 10 days
Tsay FW [22]	2017	Taiwan	naive H. pylori-positive and peptic ulcer disease or gastritis	HT versus BQT	pantoprazole 40 mg bid, amoxicillin 1 g bid, 14 days; metronidazole 500 mg bid, clarithromycin 500 mg bid, final 7 days	pantoprazole 40 mg bid, bismuth subcitrate, 120 mg qid, tetracycline, 500 mg, qid, metronidazole 250 mg qid, 14 days
He XJ [23]	2017	China	naive H. pylori-positive and peptic ulcer disease or gastritis	HT versus BQT	esomeprazole 20 mg bid, amoxicillin 1 g bid, 14 days; metronidazole 400 mg bid, clarithromycin 500 mg bid, final 7 days	esomeprazole 20 mg bid, amoxicillin 1 g bid, colloidal bismuth pectin 200 mg tid, clarithromycin 500 mg bid, 14 days
Hsu PI [24]	2018	Taiwan	naive H. pylori-positive and gastrointestinal symptom	HT versus BQT	pantoprazole 40 mg bid, amoxicillin 1000 mg bid, 14 days; clarithromycin 500 mg bid, and metronidazole 500 mg bid, initial 7 days	pantoprazole 40 mg bid, bismuth tripotassium dicitrate 300 mg qid, tetracycline 500 mg qid, and metronidazole 250 mg qid

Table 1. *Continued.*

Study	Treatment duration	Infection confirmative test	Follow-up	Eradication confirmative test	Number
Hsu PI [15]	12 days	rapid urease test, histology, or culture (at least two positive)	6 weeks	UBT, or three tests negative (histology, rapid urease test and culture)	440
Makhlough A [16]	14 days	rapid urease test and fecal H. pylori antigen test (both positive)	8 weeks	fecal H. pylori antigen test	40
Oh DH [17]	14 days	histology or rapid urease test positive	4 weeks	13C-UBT	184
Hwang JJ [18]	14 days	13C-UBT, rapid urease test or histology positive	4 weeks	13C-UBT	284
Kefeli A [19]	14 days	Histology or rapid urease test positive	6 weeks	13C-UBT	340
Molina-Infante J [20]	14 days	13C-UBT positive or at least two methods positive (rapid urease test, culture, or histology)	8 weeks	13C-UBT	340
Heo J [21]	10 days	13C-UBT, rapid urease test or histology (at least two positive)	4 weeks	UBT	479
Tsay FW [22]	14 days	rapid urease test, histology, and culture (at least two positive)	6 weeks	13C-UBT or both tests negative (rapid urease test and histology)	330
He XJ [23]	14 days	13C-UBT or histology positive	4 weeks	13C-UBT or 14C-UBT negative	152
Hsu PI [24]	14 days	rapid urease test, culture and histology (at least two positive) or both 13C-UBT and serological tests positive	6 weeks	UBT or three tests negative (histology, rapid urease test and culture)	352

HT, hybrid therapy; STT: standard triple therapy; CT: concomitant therapy; ST: sequential therapy; BQT: bismuth quadruple therapy; UBT, urea breath test.

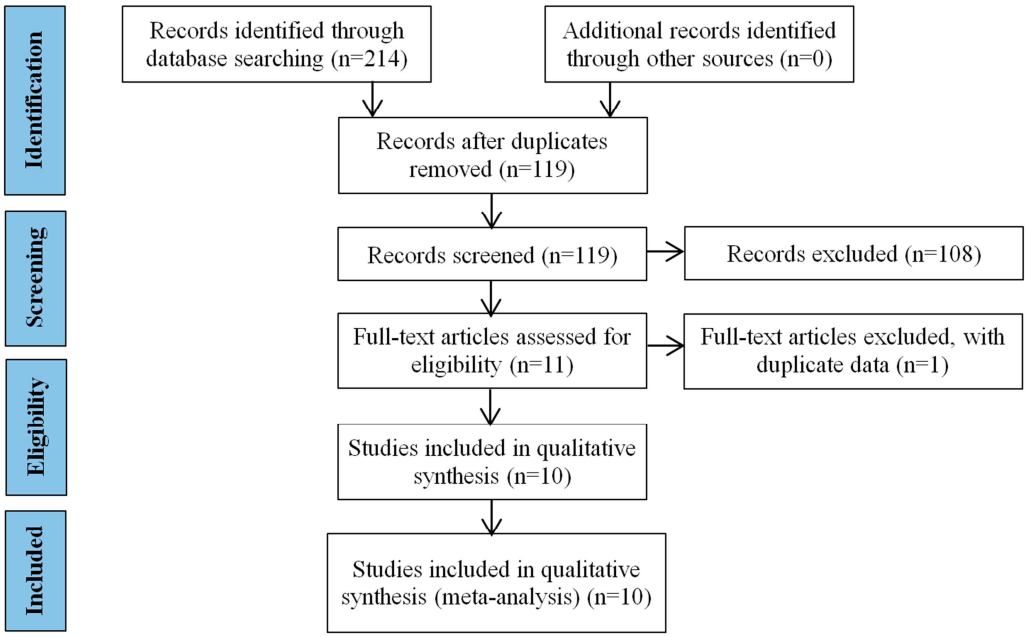

Figure 1. *Flow chart showing study selection.*

Table 2. *Efficacy of hybrid therapy (HT) versus other therapies for H. pylori eradication in per-protocol analysis.*

Groups	Eradication rate of HT	Eradication rate of other therapies	P value	OR, 95%CI	Heterogeneity test	Model
HT versus STT	96.1%	86.8%	0.0008	3.59, 1.70–7.57	P=0.24, I^2=29%	fixed-effect
HT versus ST	88.8%	90.0%	0.67	0.97, 0.29–3.29	P=0.003, I^2=83%	random-effect
HT versus CT	90.7%	92.6%	0.35	0.77, 0.45–1.32	P=0.21, I^2=35%	fixed-effect
HT versus BQT	96.2%	95.5%	0.63	1.19, 0.59–2.41	P=0.16, I^2=46%	fixed-effect

HT, hybrid therapy; STT: standard triple therapy; CT: concomitant therapy; ST: sequential therapy; BQT: bismuth quadruple therapy.

3.2 Risk of Bias

The blinding issue was least fulfilled since design of seven studies were open-label and three studies were unclear. Almost ten studies described randomized method and follow-up data. Totally, ten RCTs showed low risk of bias according to the Cochrane Risk of Bias tool (Figure 2).

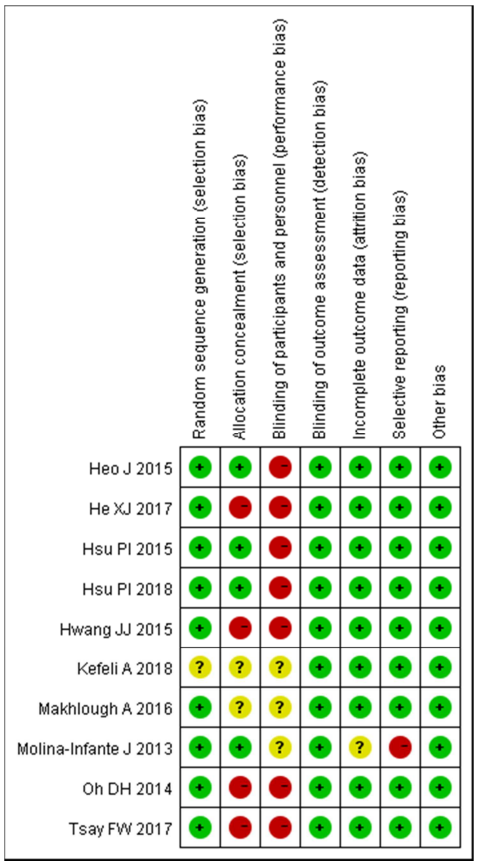

Figure 2. *Assessment of bias risk.*

3.3. Efficacy of Hybrid Therapy (HT) Versus Other Therapies (STT, ST, CT or BQT)

No significant heterogeneity was identified in the comparative analyses of HT and STT, CT or BQT (P>0.1, I^2<50%)), except in the comparative analysis of HT and ST (Cochrane's Q test, df=2, P<0.1, I^2=76%). In the ITT analysis (Figures 3-6), *H. pylori* eradication rate of HT was higher than that of STT (pooled eradication rates, 94.2% vs 85.4%; OR, 2.68; 95%CI: [1.42–5.06]; P<0.05). However, there were no significant differences of eradication rates between HT and ST, CT or BQT (HT vs ST: pooled eradication rates, 82.7% vs 84.9%; OR, 0.97; 95%CI: [0.85–1.11]; HT vs CT: pooled eradication rates, 83.5% vs 84.1%; OR, 0.96; 95%CI: [0.66–1.40]; HT vs BQT: pooled eradication rates, 95.2% vs 94.0%; OR, 1.28; 95%CI: [0.70–2.34]; P>0.05).

Interestingly, similar tendencies were found in the PP analysis (Table 2). Except the higher *H. pylori* eradication rate of HT compared with STT, we found no significant differences of eradication rates between HT and ST, CT or BQT (HT vs STT: pooled eradication rates, 96.1% vs 86.8%; OR, 3.59; 95%CI: [1.70–7.57], P<0.05; HT vs ST: pooled eradication rates, 88.8% vs 90.0%; OR, 0.97; 95%CI: [0.29–3.29], P>0.05; HT vs CT: pooled eradication rates, 90.7% vs 92.6%; OR, 0.77; 95%CI: [0.45–1.32], P>0.05; HT vs BQT: pooled eradication rates, 96.2% vs 95.5%; OR, 1.19; 95%CI: [0.59–2.41], P>0.05).

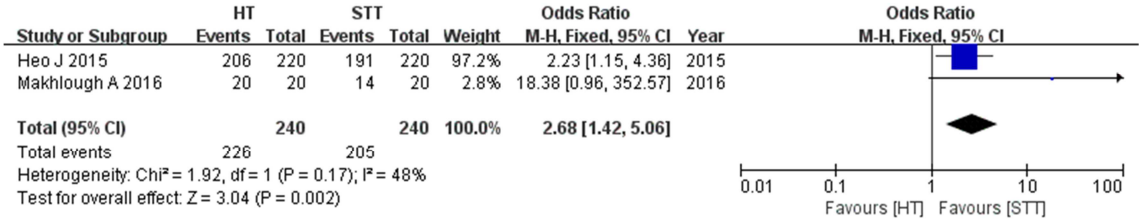

Figure 3. *Efficacy of hybrid therapy (HT) versus standard triple therapy (STT) for H. pylori eradication in intention-to-treat analysis (fixed-effect model).*

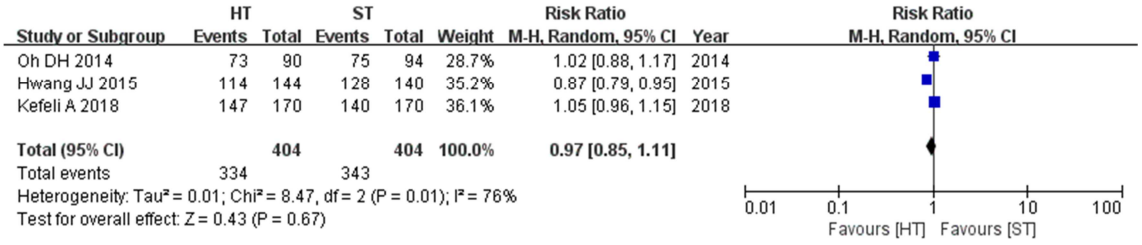

Figure 4. *Efficacy of hybrid therapy (HT) versus sequential therapy (ST) for H. pylori eradication in intention-to-treat analysis (random-effect model).*

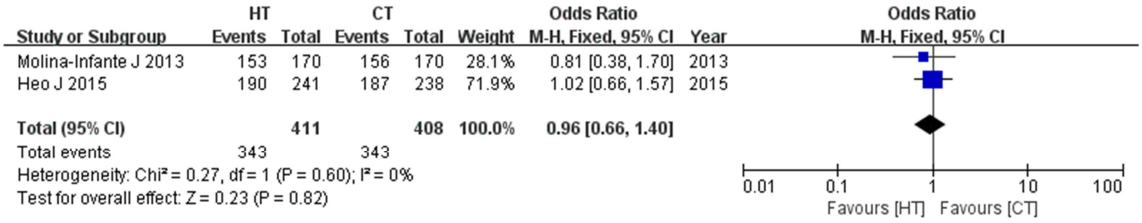

Figure 5. *Efficacy of hybrid therapy (HT) versus concomitant therapy (CT) for H. pylori eradication in intention-to-treat analysis (fixed-effect model).*

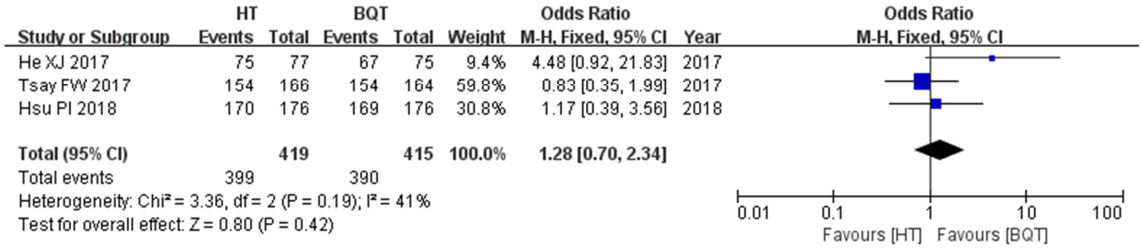

Figure 6. *Efficacy of hybrid therapy (HT) versus bismuth quadruple therapy (BQT) for H. pylori eradication in intention-to-treat analysis (fixed-effect model).*

3.4. Safety of Hybrid Therapy (HT) Versus Other Therapies (STT, ST, CT or BQT)

Because no safety data could be extracted between HT and CT, descriptive analysis were chose according to data from original articles. Additionally, since significant heterogeneity was found, random-effect model were used in the comparative analyses of HT and STT or BQT (P<0.1, I^2>50%). However fixed-effect model was used in the comparative analysis of HT and ST because of no significant heterogeneity (P=0.17, I^2=43%). As were shown in figures 7-9, the incidences of overall adverse events were similar between HT compared with STT, ST or BQT (HT vs STT: pooled adverse events, 13.8% vs 11.3%; OR, 0.77; 95%CI: [0.14–4.29]; HT vs ST: pooled adverse events, 27.4% vs 24.7%; OR, 1.18; 95%CI: [0.85–1.63]; HT vs BQT: pooled adverse events, 19.6% vs 45.1%; OR, 0.42; 95%CI: [0.11–1.63]; P>0.05). Also, the incidence of overall adverse events of HT was similar to that of CT, 47% vs 56%, respectively. [20].

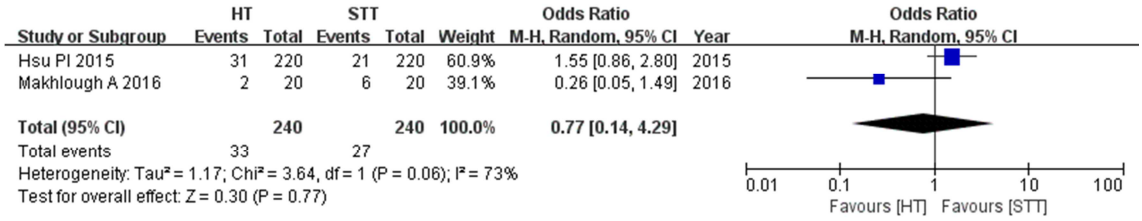

Figure 7. *Overall adverse events between hybrid therapy (HT) versus standard triple therapy (STT).*

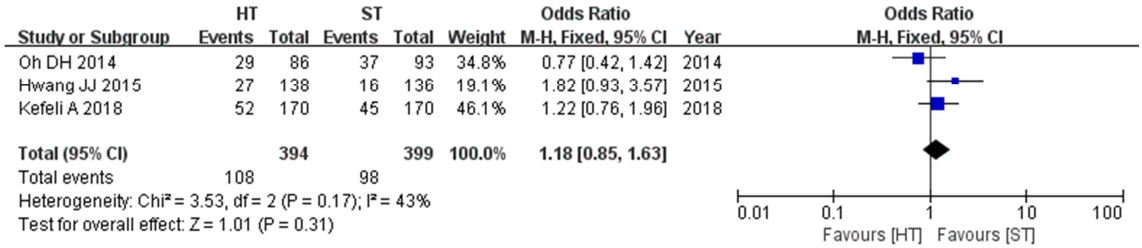

Figure 8. *Overall adverse events between hybrid therapy (HT) versus sequential therapy (ST).*

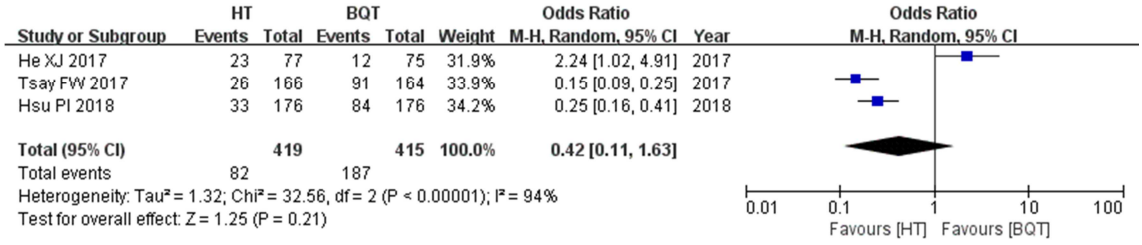

Figure 9. *Overall adverse events between hybrid therapy (HT) versus bismuth quadruple therapy (BQT).*

4. Discussion

With the rising prevalence of clarithromycin resistance to *H. pylori*, eradication rate of standard triple therapy has declined to an unacceptable level (<80%) in many countries [25, 26], possibly since clarithromycin is a key component of standard triple therapy. Therefore, several therapies were proposed to overcome the decreasing eradication rates by clarithromycin resistance, including bismuth quadruple therapy, concomitant therapy, sequential therapy, hybrid therapy and so on. Hybrid therapy was first proposed by Hsu PI et al and achieved an excellent eradication rates of 99.1% (PP analysis) and 97.4% (ITT analysis) in a pilot clinical trial. [27].

Our meta-analysis found hybrid therapy indeed had a higher eradication rate than standard triple therapy did (94.2% vs 85.4% in ITT analysis; 96.1% vs 86.8% in PP analysis). Interestingly, two studies of our meta-analysis comparing hybrid therapy with standard triple therapy were conducted in Taiwan and Iran. Taiwan and Iran were two high clarithromycin resistance regions with 22.9% and 23.6%, respectively. [28, 29] Additionally, our meta-analysis showed hybrid therapy had the same eradication rate as sequential therapy, concomitant therapy, bismuth quadruple therapy, 82.7% vs 84.9% (ITT analysis), 83.5% vs 84.1% (ITT analysis), 95.2% vs 94.0% (ITT analysis), respectively. Similarly, these studies were basically performed in areas with high clarithromycin resistance (>15%), such as Korea, Taiwan, China, Turkey, Spain and Italy. [30-33] Our meta-analysis found efficacy of hybrid therapy was similar to those of sequential therapy and concomitant therapy, which was consistent with the results of other meta-analyses. [8-11] Hybrid therapy overcame increasing clarithromycin resistance and eradication failures, some reasons may explain it: (1) whole usage of low-resistance amoxicillin in treatment duration. (2) the combined use of other antibiotics such as metronidazole. Moreover, the mean eradication rate of hybrid therapy of all included 10 studies was 88.3% (1302/1474, ITT analysis) and approached 90%. According to effectiveness grade of *H. pylori* therapy introduced by Graham DY [34], hybrid therapy reached to a fair level. In Maastricht V/Florence Consensus Report (2), concomitant therapy and bismuth quadruple therapy were the empirical first-line treatments when clarithromycin resistance was >15%. Similar to concomitant therapy and bismuth quadruple therapy, hybrid therapy can then replace the standard triple therapy as the standard regimen in the empirical first-line eradication of *H. pylori* infections in the regions with high clarithromycin resistance (>15%), as new Taiwan *Helicobacter Pylori* Consensus Report recommended. [35].

Furthermore, hybrid therapy had the same safety as standard triple therapy (incidences of adverse events: 13.8% vs 11.3%), sequential therapy (incidences of adverse events: 27.4% vs 24.7%), concomitant therapy (incidences of adverse events: 47% vs 56%) and bismuth quadruple therapy (incidences of adverse events: 19.6% vs 45.1%), indicating hybrid therapy would be well-tolerated. Moreover, most of adverse effects were mild-moderate adverse symptoms from digestive system including nausea and vomiting, and serious side effects were rare. Lastly, patients who discontinued the regimen due to adverse events were rather sparse in all 10 studies, because compliance of hybrid therapy in all 10 studies surpassed 90%. These facts further suggested hybrid therapy was indeed well-tolerated.

Of course, there were several limitations in our meta-analysis. First, the numbers of RCTs included were small, which precluded the confirmed outcome. Second, severe heterogeneity was exhibited on comparison of hybrid therapy and sequential therapy. Diversity of treatments may account for this heterogeneity. Third, because all trials were implemented in Asian and European regions, it may have increased selection bias. Whether the same results could be obtained in the American or African regions still need to be validated in additional RCTs. Fourth, hybrid therapy as second-line treatments were not investigated when compared with other therapies. Lastly, language restricted to Chinese and English would lead to selection bias.

5. Conclusions

In conclusion, hybrid therapy had the same efficacy and safety as sequential therapy, concomitant therapy and bismuth quadruple therapy, but were superior to standard triple therapy in *H. pylori* eradication. Therefore, hybrid therapy could be an excellent alternative to sequential therapy, concomitant therapy and bismuth quadruple therapy in first-line regimens, which should be then recommended as empirical first-line regimen 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, especially hybrid therapy versus concomitant therapy or bismuth quadruple therapy recommended by guidelines.

Competing Interests

The authors have declared no conflicts of interest.

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