Comparison of lansoprazole-based triple and dual therapy for treatment of *Helicobacter pylori*-related duodenal ulcer: An Asian multi-center prospective double blind randomized placebo controlled study

BCY Wong, SD Xiao[1], FL Hu[2], SC Quian[3], NX Huang[4], YY Li[5], PJ Hu[5], Daldiyono[6], C Manan[7], L Lesmana[7], RE Capio[8], JY Perez Jr.[9], KM Fock[10], U Kachithorn[11], K Phornphutkul[12], P Kullanvanijaya[13], J Ho[14], SK Lam.

Departments of Medicine and [14]Pathology, University of Hong Kong, Hong Kong, China, [1]Shanghai Second Medical University, China, [2]Beijing Medical University First Teaching Hospital, China, [3]Tianjin Medical University Third Central Hospital, China, [4]Tianjin Medical University, China, [5]First Municipal People's Hospital of Guangzhou, China, [6]RSUPN Cipto Mangunkusumo Hospital, [7]Husada Medical Hospital, [8]St. Luke's Medical Center, the Philippines, [9]University of Santo Tomas Hospital, the Philippines, [10]Changi General Hospital, Singapore, [11]Siriraj Hospital, Thailand, [12]Chiangmai University Hospital, Thailand, and [13]Chulalongkorn University Hospital, Thailand.

Running title: One week triple therapy with Lansoprazole in Asia

Correspondence to: Professor SK Lam

Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong, China.

Tel : (852)-28553348

Fax: (852)-28551143

Summary

Background: In Asian countries with limited resources, clarithromycin-based triple therapy may not be readily available. There is also limited data on direct comparison of different regimes in Asia.

Aim: To compare two lansoprazole-based non-clarithromycin triple therapy and one dual therapy in a prospective double-blind placebo-controlled study on the efficacy of *Helicobacter pylori* eradication and duodenal ulcer healing.

Methods: Fourteen centers in Asia participated in this study. Patients with acute duodenal ulcer and were *H. pylori* positive were recruited. They were randomized to receive: A) lansoprazole 30mg bid, amoxycillin 1 g bid and metronidazole 500mg bid for two weeks (LAM-2W), or B) LAM for one week and placebo (LAM-1W) , or C) LA and placebo for two weeks (LA). Upper endoscopy was repeated at week 6 to check for duodenal ulcer healing. Symptoms and side effects were recorded.

Results: A total of 228 patients were recruited, and two patients took less than 50% of the drugs. *H. pylori* eradication rates (intention to treat) were 68/82 (83%) with LAM-2W, 55/71 (78%) with LAM-1W and 43/75 (57%) with LA. There were significant differences (p=0.001) in eradication rates when comparing either LAM-2W or LAM-1W with LA. The eradication rate in patients with metronidazole resistant *H. pylori* strains were significantly lower than those with metronidazole sensitive strains (P=0.0001). The duodenal ulcer healing rates at week 6 were 85%, 85% and 72% in LAM-2W, LAM-1W and LA respectively (p=0.065). Side effects occurred in 13%, 11% and 9% in LAM-2W, LAM-1W and LA respectively. *H pylori* eradication and initial ulcer size were factors affecting duodenal ulcer healing.

Conclusions: This Asian multi-center study showed that one week lansoprazole-based triple therapy without clarithromycin has similar efficacy in *H. pylori* eradication and

ulcer healing compared with two week regime. Both triple therapies were significantly better than dual therapy in *H. pylori* eradication. Therefore one week lansoprazole-based triple therapy is as safe and effective as two week therapy in eradication of *H. pylori* infection and healing of duodenal ulcer in these Asian centers.

Key words: Helicobacter pylori, duodenal ulcer, therapy, Asia.

Introduction

The Asian Pacific Consensus meeting has recommended the use of triple therapy as a standard in the treatment of *Helicobacter pylori* related duodenal ulcer diseases in Asian countries (1). The recommendation included the use of a proton-pump inhibitor together with clarithromycin and either amoxycillin or metronidazole. This regime is much more expensive than the classical triple therapy consisting of bismuth, metronidazole and tetracycline. In parts of Asia where clarithromycin is not readily available for financial or other reasons, an alternative regime with proven efficacy in *H. pylori* eradication and ulcer healing is needed. On the other hand, metronidazole resistance is a major problem in some Asian countries and this may potentially affect the result of metronidazole containing regimes. The aim of this study was to evaluate two lansoprazole-based triple therapy and one dual therapy without clarithromycin for curing of *H. pylori* infection and healing of duodenal ulcer.

Materials and Methods

Patients aged between 18-80 years inclusive, with active duodenal ulcer of at least 5mm in diameter who were *H. pylori* positive (as determined by at least two positive results from CLO test(Delta West, Bentley, West Australia), histology and culture) were invited to participate in the study. Patients were excluded if they had acute ulcer bleeding, previous gastric or duodenal surgery, underlying malignant conditions, allergy to proton pump inhibitors or amoxycillin or metronidazole, been on treatment with bismuth compounds and/or antibiotics for the last 4 weeks before study, regular intake of nonsteroidal antiinflammatory drugs for the last 4 weeks before study, regular intake of proton-pump inhibitors or H2-receptor antagonists for

the past 2 weeks before study, history of bleeding tendency, or had significant gastrointestinal, renal , hepatic, cardiovascular, metabolic or hematological disease.

The study consisted of a double-blind, prospective randomized, placebo-controlled multicentre study carried out between July 1996 and June 1998 in 14 hospitals in Hong Kong, China, Indonesia, the Philippines, Singapore and Thailand. Randomization was performed individually in the 14 centers by drawing the code (Group A, B or C) from an envelope. The code was placed back to the envelope after the draw. The study was approved by the local Ethics Committee at each participating centre and written informed consent was obtained from patients before entering the study.

Treatment

Patients were randomized to one of the following three regimes: a) lansoprazole 30mg bid plus amoxycillin 1 g bid plus metronidazole 500mg bid all for two weeks (LAM-2W); b) lansoprazole 30mg bid plus amoxycillin 1 g bid plus metronidazole 500mg bid all for one week with three placebos for another week (LAM-1W); or c) lansoprazole 30mg bid plus amoxycillin 1 g bid for two weeks with metronidazole placebo for two weeks (LA-2W). All medication was taken each day.

Follow up

Patients returned at week 6 to return the symptom diary and bottles for drug count. They were also asked for presence of adverse events. Endoscopy was performed on that day to check for ulcer healing. The duodenal ulcer was defined as healed when there was complete epithelialization of ulcer site; partially healed when the size of ulcer is reduced by over 50%; and not healed when the ulcer size is

reduced by less than 50%. During endoscopy, two antral and one corpus biopsy were used for CLO test; two antral and two corpus biopsies were sent for histology, and one antral biopsy was sent for culture test at week 0. ^{13}C urea breath test were also performed in all patients, as detailed below. All biopsies for histology were sent to the Department of Pathology, Queen Mary Hospital, Hong Kong for examination of presence of *H. pylori* by a single pathologist (JH). Patients were considered *H. pylori* negative at week 6 if the results of all three tests were negative.

^{13}C-urea breath test

A ^{13}C-urea breath test for the detection of *H pylori* infection was performed on all patients at week 6. Briefly, after an overnight fast, a breath sample was collected in a sterile vacutainer 5 minutes after drinking a standard test meal for delay gastric emptying. The patient then took a test drink containing 75 mg ^{13}C-urea dissolved in 50 ml water, and underwent various simple postural positioning maneuvers to allow contact of the solution with the various parts of the stomach. A second breath sample was collected 30 minutes after the drink. The results of the breath test theoretically, therefore, represented the *H. pylori* status of the stomach as a whole. All breath samples were then sent to the Simon KY Lee Digestive Disease Laboratory, Queen Mary Hospital, University of Hong Kong, Hong Kong and analyzed with a purpose designed isotope ratio mass spectrometer (Fison Instruments, UK). A delta value of greater than 5 $^{0}/_{00}$ was considered positive for *H. pylori* infection. The results of the breath tests were not disclosed to the investigators, including the research nurses and endoscopists.

Bacterial culture

Antral biopsies were obtained from patients at week 0 and were totally embedded into Stuart transport medium (Oxoid, U.K.), stored at 4^0C and sent to the regional microbiology laboratories within two hours. Culture was performed using Columbia blood agar with 7% horse blood and incubated at 37^0C under microaerophilic condition (5% CO_2). *H. pylori* colonies were confirmed by positive urease, oxidase and catalase test together with the identification of Gram negative spiral looking organism on microscopy. Metronidazole susceptibility was determined by modified Kirby-Bauer disc diffusion procedure. An inhibition zone diameter of > 15 mm is regarded as metronidazole susceptible.

Statistical Analysis

To confirm a homogeneity of three treatment groups, patient characteristics were compared with chi-square test for the categorical data, Kruskal-Wallis test for ranking data and analysis of variance for quantitative data. The per protocol and intention to treat populations were included in the efficacy analyses. The per protocol population included only those eligible patients who had undergone an upper endoscopy with testing of *H. pylori* status and had taken at least 50% of the study medication. The intention to treat population included all evaluable patients who had taken at least one dose of study medication. Eradication rates, ulcer healing rates and adverse event rates of the groups were compared based on a closed testing procedure. That is if a statistically significant difference was detected with chi-square test among the three groups, pair wise comparisons were carried out, using the chi-square test without correction of continuity. The 14 institutions were grouped into 6 regions

geographically, namely South China (Hong Kong and Guangdong); North China; Indonesia; the Philippines; Singapore; and Thailand. P-values of < 0.05 were considered significant. In order to evaluate factors that may affect duodenal ulcer healing at week 6, logistic regression analysis was performed, with results expressed as odds ratios and 95% confidence interval.

Results

Two hundred and twenty eight patients with uncomplicated active duodenal ulcers at endoscopy fulfilling the inclusion and exclusion criteria were enrolled in the study. The mean age of these patients was 47.5 years (range 18 to 80 yrs). Eighty two patients were randomized to receive treatment under LAM-2W; seventy one patients received treatment under LAM-1W and seventy five patients received treatment under LA. These patients' data was all included in the intent-to-treat analysis. Two patients in LA did not finish more than 50% of the drugs, was classified as non-compliance and excluded from the per protocol analysis. The demographic data and endoscopic findings were summarized in Table 1.

H. pylori eradication

According to the intent-to-treat analysis at week 6, *H. pylori* eradication was achieved in 68 patients (82.9%), 55 patients (77.5%) and 43 patients (57.3%) in LAM-2W, LAM-1W and LA respectively (P=0.001). For the per protocol analysis, *H. pylori* eradication was achieved in 68 patients (82.9%), 55 patients (77.5%) and 43 patients (58.9%) in LAM-2W, LAM-1W and LA respectively (P=0.002). In both

intention-to-treat and per protocol analysis, the eradication rates of two week triple therapy were significantly better than that of dual therapy with p-value of 0.0008 and 0.0012 respectively. Similarly, the eradication rates of one week triple therapy in both intention-to-treat and per protocol analysis were significantly better than that of dual therapy with p-value of 0.01 and 0.02 respectively. But there was no significant difference in the eradication rates between both triple therapy regimes. (Table 2)

Metronidazole resistance

Results of *H. pylori* culture and sensitivity testing were available in 105 patients. The overall metronidazole resistance rate was 40%. The intent to treat eradication rate for patients with metronidazole sensitive strains were significantly higher than that for patients with metronidazole resistant strains (85.7% vs 50% respectively, p= 0.0001).

Ulcer healing

The ulcer healing rates (intent-to-treat) were 85.4%, 84.5% and 72% for LAM-2W, LAM-1W and LA respectively. There were no significant difference among the three groups both in intent-to-treat and per protocol analysis (Table 2).

Side effects

The total numbers of events of side effects were 12, 10, and 7 in LAM-2W, LAM-1W and LA respectively. The total number of patients experiencing side effects were 11 (13.4%), 8 (11.3%) and 7 (9.3%) in groups A, B and C respectively (*P*=

0.72). The common side effects reported included flatulence (3%), epigastric pain (3%), diarrhea (1%), nausea (1%), malaise (1%) and dizziness (1%) (Table 3). There were no severe side effects and no hospitalization or mortality related to treatment. There were no significant differences in the number of patients having side effects among the three groups.

Factors affecting ulcer healing

After logistic regression analysis, *H pylori* status at week 6 and size of ulcer were shown to affect ulcer healing. The odds ratio for *H pylori* status was 3.81 (95% C.I. : 1.86 – 7.81) and for size of ulcer was 2.13 (95% CI: 1.06 –4.28) (Table 4).

Institution

The ulcer healing rates varied from the lowest 45.5% in Indonesia to the highest 86.4% in Singapore and Thailand (p=0.012). The ulcer healing rates showed a trend of correlation with *H. pylori* eradication rates, with Indonesia having the lowest eradication rate of 63.6% and Thailand having the highest eradication rate of 86.4%, but there was no significant difference in *H. pylori* eradication rate among different institutions overall. Looking at other parameters, there were significant differences in age, smoking habit, disease onset and past ulcer history among the 6 regions.

The number (%) of patients with metronidazole resistant strains in various regions were: Hong Kong and Guangdong 20 (37.7%); China 18 (43.9%); Indonesia 1 (33.3%); Phillipines 2 (66.7%) and Thailand 1(20%). Hong Kong and Guangdong region has a significantly higher eradication rate in patients with metronidazole sensitive strains (94%) than patients with metronidazole resistant strains (45%) (p=0.0001). For other parts of China, the eradication rate was also higher in patients

with metronidazole sensitive strains (74%) than patients with metronidazole resistant strains (50%) but did not reach statistical significance (p=0.1). The other countries each has less than five cases and were not analyzed here.

Discussion

H. pylori eradication has become the standard treatment in the management of *H. pylori*-related duodenal ulcer diseases(1). Curing of the infection not only resulted in duodenal ulcer healing but significantly reduced the risk of ulcer recurrence (2). One of the preferred regime according to the Asia Pacific Consensus report was triple therapy which consists of a proton pump inhibitor, clarithromycin and either amoxycillin or metronidazole(1). These regimes have been able to attain eradication rates of 90% or greater by per protocol analysis and 80% or greater by intention-to-treat analysis in this region (3-5). Particularly in this part of the World, metronidazole resistance of *H. pylori* is a serious problem. In Hong Kong, we reported a metronidazole resistance of 53.5% overall and 38.6% in duodenal ulcer patients (6). In other parts of Asia, resistance rates varies from 54% in Malaysia to 95% in Korea and Bangladesh. A few studies have shown that the eradication rates using a proton pump inhibitor plus amoxicillin and metronidazole were significantly lower for metronidazole resistant strains than metronidazole susceptible strains (7-10). The eradication rates for resistant strains varied from 45% to 77% while those for susceptible strains varied from 90% to 96%. There are reports stating that a clarithromycin-containing triple therapy regime may partly overcome the primary resistance to metronidazole (3, 11). Although there are two studies which showed comparable eradication rates of around 94% between both metronidazole resistant and

susceptible strains (8, 12), majority reported a less favorable eradication rates of around 75% in metronidazole resistant strains (13-15). Hence the addition of clarithromycin can only increase the eradication rate for metronidazole resistant strains by around 10-25%. In this part of the World where clarithromycin may not be readily available, it is necessary to test out the efficacy of non-clarithromycin containing triple therapy.

Our study was a randomized double-blind placebo-controlled trial involving fourteen centers throughout five Asian countries. Our controlled study with three arms and an adequate number of subjects in each group showed that the eradication rates for both lansoprazole-based triple therapies were significantly better than the lansoprazole plus amoxicillin dual therapy used. Although there was a slightly higher eradication rate of using two week triple therapy, the difference did not reach statistical significance. These results were in agreement with previous lansoprazole-based regimes. In the study by Harford et al, the per protocol eradication rate for lansoprazole twice daily plus amoxicillin dual therapy was 57% while an increase of lansoprazole to three times daily raised the eradication rate to 67% (16). Our results of lansoprazole-based dual therapy were also comparable to those from omeprazole plus amoxicillin from recent studies (17,18). In comparing lansoprazole-based triple therapy using amoxicillin and metronidazole, we observed an eradication rate of around 80% in our two arms, which was slightly better than previous studies. For example a study from Misiewicz et al showed a per protocol eradication rate of 73.5%(11). A similar study showed an intent-to-treat eradication rate of 76%, which included 61% in resistant strains and 86.5% in susceptible strains (19). For regimes using omeprazole instead of lansoprazole, the results from the MACH 1 study showed a per protocol eradication rate of 81.6%, similar to our result (20).

The ulcer healing rates in our study were around 85% for the two triple therapy regime but around 70% for the dual therapy regime. After analysis of factors affecting ulcer healing, we found that the *H. pylori* status at week 6 was a crucial factor. In our study, the group using dual therapy has a significantly lower *H pylori* eradication rate and therefore affected the rate of ulcer healing. This was in agreement with our earlier study that duodenal ulcer healed in 86% in whom *H pylori* eradication was achieved but in 52% in whom eradication failed (21). Other recent studies also suggested that eradication of *H pylori* improved the healing of duodenal ulcer (22,23). After logistic regression analysis, apart from *H. pylori* status at week 6, the ulcer size at presentation was also associated with the rate of ulcer healing. This was also in agreement with our earlier study and from others (21, 24)

We observed a similar incidence of side effects among the triple therapy groups and the dual therapy group. Most of the side effects were well tolerated. This showed that most patients tolerated these two triple therapy regimes well and showed also that similar side effects occurred also in treatment with amoxicillin and lansoprazole. Other studies showed similar findings to ours (25,26). Hence one week or two week lansoprazole-based triple therapy were both well tolerated and comparable to two week dual therapy.

This study included 14 institutions from 5 different countries in Asia. These countries are situated at the proximity to each other. However, there were significant differences in patient demographics as well as eradication rate and ulcer healing rates. Our study confirmed the significantly lower eradication rate of 50% in patients with metronidazole resistant strains than 85.7% in patients with metronidazole sensitive strains. Hong Kong and the rest of China have similar prevalence of metronidazole

resistance and showed lower eradication rates in patients with metronidazole resistant strains. Unfortunately bacterial culture tests were performed in a small subset of patients in Indonesia, the Philippines and Thailand. We therefore could not draw any conclusion to the effect of prevalence of metronidazole sensitivity on the differences in eradication rate and ulcer healing observed in these countries. The difference in patient demographics also suggested that more studies need to be done to find out the most suitable and cost-effective anti-*H. pylori* regime in different populations in Asia.

In conclusion, one week and two week lansoprazole-based triple therapy without clarithromycin have similar efficacy in *H. pylori* eradication and duodenal ulcer healing, and both are significantly better than the lansoprazole plus amoxycillin dual therapy. All regimes were safe and well tolerated. The eradication of *H pylori* and initial ulcer size were factors affecting duodenal ulcer healing. Hence the use of one week regime of lansoprazole, amoxycillin and metronidazole conforms with the recommendation of Asia Pacific Consensus on *H pylori*.

Acknowledgement

We thank Takeda Chemical Industries, Ltd, Japan, for supporting this study. We are also grateful to the following individuals for their help: Dr. MMT Ng and Mr. S Yeung, Hong Kong, for statistical analysis, Ms. MY Lee and VSY Tang for ^{13}Carbon-urea breath test analysis, Ms. A Wong for data entry, and participating endoscopists and endoscopy nurses in all 14 centers.

References

1. Lam SK, Talley NJ. Report of the 1997 Asia Pacific Consensus Conference on the management of Helicobacter pylori infection. J Gastroenterol Hepatol 1998; 13: 1-12.

2. Wong BCY, Lam SK, Lai KC, Hu WHC, Ching CK, Ho J, et al. Triple therapy for Helicobacter pylori eradication is more effective than long-term maintenance anti-secretory treatment in the prevention of recurrence of duodenal ulcer: a prospective long-term follow-up study. Aliment Pharmacol Ther 1999: 13: 303-9.

3. Goh KL, Parasakthi N, Chuah SY, Cheah PL, Lo YL, Chin SC. Comparison of two 1-week low-dose omeprazole triple therapies--optimal treatment for Helicobacter pylori infection? Aliment Pharmacol Ther 1997; 11(6): 1115-8.

4. Habu Y, Mizuno S, Hirano S, Kiyota K, Inokuchi H, Kimoto K, et al. Triple therapy with omeprazole, amoxicillin and clarithromycin is effective against Helicobacter pylori infection in gastric ulcer patients as well as in duodenal ulcer patients. Results of a randomized controlled trial in Japan. Digestion. 1998 ; 59(4): 321-5.

5. Chu KM, Choi HK, Tuen HH, Law SY, Branicki FJ, Wong J. A prospective randomized trial comparing the use of omeprazole-based dual and triple therapy for eradication of Helicobacter pylori. Am J Gastroenterol. 1998 ; 93(9): 1436-42

6. Ching CK, Leung KP, Yung RW, Lam SK, Wong BCY, Lai KC, Lai CL. Prevalence of metronidazole resistant Helicobacter pylori strains among Chinese peptic ulcer disease patients and normal controls in Hong Kong. Gut 1996; 38: 675-8.

7. Bell GD, Powell KU, Burridge SM et al. H. pylori eradication: efficacy and side effect profile of a combination of omeprazole, amoxycillin and metronidazole compared with four alternative regimens. Q J Med 1993; 86:743-50.

8. Lerang F, Moum B, Haug JB et al. Highly effective twice-daily triple therapies for H. pylori infection and peptic ulcer disease: does in vitro metronidazole resistance have any clinical relevance? Am J Gastroenterol 1997; 92: 248-53.

9. Thijs JC, Van Zwet AA, Thijs WJ et al. One-week triple therapy with omeprazole, amoxicillin and tinidazole for Helicobacter pylori infection: the significance of imidazole resistance. Aliment Pharmacol Ther 1997;11:305-9.

10. Bouchard S, Birac C, Lamouliatte H, et al. Correlation between the MICS of metronidazole on H. pylori strains and the outcome of a lansoprazole-amoxicillin-metronidazole therapy [abstract]. Gut 1996; 39(suppl 2):A6.

11. Misiewicz JJ, Harris AW, Bardhan KD, Levi S, O'Morain C, Cooper BT, et al. One week triple therapy for Helicobacter pylori: a multicentre comparative study. Gut 1997; 41:735-739.

12. Moayyedi P, Tompkins DS, Ragunathan PL, et al. Prevalence of metronidazole in predicting failure of omeprazole, clarithromycin and tinidazole to eradicate H. pylori [abstract]. Gut 1996; 39(suppl 2):A6.

13. Xia HX, Keane CT, Beattle S et al. Standardisation of disk diffusion test and its clinical significance for susceptibility testing of metronidazole against H, pylori. Antimicrob Agents Chemother 1994; 38: 2357-61.

14. Peitz U, Nush A, Tillenburg B et al. High cure rate of H. pylori infection by one week therapy with omeprazole, metronidazole and clarithromycin despite a negative impact by metronidazole resistance. [abstract] . Gut 1996;39 (Suppl 2): A5.

15. Harris AW, Pryce DI, Gabe SM, et al. Lansoprazole, clarithromycin and metroidazole for seven days in H. pylori infection. Aliment Pharmacol Ther 1996; 10:1005-8.

16. Harford W, Lanza F, Arora A, Graham D, Haber M, Weissfeld A et al. Double-blind, multicenter evaluation of lansoprazole and amoxicillin dual therapy for the cure of Helicobacter pylori infection. Helicobacter 1996; 4: 243-50.

17. Graham KS, Malaty H, El-Zimaity HM et al. Variability with omeprazole-amoxicillin combinations for treatment of Helicobacter pylori infection. Am J Gastroenterol 1995; 90:1415-8.

18. Al-Assi MT, Cole RA, Karttunen TJ, El-Zimaity H, Genta RM, Graham DY. Treatment of Helicobacter pylori infection with omeprazole-amoxicllin combination therapy versus ranitidine/sodium bicarbonate-amoxicillin. Am J Gastroenterol 1995; 90:1411-14.

19. Lamouliatte H, Florent Ch, Vicari F, Megraud F, Forestier S. Effect of lansoprazole and amoxicillin plus metronidazole on the eradication of Helicobacter pylori : a randomized, double blind, multicenter study. Gastroenterol 1996:110 (4) (Suppl): 170.

20. Lind T, van Zanten SV, Unge P, Spiller R, Bayerdorffer E, O'Morain C, et al. Eradication of Helicobacter pylori using one-week triple therapies combining omeprazole with two antimicrobials: the MACH 1 Study. Helicobacter 1996; 1: 138-44.

21. Lam SK, Ching CK, Lai KC, Wong BCY, Lai CL, Chan CK, et al. Does treatment of Helicobacter pylori with antibiotics alone heal duodenal ulcer? A randomised double blind placebo controlled study. Gut 1997;41: 43-8.

22. Graham DY, Lew GM, Evans DG, Evans DJ, Klein PD. Effect of triple therapy (antibiotics plus bismuth) on duodenal ulcer healing. Ann Intern Med 1991; 115:266-9.

23. Hosking SW, Ling TKW, Chung SCS, Yung MY, Cheng AFB, Sung JJY, et al. Duodenal ulcer healing by eradication of Helicobacter pylori without anti-acid treatment: randomised controlled trial. Lancet 1994; 343: 508-10.

24. Massarrat S, Eisenmann A. Factors affecting the healing rate of duodenal and pyloric ulcers with low-dose antacid treatment. Gut 1981; 22:97-102.

25. Thijs JC, Van Zwet A. Oey HB. Efficacy and side effects of a triple drug regimen for the eradication of Helicobacter pylori. Scand J Gastroenterol 1993; 28:934-8.

26. Saberi-Firoozi M, Massarrat M, Zare S, Fattahi M, Javan A, Etaati H, et al. Effect of triple therapy or amoxycillin plus omeprazole or amoxycillin plus tinidazole plus omeprazole on duodenal ulcer healing, eradication of Helicobacter pylori, and prevention of ulcer relapse over a 1-year follow-up period: a prospective, randomized, controlled study. Am J Gastroenterol 1995; 9: 1419-23.

Table 1. Demographic data of patients

	LAM-2W	LAM-1W	LA	*p value*
Total number	82	71	75	
Age, (yr)(mean ± SD)	47.1 ± 14.6	50.0 ± 14.1	45.6 ± 13.7	0.17
M:F	66:16	48:23	61:14	0.20
Smoking (%)	50	38	40	0.42
Alcohol (%)	35	24	31	0.69
Coffee (%)	33	35	33	0.67
Pain score (mean ± SD)	1.8 ± 0.7	2.3 ± 1.0	2.1 ± 0.9	0.42
DU size (mm) (mean ± SD)	9.8 ± 4.6	9.2 ± 3.8	9.0 ± 4.2	0.45

Table 2
Outcome of *H. pylori* eradication and ulcer healing in relation to treatment groups

					p value			
	LAM-2W (A)	LAM-1W(B)	LA(C)	Overall	Among 3 gps	Pairwise comparison		
						A v B	A v C	B v C
Intention to treat								
Hp eradication, (%)	68/82 (82.9)	55/71 (77.5)	43/75 (57.3)	166/228 (72.8)	0.001	0.42	0.0008	0.01
Ulcer healing, (%)	70/82 (85.4)	60/71 (84.5)	54/75 (72.0)	184/228 (80.7)	0.065	-	-	-
Per protocol								
Hp eradication, (%)	68/82 (82.9)	55/71 (77.5)	43/73 (58.9)	166/226 (73.4)	0.002	0.42	0.0012	0.02
Ulcer healing, (%)	70/82 (85.4)	60/71 (84.5)	52/73 (71.2)	182/226 (80.5)	0.051	-	-	-

Note: The groups were compared based on a closed testing procedure. If a statistically significant difference was detected among the three groups, pairwise comparison were carried out, using the chi-square test without correction of continuity.

Table 3.

Side effects experienced by patients

	LAM-2W	LAM-1W	LA	Total
Epigastric pain	3	3	1	7
Flatulence	3	2	1	6
Diarrhoea	0	1	2	3
Malaise	2	1	0	3
Nausea	0	1	2	3
Dizziness	1	1	0	2
Heartburn	1	1	0	2
Pruritus	1	0	0	1
Regurgitation	1	0	0	1
Bloating	0	0	1	1
Total episodes	12	10	7	29
Total patient, (%)	11 (13.4%)	8 (11.3%)	7 (9.3%)	26 (11.4%)*

*p = 0.72 (chi-square test)

Table 4.

Factors affecting duodenal ulcer healing

Logistic regression analysis

Parameter Estimate

Model	level	parameter		test		
		estimate	s.e.	Wald	df	p-value
Constant	-	- 3.42	0.76	20.18	1	0
Hp eradication	negative	1.33	0.37	13.29	1	0.0003
Ulcer size		0.76	0.35	4.56	1	0.033

Goodness-of-Fit

	chi-square	df	p-value
deviance	17.85	2	0.0001

Odds Ratio

	Odds ratio	95% Confidence interval .
Hp Eradication	3.81	1.86 – 7.81
Ulcer size	2.13	1.06 – 4.28