

Comparative Study of Using Different Dosages and Regimens of Esomeprazole in Treating *Helicobacter pylori*-related Peptic Ulcer Disease

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Abstract

Proton-pump inhibitor-based triple therapy is currently the mainstay for eradication of *H. pylori* infection and peptic ulcer disease. Esomeprazole-based triple therapy was verified in many publications to achieve acceptable ulcer healing rate and eradication rate of *H. pylori* infection. However, comparison of different triple therapy in eradication of *H. pylori* infection is seldom mentioned. This clinical trial is aimed to compare the effects of two different dosage of esomeprazole (40 mg or 20 mg twice daily) and different antibiotic combination in eradication rate of *H. pylori* infection and peptic ulcer healing rate. From Feb. 2003 to Oct. 2009, we collected 272 patients (female: 42%; age: 53.8 ± 15.2 yr) with investigated *H. pylori* related peptic ulcer disease (gastric ulcer or duodenal ulcer) and then randomly assigned all the patients into four groups for treatment. Group A: E 40mg, M 500mg, C 250mg; Group B: E 20mg, M 500mg, C 250mg; Group C: E 40mg, A 1000mg, C 500mg; Group D: E 20mg, A 1000mg, C 500mg (E: esomeprazole, M: metronidazole, C: clarithromycin, A: amoxicillin). Diagnosis of peptic ulcer disease was made via esophagogastroduodenoscopy (EGD). Eradication was confirmed at least four months after completion of treatment by means of urea breath test (UBT), rapid urease test or histology. After treatment, repeated EGD was performed in 170 patients for confirmation of ulcer healing in addition to the rapid urease test or biopsy which is mandatory for confirmation of eradication. Another seven patients who were reluctant to receive secondary EGD underwent UBT only. Based on per-protocol analysis, *H. pylori* eradication among group A is 89.6%, group B 86.7 %, group C 97.5% and group D 93.2%. Ulcer healing rate among group A is 95.6%, group B 91.1%, group C 97.4% and group D 100%. There was no statistically significant difference in either eradication or ulcer healing rate among 4 groups. By intention-to-treat analysis, *H. pylori* eradication rates among four groups are much lower and reported 63.2%, 57.4%, 57.4% and 60.3% respectively. Moreover, the per-protocol overall eradication rate was 91.53% (162/177); while overall ulcer healing rate was 95.88% (163/170). Esomeprazole 20 mg based triple therapy appears to be as effective as standard esomeprazole 40 mg based triple therapy. In the era of high health care expenditure, reducing the cost of treatment but not sacrificing efficacy may be worthwhile. (J Intern Med Taiwan 2011; 22: 183-191)

Key Words: *H. pylori*, Esomeprazole, Peptic ulcer disease

Introduction

Helicobacter pylori infection is one of the most common worldwide infections. The bacterium causes peptic ulcers, gastric mucosa-associated lymphoid tissue lymphoma, and gastric cancer. As the majority of cases with peptic ulcer disease are caused by infection with *H. pylori*^{1,2}, eradication therapy is the current universally accepted recommendation for peptic ulcer disease associated with *H. pylori* infection^{3,4}. The World Health Organization has categorized *H. pylori* infection as a category I carcinogen and causal agent of human gastric cancer⁵, so it is important to eradicate *H. pylori* infection in patients with peptic ulcer disease. Moreover, a recent Taiwan study eluded that early *H. pylori* eradication is associated with decreased risk of gastric cancer in patients with peptic ulcer diseases based on a nationwide cohort study⁶.

The treatment of *H. pylori* remains a challenging clinical problem despite extensive research over the last 25 years. Benzimidazole compound such as esomeprazole was the first gastric parietal cell proton pump inhibitor (PPI) widely used for the treatment of acid-related gastric diseases due to their ability to inhibit acid secretion. Esomeprazole, the S-isomer of omeprazole (a racemic mixture of S- and R-optical isomers), was the first PPI to be developed as a single optical isomer⁷⁻¹¹. On one hand, esomeprazole provides better control of intra-gastric pH than other PPIs¹². On the other hand, esomeprazole has a higher degree of activity against *H. pylori* than other PPIs such as omeprazole¹³. Therefore, these characteristics support its efficacy in the treatment of acid-related diseases, as well as for *H. pylori* treatment regimens¹⁴⁻¹⁶.

The second Maastricht Consensus Report agreed that effective treatment for *H. pylori* should achieve an intention-to-treat (ITT) eradication rate of over 80%³. Proton pump inhibitor (PPI)-based

triple therapy has been the first-line treatment of choice for over two decades. The traditional first-line treatment is a PPI (twice a day), amoxicillin (1 g twice a day) or metronidazole (500 mg twice a day), and clarithromycin (250 or 500 mg twice a day) for 7 days. This regimen was still recommended at the Maastricht III Consensus Conference held in 2005 and in the recently published report¹⁷.

Determining a comparable dosage of esomeprazole, several large-scale studies¹⁸⁻²¹ disclosed that the equivalent 20-mg dosage of omeprazole and esomeprazole (instead of current 40-mg esomeprazole) in triple therapy both achieved a similarly high *H. pylori* eradication rate for duodenal ulcer patients. More recent studies focused on 40-mg esomeprazole based triple therapy in eradication of *H. pylori* and reported equivalent or slightly higher eradication rate in certain circumstance^{22,23}.

The reimbursement of medication is the largest part of health care expenditure in Taiwan and other countries. Together with these antecedents and the goal of decreasing the health care expenditure worldwide, our aim was to study the efficacy of esomeprazole-based triple therapy in *H. pylori* eradication and to evaluate, by a randomized trial, the effect of decreasing the dose of esomeprazole (from 40 to 20 mg), and the different combination of antibiotics.

Materials and methods

Design overview

This was a prospective, randomized, comparative study with intention-to-treat and per-protocol analysis of eradication and ulcer healing rate. Written informed consent was obtained from all patients. This study was performed according to good clinical practice and the Declaration of Helsinki; also, study protocol was approved by the ethics institutional review board of our hospital.

Settings and participants

Between March 2003 and June 2005, patients

with investigated (all by esophagogastroduodenoscopy) gastric or duodenal ulcer who were at least 18 years of age, who had never received treatment for *H. pylori* infection, were enrolled from outpatient department in one medical center in Taipei, Taiwan. The exclusion criteria are as followings: (a) use of antibiotics, bismuth salts or nonsteroidal anti-inflammatory drugs during the previous two weeks; (b) severe or unstable cardiovascular, pulmonary, or endocrine disease; clinically significant renal or hepatic disease or dysfunction; (c) documented allergy to any of the antibiotics used in triple therapy; (d) pregnancy.

After completion of eradication regimen, daily esomeprazole 40 mg for additional 3 to 4 weeks was allowed to relieve patient's pain and accelerate ulcer healing. Repeated EGD was mandatory to evaluate ulcer healing and simultaneously confirmation for *H. pylori* eradication by rapid urease test at least four months after the initiation of eradication therapy according to our study protocol. The end of follow up period for last patient was in April, 2008.

Therapy

Four regimens were administered for 7 days in a randomized order: (a) esomeprazole (40 mg b.i.d.), metronidazole (500 mg b.i.d) and clarithromycin (250 mg b.i.d.) (E40 M500 C250); (b) esomeprazole (20 mg b.i.d.), metronidazole (500 mg b.i.d) and clarithromycin (250 mg b.i.d.) (E20 M500 C250); (c) esomeprazole (40 mg b.i.d.), amoxicillin (1 g b.i.d.), clarithromycin (500 mg b.i.d) (E40 A1000 C500); and (d) esomeprazole (20 mg b.i.d.), amoxicillin (1 g b.i.d.), clarithromycin (500 mg b.i.d) (E20 A1000 C500). Randomization was carried out using a table of contingent numbers, by blocks, and patients were blinded to the therapy. Concealment of allocation of the sequence of randomization was performed. Patients were advised of the possibility of having a metallic taste and diarrhea during the treatment period. Adverse events were assessed

after completion of therapy when returned to outpatient department.

Confirmation of *H. pylori* eradication

H. pylori infection at entry was determined by at least one of the following tests: urea breath test (UBT), histology or rapid urease test. Among patients who agreed to receive second EGD, ulcer healing was observed and eradication was evaluated with the rapid urease test (N=162) or biopsy (N=8) except for 7 patients (3 in Group A, 2 in Group C and 2 in Group D) who refused second EGD received UBT for confirmation of eradication only. UBT was done after an overnight fast. A baseline breath sample was obtained, and 75 mg of ¹³C urea with citric acid (1.5 g) was administered as an aqueous solution. The results of the test were considered positive if the difference between the baseline sample and the 30-minute sample exceeded 4.5 parts per 1000 of ¹³CO₂. The sensitivity and specificity values of UBT were reported 94.7% and 95.7%, respectively²⁴.

Measurements and outcomes

This analysis assumed a 90% eradication rate in the E₄₀ A₁₀₀₀ C₅₀₀ group and a 85% eradication rate in other groups, with the use of a two-sided t-test, a significance level of 5%. Quantitative variables were given as means ± SD, and *p*-values lower than 0.05 were considered significant. All the calculations were performed using the STATA version 11 software (Stata Corporation, Texas, USA).

Results

Patients

In total, two hundred seventy-two (272) peptic ulcer patients were initially included in the study and randomly assigned to four regimen groups. Each group had 68 patients. The distribution of the demographic characteristics in the four groups is summarized in Table 1.

Compliance with the Protocol and Loss from

Follow-up

Twenty three patients (33.8%) in group A, 23 (33.8%) in group B, 30 (44.1%) in group C and 26 (38.2%) in group D did not return for second endoscopy and confirmation of *H. pylori* eradication. All patients but four (two in group A, one in group C and one in group D) were compliant (>80% of the prescribed treatment were taken). Therefore, compliance of four regimen group was comparable and similar. Totally, one hundred and seventy patients (170) returned for second EGD for ulcer healing assessment (Table 2) and simultaneously for confirmation of *H. pylori* eradication by rapid urease test. Seven patients who refused second EGD agreed self-paid UBT for confirmation of *H. pylori* eradication (Figure 1).

Effect of therapy on *H. pylori* eradication and ulcer healing

By per-protocol analysis, *H. pylori* eradication in group A is 89.6 % (95% CI = 81–98%), group B 86.7 % (95% CI = 76–96%), group C 97.5% (95% CI = 93–99%) and group D 93.2% (95% CI = 85–99%). The overall eradication rate was 91.53% (162/177). The highest eradication rate (97.5%) is found in group C regimen, but not superior to the lowest one (86.7 %) in group B (p=0.07). Figure 2 shows the comparison and efficacy among the four regimen groups. They are all statistically insignificant between related groups. By intention-to-treat analysis, *H. pylori* eradication rates among four groups are 63.2%, 57.4%, 57.4% and 60.3% respectively and similarly, none is superior to one another.

Table 1. Distributions of demographic characteristics

Group	No.	M/F	Age (Mean ± SD) y/o	Follow up months	No. Eradication (n=177)	No. Healed (n=170)
A	68	29/39	53.5 ± 14.7	9.4 ± 10.5	43/48	43/45
B	68	27/41	54.8 ± 14.2	7.9 ± 8.7	39/45	41/45
C	68	29/39	58.6 ± 13.7	12.6 ± 15.6	39/40	37/38
D	68	26/42	53.6 ± 15.6	8.8 ± 8.9	41/44	42/42

Male to female ratio (M/F), age and follow up months are not statistically different in each group.

Table 2. Details of distribution of ulcer types (First and second EGD) in each treatment group

	Group A		Group B		Group C		Group D		Total	
	ITT	PP	ITT	PP	ITT	PP	ITT	PP	ITT	PP
GU	16	9	15	12	17	12	22	12	70	45
DU	48	31	49	30	43	23	39	25	179	109
GU+DU	6	5	4	3	8	3	7	5	25	16
	68	45	68	45	68	38	68	42	272	170

GU: Gastric ulcer; DU: Duodenal ulcer.

Table 3. Results of intention-to-treat and per-protocol analysis

	A		B		C		D		Overall	
	<i>H. pylori</i> erad. %	Ulcer healed %								
Intention-to-treat	63.2	67.6	57.4	60.3	57.4	57.4	60.3	64.7	59.6	62.5
Per-protocol	89.6	95.6	86.7	91.1	97.5	97.4	93.2	100	91.53	95.88

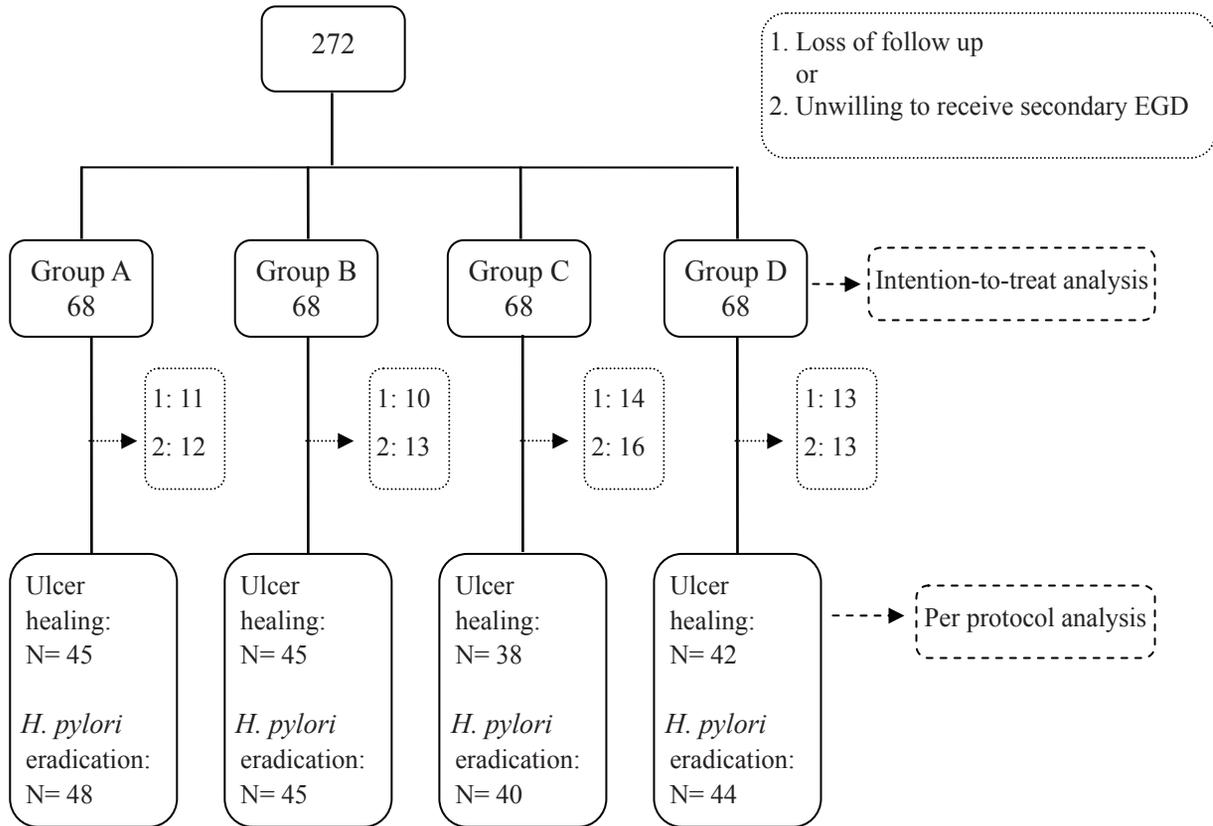


Figure 1. Shows the *H. pylori* eradication flow diagram of subject progress through the phases of the study.

By per-protocol analysis, ulcer healing rate in group A is 95.6% (95% CI = 91–99%), group B 91.1% (95% CI = 83–99%), group C 97.4% (95% CI = 93–99%) and group D 100% (Figure 3). The overall ulcer healing rate was 95.88 % (163/170). All ulcer healing rates among the four groups are over 90% and are also not statistically significant between related groups.

Adverse events

Of the total two hundred seventy-two (272) patients initially enrolled in this study, no severe adverse effect was reported. Two patients in group A reported dizziness and abdominal discomfort respectively and thus failed to be compliant while none in group B had any adverse effect. In group C, seven patients experienced metallic taste alternation while another two had nausea, dizziness sensation and one suffered from muscle cramping. In group D, five patients reported metallic taste, two had

loose stool and two had mild diarrhea. No differences according to type of symptoms were found among the four groups. Symptoms were limited to the duration of treatment in most patients, and no differences in the duration of symptoms were found between groups.

Discussion

As all comparative trials included in the meta-analysis²⁵ used esomeprazole at a dosage of 20 mg b.i.d., it was desirable to have further studies evaluating the current "standard" dose for this PPI of 40 mg given b.i.d., as our study. In group A and B, as we can see from the results, the eradication rate is quite similar among these two groups with different dosage of PPI (89.6% v.s. 86.7%, p=0.398). Although higher eradication rate is observed in group C (97.5%) with standard dosage of esomeprazole, it is still not statistically significant.

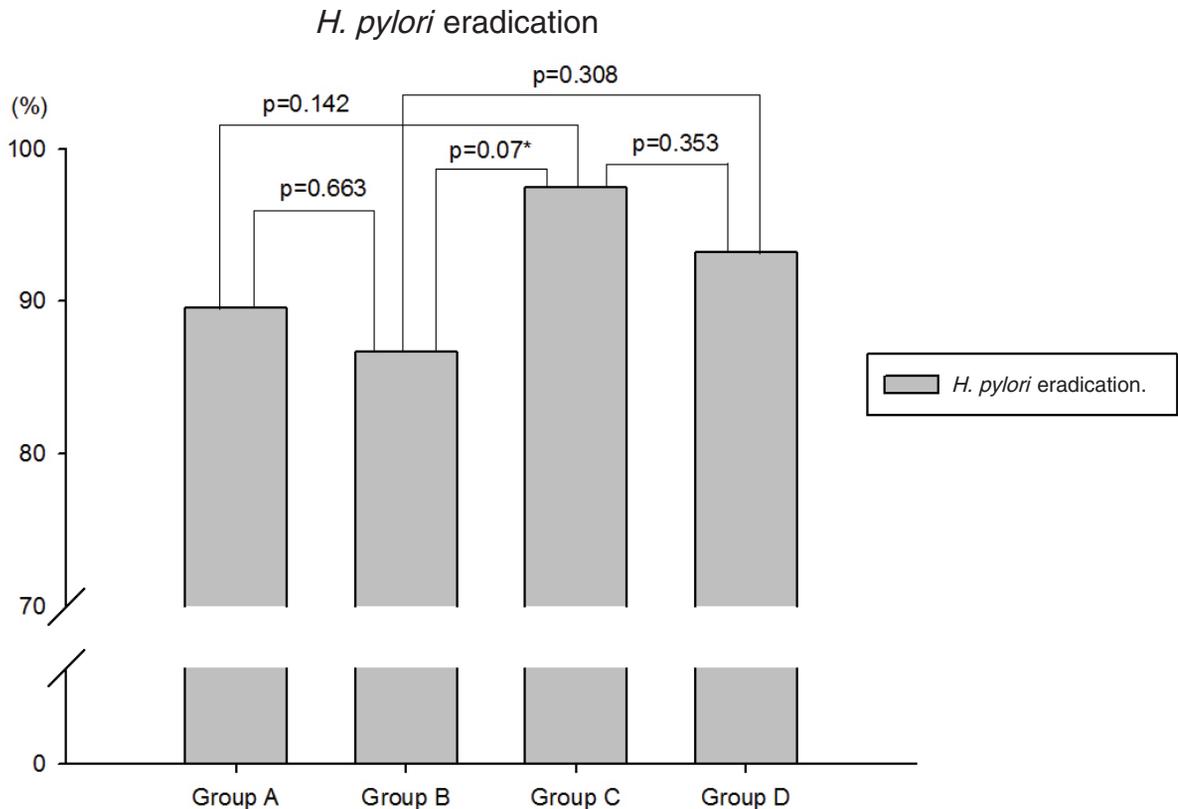
(97.5% v.s. 93.2%. $p=0.29$). Concerning about the eradication rate of *H. pylori*, we found from this study that half dosage (20mg) of esomeprazole-based triple therapy does not appear to be inferior to standard dosage of esomeprazole-based triple therapy.

In this study, group C and D regimen both achieved excellent eradication rates (>93%) and seemed to be more effective than the other treatment regimen in eradication of *H. pylori*. Therefore, we further analyze the effectiveness of the two regimens by pooling group A with B and group C with D. Although the pooled eradication rate of esomeprazole, metronidazole and clarithromycin (250mg) is a little bit lower than that of

esomeprazole, amoxicillin and clarithromycin (500 mg), we still can't see any significance of inferiority (88.2% v.s. 95.2%, $p=0.196$).

As for the concern of case numbers enrolled and the power to distinguish the four treatment groups for superiority; based on the results from our study, using Z test for power calculation, the power was 65% for Group B vs. C, 47% for Group A vs. C, and 22% for Group C vs. D, respectively and somewhat underpowered.

One may doubt the use of different clarithromycin dosage. As we can see from a meta-analysis study [26] which included dozens of published data, most studies used clarithromycin (250mg b.i.d.) to couple with metronidazole and clarithromycin (500



* $E_{40}A_{1000}C_{500}$ is superior to $E_{20}M_{500}C_{250}$ with marginal statistical Significance.

Group A: E 40mg, M 500mg, C 250mg; Group B: E 20mg, M 500mg, C 250mg;
 Group C: E 40mg, A 1000mg, C 500mg; Group D: E 20mg, A 1000mg, C 500mg

Figure 2. The comparison and efficacy of *H. pylori* eradication among the four regimen groups (Total: 177).

mg b.i.d) to couple with amoxicillin. From our study, neither different dosage of clarithromycin nor different regimen can be superior to the others.

Cost is a major consideration in many countries with high health care expenditure. For the less expensive, lower dose of esomeprazole-based triple therapy (group B: 86.7% eradication rate), the eradication rate is fair and not inferior to the more expensive standard dose esomeprazole-based triple therapy (group C: 97.5%) ($p=0.07$). The total cost is actually much less (US \$:22 v.s US \$:42, calculated based on the reimbursement price of Taiwan Bureau of National Health Insurance).

There are some limitations in this study. First, eradication rate of intention-to-treat analysis is quite low and did not reach the level of 80%, which is much lower than other published data.

The difference results from the cost of confirmation of eradication as the UBT is paid by patients themselves since this study was not sponsored by any organization or through agent. The other reason why the patients are not willing to return for confirmation despite initial agreement to return for second EGD, is that the patients tended to refuse because of relieved symptoms subjectively after treatment. Furthermore, there is no incentive for them to return for confirmation. Another limitation of this study is that we were not able to analyze the risk factors associated with treatment failure, such as clarithromycin or metronidazole resistance, the absence of the CagA gene, smoking habit etc.

In conclusion, esomeprazole 20 mg based triple therapy is as effective as standard esomeprazole 40 mg based triple therapy. In areas or

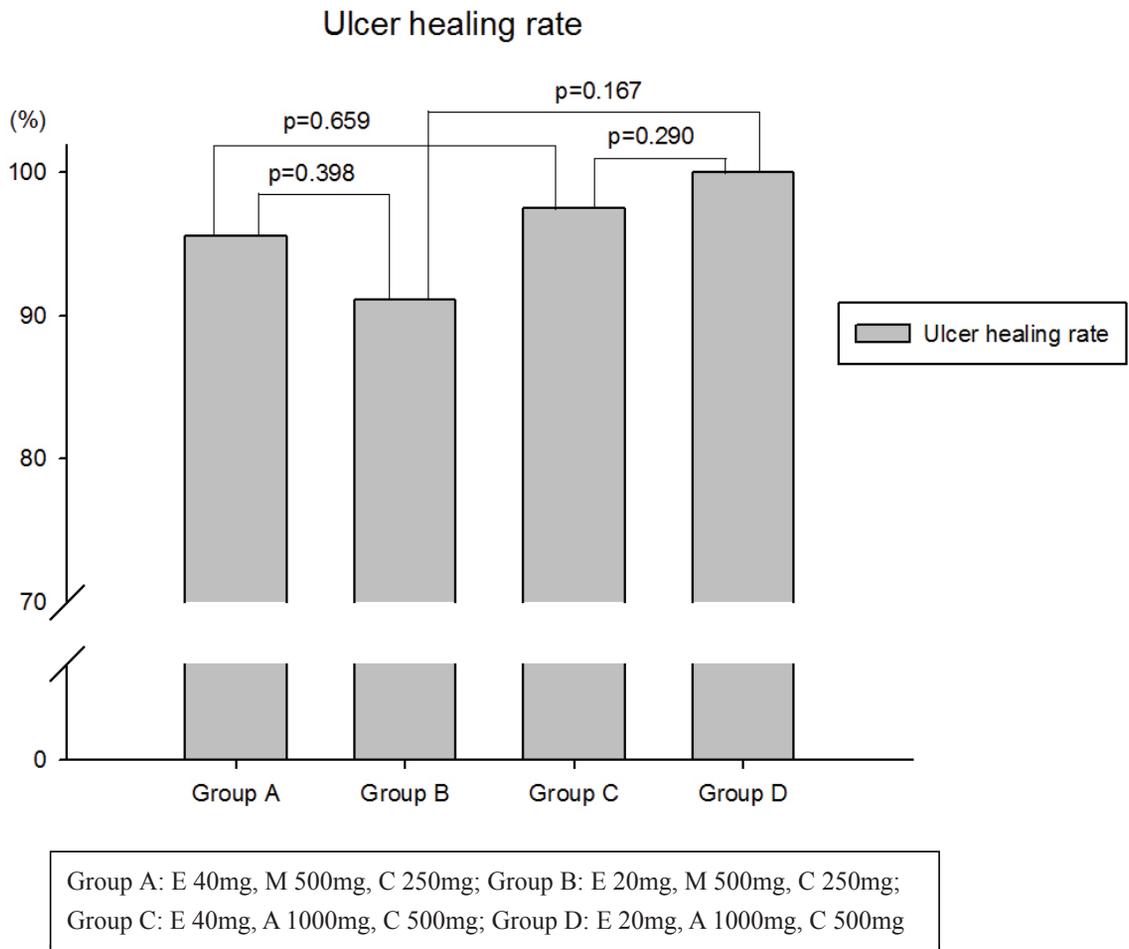


Figure 3. The comparison and efficacy of ulcer healing among the four regimen groups (Total: 170).

countries where the health care funding is limited or the patients have to pay for the *H. pylori* eradication therapy by themselves, the esomeprazole 20 mg based triple therapy is worthwhile in considering *H. pylori* eradication.

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比較耐適恩 (Esomeprazole) 不同劑量及 配方對於幽門螺旋桿菌相關的消化道潰瘍之療效

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摘要

以氫離子幫浦抑制劑為基礎的三合一療法是目前根除幽門螺旋桿菌感染與治療消化性潰瘍疾病的主流療法。其中以 Esomeprazole 為基礎的三合一療法在許多已被發表文章證實了可以達到良好的潰瘍癒合率和幽門螺旋桿菌根除。然而，比較不同劑量及配方的三合一療法根除幽門螺旋桿菌感染則很少被提及。這項臨床試驗的目的是比較兩種不同劑量的 Esomeprazole (40 毫克或 20 毫克，每天兩次) 和不同的組合的抗生素對於幽門螺旋桿菌感染根除和消化道潰瘍癒合率的成效。從 2003 年 2 月至 2009 年 10 月，我們收集了 272 例 (女：42%，平均年齡：53.8±15.2 歲) 證實幽門螺旋桿菌相關的消化性潰瘍病 (胃潰瘍或十二指腸潰瘍)，然後將所有的病人隨機分配到四組進行治療。A 組：E 40 毫克，M 500 毫克，C 250 毫克；B 組：E 20 毫克，M 500 毫克，C 250 毫克；C 組：E 40 毫克，A 1000 毫克，C 500 毫克；D 組：E 20 毫克，A 1000 毫克，C 500 毫克 (E：Esomeprazole，M：Metronidazole，C：Clarithromycin，A：Amoxicillin)。消化性潰瘍病的診斷是經由上消化道內視鏡確認。滅菌成功與否則是經過至少四個月的治療後，經由尿素呼氣試驗 (Urease Breathing Test)、快速尿素酶試驗或組織學確認。所有隨機分組患者再經過治療後，有 170 名患者接受第二次上消化道內視鏡來確認潰瘍癒合及加上快速尿素酶試驗確認滅菌成功與否。另外有七名不願意接受第二次上消化道內視鏡的檢查則只用尿素呼氣試驗確認滅菌成功與否。以完成實驗設計流程 (per protocol) 來分析，A 組的幽門螺旋桿菌滅菌成功率為 89.6%，B 組 86.7%，C 組 97.5%，D 組 93.2%。在潰瘍癒合率 A 組為 95.6%，B 組 91.1%，C 組 97.4%，D 組 100%。以完成實驗設計流程的整體滅菌率為 91.53% (一百七十七分之一百六十二)，而整體的潰瘍癒合率分別為 95.88% (170 分之 163)。以減半劑量 20 毫克的 Esomeprazole 為基礎的三合一療法在我們的實驗被證實和原始劑量 40 毫克的標準三合一療法是一樣有效的。在這醫療開支高漲的時代，降低治療的成本且不犧牲療效的療法是值得臨床上採用的。