

Concise Review

Periodontal Treatment Is Associated With Improvement in Gastric *Helicobacter pylori* Eradication: An Updated Meta-analysis of Clinical Trials



Ayla Ozturk*

Department of Periodontology, School of Dentistry, Ondokuz Mayıs University, Samsun, Turkey

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ABSTRACT

Objectives: The efficacy of conventional systemic antibiotic therapy for eradication of *Helicobacter pylori* has been seriously challenged by antibiotic resistance. Identification of alternative therapeutic strategies might help to overcome this limitation. The aim of this study was to update previous meta-analyses that investigated the effect of periodontal treatment on gastric *H. pylori* eradication.

Methods: A systematic electronic search of the literature was conducted to identify all published clinical trials that compared the effect of adjunct periodontal treatment on conventional systemic *H. pylori* eradication therapy.

Results: The updated analysis (consisting of 541 participants representing six studies) demonstrated that, compared with conventional systemic eradication therapy alone, the addition of periodontal treatment resulted in improvements in gastric *H. pylori* eradication rates with OR 4.11 ($P=0.01$). Moreover, not to lose any data, the previously presented Chinese results that could not be assessed by any available mechanism deduced from previously published meta-analysis and with other records were re-analysed. Similarly, the second meta-analysis adding up to a final cluster of 10 studies (909 participants) gives further credence to periodontal treatment as a useful concomitant therapy in the *H. pylori* eradication therapy (odds ratio [OR]=2.65; $P=0.0002$). Finally, the meta-analysis of four trials consisting of 177 cases and 161 controls showed that periodontal treatment also improved non-recurrence rates of gastric *H. pylori* infection, with an OR of 5.36 (P -value = 0.0002).

Conclusion: Although the inclusion of five additional clinical trials in this updated meta-analysis has not changed the result of the previous review, the current meta-analysis is superior for having removed one study involving the use of chlorhexidine, which did not meet appropriate criteria for inclusion. Our results strengthen the value of periodontal treatment as an adjunctive remedy. Consistency of these results suggests that the incorporation of professional periodontal treatment with systemic eradication therapy may be a wise strategy, enhancing the efficacy of *H. pylori* eradication therapy. Systematic review registration: in PROSPERO ID number: CRD42019119347.

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* Corresponding author. Ayla Ozturk, Department of Periodontology, School of Dentistry, Ondokuz Mayıs University, OMÜ Kuru-pelit Kampüsü, Diş Hekimliği Fakültesi, 55139 Atakum, Samsun, Turkey.

E-mail address: aylao@omu.edu.tr

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Introduction

Helicobacter pylori, a Gram-negative, highly motile, spiral-shaped bacterium, is an important gastrointestinal pathogen whose presence can result in a range of diseases, including chronic gastritis, peptic ulcer, and gastric cancers. *H. pylori* is among the most common chronic bacterial infections in

humans, affecting almost half of the world's population. The presence of the microorganism was first reported in 1982 in the human stomach,^{1,2} which had commonly been considered a sterile environment because of its low pH. Since then, the diagnosis and treatment of gastrointestinal diseases have changed dramatically. Gastrointestinal diseases are now approached clinically as an infectious disease for which elimination of the causative agent is curative. Treatment of *H. pylori* infection involves the administration of systemic antibiotics in combination with other drugs. A 10- to 14-day triple regimen combining a proton pump inhibitor (PPI) with two antibiotics (clarithromycin and amoxicillin or metronidazole) is currently accepted as first-line treatment.³

Taking into account the increasing prevalence of antibiotic resistance, the efficacy of triple regimens has been seriously challenged, and the drugs are gradually becoming ineffective.^{4–6} Current studies have documented the lowest eradication rates in the past decade.⁷ Several strategies have been proposed to overcome increases in the *H. pylori* eradication failure rates, such as to prescribe the drugs sequentially; to prescribe the four drugs concomitantly; or to use bismuth-based quadruple therapy.⁸ However, these treatment regimens are limited by poor patient compliance and bacterial resistance.⁹ To overcome this limitation, alternative therapeutic strategies such as probiotic supplementation¹⁰ or periodontal treatment¹¹ during anti-*Helicobacter pylori* treatment have attracted substantial interest. Unfortunately, according to the Maastricht 2017 Consensus Conference guidelines,¹⁰ probiotics improve *H. pylori* eradication rates by reducing treatment-related side effects rather than through direct effects on *H. pylori*.

Apart from the stomach, *H. pylori* has been found in the oral cavity, including dental plaque,^{12,13} saliva,¹⁴ mucosal lesions,¹⁵ and sites of periodontitis,¹⁶ suggesting the oral environment may be one of many potential reservoirs for *H. pylori*. Thus, the presence of the organism in the oral cavity may affect the outcome of eradication therapy by serving as a source of both gastric reinfection and bacterial transmission.¹⁷

Although systemic antibiotic treatments are effective in eliminating *H. pylori* in the stomach, the same treatment regimens have little or no effect on dental plaque.^{14,18,19} Because dental plaque is a biofilm, the microorganisms in it are protected from systemic antimicrobials and must be removed mechanically. Removal of oral *H. pylori* can improve the gastric eradication rate by reducing the chance of reinfection and thus decrease the need for repeated antibiotic use.

Because of the inefficacy of systemic eradication therapy on dental plaque-associated *H. pylori*, studies were carried out to investigate the effect of periodontal treatment on such organisms.²⁰ Additionally, two meta-analyses were conducted to systematically review the effectiveness of adjunct periodontal treatment on gastric *H. pylori* eradication. Whereas the original meta-analysis covered three studies, the second meta-analysis included, to its detriment, a study²¹ that reported on the use of a daily chlorhexidine mouth rinse without any professional periodontal treatment as a means of acceptable therapy for gastric *H. pylori* eradication. Although chlorhexidine mouth rinse is a useful antiplaque agent, it is no replacement for brushing or professional periodontal treatment. Chlorhexidine is more efficacious in

impeding plaque formation on a clean tooth surface than in reducing established plaque deposit.²² The inclusion of this chlorhexidine treatment study in the meta-analysis not only may compromise the homogeneity of intervention groups but may also underestimate or overestimate the effectiveness of professional periodontal treatment. Indeed, when the chlorhexidine study²¹ was excluded from Ren et al.²³ study and their data was re-analysed,²³ the result become non-significant ($P = 0.20$). Moreover, the quality of the previously presented Chinese results in this meta-analysis could not be assessed by any available mechanism. Further, an update of Cochrane reviews is required every 2 years or the absence of the required update needs to be rationalised in the systematic review.²⁴

Accordingly, an updated systematic review of studies was undertaken to investigate whether periodontal therapy is a useful adjunct to systemic therapy for eradication of gastric *H. pylori* infection.

Materials and methods

Meta-analysis

Literature search

A systematic search of the literature was performed using electronic databases including Medline (PubMed), the Web of Science, U.S. clinical trials registries (ClinicalTrials.gov) and published abstracts from major scientific meetings for all articles published by November 2018 on the effect of periodontal treatment on gastric *H. pylori* eradication. The following MeSH terms were used in this search: (“*helicobacter pylori*” [MeSH Terms]) AND “periodontics/instrumentation” [MeSH Terms]; (“*helicobacter pylori*” [MeSH Terms]) AND “root planing” [MeSH Terms]; (“*helicobacter pylori*” [MeSH Terms]) AND scaling, dental [MeSH Terms]; (“*helicobacter pylori*” [-MeSH Terms]) AND “periodontics” [MeSH Terms]; (“*helicobacter pylori*” [MeSH Terms]) AND “periodontal debridement” [MeSH Terms]; (“*helicobacter pylori*” [MeSH Major Topic]) AND “periodontitis” [MeSH Terms]. For publications that had not yet been subjected to MeSH-indexing, the following query was used: “*Helicobacter pylori*” or “*Helicobacter pylori* infection” or “*H. pylori*” concatenated with “periodontal treatment” or “initial periodontal therapy” or “scaling and root planing.” The ClinicalTrials.gov website was searched to identify unpublished trials. Additional articles were searched through the references cited in the articles selected. No language restrictions were applied. If any overlapping studies were identified, only the one containing comprehensive data was included. The flow of the study selection, according to PRISMA guidelines,²⁵ is presented in Figure 1.

Study selection

This meta-analysis followed PRISMA reporting guidelines²⁶ and the Cochrane Handbook for Systematic Reviews of Interventions.²⁷ These PICOS criteria were used to select studies:

- **Population:** Adults who had *H. pylori* infection;
- **Intervention:** Professional periodontal treatment (initial periodontal treatment consisting of scaling and root planing) plus conventional systemic eradication therapy;

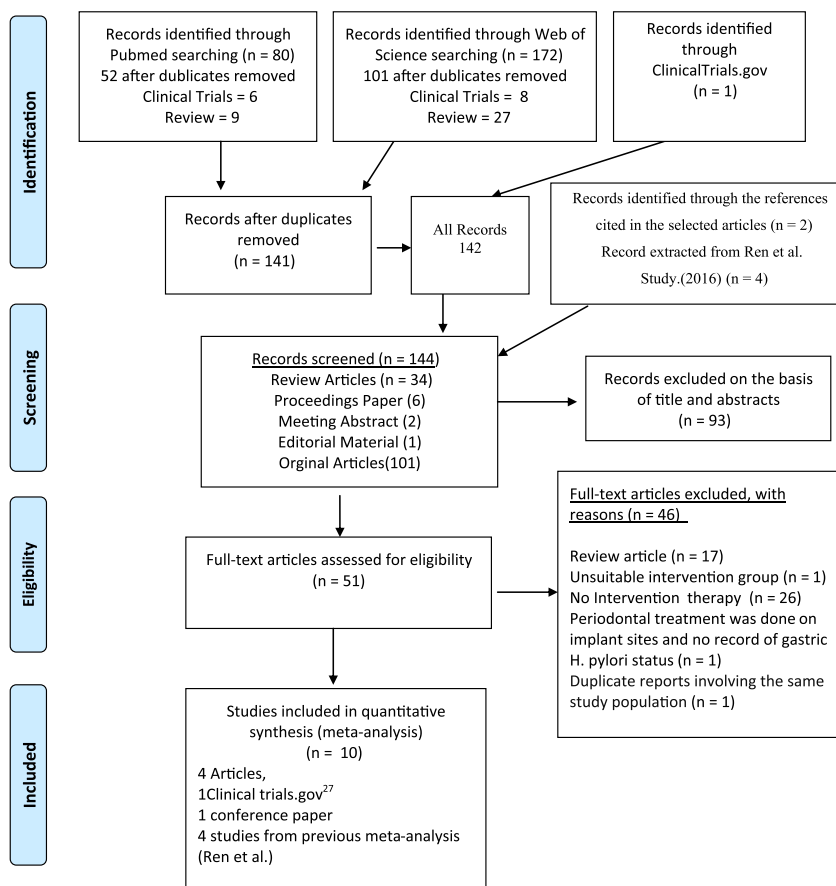


Fig. 1 – Flowchart of study selection according to the PRISMA guidelines.

- **Comparator:** Conventional systemic eradication therapy. (*H. pylori* eradication regimens included trials consisted of triple therapy, quadruple therapy, sequential therapy, and concomitant therapy).
- **Outcome measures:** The primary outcome measure of the meta-analysis was the eradication rate of gastric *H. pylori* infection. The secondary outcome measure was the recurrence rate of gastric *H. pylori* infection.
- **Study design sought for inclusion:** All clinical trials were included.

Excluded were studies that used oral mouth rinse without any professional periodontal treatment as the intervention group; studies that used oral hygiene measures without any professional periodontal treatment as the intervention group; trials with periodontal surgical treatment; letters to the editor; updates, interviews, commentaries and review papers; and animal studies.

Quality assessment

Methodological qualities of the included studies were assessed using criteria from the Cochrane Collaboration's handbook version 5.1.0 (*Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*, Higgins and Greene).²⁷ These parameters were considered: (i) random sequence generation (selection bias); (ii) allocation concealment (selection bias); (iii) blinding of participants and personnel

(performance bias); (iv) blinding of outcome assessment (detection bias); (v) incomplete outcome data (attrition bias); (vi) selective reporting (reporting bias); and (vii) other sources of biases (see Table 2.). The Cochrane Collaboration tool was used to assess the risk of bias.

Statistical analysis

This meta-analysis was performed with the Meta package (<http://www.cran.r-project.org/bin/windows/base>). OR and 95% confidence intervals (CI) were calculated for combined treatment versus systemic therapy for gastric eradication. The pooled OR was estimated using fixed-effects of Mantel-Haenszel and random-effects²⁸ models.²⁹ The extent of heterogeneity was quantified using I^2 . Publication bias was evaluated by funnel plot analysis. Meta-regression analysis was performed where possible to explore the role of potential sources of heterogeneity.

Results

Study identification

A total of 153 studies were identified from the electronic database using the aforementioned search criteria, and one clinical trial³⁰ (later published) was identified through the

ClinicalTrials.gov registry platform (Figure 1). Review articles, one of two overlapping studies^{31,32} and irrelevant studies were excluded. The study by Wang et al.²¹, included in the previous meta-analysis,²³ was excluded here because no professional periodontal treatment was performed as part of the treatment protocol in the intervention arm. Importantly, four additional non-duplicated relevant records in Chinese were extracted from the previous meta-analysis.²³ These articles were not covered in PubMed, Web of Science or Google Scholar. Among these four Chinese studies, only the abstract of one could be retrieved³² on Google. Therefore, all data for these studies had to be extracted from the previous meta-analysis.²³ Because of the failure of these investigations to be in an accessible form in a credible international peer-reviewed forum, global researchers working independently have no choice but to exclude the data from their own systematic reviews, because there is simply no way to assess scientific and methodological quality based on the PRISMA 27-item checklist and four-phase flow diagram.^{24,26} First data from these four Chinese records were all removed from this meta-analysis, and the analysis was performed only with the studies available to all global researchers. However, not to lose any available data, a second meta-analysis of all studies including the previously excluded Chinese data that could be extracted by Ren et al.²³ were performed.

Study characteristics

The combined search yielded 10 papers that provided information on the contribution of professional periodontal therapy on the systemic gastric *H. pylori* eradication therapy (Table 1). Average length of follow-up ranged from 1 month³⁴

to 12 months.³⁵ Nine of these studies were from Asia^{31–39} and one was from Europe.⁴⁰ In the end, from those 10 clinical trials,³⁰ 473 cases, and 436 controls were evaluated (ClinicalTrials.gov).

Gastric *H. pylori* eradication

This meta-analysis showed that the adjunction of professional periodontal therapy to conventional systemic eradication therapy significantly improved the gastric *H. pylori* eradication. The pooled OR was estimated by using both fixed-effects (Mantel–Haenszel) and random-effects models. The meta-analysis was first performed in studies available to the investigator(s).^{30,31,34,35,36,40} The combined OR with a fixed-effects model was 3.86 (95% CI [2.55; 5.84] and with a random-effects model 4.11 [1.91; 8.87 P-value = 0.01] (Figure 2). Furthermore, four additional studies were cumulated from the previous meta-analysis²³ and with newly emerged data re-analysed. Similarly, the combined OR with a fixed-effects model in re-analysed data was 2.51 (95% CI: 1.84–3.43; <0.0001) and with a random-effects model 2.65 (95% CI: 1.58–4.42; =0.0002) (Figure 3). There was significant statistical heterogeneity between studies ($P < 0.006$, $I^2 = 61%$). The random-effects model is more appropriate when heterogeneity is present.^{27,41}

The effect of periodontal treatment on the recurrence of gastric eradication

In addition to the contribution of periodontal treatment on gastric *H. pylori* eradication, several studies^{31,33,35,38} examined the effect of adjunct periodontal treatment on the recurrence

Table 1 – Characteristic of included studies in meta-analysis

		Gastric <i>H. pylori</i> (+)	Gastric <i>H. pylori</i> (-)	Sample size	Percent eradication	Follow-up
Zaric et al. (2009) ⁴⁰	Triple	11	10	21	47.60%	3 months
	Triple + perio	5	17	22	77%	
Jia et al. (2009) ³² (in Chinese)	Triple	33	7	39	17.95%	6 months
	Triple + Perio after gastric eradication	9	38	47	80.85%	
Jia et al. (2009) ³¹	Triple	43	8	51	15.69%	6 months
	Triple + Perio after gastric eradication	11	45	56	81.36%	
Gao et al. (2011) ³⁵	Triple	10	27	37	73%	1 month
	Triple + perio	8	35	43	81.40%	
	Triple	16	11	37	32.40%	12 months
	Triple + perio	2	27	43	62.80%	
Song et al (2013) ³⁴	Triple	8	40	51	78.4%	1 month
	Triple + perio	13	40,54	57	94.7%	
Tongtawee et al. (2017) ³⁶	Triple	11	39	50	78%	3 months
	Triple + perio	3	45	48	93.8%	
Yuksel-Sert (2019) ³⁰	Triple	23	24	47	51.06%	3 months
	Triple + perio	18	33	51	64.71%	
Jin et al. (2003) ³³ (in Chinese)	Triple	4	26	32	81.25%	1 month
	Triple + perio	6	28	32	87.5%	
Jin et al. (2007) ³⁸ (in Chinese)	Triple	9	32	41	78%	1 month
	Triple + perio	8	38	46	82.6%	
Lv and Yao. (2006) ³⁷ (in Chinese)	Triple	13	17	30	56.6%	1 month
	Triple + perio	9	26	35	74.3%	
Liu et al. (2012) ³⁹ (in Chinese)	triple	40	34	74	45.9%	1 month
	triple + perio	30	48	78	61.5%	

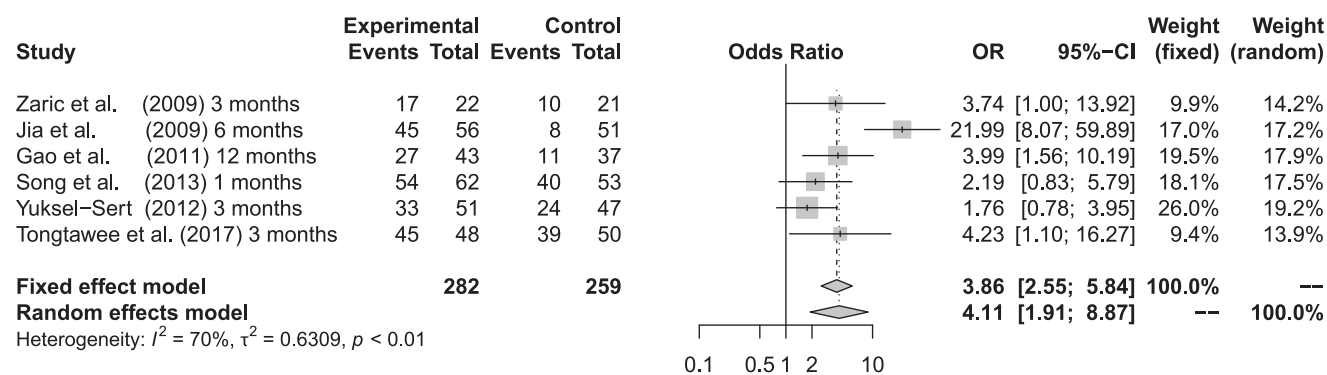


Fig. 2 – Forest plot of published studies on the contribution of professional periodontal treatment to conventional systemic gastric *H. pylori* eradication therapy.

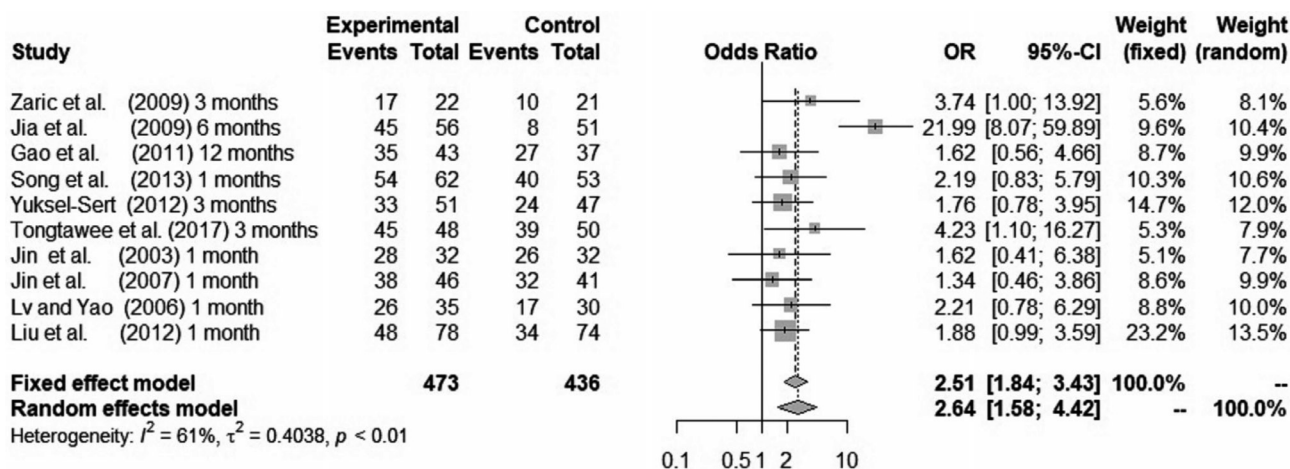


Fig. 3 – Forest plot of published studies including data of four trials from a previous review on the contribution of professional periodontal treatment to the recurrence of gastric *H. pylori* eradication.

of gastric *H. pylori* after successful eradication. Three of these trials^{33,35,38} examined recurrence rate at 12 months, and one trial³¹ examined recurrence at 6 months, adding up to 161 systemic therapy participants and 177 combined therapy participants (338 total). Meta-analyses of these clinical trials showed that adjunct periodontal treatment improved not only gastric eradication rates but also non-recurrence rates of gastric *H. pylori* infection, with an OR 5.36 (95% CI: 2.18–13.15; P -value = 0.00002) in the random effect model and an OR 5.20 (95% CI: 3.22–8.39; P -value < 0.0001) (Figure 4) in the fixed-effect model. A significant statistical heterogeneity was detected between studies ($P < 0.01$, $I^2 = 71\%$). Sensitivity analysis of these studies showed that after exclusion of the Jia et al. study³¹ in the analysis, the heterogeneity decreased from 71% to 0%. The OR was 3.39 (95% CI: 1.99–5.85, P -value = 0.0001).

The effect of oral *H. pylori* status on gastric eradication

Although most of the clinical trials evaluated oral *H. pylori* status, three of them^{33,37,38} did not. Oral *H. pylori* status can

be a potential confounder of the effect of adjunct periodontal treatment on gastric *H. pylori* status. Therefore the trials were stratified based on oral *H. pylori* status. This meta-analysis on oral *H. pylori*-positive patients showed that adjunct periodontal treatment improved the gastric eradication rates with OR 3.16 (1.59; 6.28; $P = 0.001$).

The effect of adjunct periodontal treatment on gastric eradication of unknown oral *H. pylori* status seems smaller (range = 5%–17%) but may be clinically significant. Because the number of the participants was low (216 participants) in this group, the meta-analysis did not have sufficient statistical power to detect such small differences. Thus, it was not possible to determine the effect of adjunct periodontal treatment in this group.

Trial quality

The quality assessment of the included studies is presented in Table 2. All studies described their methods as randomised yet failed to specify methods of randomisation or allocation concealment. Sert-Yuksel³⁰ used the alternate date of

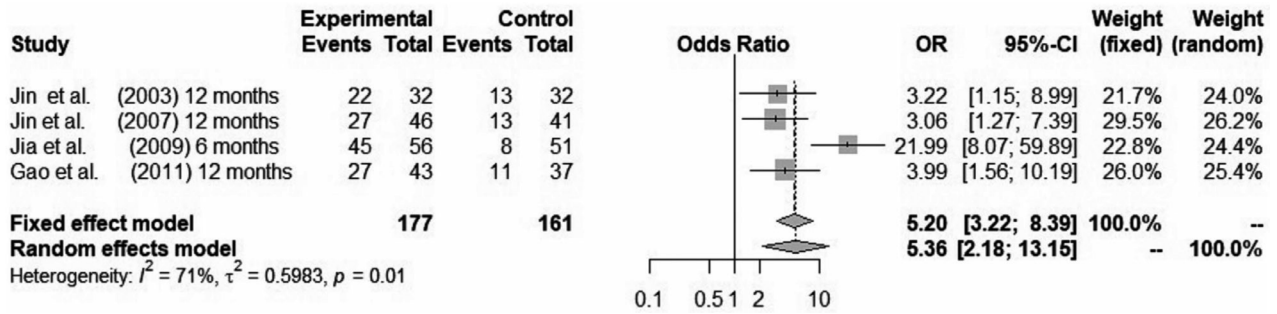


Fig. 4 – Forest plot of published studies on the contribution of professional periodontal treatment to the recurrence of gastric *H. pylori* eradication.

Table 2 – Quality measure of included studies in the meta-analysis based on the Cochrane Collaboration tool

	Random sequence generation (Selection Bias)	Allocation concealment (Selection Bias)	Blinding of the outcome assessment (detection Bias)	Incomplete outcome data addressed (Attrition Bias)	Selecting reporting (Reporting Bias)
Zaric et al. (2009) ⁴⁰	+	?	?	–	+
Jia et al. (2009b) ³²	?	?	?	–	+
Gao et al. (2011) ³⁴	?	?	?	–	+
Song et al. (2013) ³⁴	?	?	+	–	+
Tongtawee et al. (2017) ³⁶	?	?	?	–	+
Sert-Yuksel (2019) ³⁰	–	+	+	–	+
Jin et al. (2003) ³³	?	?	?	+	+
Jin et al. (2007) ³⁸	?	?	?	+	+
Lv and Yao (2006) ³⁷	?	?	?	+	+
Liu et al. (2012) ³⁹	?	?	?	+	+

Due to nature of periodontal treatment, it was not possible to blind the patient or clinician therefore, the assessment of blinding of participants and personal from the evaluation was excluded. For the Chinese studies, the quality measures were extracted from Ren et al.²³

allocation, which may be predictable, and therefore was deemed to be at a high risk of bias. Because of the nature of the periodontal treatment, it was not possible to blind the patient or clinician; therefore the assessment of blinding of participants and personnel from the evaluation was excluded. A variety of methods, such as polymerase chain reaction, urea breath test, and the stool antigen test, was used for outcome assessment. Two of these studies used an automated system for the detection of *H. pylori*, therefore deemed to be of low risk of bias. Method of detection of *H. pylori* and subsequent risk of bias was unclear in the remainder. In six of the trials data were not analysed on an intention-to-treat basis. Information in the remainder of studies (in Chinese) was extracted from the study by Ren et al.²³ Studies varied in quality. The majority of studies were small and low in quality. In this meta-analysis, except for the exclusions detailed previously, all relevant trials pertaining to the research question were included irrespective of the quality of the studies in order to provide a comprehensive review of the literature and avoid selection bias. The strength of the evidence of this meta-analysis was deemed to be moderate based on a best evidence synthesis rating system,⁴² a determination based on consistent findings in multiple low-quality studies presenting results in all studies trending in the same direction.

Sensitivity analyses

After exclusion of the data from Jia et al.³¹ in the analysis, the test of heterogeneity was not significant; I^2 decreased from 61% to 0% (Table 3). Additionally, any possible publication bias or small study effect was tested by a funnel plot analysis (Figure 5). The results showed no clear indication of funnel plot asymmetry ($P = 0.68$), suggesting no evidence of publication bias for all outcome measures.

Discussion

The goal of this investigation was to evaluate the effect of non-surgical periodontal therapy on gastric *H. pylori* eradication. In the updated analysis, excluding the problematic study using chlorhexidine discussed previously, six studies available to all investigators were analysed. Results were significant, OR for the six studies is 4.11 (P -value = 0.01; Figure 2). However, so as to include all available data, a second meta-analysis of 10 studies including the previously excluded Chinese data (that could be deduced from the analysis by Ren) was performed. Similarly, the re-updated meta-analysis evaluating a total of 909 participants has strengthened the evidence that the addition of periodontal treatment to systemic

Table 3 – Summary results of the influential analysis (random-effects model)

Study	OR [95% CI]	P-value	tau ²	I ² (%)
Omitting Zaric et al. (2009) ⁴⁰	2.8338 [1.6324; 4.9192]	0.0002	0.4467	64.9
Omitting Jia et al. (2009) ³²	2.2053 [1.5963; 3.0465]	<0.0001	0.0000	0.0
Omitting Gao et al. (2011) ³⁵	2.7901 [1.5849; 4.9119]	0.0004	0.4618	64.2
Omitting Song et al. (2013) ³⁴	2.9968 [1.6968; 5.2930]	0.0002	0.4723	64.9
Omitting Tongtawee et al. (2017) ³⁶	3.0992 [1.7571; 5.4664]	<0.0001	0.4586	64.6
Omitting Sert-Yuksel et al. (2019) ³⁰	2.8052 [1.6218; 4.8521]	0.0002	0.4392	63.1
Omitting Jin et al. (2003) ³³	3.0424 [1.7642; 5.2465]	<0.0001	0.4328	64.3
Omitting Jin et al. (2007) ³⁸	3.1491 [1.8315; 5.4146]	<0.0001	0.4099	62.1
Omitting Lv and Yao (2006) ³⁷	2.9882 [1.6991; 5.2553]	0.0001	0.4658	65.0
Omitting Liu et al. (2012) ³⁹	3.0934 [1.7295; 5.5330]	0.0001	0.4846	62.5
Pooled estimate	2.8938 [1.7397; 4.8137]	0.0002	0.59	60.9

Pooled OR and 95% CI for excluding each data set in the meta-analysis (up to July 2008). The relative contribution to heterogeneity of each study examined by a sensitivity analysis by removing one data set at a time. The pooled OR was re-calculated in the absence of each study. Iterative sensitivity analysis showed that Jia et al.³¹ accounted for the heterogeneity observed in our meta-analysis. After exclusion of this study in the analysis, the test of heterogeneity was not significant, I² decreased from 76% to 0%.

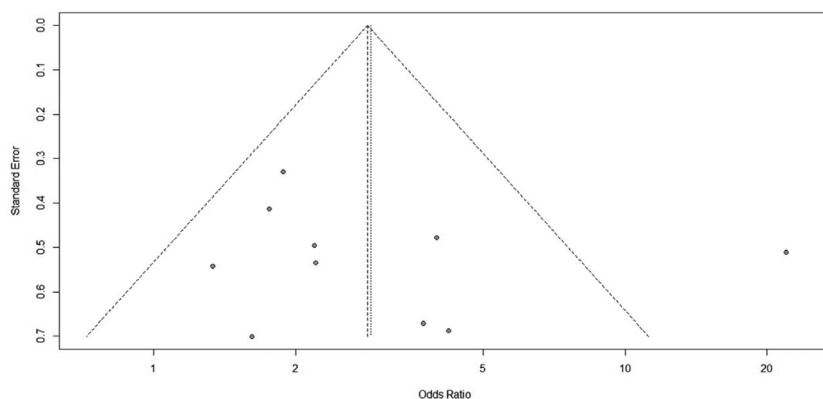


Fig. 5 – Funnel plot asymmetry used to determine publication bias. Points indicate odds ratios from the studies included in the meta-analysis. (P-value = 0.68).

eradication therapy leads to an improvement of gastric *H. pylori* eradication, with OR 2.64 (P-value < 0.0001; Figure 3). Additional meta-analysis of four clinical trials (338 participants) investigation gastric *H. pylori* recurrence showed that adjunct periodontal treatment improved not only gastric eradication rates but also improved non-recurrence rates of gastric *H. pylori* infection, OR 5.36 (P-value = 0.0002).

Systematic review and meta-analysis of the literature support the value of periodontal treatment as an adjunct. Thus, periodontal treatment combined with standard systemic therapy could be a promising approach to gastric *H. pylori* management.

Although systemic eradication therapy is effective in gastric *H. pylori*, its effect on biofilm-protected dental plaque is limited.¹⁴ Bacteria in residence in dental plaque are almost 1,000–1,500 times more resistant to antibiotics compared to planktonic (unattached) bacteria.⁴³ Elimination of oral biofilm by mechanical means by a dental professional coupled with daily oral hygiene procedures is one of the most efficient treatment options available.

A number of studies have evaluated the effect of periodontal therapy on gastric *H. pylori* eradication. The initial research by Zaric et al.⁴⁰ showed that adjunctive periodontal

therapy improves the gastric *H. pylori* eradication rate. A concurrent study by Jia et al.³¹ reinforced the role of periodontal therapy as an adjunct in gastric *H. pylori* eradication. A meta-analysis⁴⁴ covering these two studies and a third (total 298 patients) showed that adjunction of periodontal therapy significantly reduced the relative risk of persistence of gastric *H. pylori* by 63% compared with eradication therapy alone. (Bear in mind this meta-analysis was limited by the inclusion of two overlapping studies by the same group.^{31,32}) The systematic review by Ren et al. (2016)²³ covered two of three clinical trials from the previous meta-analysis and an additional four trials from China^{33,37–39} on the effect of adjunct periodontal treatment on gastric *H. pylori* eradication therapy compared to conventional systemic eradication therapy. However, the use of chlorhexidine oral rinse in combination with systemic eradication therapy was inappropriately considered as periodontal treatment, and the study was included in the analysis. In our meta-analysis, only trials with adjunct periodontal therapy consisting of professional scaling and root planning were included. Additionally, our meta-analysis also provides evidence of benefit from a larger number of studies (10 vs. 5) and more than twice as many patients (909 vs. 411) including more recent clinical trials^{30,31,34–36} (Table 1).

As with all meta-analyses, this meta-analysis has several limitations. There is the issue of potential publication bias. This meta-analysis was limited to published studies although searches of clinical trials registries (ClinicalTrials.gov) were conducted to identify unpublished and yet-ongoing trials on the effect of periodontal therapy on gastric *H. pylori* eradication. Publication bias was also assessed using the Begg and Egger test as well as funnel plot analysis. Funnel plot analysis did not show any publication bias or small study effect, indicating that the unpublished evidence did not affect the results of the meta-analysis.

Second, there was evidence of substantial interstudy heterogeneity in this meta-analysis. To examine the relative contribution of each individual study to the heterogeneity of the overall analysis, each study was excluded from the analysis consecutively. The data from Jia et al.³¹ accounted for heterogeneity in this meta-analysis. After exclusion of these data in the analysis, the test of heterogeneity was not significant, I^2 decreased from 61% to 0%.

Other factors can also act as confounders, among them variation in the assessment of oral *H. pylori* status. Of the 10 clinical trials, three^{33,37,38} did not evaluate the presence of oral *H. pylori*, whereas the rest of the studies evaluated both gastric and oral *H. pylori* status. However, these trials had small weights in this meta-analysis and excluding them only slightly altered the effects of periodontal treatment on gastric *H. pylori* eradication OR = 3.16 (1.59; 6.28; $P = 0.001$).

The quality of studies was low in the majority of the clinical trials. The vast majority of the studies evaluated failed to specify the methods of the random sequence generation, allocation concealment, and blinding, or data were analysed on an intention-to-treat basis.

Despite its limitations, the currently updated meta-analysis gives further credence that periodontal therapy has a significant effect on gastric *H. pylori* eradication. The strength of the evidence within this meta-analysis was deemed to be moderate due to the consistent findings in multiple low-quality studies presenting results in all studies trending in the same direction.⁴² Periodontal treatment is associated with improvement in non-recurrence rates of gastric *H. pylori* infection compared with systemic eradication therapy alone. Coordinated efforts by a dental professional and a gastroenterologist may be helpful to improve treatment outcomes in affected individuals.

Conflicts of interest

No conflicts of interest related to this study. The author received no funding from an external source.

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