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Retrospective Study

Efficacy and safety of modified tetracycline dosing in a quadruple therapy for *Helicobacter pylori*: A retrospective single center study

Ying-Chao Sun, Meng-Jia Zhu, Xue-Qin Chen, Lei Yue, Yi-Ru Zhao, Xin-Jie Wang, John J Kim, Qin Du, Wei-Ling Hu

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Abstract**BACKGROUND**

Although highly effective as a component of *Helicobacter pylori* (*H. pylori*) treatment regimen, tetracycline is associated with a high incidence of medication-related adverse events. Modified dosing of tetracycline as part of quadruple therapy may improve safety while providing comparable eradication rates.

AIM

To evaluate the efficacy and safety of modified dosing of tetracycline in patients receiving tetracycline and furazolidone-containing quadruple therapy in patients with *H. pylori* infection.

METHODS

Consecutive patients (10/2020-12/2021) who received tetracycline and furazolidone quadruple therapy for *H. pylori* infection at Sir Run Run Shaw Hospital were identified. All patients received tetracycline, furazolidone, proton pump inhibitor, and bismuth for 14 d as primary or rescue therapy. Modified tetracycline dose group received tetracycline 500 mg twice daily while standard group received 750 mg twice daily or 500 mg three times daily.

RESULTS

Three hundred and ninety-four patients [mean age = 46.3 ± 13.9 , male = 137 (34.8%), and 309 (78.4%) primary therapy] completed tetracycline and furazolidone quadruple therapy for *H. pylori* infection including those who received modified tetracycline dose in 157 and standard doses in 118 (750 mg twice daily) and 119 (500 mg three times daily). Eradication rates in the modified tetracycline dose group were 92.40% and in the standard groups, eradication rates were 93.20% for 750 mg twice daily group and 92.43% for 500 mg three times daily group, respectively, without statistical difference ($P = 0.959$). The incidence of adverse events was lower in the modified tetracycline dose (15.3% *vs* 32.3% and 29.4%; $P = 0.002$) compared to the standard dose group.

CONCLUSION

In a real-world experience, modified tetracycline dosing as part of tetracycline and furazolidone quadruple therapy for 14 d demonstrated high efficacy, comparable to standard tetracycline dose regimens, with a favorable safety profile.

Key Words: *Helicobacter pylori*; Tetracycline; Furazolidone; Eradication; Penicillin allergy; Bismuth quadruple therapy

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Core Tip: To our knowledge, this is the first real-world study to evaluate the efficacy and safety of modified dosing of tetracycline as part of tetracycline and furazolidone-containing bismuth quadruple therapy in patients with *Helicobacter pylori* infection.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is associated with the development of chronic gastritis, peptic ulcer, and gastric cancer. Approximately 75% of gastric cancers worldwide can be attributed to *H. pylori*-induced inflammation and injury[1]. China is in a geographic area with high prevalence of *H. pylori* infection which parallels to high incidence of gastric cancer. Prevalence of *H. pylori* infection is estimated to be as high as 50%, and the number of incident cases of gastric cancer accounts for about 44% all patients newly diagnosed with gastric cancer globally[2,3]. Following the recognition of *H. pylori* gastritis as an infectious disease in 2015, guideline recommend that all patients diagnosed with infection should receive eradication therapy. Unless there are competing considerations such as comorbidities, re-infection rates in their communities, competing health priorities of society and financial cost[4].

With the alarming rise in the prevalence of clarithromycin-resistant *H. pylori* infection, increased incidence of treatment failure has been observed[5,6]. In addition, other proposed causes of treatment failure of *H. pylori* eradication therapy include poor patient adherence, host genetics (low gastric pH and metabolism-enhancing phenotypes of CYP2C19), and high bacterial load[7,8]. A systematic review and meta-analysis that included data from 45 countries, found that secondary resistance rates by regions ranged from 15% to 67% for clarithromycin, 19% to 30% for levofloxacin, and 30% to 65% for metronidazole[9]. However, resistance rate remains low for tetracycline, generally occurring in less than 5%. The proportion of strains with dual resistance to tetracycline and furazolidone was 0.5%[10]. Given high efficacy, tetracycline-based bismuth quadruple therapy is the preferred first-line therapy in China [3]. All major society guidelines including Maastricht VI/Florence Consensus Report[11], Toronto Consensus[12], and American College of Gastroenterology guidelines[9] recommend tetracycline-based quadruple therapy as first-line therapy in areas with high (> 15%) prevalence of clarithromycin resistance or in patients with previous macrolide exposure.

Tetracycline exhibits activity against *H. pylori* by binding reversibly to a pocket in the 30S subunit of bacterial ribosomes containing 16S rRNA, causing bacteriostatic and bactericidal effects by inhibiting protein synthesis and bacterial growth[13]. Furazolidone is a nitrofurantoin antibiotic with activity against *H. pylori* with a high absorption and distribution profile[14]. Tetracycline and furazolidone-based quadruple therapies have achieved high eradication rates in China of 91.7% and 95.2% on intention-to-

treat (ITT) and per-protocol (PP) analyses[15]. However frequent dosing requirements (three to four times daily) and high incidence of antibiotic related adverse events have resulted in reduced adherence and treatment failure[15,16], limiting effectiveness in clinical practice.

The aim of the study is to compare the efficacy and safety of modified twice daily dosing of tetracycline compared to standard tetracycline, furazolidone-containing bismuth quadruple therapy in *H. pylori* infection patients. Our goal is to determine whether lower and simplified dosing of tetracycline can achieve similar eradication rate as standard tetracycline, furazolidone quadruple therapy in a real-world setting.

MATERIALS AND METHODS

Study design and participants

Consecutive patients age > 18 years of age who were diagnosed with *H. pylori* infection and received tetracycline, furazolidone-containing quadruple therapy for 14 d at Sir Run Run Shaw Hospital (Hangzhou, China) between October 2020 to December 2021 were identified. This study was approved by the Institutional Review Board of Sir Run Run Shaw Hospital, Medical School, Zhejiang University, Hangzhou (SRRSH: 2022-431).

All patients were diagnosed as *H. pylori* infection by positive ¹³C-urea breath test (UBT) and ¹³C-UBT was performed again one month after completion of the planned treatment. Patients who had prior use of PPI, bismuth, or antibiotics one month prior to initiation of tetracycline, furazolidone-containing quadruple therapy were excluded. Furthermore, patients who had previous surgical history of upper gastrointestinal diseases; pregnant, severe medical comorbidities, allergies to any component of the tetracycline, furazolidone-containing quadruple regimen, or incomplete information were excluded for the analysis.

Diagnosis of *H. pylori* infection and treatment regimen

H. pylori infection was diagnosed by positive ¹³C-UBT (75 mg ¹³C-urea, Shenzhen Zhonghe Headway Bio-Sci & Tech Co., Ltd.) and ¹³C collection time was 30 min. Eradication was defined as negative urea breath test (< 0.4%; 0.4% as the cutoff value) according to previous Chinese studies[17-19]. Three treatment groups consisting of tetracycline-furazolidone-PPI and bismuth for 14 d with differing doses and frequency of tetracycline administration were examined. Tetracycline was given as 500 mg twice daily in the modified tetracycline dose group, and 750 mg twice daily or 500 mg three times daily in the standard tetracycline dose group[3]. Tetracycline and furazolidone were prescribed half an hour after meals; proton pump inhibitors (PPIs) included esomeprazole, rabeprazole, lansoprazole, and pantoprazole, were given 30 min before morning and evening meals; colloidal bismuth pectin capsules and bismuth potassium citrate capsules were also prescribed 30 min before morning and evening meals. Specific drugs dosage information is as follows: Furazolidone 100 mg twice daily, colloidal bismuth pectin capsules 400 mg twice daily, bismuth potassium citrate capsules 600 mg twice daily, esomeprazole 20 mg twice daily, rabeprazole 10 mg twice daily, lansoprazole 30 mg twice daily, pantoprazole 20 mg twice daily.

Medication adherence and adverse events

¹³C-UBT result medication adherence and adverse events were obtained by reviewing electronic medical records and telephone surveys when patients were at completion of 14-d *H. pylori* therapy and 4 wk after completion of the treatment. Medication adherence was defined as poor when they had taken < 80% of the total medication.

Endpoint

The primary outcome was the eradication rate of *H. pylori* infection in each treatment group, the secondary endpoint was the incidence of adverse events and medication adherence rate.

Statistical analysis

Continuous variables were expressed as the mean ± SD, and categorical variables were expressed as numbers and percentages. Continuous variables were evaluated using one-way ANOVA and categorical variables using Pearson χ^2 or Fisher's exact test. Furthermore, adjusted for age, gender, education, smoking, alcohol drinking, hypertension, hyperlipidemia, diabetes, treatment line, bismuth type, PPI type, and treatment regimen into multivariate logistic regression model to identify independent risk factors associated with eradication failure. Two-sided $P < 0.05$ was considered significant. IBM SPSS Statistics SPSS 26.0 software (IBM Corp.) was used for all analysis.

RESULTS

Patients enrolled and baseline characteristics

During the study period, 394 patients received tetracycline, furazolidone-containing quadruple therapy for *H. pylori* infection met study criteria. The mean age was 46.3 ± 13.9 , male = 137 (34.8%), and 309 (78.4%) received treatment as primary therapy for *H. pylori* infection. Of the 85 patient who had prior *H. pylori* therapy, 72 (18.3%) had one and 13 (3.3%) had two or more previous therapies. Most common failed *H. pylori* regimens among those with available data included amoxicillin-furazolidone in 25 (34.7%) and furazolidone-clarithromycin in 8 (11.1%) (Supplementary Table 1).

In this study, eradication of *H. pylori* infection was successful in 365 patients and failed in 29 patients. Patients with successful or failed eradication did not differ between groups in demographic characteristics such as age, sex, smoking history, drinking history, educational background, and family history of gastric cancer. A total of 316 patients completed gastroscopy, of which 67.7% and 12.3% were endoscopy diagnosed with gastritis or peptic ulcer in the successful eradication group, respectively, with no difference between the two groups ($P = 0.597$). Pathological diagnosis of intestinal metaplasia was present in 30.9% and 24.1% of patients between the two groups, respectively, with no difference between groups ($P = 0.557$). A total of 157 patients received low-dose tetracycline and 237 patients received standard-dose tetracycline, including 118 and 119 patients in the 750 mg twice daily and 500 mg three times daily groups, respectively. There was no difference in the distribution of treatment regimens between eradication success or failure groups ($P = 0.959$). Initial treatment was achieved in 79.7% of patients in the eradication success group and 66.7% of patients in the failure group. Specific patient demographics and clinical data are presented in Table 1.

When stratified by tetracycline dose, 157 (39.8%) patients received modified tetracycline dose and 237 (60.2%) received standard tetracycline dose including 118 (49.8%) and 119 (50.2%) who received 750 mg b.i.d. and 500 mg t.i.d. dosing, respectively (Supplementary Table 2). Demographic data including age, gender, education, and alcohol/tobacco use were similar among the three groups (Supplementary Table 2). However, a higher proportion of patients who received modified tetracycline dose (87% vs 57% and 79%, $P = 0.003$) compared to standard tetracycline dose received primary therapy for *H. pylori*.

Eradication of *H. pylori* infection

The eradication rates in the modified tetracycline dose group were 92.4% compared to 93.2% in the 750 mg b.i.d. group and 92.4% in the 500 mg t.i.d. group without difference ($P = 0.959$).

Eradication of *H. pylori* infection as primary or rescue therapy: Of the 309 patients naïve to prior *H. pylori* treatment, eradication rates for those receiving 500 mg b.i.d., 750 mg b.i.d., and 500 mg t.i.d. dosing were 93.4%, 97.5%, and 92.6%, respectively, without difference ($P = 0.338$) (Table 2).

Of the 85 patients who had prior *H. pylori* treatment as rescue therapy, eradication rates for those receiving 500 mg b.i.d., 750 mg b.i.d., and 500 mg t.i.d. dosing were 85.7%, 84.6%, and 92.0%, respectively, with difference $P < 0.0001$.

Among subgroup of patients who previously received amoxicillin-furazolidone regimen, eradication rates for those receiving 500 mg b.i.d., 750 mg b.i.d., and 500 mg t.i.d. dosing were 83.3%, 88.2%, and 83.3%, respectively, without difference ($P = 0.918$) (Supplementary Table 1).

Eradication of *H. pylori* infection with penicillin allergy: Of the 76 (19.3%) patients with penicillin allergy, eradication rates for those receiving 500 mg b.i.d., 750 mg b.i.d., and 500 mg t.i.d. dosing were 91.7%, 95.5%, and 93.1% by ITT analysis, respectively, without difference ($P = 0.770$) (Table 3).

Of the 63 patients with penicillin allergy naïve to *H. pylori* therapy, eradication rates for those receiving 500 mg b.i.d., 750 mg b.i.d., and 500 mg t.i.d. dosing were 95.0%, 100%, and 90.0%, respectively, without difference ($P = 0.372$) (Supplementary Table 3).

Eradication rates of removing the discontinued treatment population: Of all 394 patients, a total of 14 discontinued treatment due to serious adverse events or arbitrarily, including 5, 3, and 6 in the three treatment groups, respectively. Five patients in the 500 mg twice daily group and six patients in the 500 mg three times daily group discontinued treatment due to adverse reactions, but eradication of *H. pylori* infection was eventually successful. Three patients in the 750 mg twice daily group discontinued treatment, and eventually two patients failed eradication therapy. After removing these 14 patients, the eradication efficacy of the population was re-counted. The eradication rates in the three treatment groups were 92.10% (140/152), 95.65% (109/115), and 92.04% (104/113), respectively, with no statistically significant difference ($P = 0.447$).

Of the 298 patients naïve to prior *H. pylori* treatment, eradication rates among those 500 mg b.i.d., 750 mg b.i.d., and 500 mg t.i.d. dosing were 93.1%, 97.4%, and 92.1%, respectively, without difference ($P = 0.310$). Of the 82 patients who had prior *H. pylori* treatment as rescue therapy, eradication rates those receiving 500 mg b.i.d., 750 mg b.i.d., and 500 mg t.i.d. dosing were 85.7%, 89.2%, and 91.7%, respectively, with difference $P < 0.0001$. Of the 75 patients with penicillin allergy, eradication rates those receiving 500 mg b.i.d., 750 mg b.i.d., and 500 mg t.i.d. dosing were 91.7%, 95.5%, and 93.1%, respectively, without difference ($P = 0.870$).

Table 1 Demographic and clinical data of patients according to eradication outcome

Outcome	Successful	Failed	P
N	365	29	
Age (mean ± SD)	45.90 ± 13.95	52.5 ± 12.2	0.319
Age range	(20-77)	(27-68)	
Age (≤ 50)	221	15	0.046
Gender (M/F)	122/243	44/74	0.685
Smoking (Yes/No)	31/334	5/29	0.168
Drinking (Yes/No)	61/304	8/29	0.138
Education			0.099
Primary school	61	19	
Middle school	138	40	
College	158	57	
GC family history			0.361
Yes/No	15/350	2/27	
Endoscopy diagnosis			0.597
Gastritis	247	22	
Ulcer	45	2	
Unknown	73	5	
Intestinal metaplasia			0.557
No	176	17	
Yes	113	7	
Unknown	76	5	
Treatment			0.959
500 mg b.i.d.	145	12	
750 mg b.i.d.	110	8	
500 mg t.i.d.	110	9	
Treatment line ¹			0.026
First line	291	18	
Rescue therapy	74	11	
PPI			0.762
Pantoprazole	151	14	
Esomeprazole	69	4	
Rabeprazole	139	11	
Lansoprazole	6	0	
Bismuth			0.351
Bismuth potassium citrate	302	22	
Colloidal bismuth pectin	63	7	
Type 2 diabetes	18	6	0.020
Hypertension	48	15	< 0.0001
Hyperlipidemia	19	7	< 0.0001
Penicillin allergy	70	6	0.843

¹Recording this treatment as start of frequency. Rescue therapy was defined as patients who had eradicated therapy once or more but failed. *P* values were from two-side comparisons the differences between two groups. M: male; F: female; 500 mg b.i.d.: Tetracycline twice daily; 750 mg b.i.d.: Tetracycline twice daily; 500 mg t.i.d.: Tetracycline three times daily.

Table 2 Treatment times previously of the enrolled patients and its eradication rates

Treatment times	500 mg b.i.d.	750 mg b.i.d.	500 mg t.i.d.
1	93.4% (127/136)	97.5% (77/79)	92.6% (87/94)
2	83.3% (15/18)	87.5% (28/32)	90.9% (20/22)
≥ 3	100% (3/3)	71.4% (5/7)	100% (3/3)
Rescue therapy ¹	85.7% (18/21)	84.6% (33/39)	92.0% (23/25)

¹Rescue therapy was defined as patients who had eradicated therapy once or more but failed. 500 mg b.i.d.: Tetracycline twice daily; 750 mg b.i.d.: Tetracycline twice daily; 500 mg t.i.d.: Tetracycline three times daily.

Table 3 Penicillin allergy of the enrolled patients and its intention-to-treat eradication rates

Penicillin allergy	500 mg b.i.d.	750 mg b.i.d.	500 mg t.i.d.
Yes	91.7% (22/24)	95.5% (21/22)	90.0% (27/30)
No	92.5% (123/133)	92.7% (89/96)	93.3% (83/89)

500mg b.i.d.: Tetracycline twice daily; 750 mg b.i.d.: Tetracycline twice daily; 500 mg t.i.d.: Tetracycline three times daily.

Medication adherence and adverse events

Of 394 patients, 380 (96.4%) demonstrated good adherence to prescribed therapy. Furthermore, 79 patients (20.1%) experienced at least one adverse event with a cumulative number of 98 adverse events during the treatment period (Table 4). Subsequently, 14 (3.6%) patients discontinued the treatment.

The rates of adverse events among those receiving 500 mg b.i.d., 750 mg b.i.d., and 500 mg t.i.d. dosing was 5.3%, 32.3%, and 30.3%, respectively. The incidence of adverse events in the modified dose group was lower than the standard dose group ($P = 0.002$). The most frequent adverse event was fever in 18 (4.7%), bitter taste in 16 (4.1%), nausea in 12 (3.0%), and rash in 10 (2.5%) (Table 4).

Predictors of failed *H. pylori* eradication

On univariate analysis, age > 50 years (OR = 1.821, 95%CI: 0.841-3.943, $P = 0.128$), male gender (OR = 2.314, 95%CI: 0.998-4.564, $P = 0.051$), smoking status (OR = 2.245, 95%CI: 0.800-6.296, $P = 0.124$), alcohol use (OR = 1.899, 95%CI: 0.804-4.484, $P = 0.144$), rescue therapy (OR = 2.403, 95%CI: 1.088-5.307, $P = 0.03$), type 2 diabetes (OR = 4.016, 95%CI: 1.373-11.752, $P = 0.011$), hyperlipidemia (OR = 6.937, 95%CI: 2.720-17.691, $P < 0.0001$), and hypertension (OR = 6.964, 95%CI: 3.163-15.333, $P < 0.0001$) were associated failed *H. pylori* eradication. On multivariate analysis model, hyperlipidemia (aOR = 3.697, 95%CI: 1.149-11.899, $P = 0.028$) and hypertension aOR = 7.885, 95%CI: 2.582-24.081, $P < 0.0001$) were associated with failed *H. pylori* eradication (Supplementary Table 4).

DISCUSSION

To our knowledge, this is the first real-world study to evaluate the effectiveness and safety of modified dosing of tetracycline as part of tetracycline and furazolidone-containing bismuth quadruple therapy in patients with *H. pylori* infection. Our study demonstrated high *H. pylori* eradication rates of in the modified tetracycline dose of utilizing tetracycline 500 mg twice daily were 92.4%, similar to standard dosing utilizing tetracycline 750 mg twice daily or 500 mg three times daily regimens. Furthermore, the incidence of adverse events was lower in the modified tetracycline dosing (15.3% vs 32.3% and 29.4%; $P = 0.002$) compared to the regimen with standard tetracycline dosing.

Previous studies demonstrated that tetracycline and furazolidone quadruple therapy provide high eradication rates of 91.7% and 95.2% per ITT and PP analysis[15]. A randomized trial performed China demonstrated robust eradication rates of tetracycline and furazolidone quadruple therapy, even as rescue therapy of 77.5% and 85.0% per ITT and PP analysis[16]. Lower eradication rates may be

Table 4 Drug adverse events in different treatment groups (n/N)

Group	500 mg b.i.d.	750 mg b.i.d.	500 mg t.i.d.	All	P
Taste distortion	2	6	8	16	0.060
Nausea	2	6	4	12	0.190
Abdominal pain	1	2	0	3	0.320
Vomiting	0	1	0	1	0.310
Bloating	3	0	1	4	0.290
Diarrhea	4	2	1	7	0.570
Dizziness	1	2	1	4	0.670
Skin rash	3	4	3	10	0.740
Fatigue	1	4	1	6	0.140
Fever	4	6	8	18	0.250
Constipation	1	1	0	2	0.630
Decreased appetite	0	3	7	10	0.009
Chills	0	1	0	1	0.310
Melena	0	0	1	1	0.310
Abdominal discomfort ¹	2	0	1	3	0.480
All ²	15.3% (24/157)	32.3% (38/118)	30.3% (36/119)	98/394	0.002

¹Abdominal discomfort, but not of specified.

²The symptoms of a single adverse reaction are counted as 1, and a patient may have multiple adverse events.

P values were from two-side comparisons the differences among three treatment group. N: Total patient number; n: Patient number with side effects; 500 mg b.i.d.: Tetracycline twice daily; 750 mg b.i.d.: Tetracycline twice daily; 500 mg t.i.d.: Tetracycline three times daily.

attributed to clinical or agricultural overuse of antibiotics in northwest China where the primary resistance rates of *H. pylori* for furazolidone and tetracycline reached 21.0% and 19.3% [10]. Another study using *Lactobacillus acidophilus* (1 g t.i.d.) for 2 wk followed by bismuth-containing quadruple regimen (tetracycline 750 mg b.i.d. + furazolidone 100 mg b.i.d.) for 10 d as rescue therapy in patients showed eradication rates of 92.0% and 91.8% in ITT and PP analysis, respectively, suggesting that patients with refractory infection may benefit from tetracycline-containing bismuth quadruple regimen therapy [20].

Tetracycline exert bacteriostatic activity by binding bacterial ribosome and inhibit protein synthesis [13]. Pharmacokinetic properties including time over MIC ($T > MIC$) and maximum concentration (C_{max}/MIC) are vital to antimicrobial activity of tetracycline leading to recommendations for frequent dosing regimens [21]. Interestingly our results demonstrated that tetracycline twice a day dosing was comparable to three times a day dosing. Our findings are consistent with a previous Korean study [22] that demonstrated that comparable high eradication rates of 93.9% with twice a day dosing of tetracycline comparable to four times a day dosing of 92.9% when maintaining a total tetracycline dose of 2 g a day utilizing tetracycline and metronidazole quadruple therapy. Furthermore, tetracycline concentrations in blood follow a plateau-shaped course with a slow rise and a slower drop, the serum half-life ($t_{1/2}$) being in the range 6 h to 10 h. Although sparse data, previous study demonstrated that tetracycline dose of 300 mg produced a consistent and robust areas under the serum time curves of $26.9 \text{ mg} \times \text{h/L} \pm 6.0 \text{ mg} \times \text{h/L}$ [23]. Our study demonstrated no appreciable difference in *H. pylori* eradication with tetracycline 750 mg and 500 mg twice daily dosing regimens. However, studies evaluating pharmacokinetics and pharmacodynamics of tetracyclines in *H. pylori* infection is limited and are mainly derived from treatment of primary or secondary syphilis [21].

Previously studied explored the optimal dose and interval of tetracycline as a component of tetracycline and furazolidone triple therapy for *H. pylori* infection. For example, an Iranian study of 52 patients receiving tetracycline 500 mg twice a day combined with furazolidone and PPI for 14 d resulted in an eradication rate of 96.3% with only occasional serious side effects [24]. Furthermore, a Chinese study of 60 patients evaluating 7-d therapy tetracycline 500 mg twice daily with furazolidone, ranitidine, and bismuth citrate demonstrated eradication rate of 85% in the ITT analysis and 91% in the PP analysis [25]. Studies evaluating tetracycline twice a day dosing as a component of tetracycline and metronidazole quadruple therapy resulted in high eradication rates of over 90% [22,26,27]. However, they were not comparative studies [22,27] or agents at doses different from that of standard BQT [26]. A

Korean study comparing tetracycline twice a day compared to four times a day as part of tetracycline and metronidazole quadruple therapy demonstrated eradication rate of 90.1%, similar to four times a day dosing but also similar adherence and incidence of adverse events (32.4% and 43.1%, $P = 0.254$) [28]. This study raised the possibility that dose reduction of tetracycline to improve adherence and reduce adverse events is possible while maintaining high eradication rates.

The minority (22.6%) of patients in our study population received tetracycline and furazolidone quadruple therapy for previous failed treatment. As expected, eradications appeared reduced among patients receiving rescue therapy. This may be related to development of resistance to furazolidone with recent study in China demonstrating alarming prevalence of 63.1% (736/1167) of furazolidone-resistance *H. pylori* strains among those who experienced prior treatment failure [29].

Safety of tetracycline-containing regimen have raised concern given high incidence of adverse events including gastrointestinal symptoms, allergies, asthma, and hemolytic anemia, loss of appetite, and severe liver injury. Early studies have reported impaired bone growth and maturation as well as deposition in teeth with tetracycline leading to avoidance of use in the pediatric population [30]. In previous studies evaluating tetracycline-containing bismuth quadruple regimens used as rescue therapy in penicillin-allergic patients, approximately one-third developed adverse events leading to discontinuation on therapy in tenth despite high (> 90%) eradication rates [15]. Standard dose of tetracycline in tetracycline and metronidazole regimens are generally lower than the doses utilize in tetracycline and furazolidone regimens given concern for compounded risk of adverse events associated with furazolidone. Our study confirmed that modified dosing and frequency of tetracycline as part of tetracycline and furazolidone therapy had a lower incidence of adverse events (15.3%) compared to the groups that received standard dosing (750 mg twice a day) or frequency (500 mg three times a day) of tetracycline of 32.3% and 29.4%, respectively. Previous studies showed similar incidence of overall adverse events (26%-32%) with *H. pylori* therapy containing standard dosing of 500 mg three times a day [15,16]. Furthermore, 14 (3.6%) patients discontinued therapy due to adverse reactions including 5 in the 500 mg twice a day group (3.2%). Previous studies have suggested as development of serious adverse effects of furazolidone (*i.e.*, fever, fatigue, and dizziness) led to discontinuation of the therapy related to high dose (*i.e.*, 200 mg twice a day) or longer duration (> 7 d) of therapy [31-33]. A recent randomized trial demonstrated that furazolidone had higher incidence of adverse events (37.6% vs 20.2%; $P = 0.003$) compared to tetracycline containing amoxicillin quadruple therapy [34]. Although unclear, some of the adverse events in the study are likely driven by the use of furazolidone rather than tetracycline.

There were limitations in our study mostly related to retrospective study design. Although categorized tetracycline and furazolidone doses were consistent across groups, variation in bismuth and PPI types and dose were observed. The differences in pharmacodynamic effects of different PPIs driven by CYP2C19 genetic polymorphism and higher proportion of patients receiving standard compared to modified dosing of tetracycline among those receiving rescue therapy may have introduced bias in the results. The treatment and eradication testing time taken in this study was 4 wk apart, but many previous studies have suggested that more accurate results can be obtained with a duration of 6-8 wk [35], and shorter testing intervals may have an impact on the results. Furthermore, lack of *H. pylori* culture and antibiotic sensitivity testing precluded determine for reasons for failed therapy.

CONCLUSION

Modified tetracycline dosing as a component of tetracycline and furazolidone quadruple therapy for 14 d demonstrated high and comparable *H. pylori* eradication rate while reducing the incidence of adverse events compared to standard tetracycline dose regimen. Randomized controlled studies comparing difference doses of tetracycline as a component of tetracycline and furazolidone quadruple therapy are needed to confirm our findings in patients with *H. pylori* infection.

ARTICLE HIGHLIGHTS

Research background

Although highly effective as a component of *Helicobacter pylori* (*H. pylori*) treatment regimen, tetracycline is associated with a high incidence of medication-related adverse events. Modified dosing of tetracycline as part of quadruple therapy may improve safety while providing comparable eradication rates.

Research motivation

To evaluate the efficacy and safety of modified dosing of tetracycline in a quadruple therapy in patients with *H. pylori* infection.

Research objectives

To compare the efficacy and safety of modified twice daily dosing of tetracycline compared to standard tetracycline, furazolidone-containing bismuth quadruple therapy in *H. pylori* infection patients. Our goal is to determine whether lower and simplified dosing of tetracycline can achieve similar eradication rate as standard tetracycline, furazolidone quadruple therapy in a real-world setting.

Research methods

Consecutive patients (10/2020-12/2021) who received tetracycline and furazolidone quadruple therapy for *H. pylori* infection at Sir Run Run Shaw Hospital were identified. All patients received tetracycline, furazolidone, proton pump inhibitor, and bismuth for 14 d as primary or rescue therapy. Statistical analysis was applied to analyze the eradication rate and the occurrence of adverse events in this population.

Research results

Eradication rates in the modified tetracycline dose group were 92.40% and in the standard groups, eradication rates were 93.20% for 750 mg twice daily group and 92.43% for 500 mg three times daily group, respectively, without statistical difference ($P = 0.959$). The incidence of adverse events was lower in the modified tetracycline dose (15.3% *vs* 32.3% and 29.4%; $P = 0.002$) compared to the standard dose group.

Research conclusions

In a real-world experience, modified tetracycline dosing as part of tetracycline and furazolidone quadruple therapy for 14 d demonstrated high efficacy, comparable to standard tetracycline dose regimens, with a favorable safety profile.

Research perspectives

Randomized controlled studies comparing difference doses of tetracycline as a component of tetracycline and furazolidone quadruple therapy are needed to confirm our findings in patients with *H. pylori* infection.

FOOTNOTES

Author contributions: Yingchao Sun, Mengjia Zhu and Xueqin Chen have contributed equally to this work. Sun YC and Hu WL contributed to conceptualization; Sun YC and Wang XJ contributed to writing-original draft preparation; Zhu MJ and Yue L contributed to writing; Chen XQ, Zhao YR, and Zhu MJ contributed to review and editing; Kim JJ contributed to manuscript polishing; Hu WL contributed to supervision; and all authors have read and agreed to the published version of the manuscript.

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