

Efficacy of dexlansoprazole-based triple therapy for *Helicobacter pylori* infections

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Abstract

Background: Dexlansoprazole has been shown to be efficacious for the treatment of gastroesophageal reflux disease. However, there is a paucity of data about its efficacy for *Helicobacter pylori* eradication. The aim of this study was to evaluate the efficacy of dexlansoprazole for *H. pylori* eradication as triple therapy in real-world practice.

Methods: Adult patients with endoscopically proven *H. pylori* related peptic ulcer diseases or gastritis were recruited for this study. The eradication status was assessed based on the results of the ¹³C-urea breath test performed 4 weeks after treatment. According to the different treatment regimens, the patients were allocated to group A: Esomeprazole 40 mg b.i.d. + amoxicillin 1 g b.i.d. + clarithromycin 500 mg b.i.d. for 7 days; group B: Esomeprazole 40 mg q.d. + amoxicillin 1 g b.i.d. + clarithromycin 500 mg b.i.d. for 7 days, or group C: Dexlansoprazole 60 mg q.d. + amoxicillin 1 g b.i.d. + clarithromycin 500 mg b.i.d. for 7 days.

Results: A total of 215 patients (49% males) were enrolled in this study, with a mean age of 55 years. The eradication rates in group A, B, and C were 94.7% (71/75), 89.6% (69/77), and 93.7% (59/63) ($p = 0.457$), respectively. The adverse events were similar between the three groups ($p = 0.068$).

Conclusions: This study suggests that dexlansoprazole-based triple therapy has an acceptable eradication rate for *H. pylori* infection.

Keywords: dexlansoprazole, *Helicobacter pylori* eradication, proton pump inhibitor

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Introduction

Helicobacter pylori infection is a key etiological factor in peptic ulcer disease, gastric mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma.^{1–3} The World Health Organization has defined *H. pylori* as a risk factor for the development of gastric cancer. The standard first-line treatment for *H. pylori* eradication is triple therapy, which consists of proton pump inhibitors (PPIs) and two kinds of antibiotics. However, recent epidemiology studies have indicated that the eradication rate for *H. pylori* is decreasing. The possible causes for eradication therapy failure include antibiotic resistance, smoking, high intragastric bacterial load before treatment, bacterial genotype, poor patient compliance, and host genetic polymorphisms of the

cytochrome P450 isoenzymes that are specifically involved in the metabolism of PPIs.⁴

PPIs play an important role in *H. pylori* eradication. They not only inhibit gastric acid secretion to increase the bioavailability of antibiotics but also have antibacterial activity.^{5,6} The acidic environment maintains *H. pylori* in a nonreplicating state. Thus, increasing the effectiveness of acid-suppressing therapy can achieve a higher eradication rate.^{7–9}

Dexlansoprazole and esomeprazole belong to a class of drugs known as PPIs, which inhibit the secretion of hydrogen ions in the stomach by inhibiting the H⁺/K⁺ ATPase enzyme (proton pump), resulting in a prolonged elevation of

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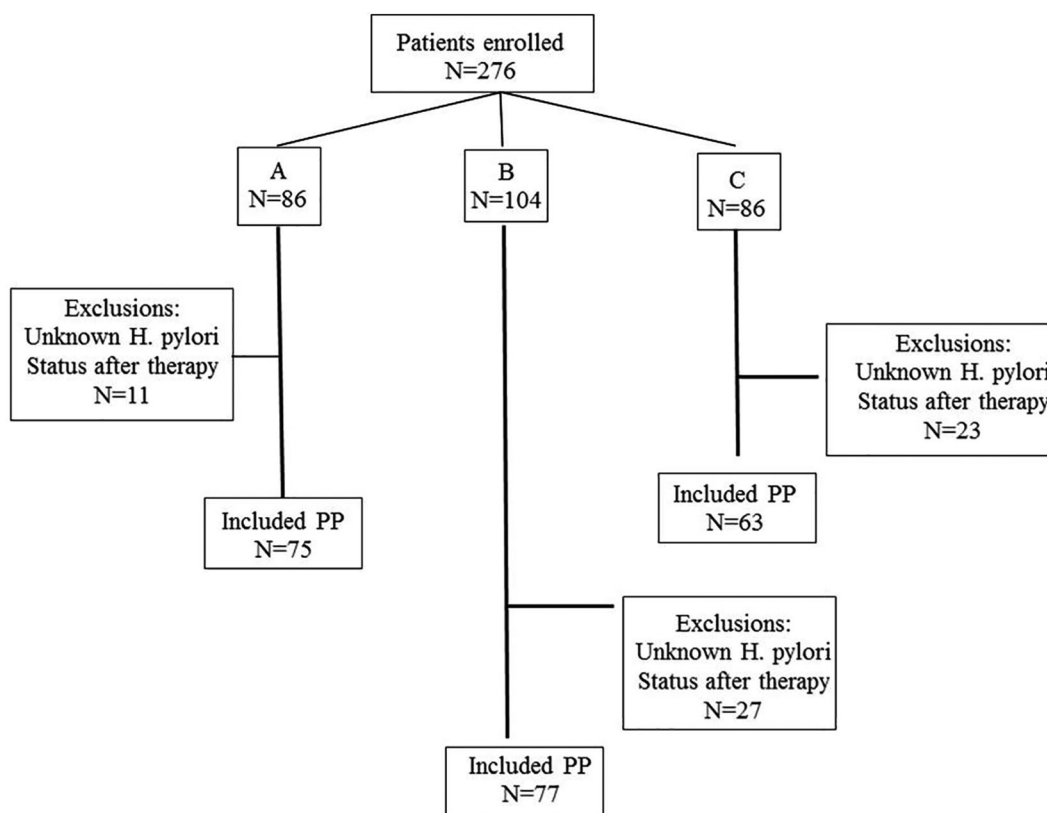


Figure 1. Schematic flow chart of the study design.

intra-gastric pH levels. Dexlansoprazole is a formulation of dual delayed-release delivery system and produces a plasma concentration time profile with two peaks. The first peak occurs 1–2 h after administration and the second peak occurs 4–5 h later.¹⁰ Esomeprazole is a delayed-release formulation with single release characteristics that produces a maximum plasma concentration at approximately 1.6 h post dose.

Dexlansoprazole has been shown to be efficacious in treating gastroesophageal reflux disease.^{11,12} However, there is a paucity of data about its efficacy for *H. pylori* eradication. Therefore, the aim of this study was to evaluate the efficacy of dexlansoprazole-based triple therapy for *H. pylori* eradication.

Materials and methods

Patient selection

From January 2016 to December 2017 the medical charts of 276 treatment naive patients, who received triple therapy for *H. pylori* eradication in

Linkou Chang Gung Memorial Hospital, were retrospectively reviewed. The inclusion criteria were: (1) patients older than 20 years with upper endoscopic examination, and (2) patients with *H. pylori* infection diagnosed by either a rapid urease test (with one specimen from the antrum and one from the corpus) or a histology evaluation of gastric biopsy tissue. The exclusion criteria were unknown *H. pylori* infection status after therapy. According to the triple therapy regimen, the patients were allocated to group A: Esomeprazole 40 mg b.i.d. + amoxicillin 1 g b.i.d. + clarithromycin 500 mg b.i.d. for 7 days, group B: Esomeprazole 40 mg q.d. + amoxicillin 1 g b.i.d. + clarithromycin 500 mg b.i.d. for 7 days, or group C: Dexlansoprazole 60 mg q.d. + amoxicillin 1 g b.i.d. + clarithromycin 500 mg b.i.d. for 7 days. Figure 1 demonstrates the schematic flow chart of the study design. The patients were allocated the different treatment regimen using a blind method. Eradication status was determined by the ¹³C-urea breath test performed 4 weeks after treatment.³ The primary outcome measure was the overall eradication rate of *H. pylori*. The secondary outcome measure was the frequency of adverse

Table 1. Demographic data and endoscopic appearances of the patients in different groups.

	A (n=75)	B (n=77)	C (n=63)
Characteristics			
Age (year) (mean \pm SD)	54 \pm 11	55 \pm 13	56.5 \pm 12.2
Gender (male/female)	30/45	45/32	31/32
Endoscopic findings			
Gastric ulcer	16 (21%)	22 (29%)	6 (10%)
Duodenal ulcer	11 (15%)	21 (27%)	7 (11%)
Gastric and duodenal ulcer	1 (1%)	7 (9%)	0 (0%)
Gastritis	47 (63%)	27 (35%)	50 (79%)

Table 2. The major outcomes of the patients in eradication therapy.

	Group A (n=75)	Group B (n=77)	Group C (n=63)	p value
Eradication rate	94.7% (71/75)	89.6% (69/77)	93.7% (59/63)	0.457
Adverse event	12.0% (9/75)	19.5% (15/77)	6.3% (4/63)	0.068

events. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB No. 104-4789A3).

Statistical analysis

The statistical calculations were performed using SPSS, version 18.0, software (SPSS Inc., Chicago, IL, USA). The *H. pylori* eradication rate was demonstrated on a per protocol analysis. Categorical variables were analyzed by using a Chi-square test (χ^2) and continuous variables were analyzed using a Student's *t* test. Differences in baseline characteristics, eradication rates, and adverse events between groups were determined by a χ^2 test or Fisher's exact test, as appropriate. The *p* values ≤ 0.05 were considered to indicate statistical significance.

Results

Characteristics of the study groups

A total of 215 patients were enrolled in the final analysis, 75 patients were in group A, 77 in group B and 63 in group C. The mean age of the patients was 55 years, 49% were male, 39% had a peptic ulcer, and 10% were smokers. The baseline

demographic data and clinical parameters of the three treatment groups are listed in Table 1. There were no significant differences in age and gender among groups A, B, and C.

Eradication of *H. pylori* infection

Among the 215 patients receiving first-line triple therapy, 199 achieved successful eradication of *H. pylori*, and the overall eradication rate was 92.6%. The eradication rates in group A, B and C were 94.7%, 89.6%, and 93.7% respectively ($p=0.457$). As shown in Table 2 univariate analysis of the clinical factors influencing the efficacy of *H. pylori* eradication revealed that there was no difference in age, gender, smoking, or previous history of peptic ulcer disease (Table 3).

Adverse events

The adverse effects in patients were investigated. As shown in Table 4, 13% of patients (28/215) experienced adverse events including abdominal pain (0.9%), taste change (0.9%), anorexia/nausea (1.9%), diarrhea (2.8%), dizziness (0.5%), skin rash (0.5%), constipation (0.9%), headache (0.9%), fullness (2.8%), heartburn (0.5%), cramping pain (0.5%), and acid reflux (0.9%).

Table 3. Univariate analysis of the clinical factors influencing the efficacy of *Helicobacter pylori* eradication.

Principle parameter	Number of cases	Eradication rate	p value
Age			
<60years	141	90.8% (128)	0.173
≥60years	74	96.0% (71)	
Sex			
Female	109	95.4% (104)	0.107
Male	106	89.6% (95)	
Smoking			
(-)	194	92.8% (180)	0.704
(+)	21	90.5% (19)	
Previous history of peptic ulcer			
(-)	132	93.2% (123)	0.182
(+)	83	94.0% (78)	
<i>Helicobacter pylori</i> eradication (per protocol)			
A	75	94.7% (71)	0.457
B	77	89.6% (69)	
C	63	93.7% (59)	

Table 4. Adverse events in patients undertaking eradication therapy.

Adverse events	Group A (n=75)	Group B (n=77)	Group C (n=63)	p value
Abdominal pain	1	0	1	0.57
Taste change	0	0	2	0.09
Anorexia/Nausea	1	3	0	0.52
Diarrhea	0	5	1	0.01
Dizziness	0	1	0	0.15
Skin rash	0	1	0	0.41
Constipation	2	0	0	0.18
Headache	2	0	0	0.41
Fullness	2	4	0	0.41
Heartburn	0	1	0	0.15
Cramp	0	1	0	0.41
Acid reflux	2	0	0	0.15

The incidence of adverse events was 12.0% (9/75) in group A, 19.5% (15/77) in group B, and 6.4% (4/63) in group C. There was no significant difference between the three groups ($p=0.068$; Table 2).

Discussion

Dexlansoprazole modified-release (MR) is an R-enantiomer of lansoprazole, with a dual delayed-release formulation. The drug has been shown to be efficacious in treating gastroesophageal reflux disease.^{11–13} However, there is a paucity of data about its efficacy on *H. pylori* eradication.

The major effect of PPIs in the treatment of *H. pylori* infection is to increase intragastric pH. Intragastric pH is important for the efficacious effect of antibiotics and the inhibition of the growth of *H. pylori*. The acidic environment maintains the *H. pylori* in a nonreplicating state. Moreover, optimal efficacy of amoxicillin requires a neutral pH. Therefore, increasing the effectiveness of acid-suppressing therapy can result in a higher *H. pylori* eradication rate.^{7–9}

Several studies have suggested that a twice daily dose of PPIs can increase the eradication rate of *H. pylori*. A meta-analysis showed that a high dose of PPIs increased the eradication rate by 6–10%.¹⁴ In addition, the eradication rate of standard triple therapy depends on the availability of PPIs. The function of the PPI depends on the CYP2C19 and MDR polymorphisms. A meta-analysis study showed that the eradication rates of rapid or extensive metabolizers (genotype RM or EM, either homozygous or heterozygous) and genotype with MDR T/T was low compared with the T/C and C/C genotypes.^{15,16} The same meta-analysis revealed that regimens containing lansoprazole or rabeprazole were unaffected. As stated in ‘The Second Asia-Pacific Consensus Guidelines for *Helicobacter pylori* infection’, in order to overcome CYP2C19 polymorphisms in the context of salvage therapy, increasing the dose of PPIs is a more practical approach than CYP2C19 genotyping in the clinical setting.¹⁷

The novel PPI, dexlansoprazole MR, has a longer elimination half-life and extends the duration of effective treatment.¹⁸ Theoretically, this can lead to a better *H. pylori* eradication rate. However, a

14-day dual therapy with dexlansoprazole 120 mg and amoxicillin 1 g, both twice a day at approximately 12 h intervals, in 2014 was shown to have a poor eradication rate (53.8%).¹⁹ A similar result of dexlansoprazole-amoxicillin dual therapy was also noted in a Korean study.²⁰ Nonetheless, dexlansoprazole-based triple therapy had a good eradication rate and a similar success rate compared with rabeprazole-based triple therapy.^{21,22} A total of 177 *H. pylori* infected patients were randomized to receive dexlansoprazole-based triple therapy, or rabeprazole-based triple therapy for 7 days. The per protocol analysis yielded comparable results (85.1% versus 81.2%; $p=0.497$). Both groups exhibited similar frequencies of adverse events (7.8% versus 4.6%; $p=0.536$) and drug compliance (98.9% versus 97.7%; $p=0.496$). Levofloxacin-dexlansoprazole-based quadruple therapy was also shown to be effective for *H. pylori* eradication in a Thai study.²³ To the best of the authors’ knowledge, no studies have compared the efficacy on *H. pylori* eradication of dexlansoprazole-based and esomeprazole-based triple therapies. The results of this study add a potentially important message that the efficacy of dexlansoprazole-based standard triple therapy was not inferior to esomeprazole-based triple therapy. The recent studies on the efficacy of dexlansoprazole for *H. pylori* eradication are listed in Table 5.

In *H. pylori* eradication, adverse gastrointestinal symptoms including abdominal pain, fullness, anorexia, and acute diarrhea are usually associated with antibiotic treatments (especially with regimens that last more than 10 days) rather than with PPIs.²⁴ In this study, most of the adverse symptoms were mild gastrointestinal symptoms. The adverse event rate in the group receiving dexlansoprazole-based triple therapy was significantly lower than in the group receiving twice daily esomeprazole-based triple therapy (6.4% versus 12.0%, $p=0.002$). A meta-analysis reported that the average incidence of adverse events and the compliance rate in patients treated by triple therapy was 13% and 92.6%, respectively.²⁵ In the once daily dexlansoprazole-based triple therapy, the adverse event rate was low and all patients underwent a 1 week course of treatment. Of interest, there was no statistical difference in the rate of adverse events in group A and B. (12.0% versus 19.5%; $p=0.2$). This finding was different from a study conducted by Anagnostopoulos and

Table 5. Recent studies on the efficacy of dexlansoprazole for *Helicobacter pylori* eradication.

Author	Country	Study design	Study group	Control group	Duration of treatment (days)	Number of Patients	Eradication rate (%)	p value	Conclusion
Attumi and Graham ¹⁹	USA	Open-label prospective pilot study	Dexlansoprazole 120 mg/12 h, Amoxicillin 1 g/12 h		14	13	53.8		High-dose dexlansoprazole was not an effective anti- <i>H. pylori</i> regimen.
Park <i>et al.</i> ²⁰	Korea	Single arm prospective study	Dexlansoprazole 30 mg/8 h, amoxicillin 750 mg/8 h		14	50	52		High and frequent doses of PPI amoxicillin dual therapy was not effective in eradicating <i>H. pylori</i> infection.
Wu <i>et al.</i> ²¹	Taiwan	Prospective, randomized, controlled study	Dexlansoprazole MR 60 mg/24 h, clarithromycin 500 mg/12 h, amoxicillin 1 g/12 h	Rabeprazole 20 mg/12 h, clarithromycin 500 mg/12 h, amoxicillin 1 g/12 h	7	90, 87	83.3 81.6	0.736	Single-dose dexlansoprazole MR-based triple therapy yields a similar eradication rate as double-dose rabeprazole-based therapy.
Chotivitaya-tarakorn <i>et al.</i> ²²	Thailand	Prospective, randomized, placebo-controlled study	Dexlansoprazole 60 mg/12 h, moxifloxacin 400 mg/24 h, clarithromycin MR 1 g/24 h, once daily, <i>Saccharomyces boulardii</i> 282.5 mg/12 h	Dexlansoprazole 60 mg/12 h, moxifloxacin 400 mg/24 h, clarithromycin MR 1 g/24 h, once daily, placebo/12 h	7 or 14	108 [27 in each group]	7D (100, 88.9) 14D (92.6, 96.3)	7D (0.24) 14D (1.00)	There was no significant difference between eradication rate of 7-day and 14-day regimen with or without probiotics.
Prapitpaiboon <i>et al.</i> ²³	Thailand	Prospective randomized control study	Dexlansoprazole 60 mg/ q12 h, levofloxacin 500 mg/24 h, clarithromycin MR 1000 mg/24 h, bismuth subsalicylate 1048 mg/12 h	Dexlansoprazole 60 mg/ q12 h, levofloxacin 500 mg/24 h, clarithromycin MR 1000 mg/24 h, bismuth subsalicylate 1048 mg/12 h	14 versus 7	48, 42	98, 85.7	0.059	The 14-day levofloxacin-dexlansoprazole-based quadruple therapy provides high <i>H. pylori</i> eradication rate.
Prapitpaiboon <i>et al.</i> ²³	Thailand	Prospective randomized control study	Dexlansoprazole 60 mg/ q12 h, levofloxacin 500 mg/24 h, clarithromycin MR 1000 mg/24 h, bismuth subsalicylate 1048 mg/12 h	Dexlansoprazole 60 mg/ q12 h, levofloxacin 500 mg/24 h, clarithromycin MR 1000 mg/24 h, bismuth subsalicylate 1048 mg/12 h	14 versus 7	48, 42	98, 85.7		

MR, modified-release; PPI, proton pump inhibitor

colleagues²⁶ where the rate of adverse events was higher in the group with esomeprazole 40 mg twice daily than in the group with esomeprazole 40 mg once daily (46% *versus* 17%). Although the possible mechanism was uncertain, and beyond the scope of this study, the authors speculated that the metabolic rate of esomeprazole by CYP2C19 might lead to this difference between patients from Asia and Europe. Further studies are required to investigate this hypothesis.

This study has some limitations that need to be considered when interpreting the results. First, it is a retrospective study carried out at a single medical center. Second, *H. pylori* culture was not routinely applied to patients before triple therapy. It is generally believed that the main cause of *H. pylori* eradication failure is antibiotic drug resistance, especially clarithromycin.²⁷ Third, the genetic factors of the patients, including CYP2C19 and MDR polymorphisms, were not available. Finally, this study did not investigate the other medications being taken by patients during the treatment period, which may have had drug-drug interactions with the triple therapy regimens under investigation.

Conclusion

This study suggests that dexlansoprazole-based triple therapy has an acceptable eradication rate for *H. pylori* infection in real-world practice.

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Conflict of interest statement

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