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META-ANALYSIS

Standard triple therapy for *Helicobacter pylori* infection in China: A meta-analysis

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Abstract

AIM: To assess the efficacy and safety of standard triple therapy compared with other pre-existing and new therapies in China.

METHODS: Literature searches were conducted in the following databases: PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, the VIP database, the China National Knowledge Infrastructure database, and the Chinese Biomedical Database. A meta-analysis of all randomized controlled trials (RCTs) comparing standard triple therapy for the eradication of *Helicobacter pylori* with pre-existing and new therapies in China was performed using Comprehensive Meta-Analysis 2.0. There were 49 studies that met our criteria and the qualities of these studies were assessed using the Jadad scale. The Mantel-Haenszel method was used for pooling dichotomous data. We also conducted subgroup analyses according to age, duration of treatment and drug type. Sensitivity analyses and a cumulative meta-analysis were also performed with CMA 2.0. Publication bias was evaluated using Egger's test, Begg's test or a funnel plot.

RESULTS: A total of 49 RCTs including 8332 patients were assessed. This meta-analysis showed that standard triple therapy with proton pump inhibitors (PPIs), amoxicillin (AMO) and clarithromycin (CLA) was inferior to sequential therapy [relative risk (RR) = 0.863; 95% confidence interval (CI): 0.824-0.904], but was not superior to quadruple therapy (RR = 1.073; 95%CI: 0.849-1.357) or other triple therapies (RR = 1.01; 95%CI: 0.936-1.089). The meta-analysis also suggested that standard triple therapy is slightly more effective than dual therapy (RR = 1.14; 95%CI: 0.99-1.31). However, the differences were not statistically significant. We removed the only trial with a regimen lasting 14 d by sensitivity analysis and found that 7-d standard triple therapy was superior to 7-d dual therapy (RR = 1.222; 95%CI: 1.021-1.461). Moreover, a sub-analysis based on the duration of quadruple therapy indicated that the 7-d and 10-d standard triple therapies were inferior to sequential therapy (RR = 0.790; 95%CI: 0.718-0.868; RR = 0.917; 95%CI: 0.839-1.002, respectively). Additionally, there were no significant differences in cure rate or adverse events among standard triple therapy, quadruple therapy, and other triple therapies (RR = 0.940; 95%CI: 0.825-1.072; RR = 1.081; 95%CI: 0.848-1.378, respectively). Standard triple therapy had a higher occurrence of side effects than sequential therapy (RR = 1.283; 95%CI: 1.066-1.544).

CONCLUSION: The eradication rates with a standard triple therapy consisting of PPI, AMO, and CLA are suboptimal in China, and new treatment agents need to be developed.

Key words: *Helicobacter pylori*; Eradication; Combination drug therapy; Amoxicillin; Clarithromycin; Adverse effects; Meta-analysis

Core tip: This study compared the efficiency of standard triple therapy with other pre-existing and new therapies on the Chinese mainland and examined the eradication rates for *Helicobacter pylori* in China. The results showed that the standard triple therapy including proton pump inhibitors, amoxicillin and clarithromycin might not be suitable for first-line therapy.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is currently very common[1], and infection plays an important role in some gastrointestinal diseases, such as peptic ulcers, chronic gastritis, gastric cancer, and gastric malignant disease[2]. Eliminating *H. pylori* can reduce the recurrence of peptic ulcers and prevent gastric cancer[2]. Standard triple therapy with a proton pump inhibitor (PPI), amoxicillin (AMO) and clarithromycin (CLA) has been extensively employed around the world, and contributed to an eradication success rate of over 90% in the 1990s[3]. However, because of the wide application in *H. pylori* infection, eradication rates have declined to less than 60%[4,5]. The primary reason for this decline is the resistance of *H. pylori* to antibiotics, particularly CLA and metronidazole[5].

The standard triple therapy with PPI, AMO and CLA is still recommended as one of the first line anti-*H. pylori* treatments when the resistance rate of *H. pylori* to CLA is less than 15%-20%[6-8]. This therapy has encountered some challenges, and although the eradication rate is decreasing[4], the resistance of *H. pylori* to CLA has increased[9]. One recent study suggested that the therapy could not achieve an acceptable eradication rate[10].

The efficacy of triple therapy consisting of PPI, AMO and CLA has been demonstrated by several studies during the past decade in China. However, the use of antibiotics for other diseases without rigorous supervision has caused a rapid increase in the prevalence of antibiotic-resistant *H. pylori* in China. A recent study showed that the resistance of *H. pylori* to CLA is more than 80% and another study suggested that the primary resistance of *H. pylori* to CLA is 17.2%[11,12]. These data indicate that the current effectiveness of standard triple therapy consisting of PPI, AMO and CLA may be diminished in some areas[13-15]. Furthermore, one study indicated that standard triple therapy was not superior to sequential therapy[16]. Despite the development of resistance, experts consider standard triple therapy effective in areas where *H. pylori* resistance rates to CLA are less than 15%[7].

Whether the standard triple therapy is suitable as a first-line therapy for *H. pylori* infection in China remains controversial. The changes in eradication rates of standard triple therapy containing PPI, AMO and CLA with time also remains uncertain in China. To further assess the efficacy and safety of standard triple therapy compared with other eradication treatments (other triple therapies, quadruple treatments and sequential treatments), we conducted this systemic review and meta-analysis. Furthermore, we also performed a cumulative meta-analysis to investigate the changes in the eradication rate of the standard triple regime over time in China.

MATERIALS AND METHODS

Data sources

We searched PubMed (to November 2013), EMBASE (to November 2013), the Cochrane Central Register of Controlled Trials (Issue 11, 2013), the VIP database, the China National Knowledge Infrastructure database (CNKI), and the Chinese Biomedical Database (CBM). The specific search algorithm used for each database was the following: PubMed - [(amoxicillin AND clarithromycin) AND triple] AND "*Helicobacter pylori*"[Mesh], Filters: Randomized Controlled Trial); Embase - "*Helicobacter pylori*"/expand "amoxicillin"/exp and "clarithromycin" /exp and triple and "human"/de and "randomized controlled trial"/de; the Cochrane Central Register of Controlled Trials - amoxicillin AND clarithromycin AND triple AND helicobacter pylori; the VIP database, CNKI database and CBM database - were searched with the following keywords: "*Helicobacter pylori*", "amoxicillin", "clarithromycin" and "triple".

Selection criteria

The articles eligible for inclusion in the meta-analysis met the following inclusion criteria: (1) randomized controlled trial; (2) inclusion of at least 2 branches of treatment, including: (1) standard triple therapy (PPI, AMO, CLA), (2) dual therapy (PPI, a type of antibiotic), quadruple therapy, sequential therapy or other triple therapy; (3) an *H. pylori* diagnosis by urea breath test (UBT), rapid urease test, histology, and/or fecal antigen testing; (4) eradication testing with UBT and/or histology at least 4 wk after completion of therapy; (5) an available eradication rate; (6) no restrictions in age or sex; (7) a study population composed of subjects who had never been treated for *H. pylori*; (8) inclusion of mainland Chinese residents; and (9) studies published in Chinese must have been published in core journals (Peking University Library Chinese Core Periodical Catalog, 2012).

Exclusion criteria

The following were exclusion criteria: (1) articles and/or abstracts not reporting tests used to diagnose infection and/or follow-up infection; (2) articles and/or abstracts

not conducted on the Chinese mainland; and (3) articles with inappropriate treatments in the control group or standard triple group, including the use of traditional Chinese medicine or probiotics.

Outcome assessment

The primary study outcomes for the meta-analysis included the following: (1) the efficacy of standard triple therapy compared with established and new therapies in eradicating *H. pylori* infection; and (2) the incidence of adverse events in standard triple therapy *vs* other therapies.

Data extraction and quality assessment

Two independent reviewers (Wang B and Lv ZF) extracted the data from the selected studies using standardized data extraction forms. Any disagreement was resolved by consensus.

The following data were extracted: study design, number of patients in each treatment arm, testing used to confirm persistent infection prior to study enrollment and eradication after the completion of treatment, drug regimen, duration of treatment, eradication rates by intention to treat (ITT) analysis, percentage of adverse effects and severe adverse effects. The study quality was assessed using the Jadad scale.

Statistical analysis

The data analysis was performed using the Mantel-Haenszel method by meta-analysis software Comprehensive Meta-Analysis 2.0 (Biostat, Englewood, NJ, United States). For each trial, we calculated the relative risk (RR) for the primary measure. The RRs were presented with 95% confidence intervals (CIs), with a P-value < 0.05 considered significant. The study endpoints were calculated by ITT. We estimated the degree of heterogeneity among the trial results using the χ^2 statistic (with a P-value < 0.10 considered significant) and the I^2 test (25%, 50%, and 75% represent low, moderate and high heterogeneity, respectively). Whenever significant heterogeneity ($P < 0.1$ or $I^2 > 50\%$) was achieved, we used the random effect model to combine the effect sizes of the included studies. If no significant heterogeneity was found, we selected a fixed effect to pool the data. The subgroup or sensitivity analyses were performed where appropriate. We assessed the presence of publication bias with Egger's test and Begg's test or a funnel plot if necessary.

RESULTS

Description of the studies

The bibliographical search yielded a total of 1283 studies. Of these studies, 1069 studies were from PubMed, Cochrane and EMBASE, while the other 214 studies published in Chinese were from CBM, VIP and CNKI. Among the studies that were found in PubMed, Cochrane and EMBASE, we excluded 553 duplicate studies and an additional 484 studies that were not conducted on the Chinese mainland. Therefore, we retrieved 32 potentially relevant articles for a more detailed assessment. After examining the titles and abstracts, we excluded 3 unrelated articles. After reviewing the full-text articles we excluded 13 articles with inappropriate treatments in the control group or standard triple group, 4 non-randomized controlled trials (RCTs) and 3 articles that were published in non-core journals. Finally, 9 English language RCTs met the inclusion criteria. For the Chinese articles, we excluded 57 duplicates and 1 study that was not conducted on the Chinese mainland. We also excluded 7 unrelated articles, 61 articles with inappropriate treatments in the control group or standard triple group, 28 non-RCTs and 20 articles that were published in non-core journals after examining all titles, abstracts and full texts. Finally, we identified 40 Chinese RCTs that met the inclusion criteria. In conclusion, 49 RCTs[14-62] met the inclusion criteria. The flowchart of reviews showed the detailed process of selection (Figure 1). The characteristics and quality score of the 49 trials included in the meta-analysis are summarized in Table 1.

Meta-analysis

Standard triple therapy *vs* dual therapy: Three studies[17-19] compared standard triple therapy with dual therapy. As shown in Figure 2, the pooled RR was 1.14 (95%CI: 0.99-1.31, $P = 0.066$). We found evidence of heterogeneity ($I^2 = 63\%$, $P = 0.07$) with funnel plot asymmetry (Egger's test coefficient 2.75 to 10.28, $P = 0.03$) (Table 2). The pooled eradication rate of dual therapy was 78.0% based on this meta-analysis. Due to the heterogeneity, we also performed sensitivity analyses and the difference became significant when the study of Gao *et al*[19] was removed (RR = 1.222, 95%CI: 1.021-1.461).

Data on adverse events were available for 2 trials. The pooled RR was 0.651 (0.276-1.539), which indicated no significant difference and no evidence of heterogeneity ($I^2 = 0\%$, $P = 0.699$).

Standard triple therapy *vs* sequential therapy: We identified 20 studies[15,16,22,41-56,61] comparing standard triple therapy with sequential therapy. As shown in Figure 3, the pooled RR was 0.863 (95%CI: 0.824-0.904, $P < 0.001$). We found evidence of heterogeneity ($I^2 = 37.4\%$, $P = 0.047$) with funnel plot asymmetry (Egger's test coefficient -4.86 to -1.57, $P < 0.001$). The pooled eradication rate of sequential therapy was 84.0% based on this meta-analysis.

In addition, we performed a cumulative meta-analysis as shown in Figure 4. The pooled RRs for the years 2008, 2009, 2010, 2011, 2012, and 2013 were 0.779, 0.846, 0.852, 0.875, 0.876, and 0.870, respectively.

Due to the heterogeneity we also performed subgroup analyses according to age, duration of standard triple therapy (7-d, 10-d and 14-d), different PPIs in the standard triple therapy and for the different drugs used in the control group (the sequential therapy group).

In the subgroup analysis by age, the summary RRs in the adult and the child subgroups were 0.899 (95%CI: 0.861-0.939) and 0.779 (95%CI: 0.722-0.840), respective-

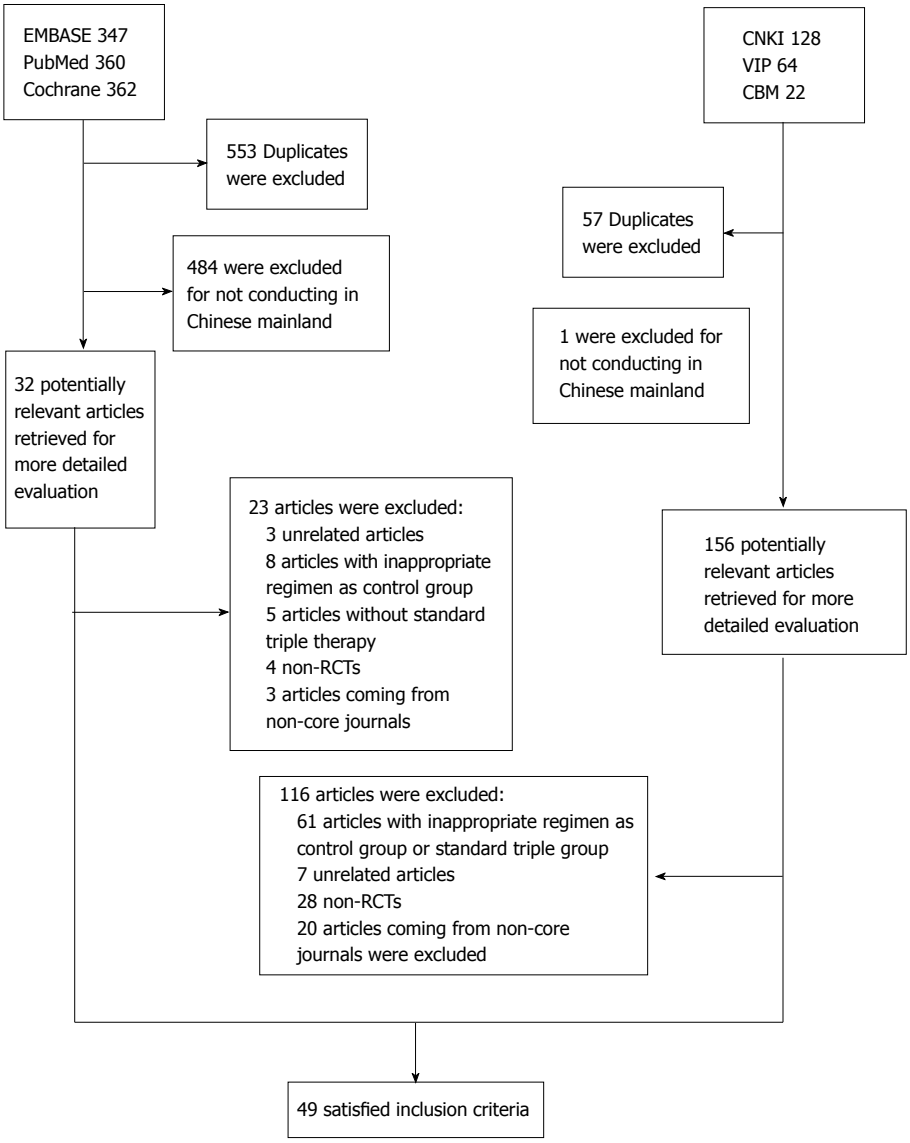

Figure 1 Flow diagram of studies identified and selected. RCT: Randomized controlled trials; CNKI: China National Knowledge Infrastructure database; CBM: Chinese Biomedical Database.

ly. The pooled eradication rates of sequential treatments in the adult and the child subgroups were 82.90% and 87.29%.

For the duration of the standard triple therapy subgroup analysis, the pooled RRs in the 7-d, 10-d, and 14-d subgroups were 0.800 (95%CI: 0.752-0.851), 0.849 (95%CI: 0.789-0.913) and 0.980 (95%CI: 0.916-1.048), respectively. The pooled eradication rates of sequential treatments in the 7-d, 10-d, and 14-d subgroups were 87.52%, 80.17%, and 89.72%, respectively.

In the PPIs subanalyses, the pooled RRs in the omeprazole, esomeprazole, pantoprazole and rabeprazole subgroups were 0.832 (95%CI: 0.772-0.898), 0.932 (95%CI: 0.871-0.998), 0.846 (95%CI: 0.746-0.960), and 0.847 (95%CI: 0.766-0.936), respectively. The pooled eradication rates of sequential treatments in the omeprazole, esomeprazole, pantoprazole and rabeprazole subgroups were 87.37%, 77.01%, 87.13%, and 91.24%, respectively.

The examination of the different drugs used in the control group subanalysis showed the pooled RRs in the tinidazole and metronidazole subgroups were 0.889 (95%CI: 0.837-0.944) and 0.810 (95%CI: 0.745-0.882), respectively. The pooled eradication rates of sequential treatments in the tinidazole and metronidazole subgroups were 81.43% and 83.20%, respectively.

We also performed sensitivity analyses and found the pooled RRs were unchanged.

Data on adverse events were available for 16 trials. The pooled RR was 1.176 (95%CI: 0.975-1.419), which indicated no significant difference and no evidence of heterogeneity (I^2 = 0%, P = 0.827).

Standard triple therapy *vs* quadruple therapy: There were 9 studies[13,37-40,42,56,60,62] comparing standard triple therapy with quadruple therapy. As shown in Figure 5, the pooled RR was 1.073 (95%CI: 0.849-1.357), P = 0.555. We found evidence of heterogeneity (I^2 = 93%, P

Table 1 Characteristics of studies included in systematic review and meta-analysis

Ref.	Age	Standard triple therapy	Control group therapy	*H. pylori* infection initial diagnosis/re-checking	Eradication rate by ITT (standard triple therapy/control group therapy)	Side effects	Jadad scores
Geng *et al*[17], 2003	Adult	P A C	O A	RUT/RUT	86.6% (71/82)/71.3% (57/80)	4 /7	1
Wu *et al*[18], 2004	Child	O A C	O C	H or C/UBT	93.3% (56/60)/76.0% (38/50)	-	1
Gao *et al*[19], 2006	Adult	R A C	R A	RUT UBT/RUT UBT	93.8% (45/48)/91.5% (43/47)	4/5	1
Huang *et al*[15], 2013	Child	O A C	ST-10 (O A/O C M)	H, RUT ST/ H, RUT ST	64.87% (157/242)/81.4% (96/118)	61/32	2
Yan *et al*[16], 2011	Adult	E A C	ST-10 (E A/E C T)	H RUT/UBT H	75.10% (220/341)/75.20% (185/281)	-	2
Liu *et al*[22], 2011	Child	O A C	ST-10 (O A/O C M) OAM group: O A M	UBT/UBT	60.61% (20/33)/91.18% (31/34) 69.70% (23/33)		3
Jia *et al*[41], 2012	Adult	E A C	ST-10 (E A/E C L)	RUT UBT/RUT UBT	76.0% (38/50)/94.0% (47/50)	3/4	1
Zhang *et al*[42], 2012	Adult	R A C	ST-9 (RA/RCOrn) R A C B	UBT RUT/UBT	80.2% (89/111)/90.2% (101/112) 91.1% (102/112)	10/6 7	2
Li *et al*[43], 2012	Child	O A C	ST-10 (O A/O C F)	UBT RUT/UBT	69.7% (23/33)/91.2% (31/34)	5/4	2
Zhou *et al*[44], 2011	Adult	O A C	ST-10 (O A/O C L)	RUT H/RUT H	79.60% (35/44)/88.9% (40/45)	-	2
Wu *et al*[45], 2011	Adult	E A C	ST-10 (E A/E C T)	UBT H RUT/UBT H RUT	90.20% (46/51)/90.40% (47/52)	18/12	2
Zhu *et al*[46], 2010	Child	O A C	ST-10 (R A/R C T)	UBT S/UBT S	70.73% (29/41)/92.68% (76/82)	7/5	1
Zhang *et al*[47], 2010	Adult	P A C	ST-10 (P A/P C T)	UBT/UBT	73.0% (61/74)/92.3% (36/39)	12/6	3
Lu *et al*[48], 2010	Child	O A C	ST-10 (O A/O C T)	S UBT RUT/UBT	82.43% (26/36)/90% (36/40)	6/7	2
Hu *et al*[49], 2009	Adult	E A C	ST-10 (E A/E C T)	RUT H/UBT	77.50% (31/40)/94.87% (37/39)	8/7	2
Pang *et al*[50], 2009	Adult	O A C	ST-10 (O A/O C T)	RUT H UBT/RUT UBT	89.60% (60/67)/91.90% (63/69)	19/10	2
Wang *et al*[51], 2009	Adult	E A C	ST-10 (E A/E C T)	RUT H/UBT	76.92% (40/52)/92.00% (46/50)	12/10	1
Zhao *et al*[52], 2009	Adult	P A C	ST-10 (P A/P C)	H/UBT	67.24% (39/58)/83.87% (52/62)	6/5	2
Huang *et al*[53], 2009	Adult	O A C	ST-10 (O A/O C T)	UBT/UBT	69.2% (36/52)/92.5% (49/53)	-	1
Ma *et al*[54], 2008	Adult	O A C	ST-10 (O A/O C T)	RUT UBT/RUT UBT	65.1% (41/63)/83.6% (56/67)	12/11	3
Huang *et al*[55], 2012	Adult	E A C	ST-10 (E A/E C M)	RUT H/RUT H	78.4% (40/51)/80.0% (40/50)	9/10	3
Gao *et al*[56], 2010	Adult	O A C	RAB L; ST-10 (O A/O C T)	RUT H/UBT	80.56% (58/71)/83.33% (60/72) 88.89% (64/72)	11/6 14	2
Huang *et al*[61], 2012	Child	O A C	ST-10 (O A/O C M)	B C/UBT	78.8% (109/160)/85.2% (46/54)	26/6	2
Zheng *et al*[60], 2005	Adult	E A C	1d-E A M B	RUT H/UBT	80.50% (33/41)/38.50% (15/39)	2/1	2
Dai *et al*[37], 2012	Adult	E A C	E A F B	UBT/UBT	78.12% (25/35)/88.57% (31/35)	4/8	2
Xu *et al*[38], 2011	Adult	E A C	E A C B	UBT/UBT	73.02% (46/69)/88.71% (55/67)	7/8	3
Liu *et al*[39], 2010	Adult	R A C	R A C B	UBT/UBT	62.90% (39/62)/88.70% (55/62)	4/5	1
Hu *et al*[13], 2012	Adult	Lan A C	Lan A C B	RUT H UBT/UBT	70.00% (70/100)/88.10% (89/101)	1/2	3
Jing *et al*[40], 2004	Adult	O/R A C	O/R A C F	UBT/UBT	85.83% (103/120)/86.7% (40/60)	4/5	2
Zhang *et al*[62], 2006	Adult	Lan A C	Lan A C M	UBT/UBT	69.59% (103/157)/26.78% (64/239)	148/229	2
Luo *et al*[20], 2012	Adult	E A C	E A L	UBT RUT/UBT	75.8% (91/120)/80.0% (96/120)	21/19	2
Chen *et al*[21], 2011	Adult	R A C	R A D	UBT/UBT	61.25% (49/80)/88.75% (71/80)	-	1
Xu *et al*[23], 2010	Adult	E A C	E L F	H UBT RUT/UBT RUT	75.51% (37/49)/93.87% (46/49)	6/5	1
Dai *et al*[24], 2010	Adult	E A C	E A L	UBT RUT/UBT	82.10% (23/28)/88.90% (26/30)	2/2	2
Xu *et al*[25], 2009	Adult	Lan A C	Lan C M	RUT UBT H/UBT	83.87% (26/31)/60.00% (21/35)	4/5	1
Wang *et al*[26], 2008	Adult	E A C	A C B	RUT H/UBT	80.0% (16/20)/85.00% (17/20)	10/10	2
Hu *et al*[27], 2008	Adult	O A C	O A L	RUT UBT/UBT	85.70% (36/45)/90.20% (37/45)	2/2	2
Su *et al*[28], 2005	Child	O A C	A M B	RUT H UBT/UBT	92.5% (74/80)/74.19% (92/124)	16/24	2
Mou *et al*[29], 2004	Adult	O A C	O C Gm	C H RUT/RUT H UBT	84.20% (16/19)/80.00% (20/25)	9/12	1
Chen *et al*[30], 2002	Adult	O A C	L B F	RUT H/RUT H	88.20% (97/110)/86.70% (92/106)	4/0	1
Chen *et al*[31], 1996	Adult	O A C	A M B	RUT H/RUT H	89.6% (43/48)/83.87% (78/93)	50/59	2
Cheng *et al*[32], 2010	Adult	Lan A C	Lan A L	UBT RUT/UBT	74.50% (111/149)/82.99% (122/148)	5/9	3
Zeng *et al*[33], 2007	Adult	O A C	O A L	UBT/UBT	68.30% (28/41)/86.50% (32/37)	6/5	1
Gao *et al*[34], 2005	Adult	O A C	A C B	H/H	83.33% (25/30)/86.67% (26/30)	0/2	2
Chen *et al*[35], 2004	Adult	O A C	O A Am	UBT/H	93.33% (42/45)/92.72% (51/55)	8/3	2
Chen *et al*[36], 2005	Adult	O A C	O A Am	UBT H/UBT H	88.50% (23/26)/86.70% (26/30)	2/2	1
He *et al*[58], 2004	Adult	R A C	R C M	C/UBT	85.90% (55/64)/54.70% (35/64)	-	2
Guo *et al*[58], 2004	Adult	O A C	O F C/O M C /O F A	RUT S H/UBT	84.90% (28/33)/73.74% (73/99)	9/19	2
Sun *et al*[59], 2005	Adult	O A C	O A M	B /RUT H	86.20% (50/58)/82.20% (37/45)	6/5	2

O: Omeprazole, A: Amoxicillin; B: Bismuth; C: Clarithromycin; M: Metrodinazole, P: Pantoprazole; E: Esomeprazole; Lan: Lansoprazole; D: Doxycycline; F: Furazolidone, L: Levofloxacin; R: Rabeprazole, T: Tinidazole; Orn: Ornidazole; Am: Azithromycin; Gm: Gentamycin; B: Biopsy based test; C: Culture; UBT: Urea breath test; H: Histology, PCR: Polymerase chain reaction; RUT: Rapid urease test; S: Serology; ST: Stool test; ITT: Intention to treat; -: Not reported; *H. pylori*: *Helicobacter pylori*. ST-10 (O A/O C T): Sequential therapy lasting 10 d (O A for the first 5 d, O C T for the remaining 5 d); ST-10 (P A/P C): Sequential therapy lasting 10 d (P A for the first 5 d, P C for the remaining 5 d); ST-10 (E A/E C T): Sequential therapy lasting 10 d (E A for the first 5 d, E C T for the remaining 5 d); ST-10 (P A/P C T): Sequential therapy lasting 10 d (P A for the first 5 d, P C T for the remaining 5 d); ST-10 (R A/R C T): Sequential therapy lasting 10 d (R A for the first 5 d, R C T for the remaining 5 d); ST-10 (O A/O C L): Sequential therapy lasting 10 d (O A for the first 5 d, O C L for the remaining 5 d); ST-10 (O A/O C M): Sequential therapy lasting 10 d (O A for the first 5 d, O C M for the remaining 5 d); ST-10 (E A/E C L): Sequential therapy lasting 10 d (E A for the first 5 d, E C L for the remaining 5 d); ST-10 (E A/E C M): Sequential therapy lasting 10 d (E A for the first 5 d, E C M for the remaining 5 d); ST-10 (O A/O C F): Sequential therapy lasting 10 d (O A for the first 5 d, O C F for the remaining 5 d); ST-9 (RA/RCOrn): Sequential therapy lasting 9 d (R A for the first 4 d, R C Orn for the remaining 5 d).

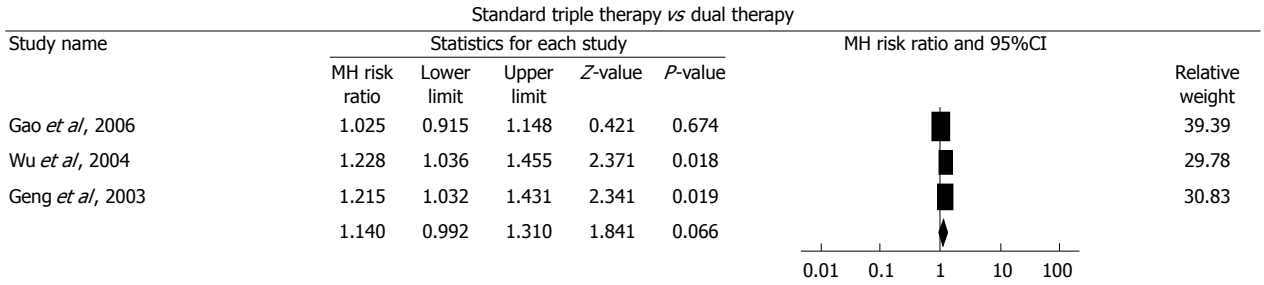

Figure 2 Forest plot of standard triple therapy *vs* dual therapy by random effect model.

Table 2 Results of meta-analysis

Meta-analyses/subgroup analyses	Eradication rate with control group	RR (95%CI)	I^2
Standard triple therapy *vs* dual therapy	78.00%	1.140 (0.992–1.310)	62.596%
7-d subgroup	73.08%	1.221 (1.084 –1.374)	0.000%
Adverse events		0.651 (0.276–1.539)	0.000%
Standard triple therapy *vs* sequential therapy	84.00%	0.863 (0.824–0.904)	37.400%
Adult subgroup	82.90%	0.899 (0.861–0.939)	25.942%
Child subgroup	87.29%	0.779 (0.722–0.840)	0.000%
7-d subgroup	87.52%	0.800 (0.752–0.851)	0.000%
10-d subgroup	80.17%	0.849 (0.789–0.913)	42.355%
14-d subgroup	89.72%	0.980 (0.916–1.048)	0.000%
Omeprazole subgroup	87.37%	0.832 (0.772–0.898)	47.049%
Esomeprazole subgroup	77.01%	0.932 (0.871–0.998)	40.061%
Pantoprazole subgroup	87.13%	0.846 (0.746–0.960)	0.000%
Rabeprazole subgroup	91.24%	0.847 (0.766–0.936)	41.871%
Tinidazole subgroup	81.43%	0.889 (0.837–0.944)	38.688%
Metronidazole subgroup	83.20%	0.810 (0.745–0.882)	43.630%
Adverse events		1.176 (0.975–1.419)	0.000%
Standard triple therapy *vs* quadruple therapy	64.90%	1.073 (0.849–1.357)	93.204%
1-d subgroup	28.42%	2.367 (1.923–2.914)	0.000%
3-d subgroup	66.67%	1.288 (1.061–1.562)	100.000%
7-d subgroup	86.79%	0.790 (0.718–0.868)	0.000%
10-d subgroup	88.04%	0.917 (0.839–1.002)	22.259%
Omeprazole subgroup	66.67%	1.250 (1.012–1.545)	100.000%
Esomeprazole subgroup	73.76%	1.098 (0.699–1.725)	88.852%
Lansoprazole subgroup	45.00%	1.391 (0.404–4.790)	98.719%
Rabeprazole subgroup	83.99%	0.948 (0.771–1.166)	84.733%
Adverse events		0.940 (0.825–1.072)	0.000%
Standard triple therapy with other triple therapies	79.90%	1.010 (0.936–1.089)	72.233%
Adult subgroup	80.92%	0.999 (0.925–1.078)	69.085%
Child subgroup	73.25%	1.079 (0.748–1.557)	74.810%
7-d subgroup	80.32%	1.022 (0.949–1.100)	60.674%
10-d subgroup	77.78%	0.933 (0.821–1.060)	0.000%
14-d subgroup	78.40%	1.050 (0.712–1.549)	93.921%
Omeprazole subgroup	80.30%	1.048 (0.976–1.125)	49.506%
Esomeprazole subgroup	84.47%	0.911 (0.831–0.999)	0.000%
Levofloxacin subgroup	82.37%	0.917 (0.852–0.987)	0.000%
Furazolidone subgroup	85.22%	0.963 (0.762–1.216)	73.898%
Metronidazole subgroup	68.84%	1.119 (0.882–1.420)	80.863%
Adverse events		1.081 (0.848–1.378)	0.000%
Eradication rate with standard triple therapy		74.5%	

< 0.00001) with funnel plot asymmetry (Egger's test coefficient -2.58 to 13.51, P = 0.15). The pooled eradication rate of quadruple therapy was 64.9% based on this meta-analysis.

We performed a cumulative meta-analysis and the pooled RRs varied little with time. We also performed sensitivity analyses and found the pooled RRs were unchanged.

Due to the heterogeneity, we performed subgroup analyses according to the course of the quadruple therapy and different PPIs in the standard triple therapy.

The pooled RRs in the 1-d, 3-d, 7-d and 10-d duration of quadruple therapy subanalysis were 2.367 (95%CI: 1.923-2.914), 1.288 (95%CI: 1.061-1.562), 0.790 (95%CI:

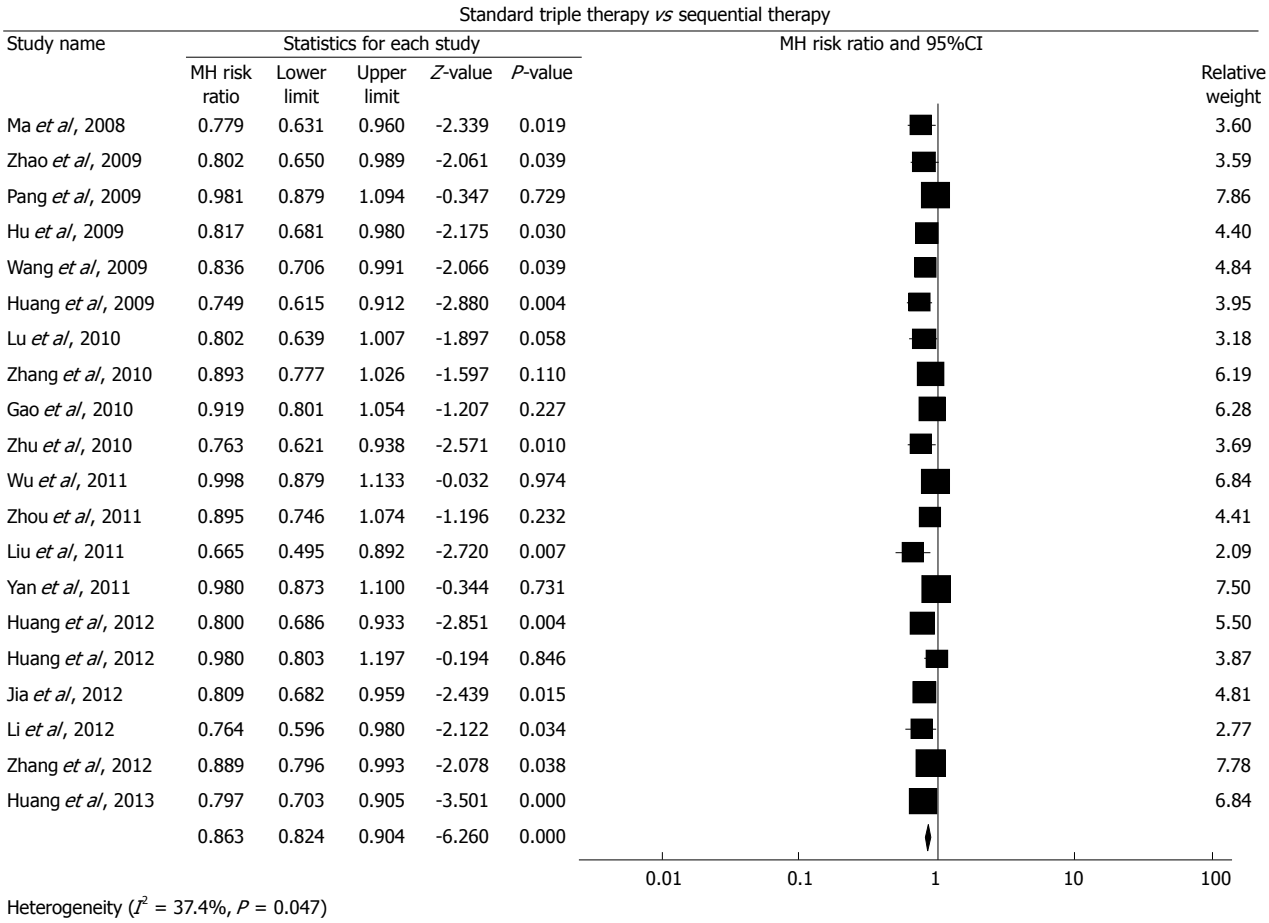

Figure 3 Forest plot of standard triple therapy *vs* sequential therapy by random effect model.

0.718-0.868), and 0.917 (95%CI: 0.839-1.002), respectively. The pooled eradication rates of quadruple treatments in the 1-d, 3-d, 7-d and 10-d subgroups were 28.42%, 66.67%, 86.79%, and 88.04%, respectively.

For the subanalysis of PPIs, the pooled RRs in the omeprazole, esomeprazole, lansoprazole and rabeprazole subgroups were 1.250 (95%CI: 1.012-1.545), 1.098 (95%CI: 0.699-1.725), 1.391 (95%CI: 0.404-4.790), and 0.948 (95%CI: 0.771-1.166), respectively. The pooled eradication rates of quadruple treatments in the omeprazole, esomeprazole, lansoprazole and rabeprazole subgroups were 66.67%, 73.76%, 45.00%, and 83.99%, respectively.

Data on adverse events were available for 7 trials. The RR was 0.940 (95%CI: 0.825-1.072), which indicated no significant difference with no evidence of heterogeneity (I^2 = 0%, P = 0.56).

Standard triple therapy *vs* other triple therapies: There were 20 studies[20-36,57-59] comparing standard triple therapy with other triple therapies. As shown in Figure 6, the pooled RR was 1.01 (95%CI: 0.936-1.089, P = 0.807). We found evidence of heterogeneity (I^2 = 72%, P < 0.00001) but no funnel plot asymmetry (Egger's test coefficient -2.35 to 3.51, P = 0.68). The pooled eradication rate of other triple therapy was 79.9% based on this meta-analysis.

As shown in Figure 7, we performed a cumulative meta-analyses and the pooled RRs varied little with time. We also performed sensitivity analyses and found the pooled RRs were unchanged.

Due to the heterogeneity, we performed subgroup analyses according to age, duration of standard triple therapy, different PPIs in standard triple therapy, and different drugs used in the control group (other triple therapy group).

The subanalysis by age showed that the summary RRs in the adult and the child subgroups were 0.999 (95%CI: 0.925-1.078) and 1.079 (95%CI: 0.748-1.557), respectively. The pooled eradication rates of other triple therapies in the adult and the child subgroups were 80.92% and 73.25%.

For the subanalysis of duration of standard triple therapy, the pooled RRs in the 7-d, 10-d and 14-d subgroups were 1.022 (95%CI: 0.949-1.100), 0.933 (95%CI: 0.821-1.060) and 1.050 (95%CI: 0.712-1.549), respectively. The pooled eradication rates of other triple therapies in the 7-d, 10-d, and 14-d subgroups were 80.32%, 77.78%, and 78.40%, respectively.

The PPI subanalysis indicated the pooled RRs in the omeprazole subgroup and the esomeprazole subgroup were 1.048 (95%CI: 0.976-1.125) and 0.911 (95%CI:

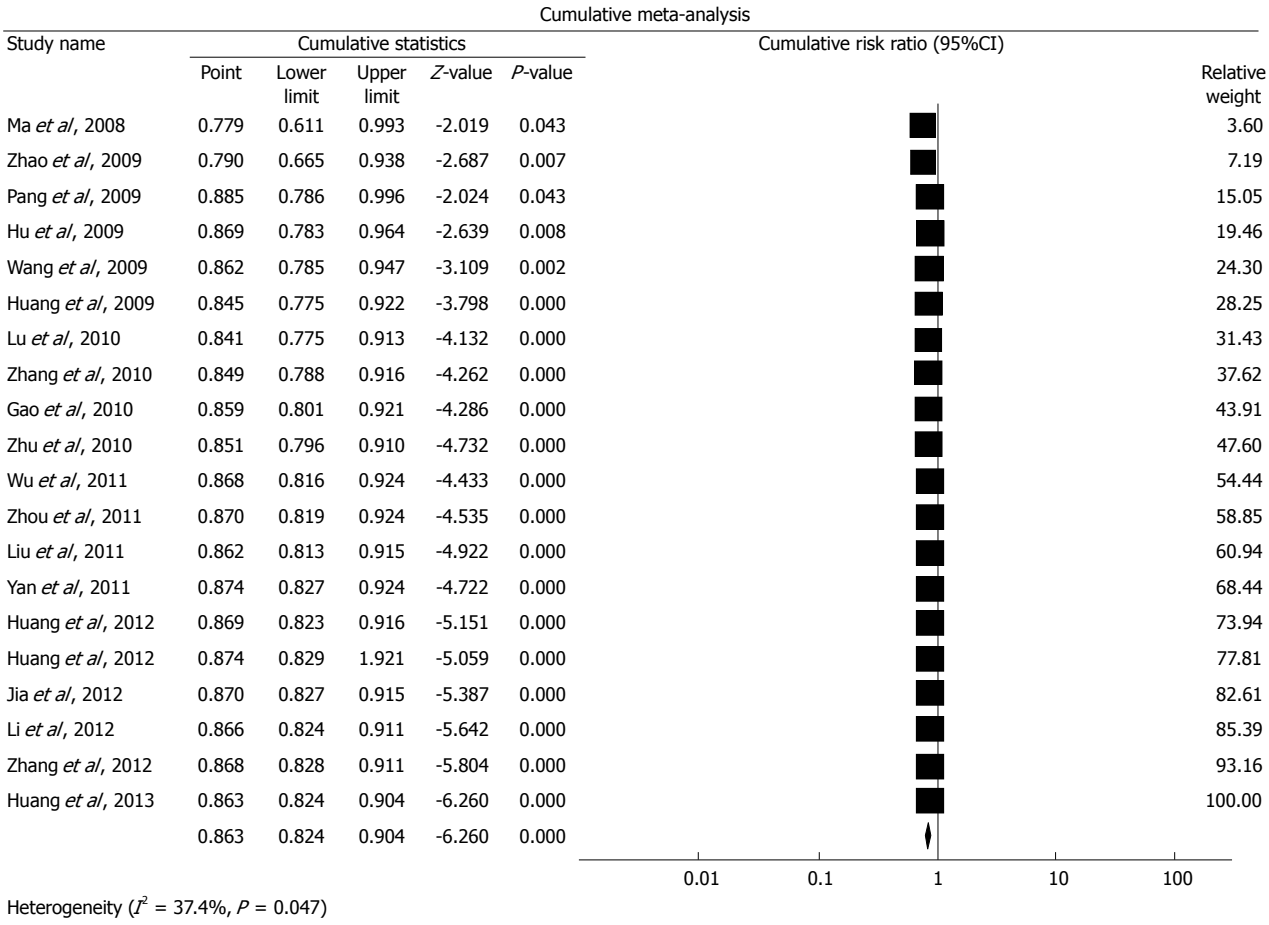

Figure 4 Cumulative meta-analysis of standard triple therapy *vs* sequential therapy by random effect model.

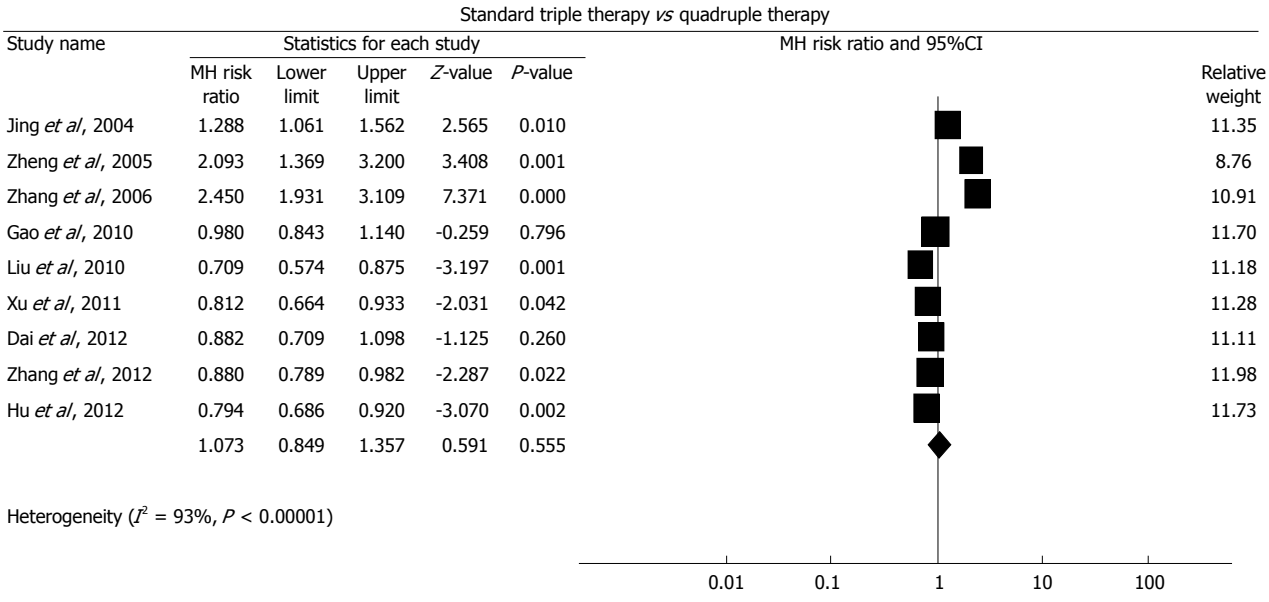

Figure 5 Forest plot of standard triple therapy *vs* quadruple therapy by random effect model.

0.831-0.999), respectively.

To examine the different drugs used in the control group subanalysis, the pooled RRs for the levofloxacin, furazolidone, and metronidazole subgroups were 0.917 (95%CI: 0.852-0.987), 0.963 (95%CI: 0.762-1.216), and 1.119 (95%CI: 0.882-1.420), respectively. The pooled eradication rates of other triple therapies in the levofloxacin, furazolidone, and metronidazole subgroups were

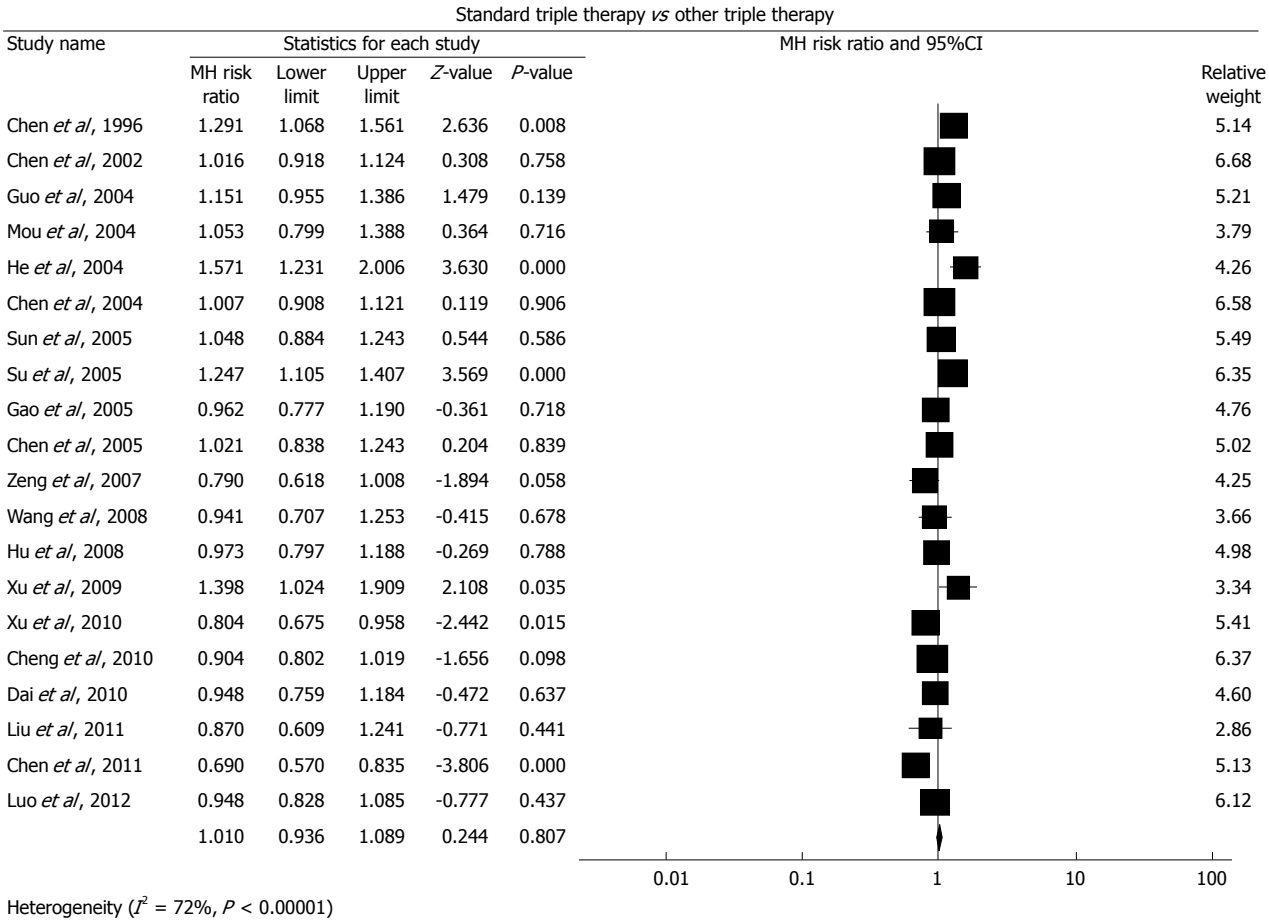

Figure 6 Forest plot of standard triple therapy *vs* other triple therapy by random effect model.

82.37%, 85.22%, and 68.84%, respectively.

Data on adverse events were available for 16 trials. The pooled RR was 1.081 (95%CI: 0.848-1.378), indicating no significant difference and no evidence of heterogeneity (I^2 = 0%, P = 0.79).

DISCUSSION

Graham *et al*[63] stratified the effectiveness of the treatment regimens for *H. pylori* infection into the following grades based on PP analysis: excellent regimen, if the eradication rate was more than 95%; good regimen, if a 91%-95% eradication rate was achieved; borderline, if the eradication rate was 85%-89%; and unacceptable if the eradication rate was less than 85%.

The standard triple treatment includes a PPI, CLA, and AMO or metronidazole to treat *H. pylori* infection. This treatment has become universal since all of the consensus conferences and guidelines worldwide recommend this treatment.

The following are the primary mechanisms of standard triple therapy: (1) AMO can impede the synthesis of the cell walls of *H. pylori* and can increase the concentration of CLA in *H. pylori* infection. Thus, the combination of the two can exert synergism; and (2) PPIs that modify the pH of gastric juice can inhibit the growth of *H. pylori* and diminish the activity of urease. Furthermore, PPIs can improve the concentration of CLA and AMO in the stomach by raising the pH of the gastric juice.

However, this triple regimen was used worldwide and the prevalence of *H. pylori* resistant to CLA has increased[7,8]. Drug resistance represents the major reason for the low eradication rate of the standard triple regimen consisting of PPIs, AMO and CLA[5]. One study conducted by the *H. pylori* Study Group of Digestive Diseases Division of the Chinese Medical Association demonstrated that the resistance rates of *H. pylori* to metronidazole, CLA, and AMO were 75.6%, 27.6%, and 2.7%, respectively[64].

The Maastricht consensus report Ⅳ indicates that triple therapy with AMO and CLA is not suitable for first-line therapy when the resistance rate of *H. pylori* to CLA is greater than 15%-20%. However, when the resistance rate of *H. pylori* is lower than 15% the regimen is still recommended as the preferred first-line regimen for *H. pylori* infection. The standard triple therapy shows a better eradication rate in CLA-sensitive strains than in CLA-resistant strains (88% *vs* 18%)[65].

Our meta-analysis and systematic review showed that the standard triple therapy might not be suitable for first-line therapy in China because the pooled eradication rate is 74.5%.

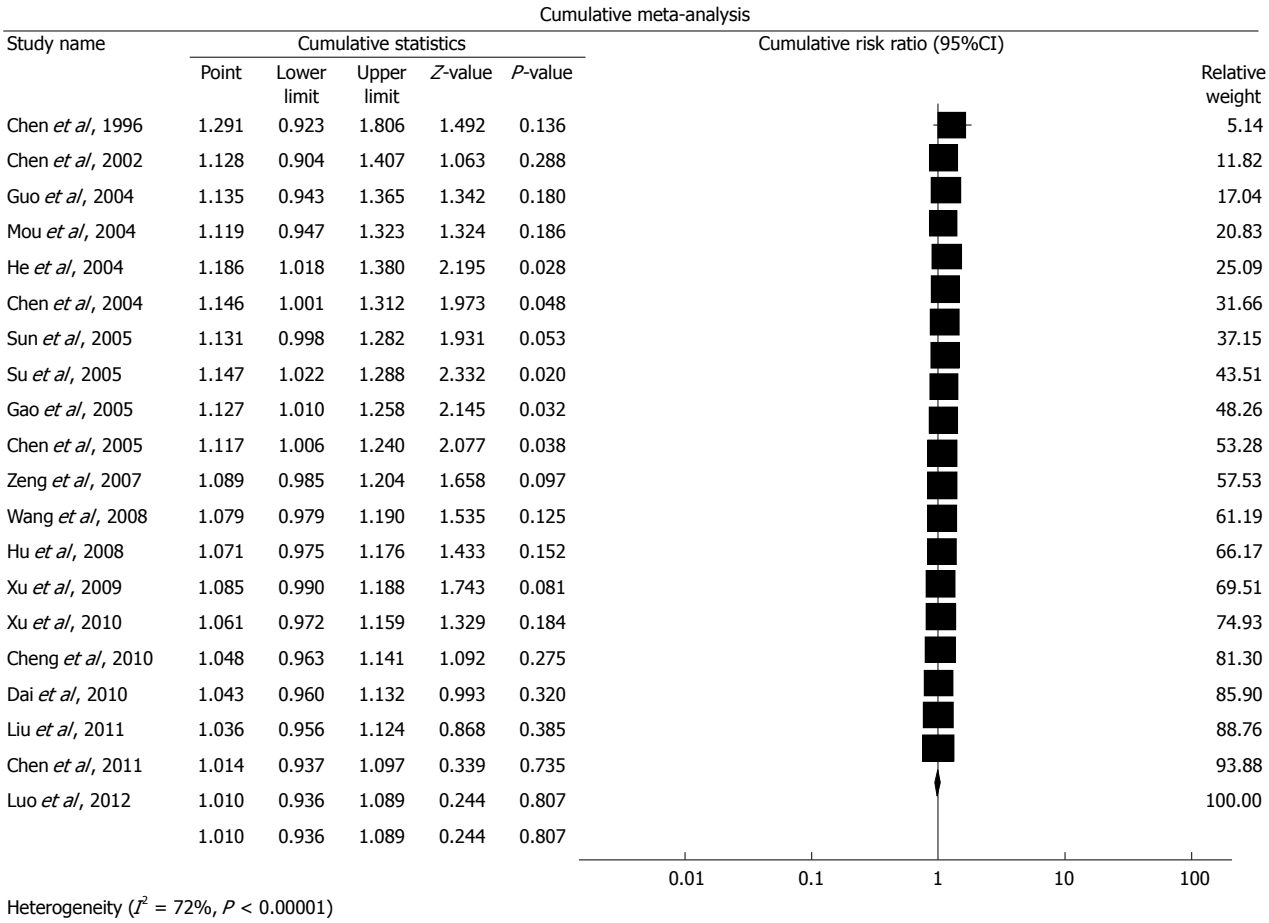

Figure 7 Cumulative meta-analysis of standard triple therapy *vs* other triple therapy by random effect model.

According to our meta-analysis comparing the standard triple therapy with dual treatments, the eradication rate of the standard triple therapy with PPIs, AMO, and CLA was slightly higher than for dual treatments (RR = 1.14, 95%CI: 0.99-1.31). However, when the study of Gao *et al*[19] was removed, the difference became significant. This result may be associated with the following causes: (1) the number of studies included in this meta-analysis was insufficient. Only 3 RCTs compared the standard triple therapy with dual treatment; and (2) the quality of the studies was low. More high quality RCTs are required to determine the actual difference between the standard triple therapies and dual treatments.

In the meta-analysis comparing standard triple therapy with sequential treatments, the outcomes demonstrated that standard triple therapy was inferior to sequential treatments (RR = 0.863; 95%CI: 0.824-0.904). The subgroup analyses showed no statistical significance among those treatments. Additionally, a recent study showed sequential treatment could achieve an 89.7% eradication rate by *per protocol* analysis in China[15]. Thus, although the guidelines of China do not recommended sequential treatment as a first-line therapy, we suggest that it is worth further study to identify the effectiveness of sequential therapy in China. Our subgroup analyses also showed that 14-d treatments were superior to 7-d treatment. These results indicate that a longer duration might be more effective when used for *H. pylori* infection. The cumulative meta-analysis showed that the RRs were stable.

Our meta-analysis comparing the standard triple *vs* quadruple treatments showed that the eradication rate of the standard triple treatment was similar to quadruple treatments. This finding conflicts with most of the pre-existing consensus. The results of subgroup analyses showed that the 7-d quadruple treatments were superior to the standard triple treatment (RR = 0.790, 95%CI: 0.718-0.868) and that the 1-d and 3-d quadruple treatments were inferior to the standard triple treatment (RR = 2.367, 95%CI: 1.923-2.914; RR = 1.288, 95%CI: 1.061-1.562, respectively). It was interesting that the effectiveness of the 10-d standard triple treatment was equivalent to that of the 10-d quadruple treatments (RR = 0.917, 95%CI: 0.839-1.002). Although we performed subgroup analyses based on the duration, age, and PPI used in the standard triple groups, the significant heterogeneity in this meta-analysis may also affect its reliability.

Based on our meta-analysis comparing standard triple treatments with other triple treatments, the eradication rate of the standard triple treatments was similar to that of other triple treatments. This result suggested that the standard triple treatment was not inferior to other triple treatments. The eradication rates of both standard triple

treatments and other triple treatments were less than 80%. We also performed subgroup analyses based on different PPIs, durations, and treatments in the control group. The results showed that the treatments containing levofloxacin were able to provide higher eradication rates than standard triple therapy and is consistent with other studies[66,67]. Interestingly, the effectiveness of the esomeprazole subgroup was inferior to the control group. There was no statistical significance in other subgroups. To determine the variations in the eradication rate of standard triple treatments compared with other triple treatments against time, we performed a cumulative meta-analysis of the chronological order of the studies' publication dates. We found that the effectiveness of the standard triple treatment with PPI, AMO and CLA gradually reduced with time. This may be related to the increasing resistance rate of *H. pylori* to CLA.

Strengths and limitations

To diminish bias there were 2 reviewers who performed the study selection, data extraction and the evaluation of study quality. We comprehensively analyzed the efficacy of the standard triple therapy with PPI, AMO and CLA in anti-*H. pylori* treatment. The subgroup analyses and sensitivity analyses made the outcomes of our meta-analyses reliable.

There were several limitations to our meta-analysis. First, most of the studies included in our meta-analysis had problems with concealing the allocation and blinding, which might have affected our results. However, we performed sensitivity analyses to determine the reliability of our results. Second, there was heterogeneity in the meta-analysis and we conducted subgroup analyses and sensitivity analyses to decrease these effects. Third, the quality of the studies included in the meta-analysis might also affect our result. Fourth, the available published languages might have exerted a bias. Thus, it is likely that our meta-analysis does not reflect all outcomes. Finally, we asked authors for unpublished data, but their lack of response may have introduced further bias.

In conclusion, the effectiveness of the standard triple therapy with PPIs, AMO, and CLA is inferior to sequential treatments and is similar to other triple treatments, but is not superior to quadruple therapy. The standard triple treatment achieves a low eradication rate for *H. pylori* infection and is not suitable as a first-line therapy for treatment of *H. pylori* infection in China.

COMMENTS

Background

The standard triple regimen with proton pump inhibitors (PPIs), amoxicillin (AMO) and clarithromycin (CLA) is still recommended as a first-line regimen for treatment of *Helicobacter pylori* infection by several groups. However, the eradication rate is decreasing and the resistance of *Helicobacter pylori* (*H. pylori*) to CLA is increasing.

Research frontiers

In China, the efficacy of the standard triple therapy consisting of PPI, AMO and CLA, has been shown by some studies to be considerable over the past decade. However, the prevalence of antibiotic-resistant *H. pylori* is increasing rapidly. It is unclear if the standard triple therapy is suitable for treatment of *H. pylori* infection in China.

Innovations and breakthroughs

This was the first meta-analysis comparing the efficiency of standard triple therapy with other pre-existing and new therapies on the Chinese mainland. Furthermore, this meta-analysis also examined the eradication rates for *H. pylori* and the changes in the eradication rate of the standard triple therapy with time on the Chinese mainland.

Applications

The results indicated that standard triple therapy of PPI, AMO, and CLA might not be suitable for first-line therapy on the Chinese mainland and new agents for treatment need to be developed.

Peer review

This meta-analysis study is well structured and has a great scientific merit. It provides an important contribution to *H. pylori* therapeutics in China.

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