META-ANALYSIS

Retrospective analysis of the clinical efficacy of minocycline regimen in the radical treatment of helicobacter pylori and its adverse reactions

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Abstract

Objective: To assess the clinical effect of minocycline regimen in the radical handling of helicobacter pylori and its adverse reactions.

Method: The meta-analysis was conducted from February to April 2024, and comprised literature search on Chinese Biomedical, Wanfang, VIP, China National Knowledge Infrastructure, Cochrane Library, ScienceDirect, EMBASE and PubMed databases for case-control studies published between January 2010 and December 2022 in which the minocycline regimen had been employed to eradicate helicobacter pylori. Two researchers retrieved the data independently, and they evaluated each study's risk of bias using the Cochrane Handbook 5.3. Data was subjected to meta-analysis using RevMan 5.3.

Results: Of the 761 studies initially identified, 281(37%) were assessed for eligibility, and 6(2.13%) of them were analysed in detail that had an overall sample of 1,650 patients; 822(49.7%) cases and 828(50%) controls. The radical treatment rate among the cases (692[84.18%]) was higher than that in the control group (678[81.88%]) (p=0.88). The incidence of adverse reactions in the two groups was not significantly different (p=0.14).

Conclusion: Minocycline was found to have a definite therapeutic effect on helicobacter pylori.

Kewords: Minocycline, Helicobacter pylori, Clearance rate, Incidence of adverse reactions.

(JPMA 75: S-162 [Suppl. 02]; 2025) **DOI: https://doi.org/10.47391/JPMA.SRPH-28**

Introduction

Helicobacter (H.) pylori is a kind of gram-negative, microaerobic helicobacter that is directly linked to the pathophysiology of stomach mucosa-associated lymphoid tissue (MALT), peptic ulcer disease, and atrophic gastritis.[1] H. pylori infection might further result in other systemic diseases through autoimmune mechanism or inflammation, such as idiopathic thrombocytopenic purpura, vitamin B12 deficiency and iron deficiency anaemia, etc.[2] H. pylori is widespread in the world, mainly through mouth-to-mouth transmission. The infection rate of H. pylori in adults in China is as high as 50%.[3] The Kyoto Consensus highlights that gastritis caused by H. pylori is an infectious illness, and recommends eradication treatment regardless of symptoms or complications.[4] Eradicating H. pylori offers significant benefits, including promoting the healing of peptic ulcers, reducing the incidence of complications, and providing relief to 80% of individuals with early-stage stomach MALT lymphoma.[5] Furthermore, it can significantly improve symptoms in individuals with H. pylori-induced dyspepsia, prevent and delay intestinal metaplasia and atrophy of the stomach mucosa, and even partly repair the atrophy of the stomach mucosa. Ultimately, it effectively prevents the onset of intestinal gastric cancer.[6,7]

In China, the recommended H. pylori treatment regimen is a quadruple treatment made up of two antibiotics, bismuth and proton pump inhibitors (PPIs), administered for a duration of 14 days.[8] However, widespread antibiotic usage has contributed to a steady rise in antibiotic resistance among commonly used drugs for H. pylori eradication in China. Research indicates that from 1999 to 2014, the resistance rates of H. pylori to levofloxacin, clarithromycin and metronidazole have risen by 45%, 16% and 50.8% respectively.[9] It is evident that these antimicrobials are exhibiting a worrying trend of increasing resistance rates over time. Conversely, the resistance levels of H. pylori in China to amoxicillin, furazolidone (FZD) and tetracycline remain relatively low at <5%.[10] Among the seven quadruple eradication schemes recommended by our guidelines,[11] the antibiotic combination contains at least one of the above three drugs, and the use of these drugs is of great significance for the elimination of H. pylori in China.

Minocycline (MINO) is a semi-synthetic tetracycline antibiotic.[12] The primary antibacterial mechanism of MINO involves binding to the bacterial ribosomal 30S subunit, thereby impeding the elongation of the peptide chain and inhibiting bacterial protein synthesis. Compared to other tetracycline antibiotics, MINO exhibits superior antibacterial efficacy and activity.[13,14] Several case-control studies[15,16] have discussed the effectiveness and security of the quadruple regimen containing minocycline in the

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eradication of H. pylori, but different studies have come to different results. The debate regarding which regimen is more effective and safer remains ongoing. As such, the results still need to be more conclusive, warranting further investigation supported by high-quality evidence. The current study was planned to assess the effectiveness and security of the MINO regimen for the complete eradication of H. pylori.

Materials and Methods

The meta-analysis was conducted from February to April 2024, and comprised literature search on Chinese Biomedical (CBM), Wanfang, VIP (VIP Database for Chinese Technical Periodicals), China National Knowledge Infrastructure (CNKI), Cochrane Library, ScienceDirect, EMBASE (Excerpta Medica Database) and PubMed databases for case-control studies published between January 2010 and December 2022 in which the MINO regimen had been employed to eradicate H. pylori. Additionally, manual search for relevant Chinese and foreign news sources, dissertations, conference papers and journals was used to supplement the literature search. The search strategy included key words such as; minocycline; Helicobacter pylori', 'H. pylori', 'clinical efficacy', 'adverse reactions', and such other related terms. The literature search was done in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) criteria.[17]

The studies were included if they were case-control trials using MINO regimen to eradicate H. pylori in the stomach, and all the selected individuals, aged 18-75 years regardless of race, nationality and gender, had been diagnosed with H. pylori infection with relevant diagnostic methods,[18] their 13C urea breath test (13C-UBT) had been positive, and the pathological section staining or the fast urease test on stomach mucosal tissue had also been positive. The subjects had not received any previous H. pylori eradication treatment. As for the interventions, the study group had been handled with radical therapy containing MINO, while the control group had been handled with other radical treatments without MINO. Also, the included studies had targetted the intention-to-treat (ITT) analysis and per-protocol (PP) analysis as two of the outcome markers. The initial approach involved calculating the H. pylori eradication rate through ITT analysis, and, it was not possible, the PP analysis had been relied upon.

The studies excluded were those without a case-control design, those with incomplete data, and those with non-significant evaluation of treatment efficacy. In case of duplicate studies focussing on the same research content, the most recent study was selected. Also, literature reviews and clinical case reports were excluded.

Two researchers retrieved the data independently, and they evaluated each study's risk of bias using the Cochrane Handbook 5.3. If there were discrepancies, the researchers resolved them through discussion or sought the assistance of a third researcher. Data was organised using Excel and NoteExpress to document details, such as the publication time, authors' name, and the number of cases involved, the treatment plan and the course of treatment, as well as the H. pylori radical cure rate and the frequency of unfavourable responses.

Data was analysed using RevMan 5.3 software. Relative risk was worked out using odds ratio (OR) with 95% confidence interval (CI).

The number of blinding, loss to follow-up, dropout cases and the reasons behind such a decision were noted, and the quality of the studies was assessed using the Jadad scale.[19] To ascertain the presence of heterogeneity among the studies, chi-square test was employed. In case of $p>0.05$ and $I^2<50\%$, the studies were deemed homogeneous, thus allowing for the collection of revised influence models for meta-analysis. However, to evaluate the homogeneity of the included studies, the combined effect was examined with $p<0.05$ and $I^2>50\%$, thereby resorting to the random effect model. In case of $p<0.05$, descriptive analysis was used instead of meta-analysis. To assess the publication bias encompassed in the literature, an inverted funnel plot was generated. Egger's test was used to examine the funnel plot's asymmetry. The TrimFill technique was used, if necessary, to rectify the funnel plot and account for the possible release deviation impact in case of $p<0.1$.

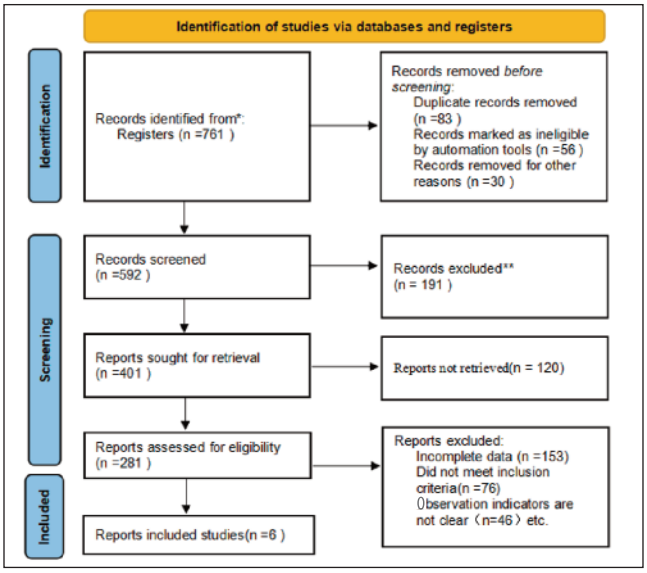

Figure-1: Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flowchart.

Results

Of the 761 studies initially identified, 281(37%) were assessed for eligibility, and 6(2.13%) of them were analysed in detail (Figure 1). The 6 studies[20-24] that had an overall sample of 1,650 patients; 822(49.7%) cases and 828(50%) controls (Table).

There were 4(66.7%) articles of high quality with Jadad score ≥3, and 2(33.3%) were of low quality with score ≤2. The risk of bias was analysed in detail (Figures 2-3).

The radical treatment rate among the cases (692[84.18%]) was higher than that in the control group (678[81.88%]) (p=0.88, I2=0%)(Figure 4).

The incidence of adverse responses in the study group (332[40.39%]) was marginally lower than that in the control group (341[41.18%]), according to the fixed-effect model (Figure 5). There was no significant difference (p=0.14).

With respect to publication bias, findings indicated that although a tiny percentage of the included literature was

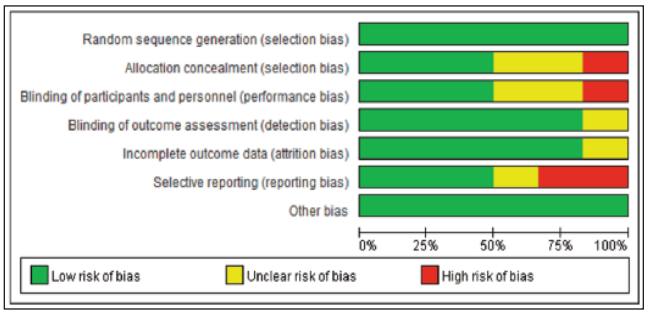

Figure-2: Risk of bias chart.

Table: Basic characteristics of the studies analysed.

Include the literature	Year of publication	Sample size C	Sample size T	Treatment scheme C	Treatment scheme T	Course of treatment	Outcome index
Huang [13]	2023	184	184	ESO 20mg bid BIS 220mg bid TET 500mg qid MET 400mg qid	ESO 20mg bid BIS 220mg bid MIN 100mg qid MET 400mg qid	14d	①②
Suo[14]	2023	217	217	ESO 20mg bid BIS 110mg bid TET 500mg qid MET 400mg qid	ESO 20mg bid BIS 110mg bid MIN 500mg qid MET 400mg qid	10d	①②
Zhang[15]	2015	62	63	Tailored therapy	RAB 20mg bid BIS 220mg bid MIN 100mg qid MET 400mg qid	14d	①②
Zhang[16]	2019	119	120	RAB 10mg bid BIS 220mg bid AMO 1000mg qid CLA 500mg qid	RAB 10mg bid BIS 220mg bid MIN 100mg qid AMO 1000mg bid RAB 10mg bid BIS 220mg bid MIN 100mg bid MET 400mg qid		①②
Zhang[17]	2023	150	150	ESO 20mg bid BIS 220mg bid MET 400mg qid CEF 500mg bid	ESO 20mg bid BIS 220mg bid MIN 100mg qid MET 400mg bid ESO 20mg bid BIS 220mg bid MIN 100mg bid CEF500mg qid	14d	①② ② ③ ④ ⑤ ⑥ ⑦ ⑧
Zhang[18]	2018	95	94	RAB 10mg bid AMO 1000mg bid CLA 500mg bid BIS 260mg bid	RAB 10mg bid MET 400mg tid MIN 100mg bid BIS 260mg bid	14d	①② ② ③ ④

bid: Twice a day (bi-daily dosing). tid: Three times a day (tri-daily dosing). qid: Four times a day (quad-daily dosing). ESO: Esomeprazole (a proton pump inhibitor). BIS: Bismuth (used in combination therapies for gastrointestinal conditions). TET: Tetracycline (an antibiotic). MET: Metronidazole (an antibiotic). MIN: Minocycline (an antibiotic). RAB: Rabeprazole (a proton pump inhibitor). AMO: Amoxicillin (an antibiotic). CLA: Clarithromycin (an antibiotic). CEF: Cefuroxime (an antibiotic). ①: Helicobacter pylori radical cure rate. ②: Incidence of adverse reactions.

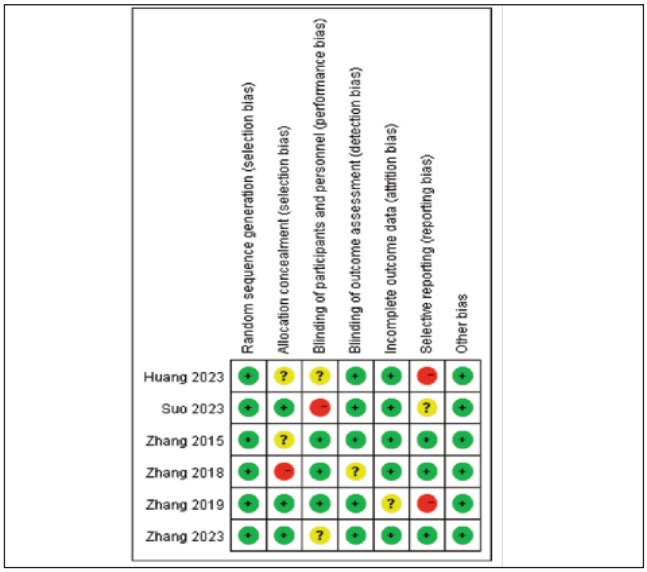

Figure-3: Risk of bias summary.

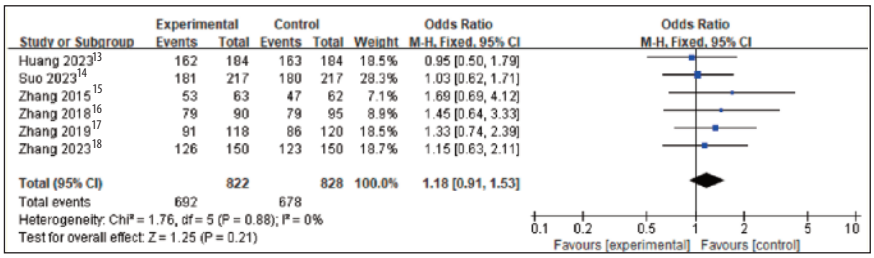

Figure-4: Forest analysis chart of helicobacter pylori eradication rate comparison.

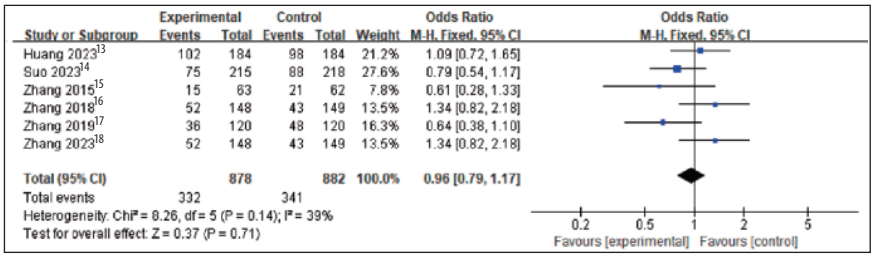

Figure-5: Forest analysis map comparing the incidence of adverse reactions.

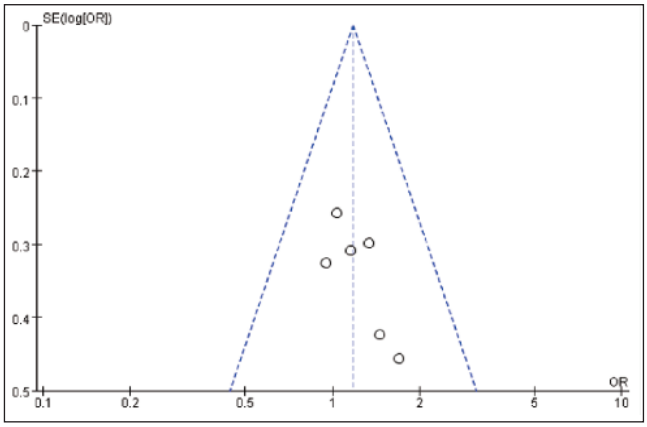

Figure-6: Funnel chart showing the eradication rate of helicobacter pylori after treatment in the two groups.

asymmetrical, the majority of the funnel charts were symmetrical (Figures 6-7). This might be attributed to the study's heterogeneity.

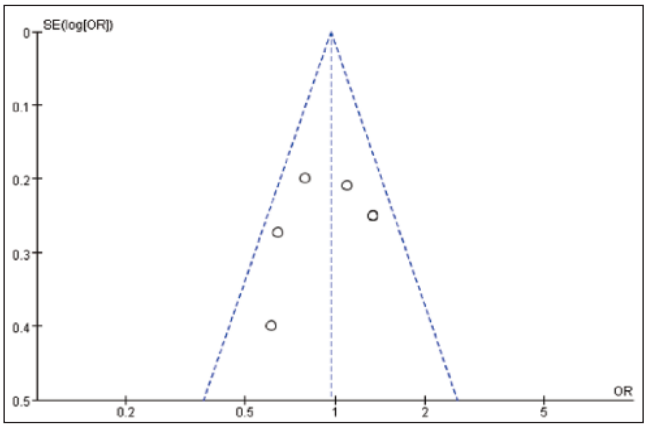

Figure-7: Funnel chart showing the incidence of adverse reactions after treatment in both the groups.

Discussion

The prevalence of H. pylori infection is relatively high worldwide, particularly in developing nations and areas. The infection rate in China has reached more than 50%.[19] Due to the close connection between H. pylori infection and MALT, gastric cancer, peptic ulcers and other illnesses, numerous international and national recommendations advocate for aggressive treatment of H. pylori infection.[25,26] However, lately, the problem of HP medication resistance has become more significant, making its eradication more challenging. H. pylori's resistance rates to amoxicillin, clarithromycin, metronidazole, levofloxacin and tetracy-cline have been reported to be 4.4%, 52.6%, 54.8%, 63.4%, and 7.3%, respectively, according to recent research in Beijing.[27] Due to high drug resistance, the 5th National Consensus in China has not recommended the empirical application of standard triple or non-bismuth quadruple scheme containing clarithromycin and metronidazole.[28] Instead, it mainly recommended the bismuth quadruple scheme based on amoxicillin or tetracycline. For those with penicillin allergies, the quadruple regimen based on tetracycline or clarithromycin is recommended. However, the resistance rate of clarithromycin is progressively rising, posing a significant limitation on its clinical utility. Consequently, the classical quadruple regimen involving tetracycline and metronidazole has regained attention and recommendation.[29,30] In recent years, the drug resistance

rate of metronidazole within this regimen has remained relatively stable, and increasing the dose has shown some effectiveness in overcoming resistance.[31] However, the clinical application of this regimen is restricted due to substantial side-effects and limited availability of tetracycline.

MINO belongs to the second-generation semisynthetic tetracycline antibiotics. Its action mechanism is mainly through binding to bacterial ribosomal 30S subunit and mitochondrial 70S subunit, thus hindering protein synthesis.[32] MINO is highly lipophilic, with antibacterial activity 8-12 times higher than that of tetracycline, and it is also sensitive to some tetracycline-resistant strains.[33] MINO is well-absorbed orally, has a bioavailability of 100%, is not affected by food, and may be affected by acid suppressants and metal ions.[34] At present, MINO has been widely used in the treatment of acne, nongonococcal urethritis, bullous dermatosis, leprosy, gingivitis and periodontitis.[35] MINO offers several advantages in medical settings, unlike tetracycline. It demonstrates more robust bacteriostatic properties, higher solubility in fat, and a longer half-life for drug metabolism. These qualities contribute to enhanced antibacterial efficacy, improved patient compliance, and reduced incidence of adverse drug reactions. As a result, MINO presents significant clinical advantages over tetracycline.

Initial treatment refers to the administration of antibiotics as the first-line approach to eradicate H. pylori infection. However, in recent years, the growing H. pylori infection rate and increasing prevalence of drug resistance have made H. pylori eradication progressively challenging. Traditional eradication regimens have proved inadequate in meeting the clinical demands. Studies have found that MINO has a significant eradication effect in the initial treatment, remedial treatment, and multiple drug resistance of H. pylori, and MINO has the advantages of adequate supply and fewer side-effects than tetracycline. However, MINO is mainly bacteriostatic, and its wide application may increase the proportion of drug-resistant strains.[36,37] When MINO is used in the handling of H. pylori infection, it is often combined with clarithromycin or metronidazole to form quadruple or triple regimens. Some clinical studies have found that MINO has considerable efficacy in the initial eradication of H. pylori infection.[38] According to the 5th National Consensus in China, quadruple regimens based on tetracycline and clarithromycin are recommended for patients with penicillin allergy. However, due to the significant rate of clarithromycin resistance in China, patients with penicillin allergy have limited treatment options available to them. The combination of MINO and metronidazole to form a "new standard quadruple" is recommended for penicillin-allergic H. pylori-positive newly treated patients. Therefore, MINO can be selectively used for the initial treatment in areas with high H. pylori resistance.

In the current study, 6 case-control studies were analysed, having an overall sample size of 1,655 cases. The incidence of adverse effects in the two groups after therapy and the radical treatment rate of H. pylori were the subjects of a meta-analysis. The findings suggested that the MINO regimen and the existing clinical treatment regimen had a similar effect on H. pylori eradication. When compared to other clinical radical treatment regimens, MINO demonstrated comparable efficacy without any significant differences. Additionally, it did not substantially increase the risk of adverse reactions, and had a higher level of safety. MINO is known for its effectiveness and safety in the radical cure of gastric H. pylori infections. If combined with clarithromycin or metronidazole, the effectiveness can be further enhanced.

The current meta-analysis has certain limitations. Some studies did not adequately describe random allocation and blinding methods, which may have introduced bias. The combination and analysis of a few outcome indicators resulted in high heterogeneity, likely due to variations in sample size and individual patient sensitivity to the drug. The duration of the included studies varied, ranging from 10 to 14 days, potentially introducing bias. Additionally, the effectiveness of many regimens has declined due to increasing antibiotic resistance.

Large-scale, high-quality randomised controlled trials (RCTs) are needed to validate the current findings.

Conclusion

The radical cure regimen including MINO demonstrated an eradication rate similar to other clinical scoring schemes in newly-diagnosed patients with H. pylori infection. This regimen is considered safe and is recommended for patients who are allergic to penicillin.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

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