

Efficacy of Moxifloxacin-Based Triple Therapy as Second-Line Treatment for *Helicobacter pylori* Infection

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Keywords

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Abstract

Background and Aim: Metronidazole and tetracycline-based second-line quadruple therapy, widely used for *Helicobacter pylori* infection, often ends up in failure due to antibiotic resistance and poor compliance in Korea. Our aim is to evaluate the efficacy and tolerability of moxifloxacin-based triple therapy as an alternative second-line treatment for *H. pylori* infection.

Methods: The subjects consisted of 85 patients infected with *H. pylori*, in whom initial proton pump inhibitor triple therapy had failed. They were randomized to receive the following 7-day therapy: 1, moxifloxacin 400 mg q.d., esomeprazole 20 mg b.i.d., and amoxicillin 1 g b.i.d.; and 2, esomeprazole 40 mg b.i.d., tripotassium dicitrate bismuthate 300 mg q.i.d., metronidazole 500 mg t.i.d., and tetracycline 500 mg q.i.d. Eradication rates, drug compliance, and side-effect rates of each group were evaluated.

Results: The eradication rates were 75.6 and 83.8% with moxifloxacin triple therapy, and 54.5 and 72.7% with quadruple therapy by intention-to-treat ($p = .042$) and per-protocol analyses ($p = .260$), respectively. Moxifloxacin triple therapy was significantly superior to quadruple therapy in terms of side-effect rates ($p = .039$). Compliance for therapy, i.e., the percentage of tablets taken ($> 85\%$), was 90.2 and 75.0%, numerically higher in moxifloxacin triple therapy group than in quadruple therapy group, but without statistical difference ($p = .065$).

Conclusions: Moxifloxacin-based triple therapy showed high eradication rates with few side effects and good drug compliance, suggesting this regimen could be a safe and effective option as second-line therapy for *H. pylori* infection in Korea.

Helicobacter pylori infection plays the major role in the pathogenesis of peptic ulcer disease, chronic gastritis, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and in gastric cancer [1]. Therefore, eradication of the bacteria has become the main therapy for these diseases. Worldwide consensus conferences have recommended triple therapy consisting of a proton pump inhibitor (PPI) and two antibiotics, mainly amoxicillin and clarithromycin, as first-line eradication therapy [2,3]. Although this treatment has been shown to be effective in numerous clinical trials, several meta-analysis revealed that the rates of eradication were widely variable, ranging from 70 to

95% [3–5]. Second-line *H. pylori* eradication therapy is necessary for patients with first-line failure, for whom the Maastricht 2-2000 Consensus Report recommended the use of minimum 7-day, PPI, bismuth, metronidazole and tetracycline-based quadruple therapy [2]. However, this regimen may vary in efficacy in different patient populations. Although a recent meta-analysis showed that such treatment for 10–14 days is highly effective [6], in some countries or areas including Korea, the quadruple therapy has been also associated with eradication failure in more than 20% of cases [5,7–10]. The main causes of treatment failures in these areas compared with Western

countries are thought to be poor patients' compliance and bacterial resistance [5,8–11]. The quadruple therapy entails complicated dosing schedules in terms of the number of tablets and interval of administrations. Moreover, considerable side-effect rates of metronidazole and tetracycline reduce patients' compliance [12]. Regarding bacterial resistance, *H. pylori* resistance to metronidazole has a negative impact on quadruple therapy [13,14]. High resistance rate of *H. pylori* to metronidazole worldwide, especially in Korea [15–20], has made the efficacy of metronidazole-containing quadruple therapy limited as a second-line therapy. Recent Korean reports revealed the eradication rates of a metronidazole- and tetracycline-containing second-line therapy were lower than 65% by intention-to-treat (ITT) analysis and 80% by per-protocol (PP) analysis [8–10]. Consequently, many therapeutic options with favorable compliance and various eradication rates are under trial [21–23], but ideal rescue regimens for a first *H. pylori* eradication failure are still uncertain.

The new generation fluoroquinolones have shown some favorable efficacies in the treatment of *H. pylori* [24–26], especially in terms of safety, simplicity of dosing schedule, and high efficacy as the initial eradication therapy. Recently, we have experienced excellent results concerning efficacy and tolerability using moxifloxacin-based triple therapy in small series of patients with two successive eradication failures [8]. With this background, we investigated whether this moxifloxacin-based triple therapy could be a strong candidate for the second-line treatment in terms of the efficacy and tolerability.

Patients and Methods

Patients

We consecutively enrolled patients, in whom a first eradication trial with PPI–amoxicillin–clarithromycin failed to eradicate *H. pylori* infection, at Seoul National University Bundang Hospital in Korea. Patients with concurrent critical illnesses, a history of previous upper gastrointestinal surgery, contraindication to any of the study medication, recent frequent intake of nonsteroidal anti-inflammatory drugs (NSAIDs), anticoagulants or steroids, an allergy to the study medications, and who were pregnant or breast-feeding women were excluded from the study. Other exclusion criteria included recent use of antimicrobials and any condition probably associated with poor compliance such as drug abusers or alcoholics. All patients enrolled in the study were aware of the study protocol and agreed to comply with the follow-up schedule, and all provided written informed consent. The study was approved by the Ethics Committee of Seoul National University Bundang Hospital.

Methods

Patients were considered as initial treatment failure if any of histology, rapid urease, or ¹³C-urea breath testing was positive before study. They were randomly assigned to one of the following two 1-week treatment regimens: 1, MEA: moxifloxacin 400 mg q.d., amoxicillin 1000 mg b.i.d., and esomeprazole 20 mg b.i.d.; and 2, EBMT: esomeprazole 20 mg b.i.d., tripotassium dicitrate bismuthate 300 mg q.i.d., metronidazole 500 mg t.i.d., and tetracycline 500 mg q.i.d. One week after the completion of therapy, compliance with therapy was evaluated by a physician both by being questioned and by pill count. The drug compliance was considered good if drug intake was more than 85%. All patients were interviewed for adverse events at the same time. *H. pylori* eradication was defined as a negative ¹³C-urea breath test 4 weeks after the completion of therapy.

¹³C-Urea Breath Test

The patient fasted for 4 hours before the test. No test meal was given, and a predose breath sample was obtained. Seventy-five micrograms of ¹³C-urea powder (Helikit™, Isotechnika, Edmonton, Canada) dissolved in 50 ml of water was administered orally. The second breath sample was collected at 30 minutes. The cut-off value used was 4‰ [27]. Collected samples were analyzed by means of isotope ratio mass spectrometer (Heliview®, Medichems, Seoul, Korea).

Statistical Analysis

Analyses of *H. pylori* eradication efficacy were performed on an ITT basis (included all patients enrolled in the study) and on a PP basis (excluding patients with poor compliance for therapy and unavailable data after therapy). The 95% confidence intervals (CI) for the differences of eradication rates between the two groups were calculated using standard methods. Continuous variables were analyzed by Student's *t*-test and categorical variables using the χ^2 test or Fisher's exact test. Analyses were performed using SPSS (Statistical Package for the Social Sciences version 11.0; SPSS Inc., Chicago, IL, USA). $p < .05$ was considered to be statistically significant.

Results

Patient Population

Eighty-five patients were enrolled in the study from June 2004 through April 2005. Of these, 41 patients were randomized to the MEA group and 44 patients to the EBMT group. The baseline characteristics were similar in

	MEA group	EBMT group	<i>p</i> value
Included in ITT analysis (n)	41	44	
Male/female (n)	24/17	23/21	.562 ^a
Mean age ± SD (years)	54.3 ± 11.7	51.6 ± 12.5	.295 ^b
Disease (n)			.932 ^a
Gastric ulcer	11	11	
Duodenal ulcer	20	24	
Gastroduodenal ulcer	2	1	
Gastric adenoma or cancer	4	3	
Nonulcer dyspepsia	4	5	
F/U loss or inadequate UBT assessment (n)	3	7	.316 ^c

ITT, intention-to-treat; SD, standard deviation; F/U, follow-up; UBT, ¹³C-urea breath test; MEA, moxifloxacin + esomeprazole + amoxicillin; EBMT, esomeprazole + bismuth + metronidazole + tetracycline.

^aTwo-sided Pearson's χ^2 test.

^bTwo-tailed *t*-test.

^cTwo-sided Fisher's exact test.

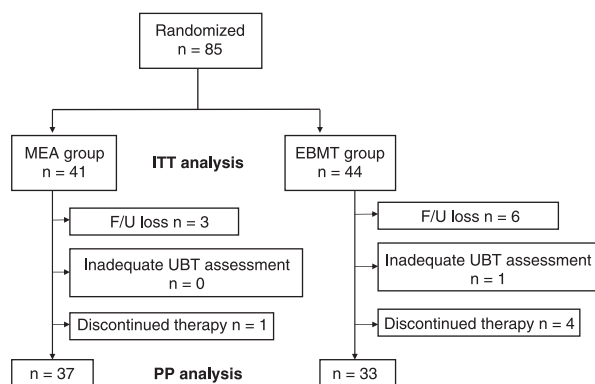


Figure 1 Flow diagram of the progress of patients included in intention-to-treat and per-protocol analysis. ITT, intention-to-treat; PP, per-protocol; MEA, moxifloxacin + esomeprazole + amoxicillin; EBMT, esomeprazole + bismuth + metronidazole + tetracycline; F/U, follow-up; UBT, ¹³C-urea breath test.

the two treatment groups (Table 1). All of them were included in the ITT analysis. Fifteen patients were excluded from the PP analysis; that is, follow-up loss and inadequate post-treatment assessment (no final UBT result) in 10 patients and protocol violation in five patients (the discontinuation of medication due to adverse events). Thus, 37 patients in the MEA group and 33 patients in the EBMT group comprised the study group for inclusion in the PP analysis. Figure 1 shows the disposition of all patients in these two groups.

***H. pylori* Eradication Rates**

The eradication rates of *H. pylori* at the end of follow-up phase were 75.6% (95% CI) in the MEA group and 54.5%

Table 1 Baseline demographic characteristics of patients

Table 2 *Helicobacter pylori* eradication rates

	MEA	EBMT	<i>p</i> value
ITT analysis			
Eradication rate	75.6% (31/41)	54.5% (24/44)	.042 ^a
95% CI	62.5–88.7%	39.8–69.2%	
PP analysis			
Eradication rate	83.8% (31/37)	72.7% (24/33)	.260 ^a
95% CI	71.9–95.7%	55.7–89.7%	

ITT, intention-to-treat; PP, per-protocol; CI, confidence interval; MEA, moxifloxacin + esomeprazole + amoxicillin; EBMT, esomeprazole + bismuth + metronidazole + tetracycline.

^aTwo-sided Pearson's χ^2 test.

in the EBMT group by ITT analysis (Table 2). Based on the PP analysis, *H. pylori* eradication was achieved in 83.8% in the MEA group and 72.7% in the EBMT group. *H. pylori* eradication rates in the MEA group were significantly higher than in the EBMT group by ITT analysis ($p = .042$), but not by PP analysis ($p = .260$).

Adverse Events and Compliance

Adverse events were described in 4 of 41 patients (9.8%) in the MEA group and in 12 of 44 patients (27.3%) in the EBMT group; the most common one was epigastric discomfort (Table 3). Side-effect rate in the MEA group was significantly lower than in the EBMT group ($p = .039$). Most adverse events were mild to moderate in intensity. Five serious adverse events were reported and they were dropped out due to the adverse events. Of these, one patient was in the MEA group (2.4%) and the adverse symptom was epigastric pain, and four patients were in

Table 3 Adverse events

Adverse events	MEA group (n = 41)	EBMT group (n = 44)
Epigastric discomfort	2 (4.9%)	6 (13.6%)
Nausea or vomiting	1 (2.4%)	2 (4.5%)
Facial spasm or paresthesia	–	2 (4.5%)
Diarrhea	1 (2.4%)	–
Chest tightness	–	1 (2.3%)
Constipation	–	1 (2.3%)
Total	4 (9.8%) ^a	12 (27.3%)

MEA, moxifloxacin + esomeprazole + amoxicillin; EBMT, esomeprazole + bismuth + metronidazole + tetracycline.

^a $p < .05$ when compared with the EBMT group (two-sided Pearson's χ^2 test).

the EBMT group (9.1%); two patients had epigastric pain, and the other two showed vomiting and paresthesia, respectively.

Compliance for therapy, i.e., the percentage of tablets taken (> 85%), was 90.2% (37/41 patients) and 75.0% (33/44 patients) in the MEA and EBMT groups, which was not significantly different between the two groups ($p = .065$).

Discussion

Quadruple therapy containing PPI, bismuth, tetracycline, and metronidazole has been generally used as a second-line therapy after initial eradication failure and chosen as the recommended regimen in several guidelines [2,3]. However, this regimen has been associated with eradication failure in more than 20% of the cases by PP analysis in some areas including Korea, the main cause of which is thought to be bacterial resistance. Moreover, poor patients' compliance due to considerable side-effect rates and complicated dosing schedules has decreased the ITT eradication rates. To overcome the bacterial resistance and poor compliance, many potential alternative therapeutic options with favorable compliance and various eradication rates have been undertaken [21–23,28–30], but the selection of an appropriate second-line therapy is still challenging for the clinician.

The background of our study was that moxifloxacin, which has several advantages in terms of safety and simplicity of dosing schedules, could decrease the dropout of patients during eradication therapy resulting in increase of the eradication by ITT analysis. In addition, in vitro studies show excellent susceptibility of *H. pylori* to newer quinolones including moxifloxacin [24,31,32]. In vitro susceptibility study performed in our hospital also revealed low resistance rate of *H. pylori* against moxifloxacin, 5.6%

(3/54) in comparison with 40.7% (22/54) of metronidazole (unpublished data), supporting these data. Thus, we hypothesized that the PP eradication rate of moxifloxacin-containing regimen could be higher or at least equal to that of conventional quadruple therapy as a second-line therapy. To prove this, we compared the efficacy and tolerability of moxifloxacin-based triple therapy with those of conventional quadruple therapy for the treatment of *H. pylori* infection after failure of a first-line eradication. The ITT and PP *H. pylori* eradication rates turned out to be 75.6/83.8% for the moxifloxacin-based triple therapy and 54.5/72.7% for the quadruple therapy. The eradication rate of triple therapy was significantly higher than that of the quadruple therapy by ITT analysis. Drug side effects were less common in the triple therapy than in the quadruple therapy, which might have influenced on the numerical difference in drug compliance and follow-up loss between the two groups. This study suggests that moxifloxacin-based triple regimen is efficacious and tolerable and could be, therefore, used as an alternative second-line eradication regimen instead of standard quadruple therapy for patients who have failed in the initial eradication therapy.

To overcome resistance problems, at least, the evaluation of drugs for a second-line *H. pylori* therapy without cross-resistance to nitroimidazoles or macrolides as components of retreatment combination therapies seems to be worthwhile. In addition to moxifloxacin, several antibiotics are suggested as candidates satisfying these conditions. Rifabutin, another potential candidate antibiotic, has been proven to exhibit high in vitro activity against *H. pylori* [33,34], and rifabutin-based clinical trials have suggested that rifabutin may be a promising second-line or rescue antibiotics for *H. pylori* eradication [22,35]. However, several concerns remain about its use as a second-line *H. pylori* therapy especially in Korea, which is still a high endemic area of tuberculosis. Its high cost, rare but serious side effect, i.e., neutropenia and thrombocytopenia, and most of all, some concern about the emergence of multidrug-resistant *Mycobacterium tuberculosis* limits its use to patients who have experienced multiple failures of *H. pylori* eradication therapies [21,35]. Besides changing the antibiotics, it is evident that the prolongation of treatment duration could cope with resistance problems. A recent meta-analysis suggested 14-day, metronidazole-containing quadruple therapy could be recommended in first-line as well as second-line anti-*H. pylori* treatment [6]. It might be valuable to compare this moxifloxacin-based triple therapy with 14-day quadruple therapy in the future if the side-effects and complexity of 14-day quadruple therapy could be overcome in Korea.

Our study has a limitation in that we did not evaluate the antibiotic resistance in relation to treatment regimens and eradication rates. The utility of the culture with

subsequent antibiotic susceptibility testing and the moment when it should be performed after eradication failure are still controversial. However, it gains more appraisal that culture after a first eradication failure is not necessary [3,7,21]. It may be pertinent to perform the bacterial culture and antibiotic susceptibility testing after two or more successive failures of eradication. From a practical viewpoint, we omitted the culture study. Another potential weakness of our study is that the compliance of quadruple therapy group was poor. The main reason of poor compliance of quadruple therapy is likely to have originated from the complexity of tablet-taking times (two, three, four times per drug) and the high tablet number of this regimen in Korea. That is, quadruple therapy consists of esomeprazole 20 mg b.i.d. (2 tablets), tripotassium dicitrate bismuthate 300 mg q.i.d. (4 tablets), metronidazole 500 mg t.i.d. (250 mg, 6 tablets), and tetracycline 500 mg q.i.d. (250 mg, 8 tablets) in comparison of MEA: moxifloxacin 400 mg q.d. (1 tablet), amoxicillin 1000 mg b.i.d. (250 mg, 4 tablets), and esomeprazole 20 mg b.i.d. (2 tablets). The tablet number of quadruple therapy is 20, nearly three times more than that of MEA, which has seven. In addition, we met the patients only two times during the second treatment, at the start point of study and after the completion of regimen, which is reflecting the usual practice pattern. This was equally applied to both treatment groups, and the compliance was not statistically different between moxifloxacin-based therapy and quadruple therapy.

In conclusion, 1-week esomeprazole, amoxicillin, moxifloxacin-based triple therapy was highly effective for a second-line *H. pylori* eradication therapy, especially, in terms of safety and tolerability. Further larger studies are needed to determine the broad application of this eradication regimen in comparison with currently approved quadruple, second-line therapy.

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