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Randomised clinical trial: a comparative study of 10-day sequential therapy with 7-day standard triple therapy for *Helicobacter pylori* infection in naïve patients

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SUMMARY

Background
The eradication rates following standard triple therapy for *Helicobacter pylori* infection are declining worldwide. Recent studies have shown that sequential therapy for *H. pylori* infection yields high cure rates.

Aim
To compare the efficacy and tolerability of a sequential regimen as first-line treatment of *H. pylori* infection with a standard triple regimen.

Methods
A total of 348 naïve *H. pylori*-infected patients from six hospitals in Korea were assigned randomly to standard triple or sequential therapy groups. Standard triple therapy consisted of 20 mg of rabeprazole, 1 g of amoxicillin and 500 mg of clarithromycin, twice daily for 7 days. Sequential therapy consisted of a 5-day dual therapy (20 mg of rabeprazole and 1 g of amoxicillin, twice daily) followed by a 5-day triple therapy (20 mg of rabeprazole, 500 mg of clarithromycin, and 500 mg of metronidazole, twice daily).

Results
The intention-to-treat (ITT) and per-protocol (PP) eradication rates were 62.2% (95% CI 54.8–69.6%) and 76.0% (95% CI 68.5–83.5%) in the standard triple group, and 77.8% (95% CI 71.4–84.2%) and 87.9% (95% CI 82.3–93.5%) in the sequential group, respectively. The eradication rate was significantly higher in the sequential group compared with the standard triple group in both the ITT and PP populations ($P = 0.002$ and $P = 0.013$ respectively), whereas the incidence of adverse events was similar.

Conclusions
Ten-day sequential therapy is more effective and equally tolerated for eradication of *H. pylori* infection compared with standard triple therapy. Sequential therapy may have a role as first-line treatment for *H. pylori* infection.

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INTRODUCTION

Helicobacter pylori is well-known as a human pathogen that plays a cardinal role in patients with chronic gastritis, peptic ulcer disease and gastric malignancies.[1] According to the recent Asia-Pacific Consensus guideline, as well as European and American guidelines, the indications for *H. pylori* eradication are steadily increasing, including gastric cancer prevention in communities with a high incidence of gastric cancer and non-ulcer dyspepsia.[2–4] Therefore, management of *H. pylori* infection is of global interest. Triple therapy, consisting of a proton pump inhibitor, clarithromycin, and amoxicillin or metronidazole, has been the most recommended and used first-line therapy for the eradication of *H. pylori* in Europe and many other countries, including Korea.[2, 4, 5] However, the eradication rates for *H. pylori* have been declining and have reached an unacceptable levels (<80%) in many countries, even if the duration of treatment was prolonged.[6–10] *Helicobacter pylori* eradication failure has increased to nearly 25% in Korea.[11, 12] This finding may be partly from the increasing prevalence of antibiotic resistance, especially clarithromycin resistance, as is the case in other countries. Accordingly, a new strategy that overcomes the falling eradication rates is needed.

A novel, 10-day sequential therapy regimen, consisting of 5 days of simple dual treatment with a proton pump inhibitor plus amoxicillin, followed by 5 days of triple treatment with a proton pump inhibitor, clarithromycin and nitroimidazole, has been the focus of several studies because of the excellent efficacy.[13, 14] Recently, in a meta-analysis of 11 randomised, controlled trials, it was shown that the sequential treatment regimen achieved significantly higher eradication rates of >90% compared with standard triple therapy.[15] In Italy, the sequential therapy is now recognised as first-line therapy in the updated Italian guidelines on *H. pylori* management.[3] The majority of studies on sequential therapy have been performed in Italy and Europe and hence publication bias may exist.[9] A definite superiority of sequential therapy over the standard triple therapy should be confirmed in other geographical areas to be widely able to recommend as first-line *H. pylori* treatment in clinical practice. We expected that the sequential regimen would be a good alternative treatment for *H. pylori* eradication in the Korean population, considering that the clarithromycin resistance rate in Korea is similar to that in Europe.

The present study compared the eradication rates of a 10-day sequential regimen with a 7-day standard triple regimen in adult patients through a randomised, controlled trial. The secondary objective of the study was to evaluate the adherence and adverse events of both regimens.

METHODS

Patients

This open-label, randomised, controlled trial involved six clinics in Daegu and Kyungpook territories, and was conducted between May 2009 and December 2010. Consecutive patients with *H. pylori* infection who were >18 years of age and had never received treatment for *H. pylori* infection were recruited for the study. Exclusion criteria were as follows: (i) use of proton pump inhibitors, H2-receptor antagonists, a bismuth preparation, and antibiotics in the 2 weeks before enrolment; (ii) concomitant anticoagulant, nonsteroidal anti-inflammatory drugs, or ketoconazole use; (iii) previous surgery of the stomach, including endoscopic mucosal or submucosal resection for an adenoma or early gastric cancer; (iv) Zollinger–Ellison syndrome; (v) severe or unstable cardiovascular, pulmonary, or endocrine disease; (vi) clinically significant renal or hepatic disease or dysfunction; (vii) a haematological disorder; (viii) severe psychiatric or neurological disorders; and (ix) pregnancy or lactation, as well as sexually active women of child-bearing years who were not willing to practise reliable contraception for the duration of the study; (x) known allergy to the prescribed antibiotics. Patients fulfilling these criteria entered the study after providing written informed consent. The study was performed according to good clinical practice and the Declaration of Helsinki, and was approved by the ethics committees at each participating centre.

Detection of *Helicobacter pylori* infection

All patients underwent upper gastrointestinal endoscopy before enrolment in this study. For the purpose of the study, peptic ulcer was defined as a mucosal ulceration >5 mm in diameter in the stomach or duodenum. *H. pylori* infection was defined as positive if the results of two of the following three tests were positive: (i) a rapid urease test (ProntoDry; Medical Instruments Co., Herford, Germany) using samples from the antrum and the distal corpus; (ii) histological assessment of *H. pylori* by modified Giemsa or cresyl violet stain according to the Sydney system; and (iii) a ^{13}C-urea breath test (^{13}C-UBT). The UBT was performed after a >8-h fast. Specifically, a baseline breath sample was obtained, and 100 mg of ^{13}C-urea was administered as an aqueous

solution. The second breath sample was collected 30 min later. The test was considered positive if there was a >2.5 per 1000 of $^{13}CO_2$ difference over baseline.

Randomisation and intervention

A randomisation list was computer-generated by an external statistician. The patients were randomised in blocks of six without stratification. The randomisation list was kept by the study coordinator. The study coordinator was only involved in the randomisation in one of the participating centres. The patients were enrolled and treatment assignment ascertained by the study investigators. The patients were randomised into two treatment groups. The first group of subjects received a 10-day sequential regimen: 20 mg of rabeprazole, and 1 g of amoxicillin, twice daily for the first 5 days, followed by 20 mg of rabeprazole, 500 mg of clarithromycin and 500 mg of metronidazole twice daily for the remaining 5 days. The second group of subjects was administered a standard triple regimen: 20 mg of rabeprazole, 1 g of amoxicillin and 500 mg of clarithromycin twice daily for 7 days. Patients with ulcers on endoscopy were treated with acid suppressants for 4–6 weeks prior to antibiotic treatment. All patients including ulcer patients did not take any medications after the end of antibiotic treatment. Patients were offered a 7- or 10-day medication personal diary, and trained to write whether or not they took their prescribed medications and any adverse events they experienced. All patients with eradication failure were offered rescue therapy according to treatment guidelines for *H. pylori* infection in Korea.[16]

Measurements and outcomes

The primary outcomes of the study were the eradication rates of *H. pylori* infections with sequential and standard triple therapy. The secondary outcomes were to assess adherence and the frequency of adverse events of the two different eradication regimens.

Follow-up procedures

Patients were asked to return 4 weeks after the end of antibiotic treatment to undergo a ^{13}C-UBT to determine the outcome of eradication therapy, and assess treatment adherence and adverse events. The infection was considered to have been successfully eradicated when the ^{13}C-UBT was negative. This test had been shown to be as accurate as biopsy examination-based methods in determining the outcome of therapy. Medication adherence was defined as consumption of >90% of the prescribed drugs and was determined by pill counts and the medication personal diary. Adverse events were evaluated using a structured questionnaire and open-ended questions in the medication personal diary. Causality was assessed by using the temporal relationship of the symptom to the start of therapy.

Statistical analysis

We calculated a sample size of 156 to detect an 10% difference between a 80% eradication rate for the standard triple therapy and 90% for the sequential therapy with a power of 0.80 and a 2-sided $\alpha = 0.05$. Eradication rates of both regimens were estimated by a recent study performed in Korea. When we assumed a dropout rate of 10%, it was calculated that at least 174 patients per treatment group were needed. Both intention-to-treat (ITT) and per-protocol (PP) analyses were used for the assessment of the eradication rates of *H. pylori* infections in the two groups. The ITT analysis included all randomly assigned patients who had taken at least one dose of the study medications. The PP analysis was limited to patients who took >90% of the study medications and completed follow-up. Statistical analysis of the results was performed using a chi-square test, Student's *t*-test and Fisher's exact test. For all analyses, *P* values <0.05 were considered significant. The 95% confidence intervals (CIs) were calculated by normal approximation. The analysis was performed using SPSS for Windows (version 18; SPSS Inc., Chicago, IL, USA).

RESULTS

Patients

Figure 1 shows the flow of patients through the study. Initially, a total of 348 patients with *H. pylori* infection were enrolled and randomly assigned to sequential ($n = 174$) or standard ($n = 174$) therapies. However, 22 subjects formally withdrew their informed consent to participate in the study shortly after randomisation. Therefore, 326 of total 348 patients (162 patients randomised to a sequential therapy group and 164 patients randomised to a standard therapy group) were included in this study. As shown in Table 1, demographic and clinical characteristics at baseline were similar between the two treatment groups. Overall, 46 patients (19 patients randomised to the sequential treatment and 27 allocated to the standard treatment) did not undergo a ^{13}C-UBT after treatment because of loss of follow-up. Twenty-three patients consumed <90% of the prescribed medications. Therefore, the final PP population consisted of 257 patients.

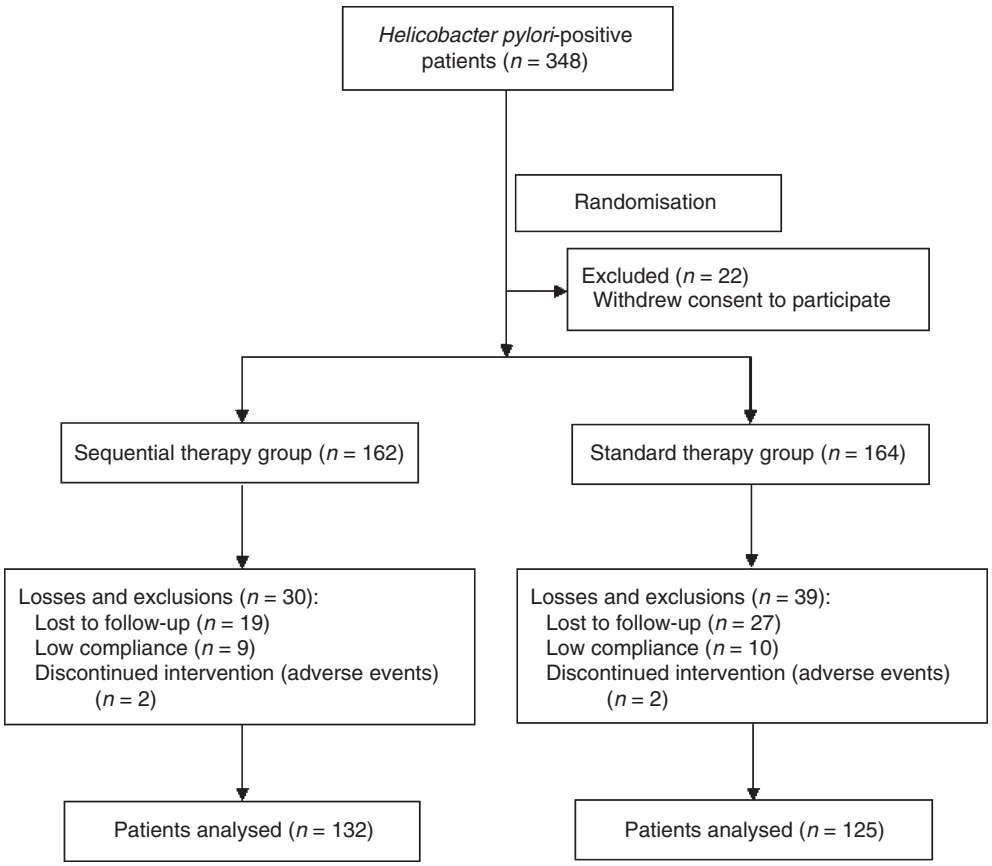

Figure 1 | Flowchart of participants through study.

Table 1 | Baseline demographic and clinical characteristics of the patients

Characteristic	Sequential therapy (*n* = 162)	Standard therapy (*n* = 164)
Gender		
Male	93 (57%)	81 (49%)
Female	69 (43%)	83 (51%)
Age (mean ± s.d.), years	52.4 ± 10.6	53.1 ± 14.3
Smoking	57 (35.2%)	42 (25.6%)
Endoscopic findings		
Gastric ulcer	58 (35.8%)	53 (32.3%)
Duodenal ulcer	7 (4.3%)	19 (11.6%)
Gastric ulcer + duodenal ulcer	2 (1.2%)	4 (2.4%)
Peptic ulcer scar	40 (24.7%)	38 (23.2%)
Gastritis	55 (34.0%)	50 (30.5%)
H. pylori colonisation*		
Mild	37 (38.1%)	32 (36.8%)
Moderate	34 (35.1%)	32 (36.8%)
Marked	26 (26.8%)	23 (26.4%)

* Data were available for 97 and 87 patients, in the sequential and standard therapy groups, respectively.

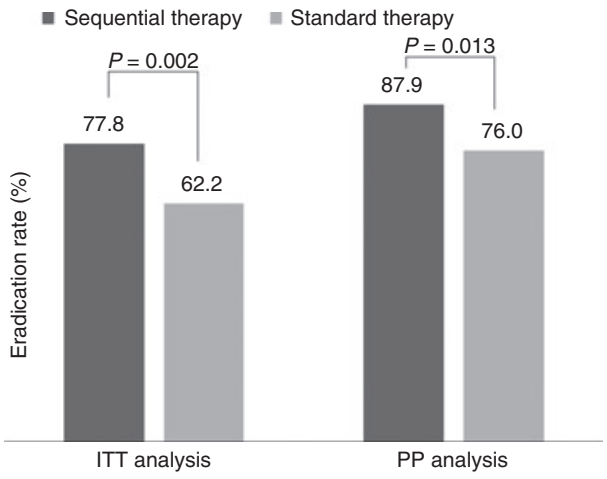

Figure 2 | *Helicobacter pylori* eradication rates of the treatment groups according to the ITT and PP analysis. ITT, intention-to-treat; PP, per protocol.

Eradication rates

As illustrated in Figure 2, the eradication rates achieved by sequential therapy were significantly higher as compared with standard therapy based on ITT (77.8%, 95% CI 71.4–84.2% vs. 62.2%, 95 CI 54.8–69.6%, $P = 0.002$) and PP analyses (87.9%, 95 CI 82.3–93.5% vs. 76.0%, 95% CI 68.5–83.5%, $P = 0.013$). The odds ratio for eradication of *H. pylori* with sequential therapy compared with standard therapy was 0.44 (95% CI 0.26–0.85). The data in Table 2 demonstrate that gender, age, smoking habit, endoscopic findings, the histologically visible degree of *H. pylori* colonisation and compliance did not influence eradication rates with sequential therapy.

Adherence and adverse events

The complete follow-up rate was not significantly different between the two groups (88.3% vs. 83.5%, $P = 0.219$). A total of 132 (92.3%) patients in the sequential therapy group and 125 (92.1%) patients in the standard therapy group adhered to the treatment (>90% of prescribed medications). There was no significantly difference between the two groups ($P = 0.745$). Forty patients (28%) treated with the sequential regimen and 35 patients (25.5%) who receive the standard therapy reported at least one adverse event. The incidence of adverse events was similar between the two groups ($P = 0.647$). In the sequential group, the most frequently reported adverse events were abdominal bloating, a bitter

Table 2 | Univariate analysis of the clinical factors influencing therapeutic outcome of the two regimens

Factor	Sequential therapy	*P* value	Standard therapy	*P* value
Gender				
Male	88.8% (71/80)	0.790	72.6% (53/73)	0.596
Female	87.3% (55/63)		76.6% (49/64)	
Age				
<60	85.3% (97/113)	0.124	72.6% (53/73)	0.125
≥60	96.7% (29/30)		76.6% (49/64)	
Smoking				
Nonsmoker	87.4% (83/95)	0.790	75.2% (76/101)	0.721
Current smoker	89.6% (43/48)		72.2% (26/36)	
Endoscopic finding				
Ulcer-related*	83.9% (78/93)	0.055	70.5% (67/95)	0.113
Non-ulcer related	96.0% (48/50)		83.3% (35/42)	
H. pylori colonisation†				
Low	87.9% (29/33)	1.000	76.9% (20/26)	0.247
High	86.3% (44/51))		63.6% (28/44)	
Compliance				
Good	87.9% (116/132)	1.000	76.0% (95/125)	0.296
Poor	90.9% (10/11)		58.3% (7/12)	

* 'Ulcer-related' endoscopic findings include a peptic ulcer scar.

† Low- and high- *H. pylori* colonisation corresponds to 'mild' and 'moderate' or 'marked' colonisation, respectively.

Table 3 | Adverse events in the sequential therapy and standard triple therapy

Adverse events	Sequential therapy (n = 143), n (%)	Standard therapy (n = 137), n (%)	P value
Diarrhoea	7 (4.9)	10 (7.3)	0.459
Abdominal bloating	9 (6.3)	7 (5.1)	0.799
Bitter taste	8 (5.6)	6 (4.4)	0.786
Regurgitation	6 (4.2)	8 (5.8)	0.591
Epigastric pain	6 (4.2)	2 (1.5)	0.283
Headache	5 (3.5)	3 (2.2)	0.723
Glossitis	4 (2.8)	3 (2.2)	1.000
Fatigue	3 (2.1)	1 (0.7)	0.623
Constipation	2 (1.4)	5 (3.6)	0.274
Vomiting	3 (2.1)	0	0.248
Abdominal pain	1 (0.7)	2 (1.5)	0.616
Nausea	1 (0.7)	2 (1.5)	0.616
Vaginitis	1 (0.7)	2 (1.5)	0.616
Rash	1 (0.7)	2 (1.5)	0.616
Itching	0	2 (1.5)	0.239
Dry mouth	0	2 (1.5)	0.239
Dizziness	0	1 (0.7)	0.489
Total	40 (28.0)	35 (25.5)	0.647
Withdrawal due to AE	2 (1.4)	2 (1.5)	1.000
Adherence<90%	9 (6.3)	10 (7.3)	0.738

AE, adverse events.

taste and diarrhoea. In the standard group, diarrhoea, abdominal bloating, and regurgitation of stomach contents were also most common. One patient each in the sequential group discontinued treatment because of a skin rash and diarrhoea. One patient each in the standard group stopped treatment due to diarrhoea and headache. All adverse events were self-limiting after therapy ended. The adverse events are summarised in Table 3.

DISCUSSION

We conducted a novel, prospective, multi-centre, randomised, controlled study to compare the efficacy of 10-day sequential therapy with 7-day standard triple therapy for the eradication of *H. pylori* infection in naïve patients in Korea. The results of this study demonstrate that sequential therapy significantly improves the eradication rate of *H. pylori* as compared with standard therapy. Moreover, the sequential regimen was equally well-accepted and tolerated with similar rates of self-limiting adverse events compared with the standard triple regimen.

Current guidelines recommend triple therapies, consisting of a proton pump inhibitor plus clarithromycin and amoxicillin or metronidazole, as the first-line treatment for eradication of *H. pylori* infections worldwide.[2, 4, 5] Early studies of first-line standard triple therapies demonstrated eradication rates of >85%.[10, 17, 18] However, over the past 10 years, a critical fall in the efficacy of these therapies has been observed in the United States, Europe and Asia.[19–24] Indeed, a meta-analysis including >53 000 patients reported that the eradication rate is below 80%[10] and a review from single centre in Korea showed that yearly eradication rates of triple therapy between 1998 and 2005 were 83.7%, 80.4%, 81.4%, 78.8%, 75.3%, 77.6%, 78.9%, and 77.6% respectively, by PP analysis.[11] Our study confirms these reports on the disappointingly low cure rates with standard triple treatment (62.2% in the ITT population and 76.0% in the PP population). This finding is most likely a result of increased bacterial resistance to antibiotics, particularly clarithromycin.[25] Indeed, a systematic review of *H. pylori* eradication therapy by Houben *et al.*[26] reported that with respect to clarithromycin

resistance, a mean drop in efficacy of 56% was found for clarithromycin-containing regimens. Another study also showed that when considering clarithromycin or nitroimidazole resistance alone, there was a 70% and 25% decrease in the success rate compared with clarithromycin and nitroimidazole susceptible strains respectively (18.3% vs. 87.8%; and 72.6% vs. 97%).[25] Thus, nitroimidazole resistance is less clinically significant than clarithromycin resistance. Several studies have reported that clarithromycin-resistant *H. pylori* strains had continuously increased from 1987–2009 in Korean patients (2.8% in 1987, 16.7% in 2005, and 38.5% in 2007–2009).[27–30]

To improve the efficacy of first-line therapy in a setting with a high prevalence of clarithromycin-resistant *H. pylori* strains, several therapeutic strategies have been proposed. Attempts to extend the duration of triple therapy from 7 days to 10 or 14 days have achieved controversial results, but in general have not resulted in a remarkable benefit.[6, 31] Indeed, a recent study conducted in Korea reported that the eradication rates of a standard triple regimen did not differ, even if the duration of treatment was prolonged from 1 to 2 weeks.[7] It has been proposed that quadruple therapy (proton pump inhibitor, bismuth salt, tetracycline, and metronidazole) may increase the success rate of eradicating *H. pylori* infections. In two large, randomised, controlled trials in which quadruple therapy was compared with triple therapy, the quadruple regimen was proven as effective as the triple regimen, but not better in the treatment of *H. pylori* infections.[32, 33] Levofloxacin-based triple therapy instead of clarithromycin may be another alternative. A recent meta-analysis of 14 studies involving 977 patients demonstrated that levofloxacin-based regimens increased eradication rates by 10% compared with quadruple therapy.[34] The problem is that the eradication rate of levofloxacin-based triple therapy is <80%, and primary levofloxacin-resistant strains are rapidly increasing.[35] In fact, a recent study showed a high prevalence of levofloxacin resistance (29.5%) in *H. pylori* strains isolated from Korean patients.[30] Nonbismuth quadruple therapy (PPI-clarithromycin-amoxicillin-nitroimidazole) for 7 or 10 days has been shown to be more effective than triple therapy.[36] However, most studies evaluating the concomitant regimen have a number of limitations, including relatively old data, small sample size and low quality of studies. So, further well-designed studies are needed to confirm the superiority of concomitant therapy.

Sequential therapy was introduced as a novel therapeutic approach for *H. pylori* eradication by Zullo *et al.*[37] in 2000. This regimen is strictly an innovative approach rather than a new strategy because it is based on a different combination of well-known drugs with an approved indication for *H. pylori* eradication. In a prospective, randomised controlled trial, Zullo *et al.*[38] reported eradication rates for sequential therapy of 92% by ITT and 95% by PP analyses. Since then, many trials have reported superiority of sequential therapy over standard triple therapy. Several meta-analyses and pooled analyses have demonstrated that eradication rates with sequential therapy were >90% compared with <80% for standard triple therapy.[9, 15, 39] Moreover, in a recent meta-analysis, which included all 15 randomised-controlled studies and >3000 patients, the sequential regimen was more effective than the standard triple therapy (91.7% vs. 76.7%) based on ITT analysis.[40] Nevertheless, American, European and Asian-Pacific guidelines do not recommend sequential therapy as an alternative first-line for *H. pylori* therapy because nearly all of the trials analysing sequential therapy have been conducted in Italy, and thus the advantage of a sequential regimen over a triple regimen lacks validation outside of Italy.[2, 4, 5] Nevertheless, there are some data which have emerged outside of Italy. A trial conducted in Turkey, where clarithromycin resistance is highly prevalent, demonstrated that sequential therapy eradicated *H. pylori* in 77.6% of patients according to PP analysis, and was 25% more effective than triple therapy.[41] An uncontrolled study in Thailand and a randomised controlled trial in Taiwan reported a high eradication rate (93–95%) with the sequential regimen.[42, 43] Only a few studies on sequential therapy have been conducted in Korea. One trial demonstrated that eradication rates of 10-day sequential treatment and triple treatment were 77.9% and 71.6% by ITT analysis, respectively, and 85.7% and 76.6% by PP analysis respectively.[8] This difference failed to reach statistical significance, which may reflect the small sample size. Indeed, a previous study and our study had similar eradication rates, but patients enrolled in our study were 2-fold greater in number than in the other study, and our results reached statistical significance. Another study showed promising data: specifically, high success rate (92%) was reported with sequential therapy in clinical practice.[44] However, the findings were limited by a retrospective study design, no complete comparison with standard triple therapy and single centre experience with a small sample size.

In the present study, eradication rates of sequential therapy were somewhat lower than >90% reported in original studies and subsequent meta-analyses.[21, 38, 43, 45] First, this may be associated with the type of nitroimidazole used. In Italian studies, tinidazole has been used, while we treated with a metronidazole-based regimen. Indeed, a recent review showed that the eradication rate achieved with a metronidazole-based regimen was significantly lower than a tinidazole-based regimen.[46] A markedly longer half-life of tinidazole as compared with metronidazole may explain such a phenomenon.[47] Second, this may be related to geographical variations in the prevalence of *H. pylori* resistance to antibiotics. In fact, in a randomised trial reporting, an eradication rate of 93% with a sequential regimen based on PP analysis, the prevalence of clarithromycin and dual resistance (i.e. clarithromycin + metronidazole) was 12.5% and 4.3% respectively.[21] Similarly, a recent study by Wu *et al.*[43] reported an eradication rate of 93.1% with a sequential regimen based on PP analysis and demonstrated that the prevalence of clarithromycin and dual resistance was 6.6% and 4.2% respectively: patients with dual resistance had significantly lower cure rates than patients without dual resistance. We did not determine *H. pylori* resistance or antibiotic sensitivity in this study, but when considering these measures in our area, clarithromycin and dual resistance have been reported to range from 16% to 38% and 7.7% respectively.[30, 48] We can assume that relatively low eradication rates with sequential therapy in the present study may, in part, be due to the high prevalence of antibiotic-resistant *H. pylori* strains, especially dual resistance, in our study population.

According to Graham *et al.*,[49, 50] sequential therapy is not an ideal regimen because our result corresponds to a grade C (cure rate: 86–89%, per protocol) in the report card for scoring the outcome of anti-*H. pylori* therapy. However, sequential therapy has been shown to achieve better eradication rates than triple therapy and triple therapy uniformly has scored as a bad therapy (grade F). Therefore, we believe that triple therapy should no longer be used as a first-line anti-*H. pylori* regimen and sequential treatment may be a promising therapeutic approach, at least for now.

In our study, the eradication rates following a sequential regimen were not significantly affected by the histologically visible degree of *H. pylori* colonisation, endoscopic findings, and smoking habit. This result is consistent with other previous studies.[14, 43, 45] No significant influence of the risk factors associated with triple therapy failure on the efficacy of sequential treatment is another possible advantage of sequential therapy.

This study had some limitations. One limitation was that culture of *H. pylori* was not performed, and no data on susceptibility of *H. pylori* to antibiotics are available. Instead, information on antibiotic resistance for *H. pylori* reported in previous studies of the Korean population was referred.[27, 48, 51] Moreover, the effect of antimicrobial resistance in standard triple and sequential therapies is well known. Another limitation was the fact that we observed a higher rate of loss to follow-up than expected, and reported in other studies. In clinical practice conditions, higher rates of noncompliance and dropout during follow-up are to be expected because sequential therapy may be rather complex.

In conclusion, this novel, large, multi-centre, randomised, prospective clinical trial on sequential therapy conducted in Asia demonstrated that 10-day sequential therapy for the eradication of *H. pylori* infections is significantly superior to standard triple therapy and well-tolerated. Considering the currently disappointing low cure rate after standard triple therapy, which was confirmed in this study, our data suggest that sequential treatment may be a valid alternative to current first-line treatment for *H. pylori* eradication, even though our study did not achieve excellent eradication rates (>90%) with sequential therapy. Further studies from other countries where data on sequential therapy is still lacking, including our area, are needed to validate sequential therapy as first-line therapy for the management of *H. pylori* infection.

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