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RAPID COMMUNICATION

Triple, standard quadruple and ampicillin-sulbactam-based quadruple therapies for *H pylori* eradication: A comparative three-armed randomized clinical trial

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Abstract

AIM: To compare the effectiveness of triple, standard quadruple and ampicillin-sulbactam-based quadruple therapies for *H pylori* eradication in a comparative three-armed randomized clinical trial.

METHODS: A total of 360 *H pylori*-positive patients suffering from dyspepsia and aging 24-79 years with a median age of 42 years were enrolled in the study and randomly allocated into the following three groups: group A (n = 120) received a standard 1-wk triple therapy (20 mg omeprazole b.i.d., 1000 mg amoxicillin b.i.d., 500 mg clarithromycin b.i.d.); group B (n = 120) received a 10-d standard quadruple therapy (20 mg omeprazole b.i.d., 1000 mg amoxicillin b.i.d., 240 mg colloidal bismuth subcitrate b.i.d., and 500 mg metronidazole b.i.d.); group C (n = 120) received the new protocol, i.e. 375 mg sultamicillin (225 mg ampicillin plus 150 mg sulbactam) b.i.d. (before breakfast and dinner), instead of amoxicillin in the standard quadruple therapy for the same duration. Chi-square test with the consideration of $P < 0.05$ as significant was used to compare the eradication rates by intention-to-treat and per-protocol analyses in the three groups.

RESULTS: The per-protocol eradication rate was 91.81% (101 patients from a total of 110) in group A, 85.84% (97 patients from a total of 113) in group B, and 92.85% (104 patients from a total of 112) in group C. The intention-to-treat eradication rate was 84.17% in group A, 80.83% in group B, and 86.67% in group C. The new protocol yielded the highest eradication rates by both per-protocol and intention-to-treat analyses followed by the standard triple and quadruple regimens, respectively. However, the differences were not statistically significant between the three groups.

CONCLUSION: The results of this study provide further support for the equivalence of triple and quadruple therapies in terms of effectiveness, compliance and side-effect profile when administered as first-line treatment for *H pylori* infection. Moreover, the new protocol using ampicillin-sulbactam instead of amoxicillin in the quadruple regimen is a suitable first-line alternative to be used in regions with amoxicillin-resistant *H pylori* strains.

Key words: Triple therapy; Quadruple therapy; Ampicillin-sulbactam; *H pylori*

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INTRODUCTION

H pylori is responsible for the majority of peptic ulcer diseases and its eradication leads to the cure of such diseases, thereby eliminating the need for surgical treatment. Eradication of *H pylori* is indicated in the management of dyspepsia in patients under the age of 45 years without alarm symptoms (the 'test and treat' strategy) and also serves as a preventive treatment in precursor lesions of gastric cancer.

According to the Maastricht 2 guidelines, first-line eradication is triple therapy with the use of a proton-pump inhibitor b.i.d., 1 g amoxicillin b.i.d., and 500 mg clarithromycin b.i.d. In the case of penicillin allergy, 500 mg metronidazole b.i.d. is substituted for amoxicillin. When first-line *H pylori* eradication fails, a second-line treatment of quadruple therapy, with a proton-pump inhibitor b.i.d., colloidal bismuth subcitrate q.i.d., 500 mg metronidazole t.i.d., and 500 mg tetracycline q.i.d, is recommended.

Antibiotic resistance is the main cause of failure for *H pylori* eradication and bata-lactamase produced

by resistant *H pylori* strains is a possible mechanism underlying the ineffectiveness of an amoxicillin-based triple or quadruple therapy[1]. Of the 153 clinical isolates of *H pylori* found in a previous study, 71.9% are resistant to amoxicillin, 77.8% to metronidazole, and 39.2% to both[2]. The resistance rate to clarithromycin is currently 2%-30%[3]. Consequently, new treatment modalities have recently emerged to overcome antibiotic resistance[4]. However, comprehensive comparisons of the effectiveness of traditional and new treatment modalities are lacking in the literature.

Antibacterial activities of beta-lactamase inhibitors such as clavulanic acid and sulbactam have been demonstrated in a number of *in vitro* studies[5,6]. However, using clavulanic acid associated with amoxicillin has not significantly increased the *H pylori* eradication rate *in vivo*[7,8]. The aim of this study was to compare the effectiveness of the following therapeutic regimens (triple therapy, standard amoxicillin-based quadruple therapy, ampicillin-sulbactam-based quadruple therapy) in eradicating *H pylori* in a three-armed randomized clinical trial for the first time.

MATERIALS AND METHODS

Patients and medications

A total of 360 *H pylori*-positive patients suffering from dyspepsia and aging 24-79 years with a median age of 42 years were enrolled in the study. *H pylori* status was determined by rapid urease test at entry. After giving written informed consent, the patients were randomly allocated into three groups: group A (n = 120) received a standard 1-wk triple therapy (20 mg omeprazole b.i.d., 1000 mg amoxicillin b.i.d., 500 mg clarithromycin b.i.d.); group B (n = 120) received a 10-d standard quadruple therapy (20 mg omeprazole b.i.d., 1000 mg amoxicillin b.i.d., 240 mg colloidal bismuth subcitrate b.i.d., and 500 mg metronidazole b.i.d.); group C (n = 120) received 375 mg sultamicillin (225 mg ampicillin plus 150 mg sulbactam, purchased from Pfizer SA, Case Postale, 8048 Zurich, Switzerland) b.i.d. (before breakfast and dinner), instead of amoxicillin in the standard quadruple therapy for the same duration. *H pylori* eradication was confirmed by C^{14}-urea breath test following 6 wk from the end of therapy.

All patients were contacted periodically, asked about the occurrence of possible side effects, and appropriate guidance was provided when needed. Those who were lost to follow up, or used antibiotics in the time period between the end of therapy and post-treatment urea breath test, or could not complete the treatment course because of severe side effects, were excluded in the per-protocol analysis.

Statistical analysis

The study was a three-armed randomized clinical trial with groups A, B and C including 110, 113 and 112 patients for the final statistical analysis (per-protocol analysis). In addition, intention-to-treat analysis was also performed. Chi-square test was used to compare the eradication rates by intention-to-treat as well as per-protocol analyses in the three groups. $P < 0.05$ was considered statistically significant.

Table 1 Demographic and clinical data of patients who completed the treatment

	Group A (Triple therapy)	Group B (Quadruple therapy)	Group C (New protocol)
Patients (*n*)	110	113	112
Male, *n* (%)	57 (52)	60 (53)	62 (55)
Female, *n* (%)	53 (47)	53 (47)	50 (45)
Age range (yr)	28-79 (median 41)	24-47 (median 39)	31-68 (median 47)
Minor side effects, *n* (%)	6 (5)	5 (4)	12 (11)
Overall eradication (*n*)	101	97	104
Intention-to-treat (%)	84.17	80.83	86.67
Per-protocol (%)	91.81	85.84	92.85

RESULTS

Five patients in group A, 3 in group B, and 4 in group C were lost to follow up. Four patients in group A, 2 in group B, and 4 in group C used antibiotics in the time period between the end of therapy and post-treatment urea breath test. One patient in group A and 2 in group B discontinued the regimen due to severe allergic reactions. Minor side effects were experienced by 6 patients in group A (vomiting, skin rash and abdominal pain), 5 patients in group B (vomiting, skin rash and pruritis) and 12 patients in group C (vomiting, diarrhea, headache, skin rash and abdominal pain).

Demographic and clinical details of the patients remaining in the three groups are shown in Table 1. The per-protocol eradication rate was 91.81% (101 patients from a total of 110) in group A, 85.84% (97 patients from a total of 113) in group B, and 92.85% (104 patients from a total of 112) in group C. The intention-to-treat eradication rate was 84.17% in group A, 80.83% in group B, and 86.67% in group C. The new protocol yielded the highest eradication rates by both per-protocol and intention-to-treat analyses followed by the standard triple and quadruple regimens, respectively. However, the differences were not statistically significant between the three groups. They were also not significantly different in the occurrence of minor side effects, either.

DISCUSSION

We opted to prescribe antibiotics for ten days because 4- and 7-d regimens have been unsuccessful in Iran[9]. In this study, the eradication rates for the triple, standard quadruple and ampicillin-sulbactam-based quadruple therapies were not significantly different. Occurrence of serious side effects necessitating termination of therapy was negligible in all three groups. Minor side effects were well tolerated among all three groups and occurred infrequently with almost the same frequency. Diarrhea and headache occurred in group C only, but other side effects were experienced in all groups.

Some recent studies have compared the efficacy of triple versus quadruple therapy, and a recent meta-analysis

has assessed these studies[10]. Eradication rates were not significantly different among patients receiving triple or quadruple therapy. The duration of therapy (7 *vs* 10 d) did not significantly change the results, either. Triple therapy given for a 10-d period achieved an intention-to-treat eradication rate of 79% compared with 77% for a 7-d period. Quadruple therapy on the other hand gave an intention-to-treat eradication rate of 83% for a 10-d period and 80% for a 7-d period[10]. The eradication rates by intention-to-treat analysis among patients receiving either triple or quadruple therapy in this study were almost similar to those obtained previously[4,10,11].

A previous preliminary study by the authors using ampicillin-sulbactam instead of amoxicillin in 10-d standard quadruple therapy on 26 patients has yielded a 92% eradication rate by per-protocol analysis which was well tolerated among patients (unpublished data). The present study is the first randomized clinical trial to evaluate the efficacy of the new protocol and to compare it with standard triple and quadruple therapies in a relatively large number of patients. Although not statistically significant, the new protocol seems to be more effective than traditional protocols.

H pylori infection has a high prevalence rate of about 90% in Iran, which emphasizes the importance of having an effective regimen to eradicate *H pylori*[12]. The metronidazole-based standard triple therapy regimen has been unsuccessful in *H pylori* eradication, yielding an eradication rate of only about 55% compared with about 90% in other countries[13,14]. This is because metronidazole-resistant *H pylori* strains are rather common in Iran as well as in other developing countries[9,15]. The high prevalence of metronidazole-resistance in Iran could be explained by the frequent use of metronidazole to treat various infections, thereby promoting antibiotic resistance in *H pylori*.

On the other hand, 7.4% of *H pylori* isolates in Iran have been reported to be resistant against amoxicillin and higher resistance rates of up to 29% have been reported in other developing countries[15,16]. Therefore, the use of ampicillin-sulbactam instead of amoxicillin in the quadruple therapy regimen, leading to an eradication rate of 92.85% by per-protocol and 86.67% by intention-to-treat analysis in this study, may be useful against metronidazole- and amoxicillin-resistant *H pylori* strains in developing countries like Iran. Consequently, there would be no need to exclude metronidazole (because of antibiotic resistance), which is an inexpensive and widely available anti-*H pylori* agent in developing countries.

Since the present study did not show the effectiveness of the new combination on ampicillin-resistant strains, we should bear in mind that some of the resistant strains do not act through beta-lactamase but rather penicillin binding proteins (PBPs)[17]. Perhaps *in vitro* study of ampicillin-resistant strains using ampicillin-sulbactam combination can help answer whether the combination is effective against the resistant strains.

In conclusion, the results of this study provide further support for the equivalence of triple and amoxicillin-based quadruple therapies in terms of effectiveness, compliance and side-effect profile when administered as a first-line treatment for *H pylori* infection. Moreover, the new protocol using ampicillin-sulbactam instead of amoxicillin in the quadruple regimen is a suitable first-line alternative to be used in regions with amoxicillin-resistant *H pylori* strains.

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