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ORIGINAL RESEARCH

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Sequential therapy versus quadruple therapy for *Helicobacter pylori* eradication: A prospective double-blinded randomized controlled trial

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Abstract

Backgrounds and Aims: This controlled randomized clinical trial was designed to compare effectiveness, side effects, and severity of symptoms before and after therapy between quadruple (QT) and sequential regimens (SQ) for *Helicobacter Pylori* (*H. pylori*).

Methods: Patients were randomly allocated into two groups. Group A received a 14-day QT including pantoprazole 40 mg q12 h, bismuth subcitrate 240 mg q12 h, clarithromycin 500 mg q12 h, and amoxicillin 1000 mg q12 h and group B received ST including pantoprazole 40 mg q12 h and amoxicillin 1000 mg q12 h for the initial 5 days followed by pantoprazole 40 mg q12 h, clarithromycin 500 mg q12 h and tinidazole 500 mg q12 h for the next 5 days. Adverse drug reactions and patients' compliance were assessed after finishing the treatment course and also 4 weeks after. All patients were naive, therefore ST and QT were first-line therapies. To evaluate severity of symptoms we used Short-Form Leeds Dyspepsia Questionnaire (SF-LDQ) before taking the first dose of regimens, at the end of therapy, and also 4 weeks after (follow-up).

Results: The mean age in Group A ($n = 83$) was 48.55 ± 12.56 and 47.24 ± 12.78 in Group B ($n = 79$). No statistically significant differences were observed between the two groups regarding age, gender, endoscopic findings, and also eradication rate. The analysis demonstrated a significant decrease in SF-LDQ score between baseline and after therapy and baseline and follow-up in both regimen groups. Both regimens were well tolerated by the majority of patients, and there were no significant differences between the two groups in terms of adverse drug reactions

Conclusion: This study showed that ST can be used as an alternative first-line therapy to QT in patients with *H. pylori* infection.

KEYWORDS

Helicobacter pylori, eradication, quadruple, sequential

1 | INTRODUCTION

Helicobacter pylori (*H. pylori*) plays a major role in the development of gastric diseases, including acute and chronic gastritis, peptic ulcer disease, and gastric cancer and eradication of this infection facilitates the treatment of these diseases and minimizes their complications.[1–3] Common recommended treatment regimens for eradication of *H. pylori* include triple therapy consisting of amoxicillin, clarithromycin, or metronidazole, and proton pumps inhibitors (PPI).[4–6] However successful eradication of *H. pylori* has been declining globally possibly due to increasing drug resistance rates, and therefore new regimens have been explored to increase successful treatment.[7,8] In Iran, bacterial resistance to clarithromycin, metronidazole, and amoxicillin is reported 28%–34%, 37%–78%, and 10%, respectively.[9,10] In such countries with higher rates of antibiotic resistance, quadruple therapy (QT) with PPI, Bismuth, amoxicillin, and clarithromycin for 14 days is considered as first-line treatment regimen.[11] Another contributing factor to the failure of these regimens may be patients' compliance due to major antimicrobial side effects and prolonged treatment course. Moreover, discontinuation of therapy may lead to the development of drug resistance.[12]

Sequential therapy (ST) is an alternative treatment regimen for *H. pylori* eradication and consists of PPI and amoxicillin for the first 5 days, followed by PPI clarithromycin and tinidazole for the next 5 days. This regimen has been shown to be highly curative and superior to standard PPI-based triple therapy by several randomized clinical trials (RCTs) and meta-analyses.[13–15] A meta-analysis based on six RCTs demonstrated that ST has an eradication rate of 79.4% in ITT analysis and 86.4% in PP analysis.[16] Use of this regimen may decrease adverse drug effects because of ST than simultaneous administration of antibiotics and therefore may improve patient adherence to therapy.

There is scant data supporting the efficacy of ST as an alternative strategy to QT, especially in regions such as Iran. We want to answer the question can the ST replace QT? Therefore this randomized clinical trial was designed to compare the effectiveness, side effects, and severity of symptoms before and after therapy between these two regimens.

2 | METHODS

2.1 | Study design and patients

This study was a prospective, double-blinded randomized controlled trial conducted at Isfahan University of Medical Sciences, Isfahan, Iran, between September 2018 and June 2020. Patients who were referred to outpatient gastrointestinal clinics with symptoms of dyspepsia, nausea and vomiting, abdominal pain, and postprandial fullness who underwent upper gastrointestinal endoscopy with confirmed *H. pylori* infection by a positive urease test were included in the study. Exclusion criteria were as follows: age under 18, history of using PPI, h2 blockers and antibiotics taken within the prior 4 weeks, previous eradication of *H. pylori* infection, previous gastric surgery, contraindications or adverse reactions to the study drugs, NSAIDS assumption, MALToma, Zollinger–Ellison syndrome and other gastrointestinal cancers, abnormal liver or kidney function and other concurrent infections requiring antibiotic administration.

The trial was approved by the ethics committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1399.264). It was conducted according to Declaration of Helsinki and subsequent revisions and was registered at the Iranian of clinical trials (IRCT20171230038142N20). The written informed consent was previously obtained from all patients.

2.2 | Randomization and treatment

The sample size of 169 eligible patients was included in the study, and one patient declined to participate (Figure 1). Then, randomization was carried out by Blocks of 4, and enrolled patients after giving informed consent, were randomly allocated into two groups; Group A received a 14-day QT including pantoprazole 40 mg q12 h, bismuth subcitrate 240 mg q12 h, clarithromycin 500 mg q12 h and amoxicillin 1000 mg q12 h and Group B received ST including pantoprazole 40 mg q12 h and amoxicillin 1000 mg q12 h for the initial 5 days followed by pantoprazole 40 mg q12 h, clarithromycin 500 mg q12 h and tinidazole 500 mg q12 h for the next 5 days. The confirmation of *H. pylori* eradication was performed by stool antigen test 4 weeks after treatment.

Adverse drug reactions and patients' compliance were assessed after finishing the treatment course and also 4 weeks after. To evaluate severity of symptoms we used Short-Form Leeds Dyspepsia Questionnaire (SF-LDQ) before taking the first dose of regimens, at the end of therapy, and 4 weeks after (follow-up). All patients were naïve, therefore ST and QT were first-line therapies.

The SF-LDQ contains four questions from the LDQ. Each question comprises two stems concerning the frequency and severity of each symptom during the last 2 months, including indigestion, heartburn, regurgitation, and nausea. It also contains a single question concerning the most troublesome symptom experienced by the patient to enable categorization of patients on the basis of predominant heartburn or epigastric pain. The SF-LDQ scores were calculated using a summed total score of the frequency and severity responses for each symptom (range: 0–32). The questionnaire has been internationally validated.[17]

2.3 | Statistical analyses

Following data collection, data were entered into SPSS (version 26.0; SPSS Inc.). Descriptive statistics, including mean, standard deviation, and frequency, were used to describe the results. The variables were compared between the two groups using Chi-square and Fisher exact tests were used for categorical variables and student's *t*-test and Mann–Whitney *U*-test for parametric and nonparametric variables,

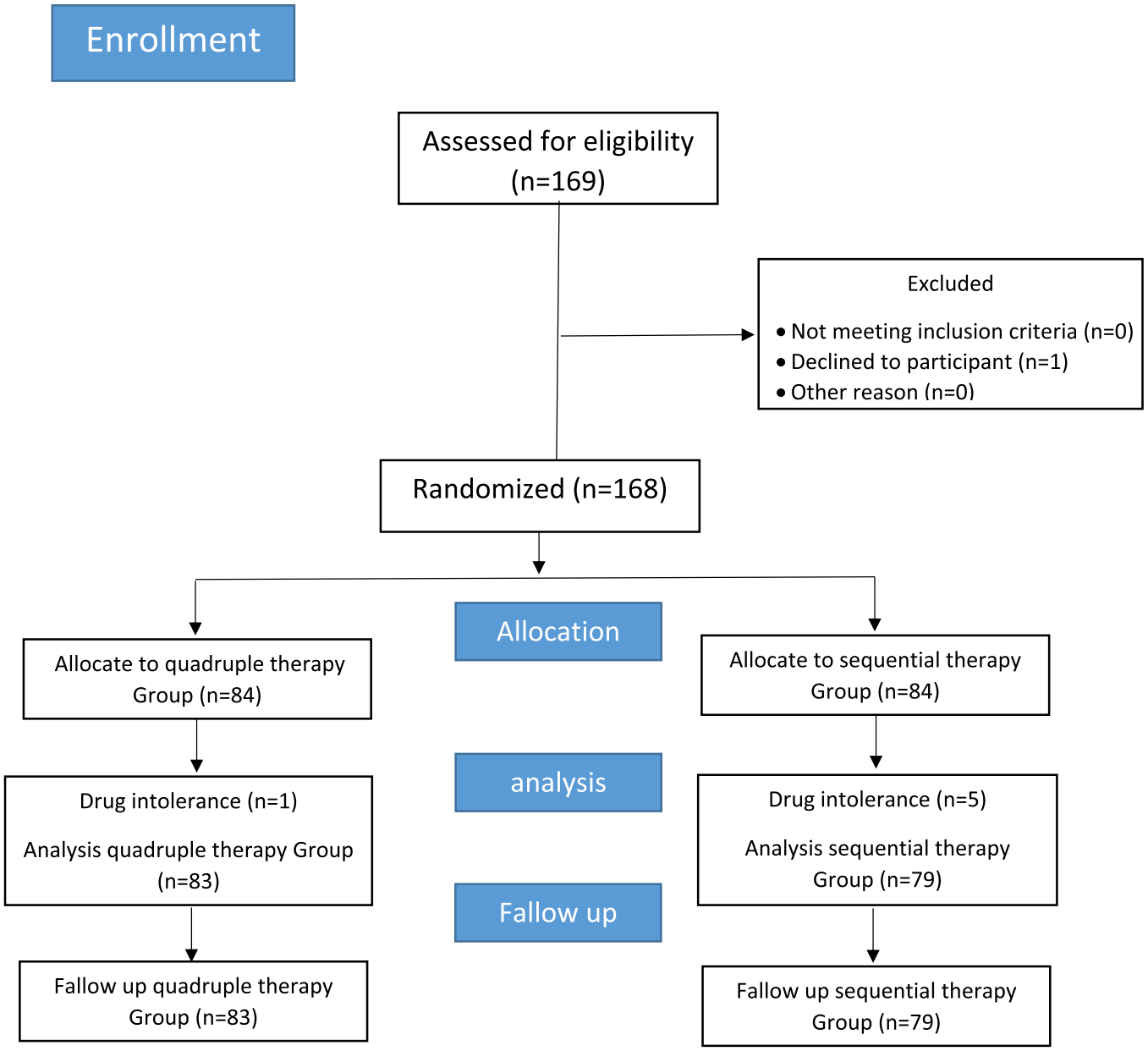

FIGURE 1 The process of the study according to the CONSORT flow diagram.

respectively. Also, a paired sample *t*-test and analyze of covariance (ANCOVA) were used. The significance level was considered <0.05 in all tests and whether tests were two-sided.

3 | RESULTS

In total, 168 patients with *H. pylori* infection were included in the study and randomly assigned to either Group A (QT) or Group B (ST). A total of six patients were excluded from the study due to poor compliance, therefore, 83 patients in Group A and 79 patients in Group B completed the follow-up. The mean age in Group A was 48.55 ± 12.56 and 47.24 ± 12.78 in Group B. In a quadruple group, 60 patients (72.3%) were females, and in the sequential group, 52 patients (65.8%) were females. No statistically significant differences were observed between the two groups regarding age and gender with *p*-values of 0.51 and 0.37, respectively. Endoscopic findings were as follows: normal, gastropathy, erosive duodenopathy, erosive gastroduodenopathy, gastric or duodenal ulcer, and sliding hiatal hernia. There were no significant differences in endoscopic findings between the two groups (Table 1).

The eradication rate in the QT group was 86.1%, while in the ST group was 81.6%, with no statistically significant difference between the two regimens (*p*-value = 0.45) (Table 2).

The severity of symptoms was evaluated using SF-LDQ questionnaire at the start of therapy (baseline), at the end of therapy (after therapy), and 4 weeks later (follow-up). The mean difference was calculated once between baseline and after therapy and once

TABLE 1 Baseline characteristics of the subjects.

	QT (*n* = 83)	SQT (*n* = 79)	*p*-Value	Mean diff (CI 95%)
Gender, *n* (%)			0.37	-
Male	23 (27.7)	27 (34.2)		
Female	60 (72.3)	52 (65.8)		
Age (mean ± SD), years	48.55 ± 12.56	47.24 ± 12.78	0.51	1.31 (−2.62 to 5.24)
Endoscopic finding, *n* (%)			0.15	-
Normal	5 (6)	3 (3.8)		
Antral gastropathy	36 (43.4)	36 (45.6)		
Other gastropathy	16 (19.2)	11 (13.9)		
Erosive duodenopathy	2 (2.4)	5 (6.3)		
Erosive gastroduodenopathy	5 (6)	1 (1.3)		
Gastric ulcer	3 (3.6)	1 (1.3)		
Duodenal ulcer	13 (15.6)	9 (11.7)		
Sliding hiatal hernia	3 (3.6)	9 (11.7)		
Others	0	4 (5.2)		

Abbreviations: CI, confidence interval; QT, quadruple therapy; SD, standard deviation; ST, sequential therapy.

TABLE 2 Eradication rates of *Helicobacter pylori* in ST and QT groups and SF-LDQ scores for severity of symptoms.

	QT (*n* = 83)	SQT (*n* = 79)	*p*-Value (CI 95%)
Eradication rate (%)	86.1	81.6	0.45***
SF-LDQ score			
Baseline	9.41 ± 3.45	8.69 ± 3.42	
	9 (4, 2)*	1(0, 11)*	
After therapy	1.61 ± 1.75	1.92 ± 1.75	
	8 (4, 19)*	2 (0, 9)*	
Mean difference (with baseline) (CI 95%)	−7.8 ± 0.35 (−8.88, −7.54)	−6.77 ± 0.37 (−7.43, −3.23)	0.087****
p-Value**	*p* < 0.001	*p* < 0.001	
Follow-up	*1.45* ± 1.81	1.8 ± 2.13	
	1 (0, 9)*	1 (0, 12)*	
Mean difference (with baseline) (CI 95%)	−7.96 ± 0.38 (−8.67, −0.612)	−6.9 ± 0.39 (−7.72, −4.56)	0.13****
p-Value**	*p* < 0.001	*p* < 0.001	

Abbreviations: CI, confidence interval; QT, quadruple therapy; SD, standard deviation; SF-LDQ, Short-Form Leeds Dyspepsia Questionnaire; ST, sequential therapy.

*Median (min, max),

**Resulted from paired sample *t*-test,

***Resulted from chi-squared test,

****Resulted from ANCOVA; adjustment was made for baseline values.

between baselines and follow-up. Results from paired sample *t*-test demonstrated a significant decrease in SF-LDQ score between baseline and after therapy and baseline and follow-up in both regimen groups (Table 2). Also, results from ANCOVA demonstrated no significant difference between the two groups in terms of a decrease in the severity of symptoms (Table 2).

Adverse drug reactions were assessed once after the end of therapy and once 4 weeks later (follow-up). Both regimens were well

TABLE 3 Adverse drug reactions.

	QT	ST	*p*-Value
Bitter taste, *n* (%)			
After therapy	Mild 13 (15.7)	Mild 9 (11.4)	
	Moderate 11 (13.3)	Moderate 16 (20.3)	0.50
	Severe 7 (8.4)	Severe 4(5.1)	
	Drug cessation 0	Drug cessation 0	
Follow up	Mild 2 (2.4)	Mild 0	
	Moderate 0	Moderate 0	0.39
	Severe 0	Severe 0	
	Drug cessation 0	Drug cessation 0	
Nausea, *n* (%)			
After therapy	Mild 6 (7.2)	Mild 6 (7.6)	
	Moderate 2 (2.4)	Moderate 4 (5.1)	0.73
	Severe 2 (2.4)	Severe 1 (1.3)	
	Drug cessation 0	Drug cessation 0	
Follow up	Mild 1 (1.2)	Mild 2 (2.5)	
	Moderate 1 (1.2)	Moderate 0	
	Severe 0	Severe 0	0.63
	Drug cessation 0	Drug cessation 0	
Vomiting, *n* (%)			
After therapy	Mild 3 (3.6)	Mild 5 (3.1)	
	Moderate 1 (1.2)	Moderate 1 (0.6)	0.55
	Severe 0	Severe 0	
	Drug cessation 0	Drug cessation 0	
Follow up	Mild 1 (1.2)	Mild 0	
	Moderate 0	Moderate 0	
	Severe 0	Severe 0	0.51
	Drug cessation 0	Drug cessation 0	
Anorexia, *n* (%)			
After therapy	Mild 8 (9.6)	Mild 5 (6.3)	
	Moderate 1 (1.2)	Moderate 2 (2.5)	0.75
	Severe 1 (1.2)	Severe 1 (1.3)	
	Drug cessation 0	Drug cessation 0	
Follow up	Mild 1 (1.2)	Mild 0	
	Moderate 0	Moderate 0	
	Severe 0	Severe 0	0.51
	Drug cessation 0	Drug cessation 0	
Abdominal discomfort, *n* (%)			
After therapy	Mild 3 (3.6)	Mild 5 (6.3)	
	Moderate 3 (3.6)	Moderate 3 (3.8)	0.79
	Severe 3 (3.6)	Severe 2 (2.5)	
	Drug cessation 0	Drug cessation 0	

(Continues)

TABLE 3 (Continued)

	QT	ST	*p*-Value
Follow up	Mild 1 (1.2)	Mild 2 (2.5)	
	Moderate 0	Moderate 0	
	Severe 0	Severe 0	0.67
	Drug cessation 0	Drug cessation 0	
Diarrhea, *n* (%)			
After therapy	Mild 4 (4.8)	Mild 3 (3.8)	
	Moderate 2 (2.4)	Moderate 1 (1.3)	0.50
	Severe 2 (2.4)	Severe 0	
	Drug cessation 0	Drug cessation 0	
Follow up	Mild 0	Mild 0	
	Moderate 0	Moderate 0	
	Severe 0	Severe 0	0.53
	Drug cessation 0	Drug cessation 0	
Constipation, *n* (%)			
After therapy	Mild 4 (4.8)	Mild 2 (2.5)	
	Moderate 6 (7.2)	Moderate 2 (2.5)	0.23
	Severe 0	Severe 2 (2.5)	
	Drug cessation 0	Drug cessation 0	
Follow up	Mild 1 (1.2)	Mild 2 (2.5)	
	Moderate 1 (1.2)	Moderate 0	
	Severe 1 (1.2)	Severe 0	0.61
	Drug cessation 0	Drug cessation 0	
Skin rash, *n* (%)			
After therapy	Mild 1 (1.2)	Mild 0	
	Moderate 0	Moderate 0	0.40
	Severe 0	Severe 0	
	Drug cessation 1 (1.2)	Drug cessation 0	
Follow up	Mild 0	Mild 0	
	Moderate 0	Moderate 0	
	Severe 0	Severe 0	0.53
	Drug cessation 0	Drug cessation 0	
Epigastric pain, *n* (%)			
After therapy	Mild 4 (4.8)	Mild 1 (1.3)	
	Moderate 1 (1.2)	Moderate 1 (1.3)	0.33
	Severe 1 (1.2)	Severe 0	
	Drug cessation 0	Drug cessation 2 (2.5)	
Follow up	Mild 3 (3.6)	Mild 1 (1.3)	
	Moderate 0	Moderate 0	
	Severe 0	Severe 0	0.52
	Drug cessation 0	Drug cessation 0	

Abbreviations: QT, quadruple therapy; ST, sequential therapy.

tolerated by the majority of patients. The most frequent side effect was a bitter taste, and other complications were nausea/vomiting, diarrhea, constipation, abdominal discomfort, skin rash, and epigastric pain. Three patients were not able to complete the therapy due to adverse drug reactions. There were no significant differences between the two groups in terms of adverse drug reactions (Table 3).

4 | DISCUSSION

Treatment of *H. pylori* still remains a challenge for clinicians, and no current first-line therapies are able to eradicate the infection in all treated patients. Current international guidelines advise *H. pylori* eradication for several clinical conditions. The ideal treatment able to cure all infected patients is not currently available. In this study, we compared the efficacy of QT and ST for eradication of *H. pylori* infection in Isfahan city, which is located in the center of Iran. The efficacy of ST as the first-line treatment in the eradication of *H. pylori* infection has been indicated in previous studies.[18–20] However, there is scant data supporting the efficacy of ST as an alternative strategy to QT, especially in regions such as Iran.

In a study on 357 cases in China, Liu et al.[21] indicated that eradication rates based on ITT in 10-day ST and modified Bismuth-contained QT were 95.2% and 98.8%, respectively, and based on PP, eradication rates were 84.9% and 92.7%, respectively. Masjedizadeh et al. reported the success rate of ST in South West Iran, comparable with QT. In this study, the QT group received omeprazole, bismuth subcitrate, tetracycline, and metronidazole.[22] In the study by Munteanu et al.[23] ST was noninferior to the standard of care QT in achieving *H. pylori* eradication, and also better compliance and fewer adverse effects were reported in the ST group. QT regimen included PPI, bismuth, metronidazole, and tetracycline/doxycycline.

In a study by Aminian et al.[24] 428 patients in Rasht city in the north of Iran with dyspepsia were included and the efficacy of four different *H. pylori* eradication regimens were assessed. The regimens were as follows: The QT group received omeprazole, amoxicillin, metronidazole, and bismuth for 14 days. The standard triple therapy group received omeprazole, amoxicillin, and clarithromycin, for 10 days. Ciprofloxacin-based triple therapy groups were given omeprazole and amoxicillin, both twice daily for 14 days, and ciprofloxacin twice a day for the first 7 days. The last group received 10 days ST with omeprazole and amoxicillin for 5 days and omeprazole, clarithromycin, and metronidazole all for the remaining 5 days. This trial showed standard 10-day triple therapy had the highest success rate while QT was the second most successful regimen. ST was not found to be an acceptable treatment option in this study.[24]

Hajian et al. compared 10-day ST to receive pantoprazole, amoxicillin, levofloxacin, and tinidazole with 14 days QT group to receive pantoprazole, clarithromycin, bismuth subcitrate, and amoxicillin. This trial revealed levofloxacin base ST does not have any advantage in comparison with QT.[25]

There are some limitations in our study that should be concerned. The absence of local antimicrobial resistance patterns is the most important limitation, therefore, results of this study may not be applicable to those who have recurrent infections. Second, some variables could not be included in the study due to availability, including socioeconomic status and smoking exposure. For a better understanding of the limitations and benefits of the two regimens in the eradication of *H. pylori* infection, further studies with bigger sample sizes are recommended.

5 | CONCLUSION

Our results indicated that there is no significant difference in eradication rates of *H. pylori* infection between the two regimens. Also, a small proportion of our cases reported adverse drug effects, but there was no significant difference between the two groups. Based on the results of this study, both regimens can significantly decrease the severity of symptoms regarding *H. pylori* infection with no significant difference between the two regimens. We recommend ST in patients who cannot tolerate QT with equal efficacy.

AUTHOR CONTRIBUTIONS

Elham Tabesh: Conceptualization; investigation; methodology; supervision; writing—original draft; writing—review & editing. **Farzad Yadmehr**: Investigation; writing—original draft; writing—review & editing. **Awat Feizi**: Formal analysis. **Farzin Khorvash**: Conceptualization. **Setayesh Sindarreh**: Formal analysis. **Atousa Hakamifard**: Conceptualization; writing—original draft; writing—review & editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. The author had full access to all of the data in this study and took complete responsibility for the integrity of the data and the accuracy of the data analysis.

ETHICS STATEMENT

The study was approved by the ethics committee of Isfahan University of Medical Sciences (ethics code: IR.MUI.MED.REC.1399.264).

TRANSPARENCY STATEMENT

The lead author Atousa Hakamifard affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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