

Influence of Different Periodontal Therapies on Eradication and Recurrence of *Helicobacter Pylori* Infection

Ke Chen¹, Gang Chen¹, Shao-Ge Liu¹, Feng-Zhen Wei¹, Sai-Zheng Lin^{2*}

1. Dept. of Stomatology, The People's Hospital of Zhenhai, Zhejiang Province, PR China.

2. Dept. of gastroenterology, The People's Hospital of Zhenhai, Zhejiang Province, PR China.

Abstract

Helicobacter pylori (*H. pylori*) infection is a crucial risk factor for chronic gastritis, peptic ulcer and gastric cancer. The presence of oral *H. pylori* might affect the efficiency of eradication therapy and act as a causal force for its recurrence. Bismuth-containing quadruple therapy has recently been the first-line treatment recommended widely but has limited efficacy in patients with periodontitis. This study aimed to evaluate efficacy of bismuth-containing quadruple therapy with different adjunctive periodontal therapies in gastric *H. pylori* eradication.

We conducted a prospective randomized trial on 160 gastric *H. pylori* infected patients who also have periodontitis, of whom 65 received quadruple therapy plus supragingival scaling (Group A) and 95 received quadruple therapy plus adjunctive periodontal therapy contained scaling and root planing (SRP) (Group B). The presence of *H. pylori* was detected by ¹³C-urea breath test (UBT).

The probe depth (PD), clinical attachment loss (CAL) and plaque index (PLI) in group A and group B both improved after treatment. The eradication rate in Group B (87.37%) is significantly higher than Group A (75.38%). However, the difference between the two groups decreased with time. The recurrence rates after one year in Group A and Group B were 12.31% and 10.53%.

This study suggests that adjunctive periodontal therapy is an effective added treatment for *H. pylori* infection. In addition, as an adjuvant treatment of quadruple therapy, the effect of SRP is significantly higher than that of supragingival scaling only.

Clinical article (J Int Dent Med Res 2023; 16(1): 204-208)

Keywords: *Helicobacter pylori*, periodontitis, infection eradication, supragingival scaling, periodontal therapy

Received date: 12 October 2022

Accept date: 07 November 2022

Introduction

H. pylori is a kind of gram-negative *Helicobacter*, which was successfully extracted from antral mucosa mucosa in 1983.¹ It was designated as a type I carcinogen by the World Health Organization in 1994 and approximately 50% of the world's population is infected.² *H. pylori* bears intimate relation with chronic gastritis, peptic ulcer and gastric cancer. However, the infection caused by gastric *H. pylori* is difficult to be completely eliminated after systemic drug therapy (triple therapy: antibiotics, antibacterial agents and proton pump inhibitors), and there is recurrent infection.³ Most scholars believe that

there are other potential repositories of *H. pylori* in the human body except the stomach.

In 1989, Kraiden isolated *H. pylori* from the dental plaque of chronic gastritis patients.⁴ Over recent years, many studies showed that oral dental plaques are an important reservoir of *H. pylori* and might be a source of re-infection with *H. pylori* in stomach.⁵ With the increasing evidence of *H. pylori* present at various parts of oral cavity, the high recurrence rate of *H. pylori* infection indicates the oral cavity is an extra-gastric *H. pylori* reservoir, as systemic antimicrobials against *H. pylori* fail to disrupt the germ-protective oral biofilm.⁶ Studies have demonstrated the permissive role of periodontal disease in the colonization of the oral cavity and gastric infection by *H. pylori*.⁷ Bismuth-containing quadruple therapy is widely used as first-line treatment for *H. pylori* infection, and previous studies have reported that bismuth-containing regimens are safe and well-tolerated for *H. pylori* eradication.⁸ These findings prompted us to

*Corresponding author:

Sai-Zheng Lin,
The People's Hospital of Zhenhai, Ningbo 315202, Zhejiang Province, PR China, Naner West Road 718, Zhenhai District, Ningbo, Zhejiang.
E-mail: linsaizheng@126.com

evaluate the effectiveness of periodontal therapy combined with quadruple therapy in the complete elimination of gastric *H. pylori* infection.

Due to the limitation of medical resources and the lack of periodontists, in many primary hospitals in developing countries such as China, a large number of patients with periodontitis can only receive supragingival scaling treatment but not adjunctive periodontal therapy contained SRP. In the study of evaluating the effect of periodontal adjuvant therapy on *H. pylori* infection, considering the directive value of our research results to the clinical practice of primary hospitals in developing countries, it is necessary to divide supragingival scaling and adjunctive periodontal therapy contained SRP into two groups for evaluation.

This study aimed to investigate the cure rate of *H. pylori* eradication treatment with Bismuth-containing quadruple therapy and adjunctive periodontal therapy in Chinese patients. The findings of this study may improve treatment efficacy and reduce the risk of *H. pylori* recurrence in this region.

Materials and methods

Patient population and inclusion/exclusion criteria

In this prospective clinical study, 160 individuals with periodontitis combine *H. pylori* infection and attending the The People's Hospital of Zhenhai, Ningbo were examined. All participants signed a volunteer consent, before undergoing research procedures, agreeing to their participation in the clinical protocol. The study protocol was approved by the Ethics Committee of the The People's Hospital of Zhenhai (IRB number: 2020003).

The inclusion criteria were as follows: ≥ 18 years of age, at least 16 natural teeth (excluding third molars and teeth with advanced caries indicated for extraction), and more than 30% of teeth with $PD \geq 5$ mm, $CAL \geq 3$ mm and BOP at baseline. The exclusion criteria were as follows: pregnancy and lactation, active tobacco smoking, SRP or antibiotic therapy within the last 6 months, medical disorders that require prophylactic antibiotic coverage or that could influence the progression or treatment of periodontitis, long term administration of anti-inflammatory or immunosuppressive medications, positive history of cardiovascular disease, elderly patients

(>70 years old). All patients underwent periodontal parameters examination before ^{13}C -urea breath test. PD, CAL and PLI were recorded at the mesiobuccal sites of the patient's four first molars (the missing first molars replaced by the second molars). The periodontal parameters examination and treatment of patients were completed by different investigators.

Study Groups

Among the patients with *H. pylori* infection, participants were randomly assigned to two treatment groups: (Group A) quadruple therapy with supragingival scaling (n=65) and (Group B) quadruple therapy with adjunctive periodontal therapy contained SRP (n=95).

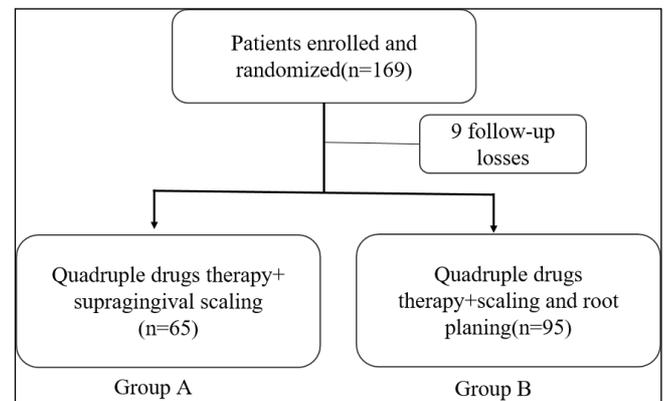


Figure 1. Study design schematic and study measures.

Figure 1 outlines the process of examinations and treatment performed. The 2-week quadruple therapy contains pantoprazole (80mg/d), amoxicillin (2g/d), furazolidone (0.2g/d) and compound bismuth and magnesium granules (12g/d). In group A, supragingival scaling using ultrasonic was completed by the same treating clinician, quadruple therapy was initiated immediately after the supragingival scaling. In group B, SRP under local anaesthesia using ultrasonic and manual Gracey scalers was completed over two 90-min half-mouth SRP sessions within 7 days, by the same treating clinician. The endpoint of SRP was defined as a smooth root surface free of calculus deposits determined by visual and tactile examination. Quadruple therapy was initiated immediately after the first half-mouth SRP session. The importance of maintaining immaculate oral hygiene through daily toothbrushing, flossing and interdental brushing was visually showed and reinforced at each appointment.

Follow-up statement

Patient follow-up was scheduled 2 months and 1 year after the completion of therapy. ¹³C-urea breath test and periodontal parameters examination were performed as per routine practice. Those who were negative for *H. pylori* underwent further examination after 1 year to establish the recurrence rate.

Statistical analysis

The effect of different treatment groups on these clinical parameters at each interval was compared by Student's t test. Within each group, the Bonferroni method (Paired-sample t test) was performed to compare the clinical parameters at different intervals. The χ^2 test was used to analyze the eradication rate of gastric *H. pylori* in each group. Data processing and analysis was performed on SPSS 23.0 (IBM, Chicago, United States). *p*-values < 0.05 were accepted for statistical significance.

Results

Clinical parameter	Mean ± SD			Within-group comparison	
	Baseline	Month 2	Month 12		
PLI	supragingival scaling +Quadruple therapy	2.45±0.95	1.52±0.66	1.49±0.53	0 versus 2: <i>p</i> < 0.0001* 0 versus 12: <i>p</i> < 0.0001* 2 versus 12: <i>p</i> = 0.727
	SRP +Quadruple therapy	2.44±0.91	1.55±0.68	1.28±0.45	0 versus 2: <i>p</i> < 0.001* 0 versus 12: <i>p</i> < 0.0001* 2 versus 12: <i>p</i> < 0.0001*
	Between-group comparison	<i>p</i> =0.978	<i>p</i> =0.823	<i>p</i> =0.008*	
PD (mm)	supragingival scaling +Quadruple therapy	6.40±2.02	5.18±1.81	4.98±1.61	0 versus 2: <i>p</i> < 0.0001* 0 versus 12: <i>p</i> < 0.0001* 2 versus 12: <i>p</i> = 0.162
	SRP +Quadruple therapy	6.42±1.88	5.28±1.67	4.48±1.29	0 versus 2: <i>p</i> < 0.0001* 0 versus 12: <i>p</i> < 0.0001* 2 versus 12: <i>p</i> < 0.0001*
	Between-group comparison	<i>p</i> =0.956	<i>p</i> =0.735	<i>p</i> =0.031*	
CAL (mm)	supragingival scaling +Quadruple therapy	7.64±2.042	6.66±1.85	6.967±1.61	0 versus 2: <i>p</i> < 0.0001* 0 versus 12: <i>p</i> = 0.0002* 2 versus 12: <i>p</i> = 0.0371*
	SRP +Quadruple therapy	7.695±1.88	6.29±1.61	6.19±1.67	0 versus 2: <i>p</i> < 0.0001* 0 versus 12: <i>p</i> < 0.0001* 2 versus 12: <i>p</i> < 0.0001*
	Between-group comparison	<i>p</i> =0.877	<i>p</i> =0.1852	<i>p</i> =0.004*	

The comparison between groups at each interval was performed with Unpaired t test (**p* < 0.05)
 The comparison within each group was performed with paired t test (**p* < 0.05); 0, baseline; 2, month 2; 12, month 12

Table 1. Mean PLI and PD of patients treated with SRP or supragingival scaling plus quadruple therapy.

Periodontal Evaluation

Table 1 showed the mean PLI, PD and CAL of sites treated with two clinical strategies at different intervals. At baseline, PLI PD and CAL between the selected sites of two treatment groups were similar, 2.44±0.91 versus 2.45±0.95 mm, 6.42±1.88mm versus 6.40 ± 2.02 mm and

7.64±2.04 versus 7.69±1.88 respectively. After 2 months, both treatment groups showed statistically significant PLI amelioration and PD, CAL reduction, and group B didn't yield additional improvement in these parameters when compared with group A (PLI: 1.55±0.68 versus 1.52±0.66, *p*=0.823; PD: 5.28±1.67 mm versus 5.18±1.81 mm, *p*=0.735; CAL: 6.66±1.85 mm versus 6.29±1.61 mm, *p*=0.1852). However, the changes in PLI, PD and CAL over the next 10 months were discrepant between two treatment groups. Compared with month 2, the PLI, PD and CAL in the group B continued to ameliorate till 12 months, while the group A failed to obtain a further amelioration in PLI and PD. Thus, at month 12, group B possessed a better PD parameter (*p*= 0.031), PLI parameter (*p*=0.008) and CAL parameter (*p*=0.004) than Group A. The group B contributed to a continuous amelioration of PLI and PD, which almost remained same in the Group A.

H. pylori eradication effect

We subsequently examined different therapies for *H. pylori* eradication and its recurrence rate. We found that in month 2, the eradication rates of group A and group B were 75.38% and 87.37% respectively. In month 12, the eradication rates were 63.08% and 76.84%, and the recurrence rate in two groups were 12.31% and 10.53% respectively (Figure 2).

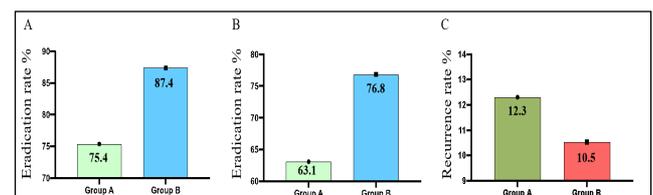


Figure 2. Therapeutic effects of different treatment methods on *H. pylori* infection. (A) Gastric *H. pylori* eradication rates of two groups 2 months after treatment; (B) Gastric *H. pylori* eradication rates of two groups 1 year after treatment; (C) Gastric *H. pylori* recurrence rates of two groups 1 year after treatment.

Moreover, the difference between the two groups was statistically significant both in month 2 and month 12. The results of paired comparison showed that in month 2, the eradication effect of group B was better than that of group A (*p*≤0.05). In month 12, the eradication effect of group B was also better than that of group A although there was no significant

statistical difference ($p=0.059$) (Table 2). Overall, periodontal therapy could increase the efficiency of *H. pylori* eradication. In addition, as an adjuvant therapy of quadruple drugs, the effect of adjunctive periodontal therapy contained SRP is better than that of supragingival scaling only.

Group <i>n</i>	Group A 65	Group B 95	<i>P</i> -value
Gastric <i>H. pylori</i> positive(+)	16	12	$p=0.050^*$
Month 2 Gastric <i>H. pylori</i> negative(-)	49	83	
Percent eradication	75.38%	87.37%	
Gastric <i>H. pylori</i> positive(+)	24	22	$p=0.059$
Month 12 Gastric <i>H. pylori</i> negative(-)	41	73	
Percent eradication	63.08%	76.84%	

The χ^2 test was used to analyze the difference of eradication effect between each group.

Table 2. Comparison of Gastric *H. Pylori* eradication rates between different groups.

Discussion

H.pylori affect about half the world's population and a higher prevalence of gastric *H. pylori* infection exists in developing countries (50.8%) compared with the developed ones (34.7%).⁹ At present, 80.0%-90.0% of gastric *H. pylori* can be cured by systemic drug therapy, but among the cured patients, gastric *H. pylori* reinfection is more common, and most of them recur in the first year.¹⁰ With the aggravation of antibiotic resistance, the eradication rate of traditional triple therapy for *H. pylori* is also gradually decreasing.^{11, 12} The average eradication rate of gastric *H. pylori* decreased from 75%-90% in 1983-1997 to 68.8% in 1996-2005.^{5, 13} In clinical practice, no treatment guarantees *H. pylori* eradication. The factors leading to the recurrence after eradication are still inconclusive, and the main view is the reinfection of residual *H. pylori*.

H. pylori can be transmitted by stomach to oral route has been recognized since 1989 when Krajde first isolated *H. pylori* from the dental plaque of patients with gastric diseases related to *H. pylori* infection.⁴ Existing studies have confirmed that oral *H. pylori* and its gastric counterpart have same or substantially same genotype and *H. pylori* at different sites might come from the same strain or be the mutants of the same bacterial strain.^{14, 15} Studies by Salazar

and shakeri have shown that poor oral health or behavior is associated with gastric cancer or precancerous lesions, such as less brushing, gum bleeding and no flossing.^{16, 17} Periodontitis is considered as an important disease, because it has been demonstrated to not only cause loosened teeth but also be associated with many systemic disorders.^{18, 19} Abdel showed that 89.0% of 75 patients with gastric *H. pylori* infection had oral *H. pylori* infection.²⁰ Boylan showed that periodontitis can increase the risk of gastric diseases such as gastric and duodenal ulcer.²¹ Therefore, improving the periodontal condition of oral cavity may help to inhibit *H. pylori* infection and reduce the recurrence rate after treatment.

In China, a considerable number of primary hospitals can only adopt supragingival scaling for patients with periodontitis because of the lack of periodontists and the constraints of medical conditions. Therefore, in our experiment to evaluate the effect of periodontal treatment on *H. pylori* eradication rate, we specially added the supragingival scaling treatment group. In our study, for patients with both periodontitis and gastric *H. pylori* infection, periodontal treatment was applied in addition to quadruple therapy. After periodontal treatment, compared with baseline group, the gastric *H. pylori* eradication rate was increased to 76.84%, while the recurrence of *H. pylori* infection was decreased to 10.53%, these results indicated that periodontal treatment could kill oral *H. pylori*. From the results of the two groups, it can be found that with the gradual improvement of periodontal conditions, the eradication rate of *H. pylori* is also rising. We speculate that the reason why simple supragingival scaling can not improve the eradication rate is that the subgingival plaque has not been effectively removed. The residual *H. pylori* in subgingival plaque will cause oral-gastric transmission and lead to the recurrence of intragastric infection.

Our study has several limitations. It was not performed in a population-based manner, because the subjects were individuals who visited a medical center for a medical checkup and testing was required for diagnosis of periodontitis. In addition, the number of subjects, especially in the examination of time-course changes after eradication for *H. pylori*, was relatively small. Thus, our results should be confirmed by an additional large scale

prospective study.

It can be seen that in the oral cavity, which is one of the possible repositories of *H. pylori*, poor periodontal conditions will be conducive to the survival and reproduction of *H. pylori* in the oral cavity, and the accumulation of dental plaque can also improve the infection rate of oral *H. pylori*. Periodontitis is a risk factor for recurrence after systemic drug therapy of gastric *H. pylori*. Therefore, in clinical practice, it is suggested to carry out routine oral examination for patients with gastric *H. pylori* infection, take effective periodontal basic treatment, reduce dental plaque and establish a good oral flora environment.²² So as to improve the eradication rate of gastric *H. pylori* infection, which is one of the development directions of clinical radical cure of gastric *H. pylori* in the future.

Conclusions

Our results indicate that for patients who both have periodontitis and *H. pylori* infection, adjunctive periodontal therapy contained SRP is an effective measure to improve the *H. pylori* eradication rate and reduce the recurrence rate. Considering the high prevalence of *H. pylori* and antibiotic resistance, periodontal evaluation and adjunctive periodontal therapy contained SRP combined with *H. pylori* eradication in gastric *H. pylori* infection are recommended.

Acknowledgements

This work was supported by Public welfare science and technology projects in Zhenhai District (Grant No. 2020S010).

Declaration of Interest

The authors report no conflict of interest.

References

1. Warren JR, Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet*. 1983;1(8336):1273-5.
2. Hatakeyama M. Helicobacter pylori CagA and gastric cancer: a paradigm for hit-and-run carcinogenesis. *Cell Host Microbe*. 2014;15(3):306-16.
3. Nam JH, Ryu KH, Park BJ, Lee CW, Park EC. Rate and predictive factors of Helicobacter pylori recurrence: Analysis of a screening cohort. *Saudi J Gastroenterol*. 2019;25(4):251-6.
4. Krajden S, Fuksa M, Anderson J, Kempston J, Boccia A, Petrea C, et al. Examination of human stomach biopsies, saliva, and dental plaque for Campylobacter pylori. *J Clin Microbiol*.

- 1989;27(6):1397-8.
5. Kadayifci A, Buyukhatipoglu H, Cemil Savas M, Simsek I. Eradication of Helicobacter pylori with triple therapy: an epidemiologic analysis of trends in Turkey over 10 years. *Clin Ther*. 2006;28(11):1960-6.
6. Gomes CC, Gomez RS, Zina LG, Amaral FR. Recurrent aphthous stomatitis and Helicobacter pylori. *Med Oral Patol Oral Cir Bucal*. 2016;21(2):e187-91.
7. Gao J, Li Y, Wang Q, Qi C, Zhu S. Correlation between distribution of Helicobacter pylori in oral cavity and chronic stomach conditions. *J Huazhong Univ Sci Technolog Med Sci*. 2011;31(3):409-12.
8. Guan JL, Hu YL, An P, He Q, Long H, Zhou L, et al. Comparison of high-dose dual therapy with bismuth-containing quadruple therapy in Helicobacter pylori-infected treatment-naive patients: An open-label, multicenter, randomized controlled trial. *Pharmacotherapy*. 2022;42(3):224-32.
9. Zamani M, Ebrahimitabar F, Zamani V, Miller WH, Alizadeh-Navaei R, Shokri-Shirvani J, et al. Systematic review with meta-analysis: the worldwide prevalence of Helicobacter pylori infection. *Aliment Pharmacol Ther*. 2018;47(7):868-76.
10. Miyabayashi H, Furihata K, Shimizu T, Ueno I, Akamatsu T. Influence of oral Helicobacter pylori on the success of eradication therapy against gastric Helicobacter pylori. *Helicobacter*. 2000;5(1):30-7.
11. Alba C, Blanco A, Alarcón T. Antibiotic resistance in Helicobacter pylori. *Curr Opin Infect Dis*. 2017;30(5):489-97.
12. Lopo I, Libânio D, Pita I, Dinis-Ribeiro M, Pimentel-Nunes P. Helicobacter pylori antibiotic resistance in Portugal: Systematic review and meta-analysis. *Helicobacter*. 2018;23(4):e12493.
13. Laheij RJ, Rossum LG, Jansen JB, Straatman H, Verbeek AL. Evaluation of treatment regimens to cure Helicobacter pylori infection--a meta-analysis. *Aliment Pharmacol Ther*. 1999;13(7):857-64.
14. Fernández-Tilapa G, Axinecuilteco-Hilera J, Giono-Cerezo S, Martínez-Carrillo DN, Illades-Aguar B, Román-Román A. vacA genotypes in oral cavity and Helicobacter pylori seropositivity among adults without dyspepsia. *Med Oral Patol Oral Cir Bucal*. 2011;16(2):e175-80.
15. Silva DG, Stevens RH, Macedo JM, Albano RM, Falabella ME, Veerman EC, et al. Detection of cytotoxin genotypes of Helicobacter pylori in stomach, saliva and dental plaque. *Arch Oral Biol*. 2009;54(7):684-8.
16. Salazar CR, Francois F, Li Y, Corby P, Hays R, Leung C, et al. Association between oral health and gastric precancerous lesions. *Carcinogenesis*. 2012;33(2):399-403.
17. Shakeri R, Malekzadeh R, Etemadi A, Nasrollahzadeh D, Abedi-Ardekani B, Khoshnia M, et al. Association of tooth loss and oral hygiene with risk of gastric adenocarcinoma. *Cancer Prev Res (Phila)*. 2013;6(5):477-82.
18. Fischer RG, Lira Junior R, Retamal-Valdes B, Figueiredo LC, Malheiros Z, Stewart B, et al. Periodontal disease and its impact on general health in Latin America. Section V: Treatment of periodontitis. *Braz Oral Res*. 2020;34(suppl 1):e026.
19. Sulaiman L, Saub R, Baharuddin NA, Safii SH, Gopal Krishna V, Bartold PM, et al. Impact of Severe Chronic Periodontitis on Oral Health-related Quality of Life. *Oral Health Prev Dent*. 2019;17(4):365-73.
20. Al-Refai AN, Fathalla SE, Nagamani R, Al-Momen S. Incidence of helicobacter pylori in dental plaque of saudi gastritis patients. *J Family Community Med*. 2002;9(2):27-36.
21. Boylan MR, Khalili H, Huang ES, Michaud DS, Izard J, Joshipura KJ, et al. A prospective study of periodontal disease and risk of gastric and duodenal ulcer in male health professionals. *Clin Transl Gastroenterol*. 2014;5(2):e49.
22. Chonnakran Suphinwong, Parichat Ong-Artborirak, Sineenart Chautrakarn. Health Behaviors, Tooth Number, and Oral Health-Related Quality of Life Among Thai Older Adults. *J Int Dent Med Res*. 2022;15(3):1248-53.