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META-ANALYSIS

Minocycline in the eradication of *Helicobacter pylori* infection: A systematic review and meta-analysis

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Abstract

BACKGROUND

Difficulty in obtaining tetracycline, increased adverse reactions, and relatively complicated medication methods have limited the clinical application of the classic bismuth quadruple therapy. Therefore, the search for new alternative drugs has become one of the research hotspots. In recent years, minocycline, as a semisynthetic tetracycline, has demonstrated good potential for eradicating *Helicobacter pylori* (*H. pylori*) infection, but the systematic evaluation of its role remains lacking.

AIM

To explore the efficacy, safety, and compliance of minocycline in eradicating *H. pylori* infection.

METHODS

We comprehensively retrieved the electronic databases of PubMed, Embase, Web of Science, China National Knowledge Infrastructure, SinoMed, and Wanfang database as of October 30, 2023, and finally included 22 research reports on *H. pylori* eradication with minocycline-containing regimens as per the inclusion and exclusion criteria. The eradication rates of *H. pylori* were calculated using a fixed or a random effect model, and the heterogeneity and publication bias of the studies were measured.

RESULTS

The single-arm meta-analysis revealed that the minocycline-containing regimens achieved good overall *H. pylori* eradication rates, reaching 82.3% [95% confidence interval (CI): 79.7%-85.1%] in the intention-to-treat analysis and 90.0% (95%CI: 87.7%-92.4%) in the per-protocol analysis. The overall safety and compliance of the minocycline-containing regimens were good, demonstrating an overall

incidence of adverse reactions of 36.5% (95%CI: 31.5%-42.2%). Further by traditional meta-analysis, the results showed that the minocycline-containing regimens were not statistically different from other commonly used eradication regimens in eradication rate and incidence of adverse effects. Most of the adverse reactions were mild to moderate and well-tolerated, and dizziness was relatively prominent in the minocycline-containing regimens (16%).

CONCLUSION
The minocycline-containing regimens demonstrated good efficacy, safety, and compliance in *H. pylori* eradication. Minocycline has good potential to replace tetracycline for eradicating *H. pylori* infection.

Key Words: *Helicobacter pylori*; Minocycline; Eradication; Safety; Resistance

Core Tip: Regarding the utilization of minocycline in the eradication therapy of *Helicobacter pylori* (*H. pylori*) infection, there is a lack of literature summarizing the potential and role of minocycline in the eradication of *H. pylori* infection. This is the first comprehensive account of the role, efficacy, and current state of research on minocycline in the eradication therapy of *H. pylori* infection by traditional meta-analysis as well as single-arm meta-analysis methods. We have summarized this minocycline in terms of bactericidal mechanism, pharmacodynamics, pharmacokinetics, drug resistance, eradication efficacy, safety and compliance.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection and its related diseases (gastric cancer, peptic ulcer, chronic atrophic gastritis/intestinal metaplasia, dyspepsia, *etc.*) are crucial global health issues. In clinics, many patients require eradication therapy for *H. pylori* infection for its effective prevention and treatment[1,2]. *H. pylori* infection eradication has become more and more difficult with the increasing resistance to antibiotics, such as clarithromycin, levofloxacin, *etc*[3,4]. The global consensuses of experts in diagnosing and treating *H. pylori* infection generally recommends the classic bismuth quadruple therapy (BQT) for eradication, *i.e.,* proton pump inhibitor, tetracycline, full-dose metronidazole, and bismuth[1,5-8]. However, this regimen demonstrated a high incidence of adverse reactions and relatively complex usage. Tetracycline is difficult to clinically obtain in many countries and regions, which has greatly limited the clinical application of BQT[9,10]. The use of other drugs to replace tetracycline to effectively eradicate *H. pylori* infection has become one of the hot research directions in this field.

Minocycline, as a semi-synthetic tetracycline[11,12], has been currently prominently used in clinical treatment of diseases such as acne, sexually transmitted diseases, and special respiratory infections. Compared with tetracycline, minocycline has demonstrated better bactericidal activity on other bacteria[13]. In 2002, scholars attempted to use the minocycline-containing regimen for eradicating *H. pylori* infection[14]. Since then, basic and clinical studies have successively investigated the efficacy, safety, compliance, and drug resistance of different minocycline-containing regimens in treatment-naive or retreated patients with *H. pylori* infection[11,12]. In general, these studies have demonstrated that minocycline demonstrated good potential and effect in eradicating *H. pylori* infection and is a very promising alternative in cases where tetracycline is difficult to obtain. Herein, we conducted a review and meta-analysis of the minocycline-containing regimens to comprehensively explore their role, effect, and research status in eradicating *H. pylori* infection.

MATERIALS AND METHODS

Bactericidal mechanism of minocycline

Chlortetracycline, the first tetracycline compound, was introduced in the 1950s. Shortly thereafter, Duggar *et al*[15] analyzed the mutant of chlortetracycline in *Staphylococcus aureus* and revealed demeclocycline, a precursor, which was further reduced and transformed into minocycline. Minocycline is a tetracycline derivative with a similar mechanism of action to that of tetracycline. It enters the bacteria mainly through the outer membrane protein channel and specifically binds to A site of the 30S subunit aminoacyl group of bacterial ribosomes, thereby blocking the aminoacyl-tRNA binding

at this site, preventing peptide chain extension and bacterial protein synthesis, and playing the bactericidal role[16] (Figure 1). The affinity between minocycline and ribosome is 20 times higher and the *in vitro* translational suppression efficiency is 2-7 times higher than that of tetracycline. Therefore, minocycline demonstrated better and more potent bactericidal effects[17,18]. Minocycline contains a broad antimicrobial spectrum covering Gram-positive cocci, Gram-negative bacilli, and cocci, as well as atypical pathogens[16].

Pharmacodynamics and pharmacokinetics of minocycline

Minocycline has a longer serum half-life than tetracycline of up to 12-18 h and can reach the peak plasma concentration within 2-3 h after oral administration. Minocycline is only taken once or twice daily and is not taken as frequently as tetracycline, which helps improve treatment compliance[12,19]. Compared with tetracycline, minocycline is not susceptible to food impact and has a high absorption rate, which is conducive to obtaining better bioavailability[19]. Minocycline demonstrated better lipid solubility and tissue permeability than other tetracyclines, which are beneficial to improving drug distribution and concentration in tissues[20]. Minocycline is almost completely absorbed in the duodenum and jejunum (95%-100%), widely distributed in body fluids, bile, and tissues, and mainly excreted through feces (20%-34%) and kidneys (5%-15%)[19].

Drug resistance of minocycline

In 2009, Horiki *et al*[21] discussed the antibiotic resistance rate of the *H. pylori* strain (n = 3521) in an investigation in Japan from 1996 to 2008, and they revealed a very low primary drug resistance rate of minocycline [0.06% (2/3, 521)]. Five studies from China, including drug resistance testing, clinical cohort, and randomized controlled trials (RCTs), discussed the drug resistance of minocycline in the Chinese mainland. The results indicated a low drug resistance rate of minocycline (approximately 0.7%-8.2%), which was similar to that of tetracycline in the same period[11,22-25]. A study in Japan evaluated the antibacterial activity, *i.e.,* the minimum inhibitory concentration (MIC) of minocycline against clarithromycin-resistant *H. pylori* strain, and revealed MIC50 and MIC90 of 0.5 μg/mL, which were similar to those of tetracycline (1 μg/mL), indicating that minocycline, similar to tetracycline, had significantly sensitive antibacterial activity against *H. pylori* strain[21]. Further, Murakami *et al*[26] concluded similar results. The in-depth study of antibiotic resistance revealed that tetracycline resistance mutation has been discovered in the stem-loop of the 31st helix of 16S rRNA of *H. pylori* strain, with the triple mutation A965U/G966U/A967C, conferring high-level resistance against tetracycline as well as an increased MIC for minocycline[27].

Methods

We conducted a comprehensive literature retrieval and meta-analysis, which was described in detail below, to explore the eradication rates, adverse reaction incidences, and minocycline-containing regimens compliance.

Literature retrieval: PRISMA statement guidelines were followed for conducting and reporting the meta-analysis data. We have conducted a comprehensive and systematic retrieval in PubMed, Web of Science, EMBASE, China National Knowledge Infrastructure, SinoMed and Wanfang database. The retrieval cut-off date was October 30, 2023. The retrieval keywords included (Minocycline) AND (Helicobacter pylori OR Helicobacter nemestrinae OR Campylobacter pylori OR Campylobacter pylori subsp. pylori OR Campylobacter pyloridis OR *H. pylori* OR Hp) AND (Eradication OR Therapeutics OR Therapeutic OR Therapy * OR Treatment * OR Eradicate * OR Regimen *).

Literature inclusion criteria were minocycline contained in *H. pylori* infection eradication regimen; adult patients over 18 years old; specific information of eradication regimens obtained, including drug types, dosages, frequencies, and treatment durations; reported numbers of successful and unsuccessful eradication in patients. Literature exclusion criteria were treatment duration of < 7 d; repeated studies; and loss to follow-up rate of > 20%.

First, preliminary screening was conducted on the included articles by titles, abstracts, and keywords. The remaining study reports passing the preliminary screening were then subjected to further review as per inclusion and exclusion criteria. Finally, the full text was thoroughly and carefully reviewed. We did not limit the minimum sample size in the analysis to reduce the bias. Figure 2 shows the process for article retrieval, screening, and inclusion.

Literature quality evaluation: Both authors (Zhou K and Li CL) used the Cochrane bias risk tool to assess bias risk in a single study across five domains, *i.e.,* selection bias, performance bias, detection bias, reporting bias, and other biases. Any disagreements were resolved through discussions with the expert (Song ZQ). The standard answers included: (1) Yes, indicating a high bias risk; (2) No, indicating a low bias risk; and (3) Unclear, indicating an uncertain bias risk.

Data extraction: All retrieved studies were loaded into the Endnote X9, which is a reference management software. Two authors (Zhou K and Li CL) extracted and recorded the following study data in pre-designed information extraction tables, including author, publication year, study country, study type, patient type, drug dose and frequency, sample size, treatment course, eradication rate, compliance, safety, and drug resistance rate. The two authors extracted the data independently and cross-checked them. Pre-extraction was performed before formal data extraction to assess the rationality of the data extraction table design and the consistent degree of understanding of the same issue. The two authors first communicated and resolved disagreements that arose during the extraction process. If disagreements persist, consensus is reached through discussions with the expert (Song ZQ).

Data analysis: The meta package of the R program (version 4.2.2) was used for the combined analysis of the single-arm eradication rates. The heterogeneity was investigated using I^2. I^2 of > 50% is considered a heterogeneity, and the random effect model was adopted to assess the effect size of included studies; otherwise, the fixed effect model was utilized. A

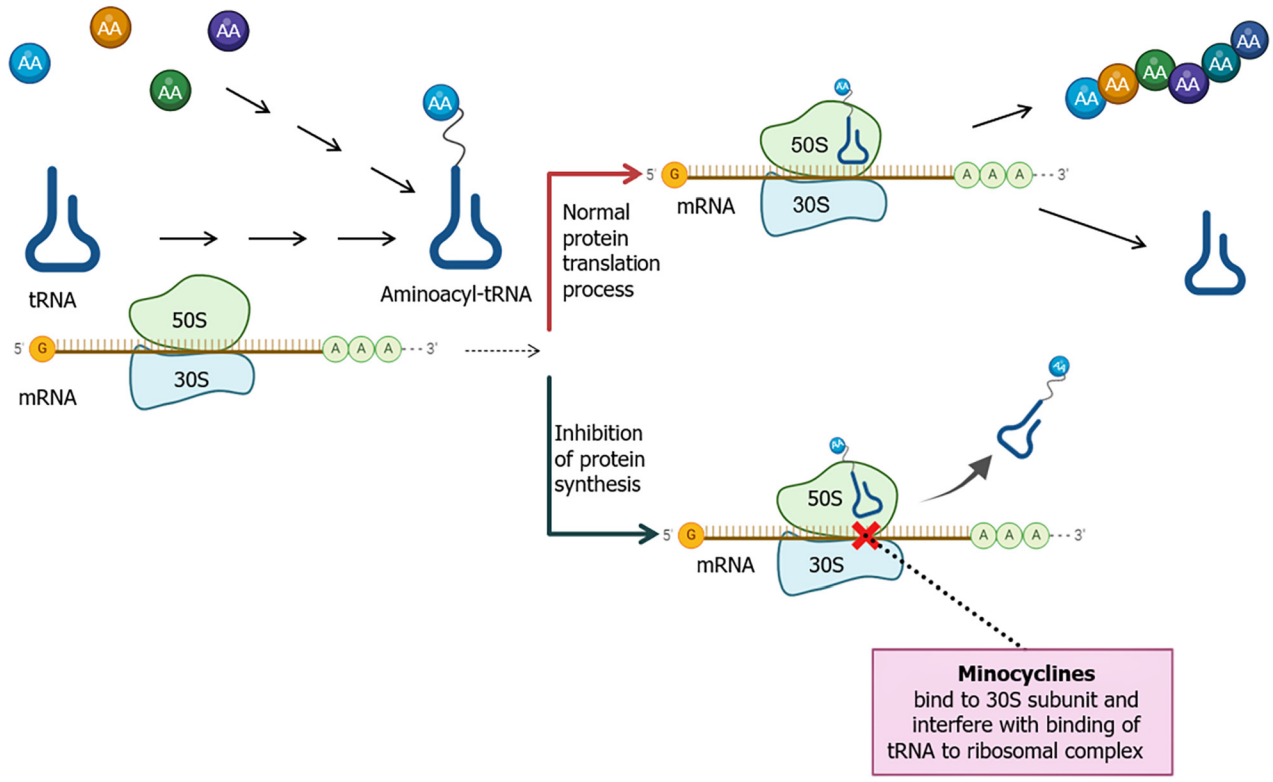

Figure 1 Scheme of the minocyclines' mechanism of action. Amino acids and tRNAs are linked together by aminoacyl-tRNA synthetase to produce specific Aminoacyl-tRNAs. ribosomes on the ribosomal complex then read the code along the 5'-3' direction of the mRNAs while linking various aminoacyl-tRNA-transported amino acids according to the instructions of the mRNA coding sequences for the process of protein synthesis. When minocycline enters into bacteria, it specifically binds to the A site of bacterial ribosomal 30S subunit aminoacyl group, thus blocking the aminoacyl-tRNA binding at this site, preventing peptide chain elongation and bacterial protein synthesis, and exerting bactericidal effects. AA: Amino acids.

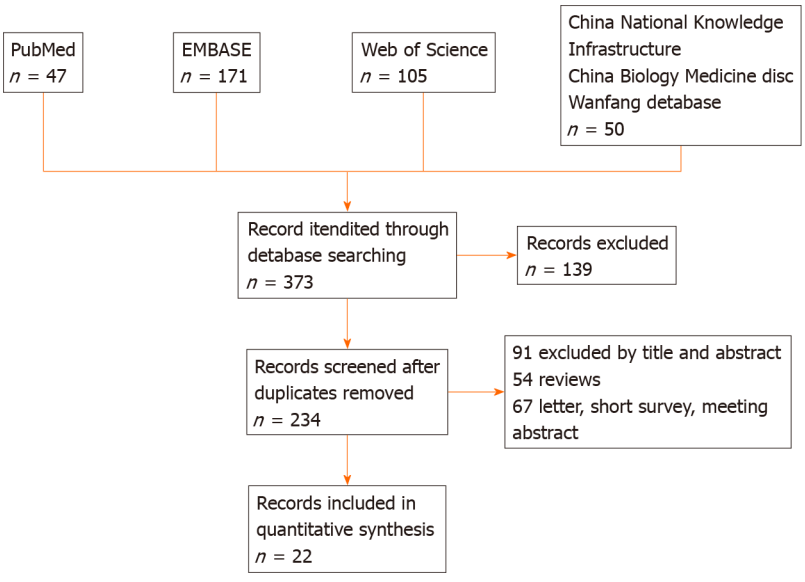

Figure 2 Literature identification process.

relatively large heterogeneity was observed in the single-arm eradication rates. Therefore, the eradication rates in intention-to-treat (ITT) and per-protocol (PP) analyses and the corresponding 95% confidence interval (CI) were respectively summarized by the random effect model. Funnel plot, Egger's test, and Begg's test were used to evaluate the publication bias, and publication bias was considered if P values were < 0.05. Sensitivity analysis was conducted by assessing the stability of the results by deleting each study in turn.

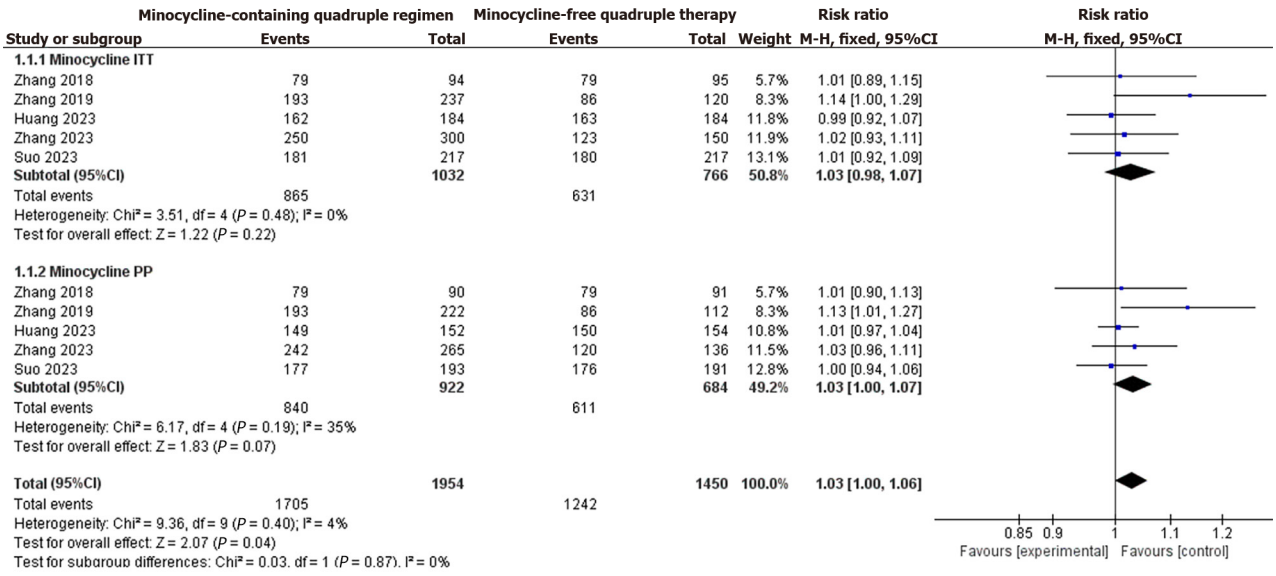

Figure 3 Forest plots comparing eradication rates for intention-to-treat and per-protocol analyses of quadruple regimens with and without minocycline. CI: Confidence interval.

RESULTS

Basic information of included studies

Table 1 shows the specific information of the included studies (n = 22)[11,12,23-26,28-43]. A total of 36 minocycline-containing treatment groups were found in 22 studies, including 19 treatment-naive and 17 retreatment groups. Regarding the eradication regimen type, 5 treatment groups in 2 studies received triplet minocycline-containing regimens, 30 treatment groups in 21 studies received quadruplet minocycline-containing regimens, and 1 treatment group received quadruple therapy combined with probiotics. Of the included studies, 20 originated from China, 1 from Japan, and 1 from Italy. Regarding treatment course, 4 treatment groups (n = 177) in 2 studies adopted a 7-d course, 7 treatment groups (n = 332) in 5 studies adopted a 10-d course, and 16 studies (n = 2588) adopted a 14-d course. Regarding study design type, 1 study used a randomized grouping approach in treatment-naive patients, and patients in the salvage treatment group were assigned to different treatment regimen subgroups according to metronidazole-resistance status. Among the remaining 21 studies, 11 were RCTs and 10 were cohort studies.

Pooled analysis of eradication rates and incidences of adverse reactions

Regarding antibiotic combinations in the minocycline-containing eradication regimens, nitroimidazole antibiotics (metronidazole, tinidazole, or ornidazole) were combined in 14 treatment groups from 12 studies[12,23-26,28,32,36-40], amoxicillin was combined in 17 treatment groups from 11 studies[11,26,29-31,33,34,36,41-43], and faropenem, levofloxacin, cefuroxime, furazolidone, and rifabutin were respectively combined in 1 treatment group[25,26,28,35,37]. Overall eradication rates of minocycline-containing eradication regimens were 82.3% (95%CI: 79.7%-85.1%, I^2 = 70%, P < 0.01) in ITT analysis and 90.0% (95%CI: 87.7%-92.4%, I^2 = 80%, P < 0.01) in PP analysis. The included studies demonstrated a high degree of heterogeneity. The pooled analysis included the overall eradication rates of the minocycline-containing regimens, the combination regimen of minocycline-containing and nitroimidazole antibiotics, the combination regimen of minocycline-containing and amoxicillin, the eradication rates in treatment-naive patients, and the eradication rates in retreated patients. Table 2 shows the results (see the appendix for details of the corresponding forest plots). Additionally, the overall incidence of adverse reactions in minocycline-containing eradication regimens was 36.5% (95%CI: 31.5%-42.2%)[9,11,12,23-25,31-33,36-38] (Supplementary Figures 1-10).

Comparative analysis of eradication rates

Comparison of efficacy of quadruplet eradication regimens with and without minocycline: The analysis included five RCTs that adopted minocycline-containing quadruple regimens[23-25,32,36]. Combinations of antibiotics in the minocycline-containing groups included metronidazole (n = 5), amoxicillin (n = 1), and cefuroxime (n = 1) and that in the control group included a tetracycline with metronidazole (n = 2), amoxicillin with clarithromycin (n = 2), and cefuroxime with metronidazole (n = 1). The figure shows no obvious heterogeneity in the ITT analysis using the fixed effect model (χ^2 = 3.51, P = 0.48, I^2 = 0), and the eradication efficacy between the quadruple regimens with and without minocycline was not statistically significantly different [risk ratio (RR) = 1.03, 95%CI: 0.98-1.07, P = 0.22]. The PP analysis revealed similar results to the ITT analysis. The two groups demonstrated no significant heterogeneity (χ^2 = 6.17, P = 0.19, I^2 = 35%) and no statistically significant difference in efficacy (RR = 1.03, 95%CI: 1.00-1.07, P = 0.07). ITT and PP analyses revealed the eradication rates of quadruple regimens with and without minocycline of 83.8% *vs* 82.4% and 91.1% *vs* 89.3%, respectively (Figure 3).

Table 1 Characteristics of included studies

Ref.	Country	Study type	Patient type	Regimen	Sample size	Duration (d)	Eradication rate (ITT analysis)	Eradication rate (PP analysis)	Compliance	Adverse effects rate	Resistance rate
Murakami *et al*[26], 2006	Japan	RCT	1st	R 20 mg bid + CLA 200 mg bid + AMX 750 mg bid	40	7	82.5% (33/40)	84.6% (33/39)			
				R 20 mg bid + MIN 100 mg bid + AMX 750 mg bid	39	7	38.5% (15/39)	40.5% (15/37)			
		Cohort study	2nd	R 20 mg bid + MIN 100 mg bid + MTZ 250 mg bid	67	7	85.1% (57/67)				
				R 20 mg bid + MIN 100 mg bid + FAR 600 mg bid	21	7	9.5% (2/21)				
Ierardi *et al*[28], 2014	Italy	RCT	≥ 2nd	R 20 mg bid + RIF 150 mg bid + MIN 100 mg bid + B 120 mg tid	27	10	77.8% (21/27)	84.0% (21/25)			
				R 20 mg bid + MIN 100 mg bid + TNZ 500 mg bid + B 120 mg tid	27	10	51.9% (14/27)	51.9% (14/27)			
Zhang *et al*[29], 2015	China	RCT	≥ 2nd	R 10 mg bid + MIN 100 mg bid + AMX 1000 mg bid + B 220 mg bid	63	10	84.1% (53/63)	88.3% (53/60)	95.2% (60/63)	23.8% (15/63)	
				Tailored therapy (triple treatment)	62	10	75.8% (47/62)	79.7% (47/59)	96.8% (60/62)	33.9% (21/62)	
Song *et al* [11], 2016	China	Cohort study	1st	R 10 mg bid + MIN 100 mg bid + AMX 1000 mg bid + B 220 mg bid	160	14	87.5% (140/160)	92.6% (137/148)	94.7% (213/225)	24.0% (54/225)	6.9% (4/58)
			2nd	R 10 mg bid + MIN 100 mg bid +AMX 1000 mg bid + B 220 mg bid	70	14	82.9% (58/70)	89.1% (57/64)	23.8% (15/63)		8.7% (2/23)
Song *et al* [12], 2016	China	Cohort study	1st	E 20 mg bid + MIN 100 mg bid + MTZ 400 mg qid + B 110 mg qid	152	14	85.5% (130/152)	92.6% (137/148)	91.3% (136/149)	35.6% (53/149)	
			2nd	E 20 mg bid + MIN 100 mg bid + MTZ 400 mg qid + B 110 mg qid	64	14	82.8% (53/64)	89.5% (51/57)	90.5% (57/63)	36.5% (23/63)	
Zhou[30], 2017	China	RCT	≥ 2nd	AMLZ 20 mg bid + MIN 100 mg bid + AMX 1000 mg bid	50	7	80.00% (40/50)				
				AMLZ 20 mg bid + MIN 100mg bid + AMX 1000 mg bid	50	10	82.00% (41/50)				
				AMLZ 20 mg bid + MIN 100 mg	50	10	84.00% (42/50)				

				bid + AMX 1000 mg bid + B 220 mg bid						
				AMLZ 20 mg bid + CLA 500 mg bid + AMX 1000 mg bid + B 220 mg bid	50	10	52.00% (26/50)			
Zhang *et al*[31], 2017	China	Cohort study	≥ 2nd	R 10 mg bid + MIN 100 mg bid + AMX 1000 mg bid + B 220 mg bid	180	14	79.4% (143/180)	84.1% (143/170)	≥ 90%	31.1% (56/180)
Zhang *et al*[32], 2018	China	RCT	1st	R 10 mg bid + MIN 100 mg bid + MTZ 400 mg tid + B 220 mg bid	94	14	84.0% (79/94)	87.8% (79/90)	≥ 90%	40.4% (38/94)
				R 10 mg bid + CLA 500 mg bid + AMX 1000 mg bid + B 220 mg bid	95	14	83.2% (79/95)	86.8% (79/91)	≥ 90%	41.1% (39/95)
Pu *et al* [33], 2018	China	Cohort study	1st	R 10 mg bid + MIN 100 mg bid + AMX 1000 mg bid + B 220 mg bid	130	14	83.9% (109/130)	94.8% (109/115)	96.2% (125/130)	41.5% (54/130)
			2nd	R 10 mg bid + MIN 100 mg bid + AMX 1000 mg bid + B 220 mg bid	96	14	86.5% (83/96)	96.5% (83/86)	97.9% (94/96)	44.8% (43/96)
Xu *et al* [34], 2019	China	Cohort study	1st	R 20mg bid + MIN 100mg bid + AMX 1000mg bid + B 300 mg bid	52	14	88.5% (46/52)	93.6% (44/47)	≥ 90%	
			2nd	R 20mg bid + MIN 100mg bid + AMX 1000mg bid + B 300mg bid	28	14	82.1% (23/28)	95.7% (22/23)	≥ 80%	
Li *et al* [35], 2019	China	RCT	≥ 2nd	E 20mg bid + RIF 150mg bid + FUR 100mg tid	74	10	82.4% (61/74)	91.0% (61/67)	90.5% (67/74)	
				E 20mg bid + MIN 100mg bid + FUR 100mg tid + B 110mg qid	72	10	84.7% (61/72)	93.8% (61/65)	90.3% (65/72)	
Zhang *et al*[36], 2019	China	RCT	1st	R 10mg bid + MIN 100mg bid + AMX 1000mg bid + B 220mg bid	119	14	85.7% (102/119)	89.5% (102/114)	96.6% (115/119)	30% (36/120)
				R 10mg bid + MIN 100mg bid + MTZ 400mg tid + B 220mg bid	118	14	77.1% (91/118)	84.3% (91/108)	94.9% (112/118)	37.5% (45/120)
				R 10mg bid + CLA 500mg bid + AMX 1000mg bid + B 220 mg bid	1020	14	71.7% (86/120)	76.8% (86/112)	95.8% (115/120)	40.0% (48/120)
Zhang *et al*[37], 2022	China	RCT	1st	R 10mg bid + MIN 100mg bid + MTZ 400mg tid + B 220mg	76	14	80.3% (61/76)	83.6% (61/73)	≥ 90%	47.4% (36/76)

				bid							
				R 10mg bid + MIN 100mg bid + LEV 500mg qd + B 220mg bid	74	14	89.2% (66/74)	90.4% (66/73)	≥ 90%	33.8% (25/74)	
Zhang *et al*[38], 2021	China	Cohort study	1st	R 10mg bid + MIN 100mg bid + MTZ 400mg tid + B 220mg bid	175	14	72.0% (126/175)	86.3% (126/146)	≥ 90%	50.9% (89/175)	
Huang *et al*[39], 2021	China	Cohort study	1st	E 20mg bid + MIN 100mg bid + ONZ 500mg bid + B 220mg bid	50	14	96.0% (48/50)		≥ 90%		
				E 20mg bid + MIN 100mg bid + ONZ 500mg bid + B 220mg bid + Bifidobacterium Lactobacillus trifecta 2000mg bid	51	14	92.2% (47/51)				
Cui *et al* [40], 2022	China	Cohort study	1st	R 10mg bid + MIN 100mg bid + MTZ 400mg tid + B 220mg bid	28	14	71.4% (20/28)	87.0% (20/23)			
Li *et al* [41], 2022	China	RCT	1st	E 20mg bid + CLA 500mg bid +AMX 1000mg bid + B 200mg bid	91	10	80.2% (73/91)	89.0% (73/82)		6.7% (9/134)	
				E 20mg bid + MIN 100mg bid + AMX 1000mg bid + B 200mg bid	43	10	81.4% (35/43)	87.5% (35/40)			
				E 20mg bid + FUR 100mg bid + AMX 1000mg bid + B 200mg bid	67	10	85.1% (57/67)	90.5% (57/63)		7.5% (5/67)	
Guo *et al* [42], 2023	China	Cohort study	1st	E 20mg bid + MIN 100mg bid + AMX 750mg tid + B 200mg tid	25	14	84.0% (21/25)		≥ 90%		
			≥ 2nd	E 20mg bid + MIN 100mg bid + AMX 750mg tid + B 200mg tid	65	14	86.2% (56/65)				
Hao *et al* [43], 2022	China	Cohort study	≥ 2nd	R 10mg bid + MIN 100mg bid + AMX 1000mg bid + B 300mg bid	80	14	78.8% (63/80)				
Suo *et al* [23], 2023	China	RCT	1st	E 20mg bid + MIN 100mg bid + MTZ 400mg qid + B 110mg qid	217	14	83.4% (181/217)	91.7% (177/193)	90.7% (195/215)	34.9% (75/215)	6.3% (4/63)
				E 20mg bid + TET 500mg qid + MTZ 400mg qid + B 110mg qid	217	14	83.0% (180/217)	92.2% (176/191)	89.7% (192/214)	41.1% (88/214)	7.0% (5/71)
Zhang *et al*[25], 2023	China	RCT	1st	E 20mg bid + MIN 100mg bid + MTZ 400mg qid + B 220mg	150	14	84.0% (126/150)	91.7% (122/133)	90.5% (134/148)	35.1% (52/148)	7% (3/43)

				bid						
				E 20mg bid + MIN 100mg bid + CEF 500mg bid + B 220mg bid	150	14	82.7% (124/150)	90.9% (120/132)	91.8% (134/146)	22.6% (33/146)	8.5% (4/47)
				E 20mg bid + CEF 500mg bid + MTZ 400mg qid + B 220mg bid	150	14	82.0% (123/150)	88.2% (120/136)	91.9% (137/149)	28.9% (43/149)	9.1% (4/44)
Huang *et al*[24], 2023	China	RCT	≥ 2 nd	E 20mg bid + MIN 100mg bid + MTZ 400mg qid + B 220mg bid	184	14	88.0% (162/184)	98.0% (149/152)	88% (162/184)	55.4% (102/184)	0.7% (1/145)
				E 20mg bid + TET 500mg qid + MTZ 400mg qid + B 220mg bid	184	14	88.6% (163/184)	97.4% (150/154)	88.6% (163/184)	53.3% (98/184)	0.7% (1/143)

RCT: Randomized controlled trial; ITT: Intention-to-treat; PP: Per-protocol; R: Rabeprazole; CLA: Clarithromycin; AMX: Amoxicillin; MIN: Minocycline; MTZ: Metronidazole; FAR: Faropenem; RIF: Rifabutin; B: Bismuth; TNZ: Tinidazole; E: Esomeprazole; AMLZ: Omeprazole; FUR: Furazolidone; LEV: Levofloxacin; ONZ: Ornidazole; TET: Tetracycline; CEF: Cefuroxime.

Table 2 Pooled eradication rates

	Overall eradication rate % (95%CI)		Eradication rate for first-treatment patients % (95%CI)		Eradication rate for retreatment patients % (95%CI)	
	Intention-to-treat analysis	Per-protocol analysis	Intention-to-treat analysis	Per-protocol analysis	Intention-to-treat analysis	Per-protocol analysis
Minocycline-containing regimen	82.3% (79.7%-85.1%)	90.0% (87.7%-92.4%)	83.6% (80.6%-86.7%)	90.5% (88.7%-92.3%)	82.3% (79.5%-85.2%)	90.8% (86.4%-95.4%)
Minocycline-containing combination regimen with nitroimidazole antibiotics	82.1% (77.9%-86.5%)	89.5% (86.0%-93.0%)	82.4% (77.9%-87.0%)	89.4% (86.9%-91.9%)	85.4% (81.0%-90.0%)	80.2% (56.8%-100.0%)
Minocycline-containing combination regimen with amoxicillin	83.8% (81.9%-85.9%)	89.9% (86.3%-93.6%)	85.9% (83.0%-89.0%)	92.7% (90.4%-95.1%)	82.7% (80.0%-85.5%)	90.9% (85.9%-96.1%)

CI: Confidence interval.

Comparison of eradication efficacy between quadruple regimens with or without minocycline and nitroimidazole antibiotics: The analysis included five RCTs that adopted minocycline-containing quadruple regimens with nitroimidazole antibiotics[23-25,32,36]. The combination of antibiotics in the control groups included tetracycline and metronidazole (n = 2), amoxicillin and clarithromycin (n = 2), cefuroxime and metronidazole (n = 1), minocycline and amoxicillin (n = 1), and minocycline and cefuroxime (n = 1). ITT analysis using a fixed effect model indicated no obvious heterogeneity (χ^2 = 0.36, P = 0.99, I^2 = 0) or statistically significant difference in the eradication efficacy between quadruple regimens with or without minocycline and nitroimidazole antibiotics (RR = 1.00, 95%CI: 0.96-1.05, P = 0.91). The PP analysis revealed similar results to those of the ITT analysis. The two groups demonstrated no obvious heterogeneity (χ^2 = 0.44, P = 0.98, I^2 = 0) and no statistically significant difference in efficacy (RR = 1.01, 95%CI: 0.98-1.04, P = 0.56). ITT and PP analyses revealed that the eradication rates of quadruple regimens with or without minocycline and nitroimidazole antibiotics were 83.7% *vs* 82.8% and 91.4% *vs* 89.6%, respectively (Figure 4).

Safety and compliance

The overall incidences of adverse reactions to minocycline-containing eradication regimens in the five studies were 22.6%-55.4%[23-25,32,36]. Most of the adverse reactions, mainly including inappetence, asthenia, abdominal discomfort, abdominal pain, diarrhea, headache, dizziness, nausea, vomiting, dysgeusia, rash, *etc.*, were mild to moderate and well-tolerated. Figure 5A shows no statistically significant difference in the incidences of adverse reactions between the quadruple regimens with and without minocycline (RR = 0.94, 95%CI: 0.84-1.06, I^2 = 0, P = 0.63). Among them, 16% of patients treated with the minocycline-containing eradication regimens developed dizziness symptoms. Further comparative analysis (Figure 5B) revealed that significantly more patients adopting eradication regimens with minocycline developed dizziness than those adopting eradication regimens without minocycline (23.4% *vs* 10.4%, P < 0.001). Additionally, minocycline-containing eradication regimens demonstrated better compliance (≥ 90%) in treatment-

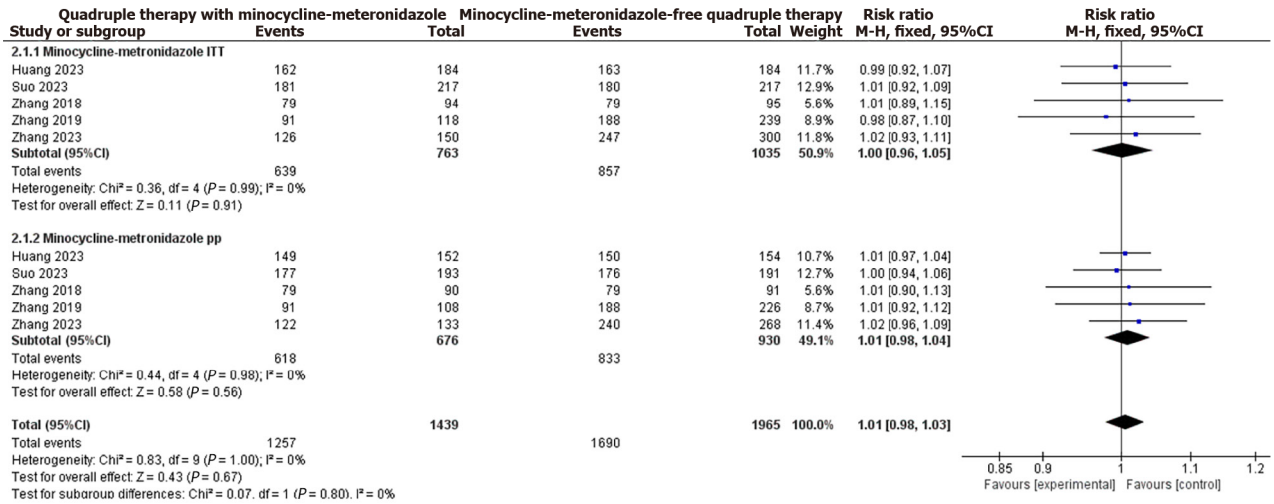

Figure 4 Forest plots comparing eradication rates for intention-to-treat and per-protocol analyses of quadruple regimens with and without minocycline-metronidazole. CI: Confidence interval.

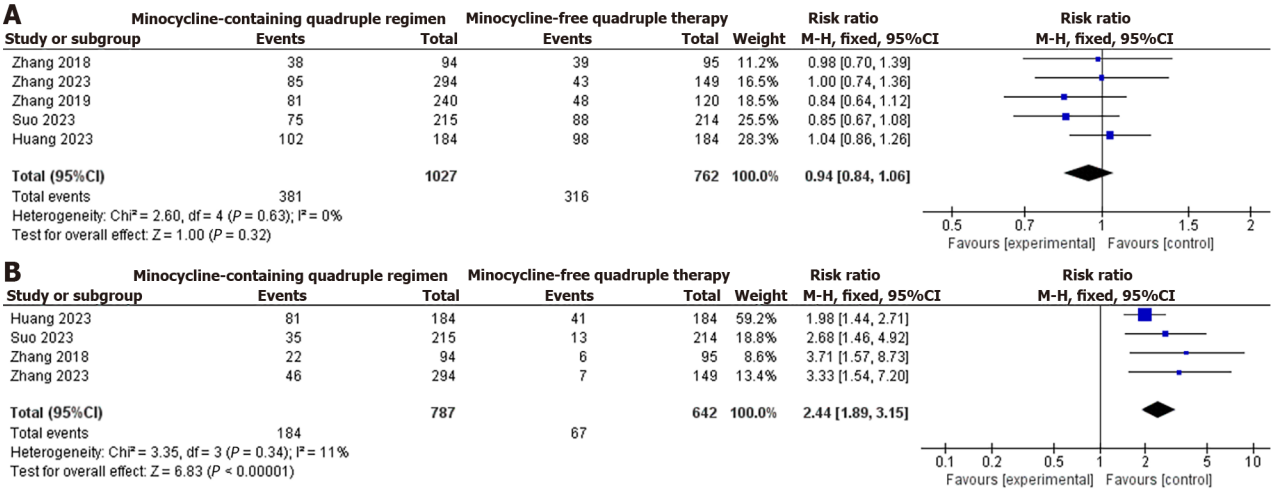

Figure 5 Comparison of the incidence of adverse reactions of quadruple therapy and dizziness in quadruple therapy with and without minocycline. A: Comparison of the incidence of adverse reactions of quadruple therapy with and without minocycline; B: Comparison of the incidence of dizziness in quadruple therapy with and without minocycline. CI: Confidence interval.

naive and retreated patients.

Publication bias analysis

Funnel plots of all included studies were plotted through ITT and PP analyses[11,12,23-26,28-43]. The funnel plots were all asymmetric, and the *P* values of Begg's test and Egger's test were < 0.05, indicating a risk of publication bias. Sensitivity analysis was conducted on the comprehensive results of the included studies by deleting each study in turn. The results were stable and the combination results fluctuated within a small range (Figures 6 and 7). We used the Cochrane Bias Risk Tool to evaluate the risk of bias in the study[23-25,32,36] and revealed that these five RCTs were mostly low risk in terms of selection, follow-up, and reporting biases, while high and unclear risks in terms of performance, measurement, and other biases (the bias risk plot was detailed in the Supplementary Figure 11).

DISCUSSION

The classic BQT has been recommended for eradicating *H. pylori* infection by many expert consensuses or guidelines globally. However, the difficulty in obtaining tetracycline clinically in many countries and regions has greatly limited its wide application[5-10]. In recent years, studies focused on the use of minocycline to replace tetracycline for eradicating *H. pylori* infection. The preliminary results have indicated good eradication efficacy, safety, and compliance. This has offered more drug options for clinical treatment and has become one of the hot spots and concerns in the current research[11,12,23]. Compared with tetracycline, minocycline has unique characteristics and advantages for eradicating *H. pylori*

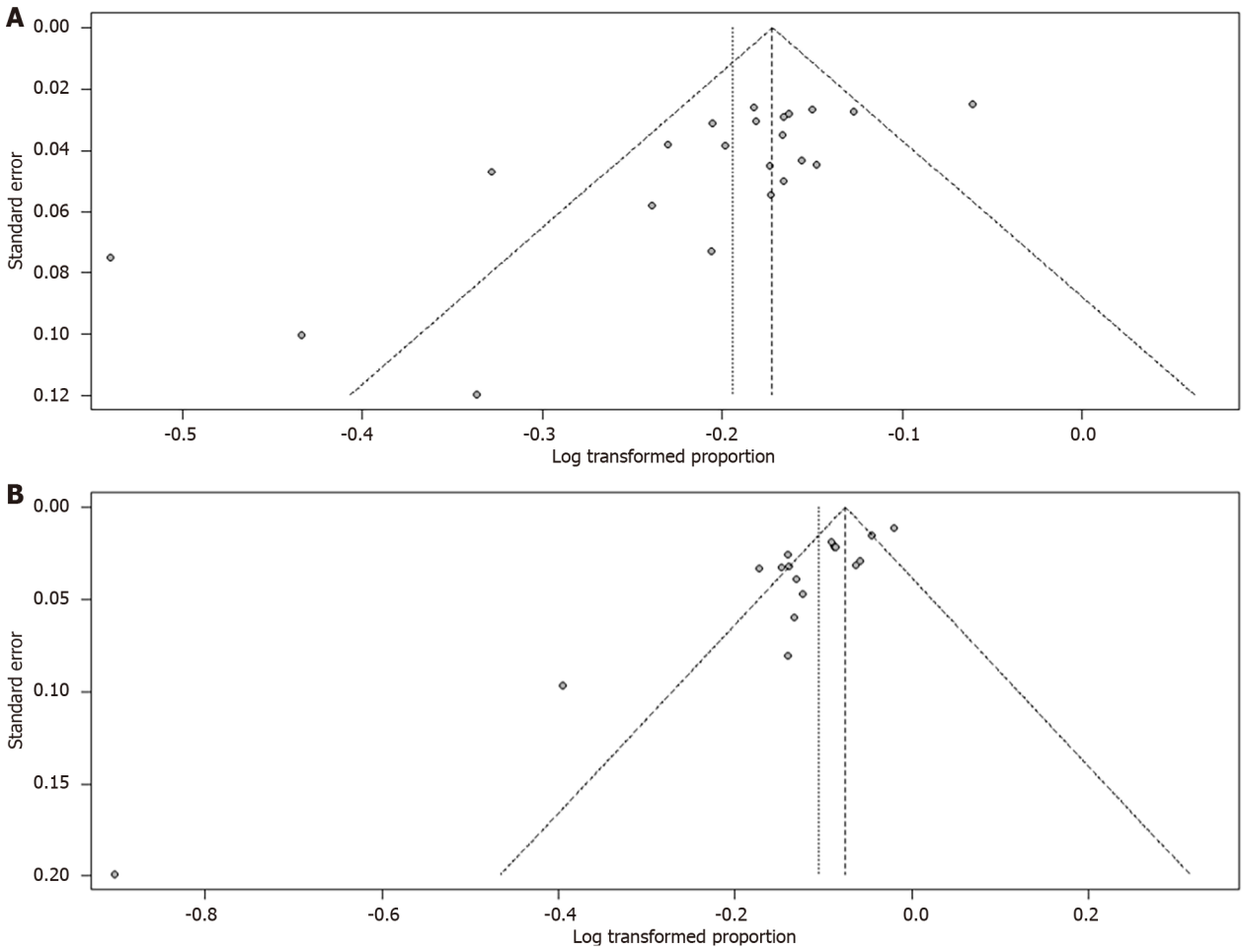

Figure 6 Funnel plots of all included studies through intention-to-treat and per-protocol analyses. A: Intention-to-treat analyses; B: Per-protocol analyses.

infection. In particular, longer half-life and dosing once or twice a day are conducive to improving the compliance of patients. Higher absorption rates, better lipid solubility, and fewer interactions with food are conducive to better bioavailability. Furthermore, minocycline demonstrated better clinical availability, bactericidal effects, and safety in studies on other bacteria[12,16,19,20].

Currently, the minocycline-containing eradication regimens are mostly in the form of a quadruple drug combination, *i.e.*, a combination of gastric acid inhibitor, bismuth agent, minocycline, and another antibiotic. We revealed through single-arm meta-analysis that the minocycline-containing regimen demonstrated good overall eradication effects, reaching an eradication rate of 82.3% (95%CI: 79.7%-85.1%) in the ITT analysis and 90.0% (95%CI: 87.7%-92.4%) in the PP analysis. The nitroimidazole combination was the most common among the antibiotic combinations, followed by the amoxicillin combination. Further, the combination with other antibiotics was relatively few. All antibiotic combinations have demonstrated good eradication efficacy. Moreover, the minocycline-containing regimens exhibited satisfactory eradication efficacy in both treatment-naive and retreated patients[12,23-26,28,30,32,36-40]. Furthermore, we compared the eradication efficacy difference between the minocycline-containing regimens and other eradication regimens through meta-analysis. The results revealed that minocycline-containing regimens or regimens containing minocycline and metronidazole were not statistically different from other commonly used eradication regimens (including the classic BQT) [23-25,32,36]. These analyses have strongly indicated that minocycline could be applied to eradicate *H. pylori* infection and used as a good alternative, especially when tetracycline is difficult to obtain.

The pooled analysis results revealed a relatively good overall safety of the minocycline-containing regimens, with an adverse reaction rate of 36.5% (95%CI: 31.5%-42.2%). Although the incidence of adverse reactions is relatively high in numerical terms, the results of this meta-analysis showed that minocycline-containing regimens were similar to other commonly used eradication regimens in terms of safety (P = 0.63). In addition, the RCT conducted by Suo *et al*[23] showed no significant difference in the incidence of adverse reactions between minocycline-containing regimen and classic BQT (combination of tetracycline and metronidazole) regimen (34% *vs* 41.1%, P = 0.18). Common adverse reactions were mild to moderate, and intolerable cases were rare. The types of adverse reactions were similar with other regimens [23-25,32,36]. However, patients who received the minocycline-containing regimens were more likely to experience dizziness (RR = 2.44, 95%CI: 1.89-3.15, P = 0.34), which might be associated with the reversible vestibular response of minocycline. Tinnitus, ataxia, nausea, vomiting, *etc.*, may accompany such a response[36]. Minocycline demonstrated strong lipophilicity and is more likely than other tetracyclines to pass through the blood-brain barrier, thereby causing

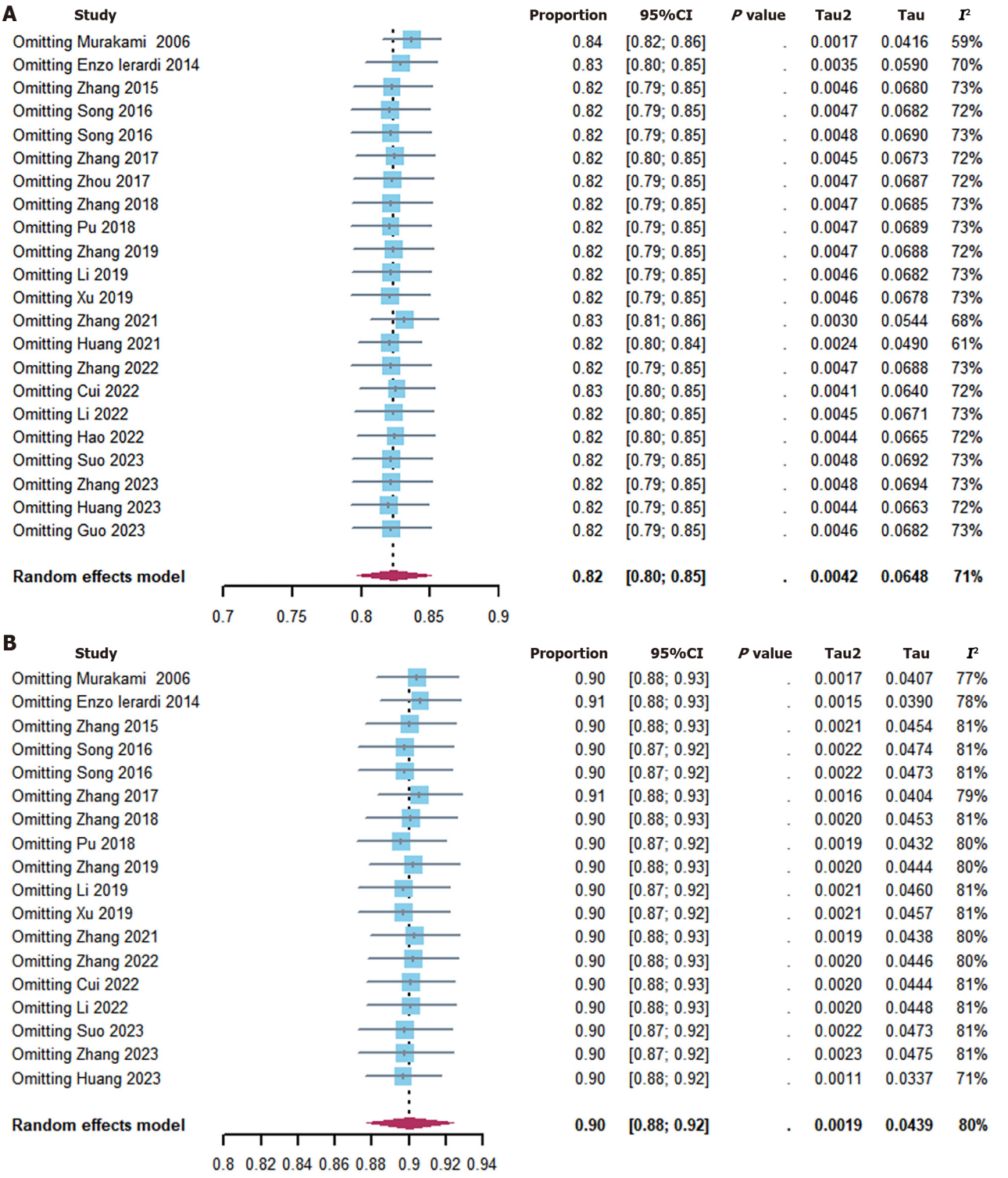

Figure 7 Sensitivity analysis of all included studies by sequentially removing each study with intention-to-treat and per-protocol analyses. A: Intention-to-treat analyses; B: Per-protocol analyses. CI: Confidence interval.

instability of the γ-aminobutyric supervisory acid loop in the cerebellar arch and resulting in vestibular dysfunction[44, 45]. This adverse reaction often occurs during initial administration and most patients recover 24-48 h after drug discontinuation[36]. Additionally, minocycline-containing regimens demonstrated good overall compliance (mostly > 90%), which was similar to other commonly used regimens.

As a relatively new drug for eradicating *H. pylori*, related pooled analyses that involve minocycline are currently lacking. We conducted a comprehensive and systematic analysis of the existing relevant literature through comprehensive literature retrieval and the use of standardized and systematic analytical methods. Both the single-arm meta-analysis method was used to summarize the eradication rate, and the traditional meta-analysis method was utilized to compare the efficacy with other commonly used regimens. This study has offered convenience and a good reference to a comprehensive understanding of the bactericidal mechanism, drug metabolism characteristics, eradication efficacy,

safety, compliance, use, and research of minocycline, and has also enhanced the rational drug selection for treating *H. pylori* infection. The recent meta-analysis on minocycline published by Gao *et al*[46] compared the efficacy and incidence of adverse reactions of the minocycline-containing quadruple regimen using the same traditional analytical methods, but two studies were repeatedly compared, which increased the weight of the article and might lead to biased results. Additionally, we further compared the efficacy of the combination of minocycline and nitroimidazole antibiotics and comprehensively summarized the efficacy and incidence of adverse reactions of minocycline in eradicating *H. pylori* infection through a single-arm meta-analysis that included more relevant research reports, thereby making the results more objective and accurate.

However, this study had certain limitations. At present, studies on minocycline-containing eradication regimens are lacking, and the countries and regions involved remain relatively small (20 studies originated from China, 1 from Japan, and 1 from Italy). The eradication regimens involved in the studies were relatively scattered, the study results had obvious heterogeneity, and the overall quality of the study design was low. These factors might affect the reliability of the obtained results. Large-sample, multi-center, RCTs from more countries and regions are warranted in the future to further determine its eradication efficacy, safety, *etc.*

CONCLUSION

Therefore, this comprehensive and systematic meta-analysis has demonstrated the satisfactory efficacy, safety, and compliance of minocycline-containing regimens in eradicating *H. pylori* infection. Compared with tetracycline, minocycline demonstrated low drug resistance and unique drug metabolism characteristics and advantages, but a few patients may experience dizziness due to vestibular dysfunction. Minocycline can be applied to clinical practice as a drug for eradicating *H. pylori* infection and used as an alternative, especially when tetracycline is difficult to obtain, but more research is needed to further confirm its effect.

FOOTNOTES

Co-first authors: Zhou Kai and Cai-Ling Li.

Co-corresponding authors: Xue-Li Tian and Zhi-Qiang Song.

Author contributions: Zhou K and Song ZQ contributed to the research design; Zhou K was involved in the literature screening, quality assessment, and manuscript writing; Zhou K, Zhang H, and Tian XL participated to the statistical analysis; Li LC, Zhou LY, Tian XL, and Song ZQ edited the manuscript; Li CL contributed to literature mining; Li CL, Suo BJ, Zhang YX, Ren XL, Wang YX, Mi CM, and Ma LL were involved in the data analysis; Song ZQ contributed to the research concepts and funding acquisition; and all authors have read and approved the final manuscript. Zhou K and Li CL contributed equally to this work as co-first authors. The reasons are the following. First, the research was performed as a collaborative effort, and the designation of co-first authors authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. Second, co-first authors contributed efforts of equal substance throughout the research process. Song ZQ and Tian XL contributed equally to this work as co-corresponding authors. The reasons are the following. First, they played a key role in coordinating the research team. Second, they made a great contribution to the original innovation of the article. In summary, we believe that designating Zhou K and Li CL as co-first authors, Song ZQ and Tian XL as co-corresponding authors is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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