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• *BRIEF REPORTS* •

Effects of killing *Helicobacter pylori* quadruple therapy on peptic ulcer: A randomized double-blind clinical trial

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Abstract

AIM: To study the therapeutic efficacy of a Chinese and Western integrated regimen, killing *Helicobacter pylori* quadruple therapy on *H pylori*-associated peptic ulcers (PU).

METHODS: With prospective and double-blind controlled method, seventy-five active PU patients with *H pylori* infection were randomized to receive one of the following three regimens: (1) new triple therapy (group A: lansoprazole 30 mg qd, plus clarithromycin 250 mg bid, plus amoxycillin 500 mg tid, each for 10 d); (2) killing Hp quadruple therapy(group B: the three above drugs plus killing *H pylori* capsule 6 capsules bid for 4 wk) and (3) placebo(group C: gastropine 3 tablets *bid* for 4 wk). *H pylori* eradication and ulcer healing quality were evaluated under an endoscope 4 wk after treatment. The patients were followed up for 5 years.

RESULTS: Both the healing rate of PU and *H pylori* eradication rate in group B were significantly higher than those in group C (100% and 96.4% *vs* 20% and 0%, respectively, $P<0.005$), but there was no significant difference compared to those in group A (88% and 92%, $P>0.05$). The healing quality of ulcer in group B was superior to that in groups C and A ($P<0.05$). The recurrence rate of PU in group B (4%) was lower than that in group A (10%) and group C (100%, $P<0.01$).

CONCLUSION: Killing *Helicobacter pylori* quadruple therapy can not only promote the eradication of *H pylori* and healing quality of ulcer but also reduce recurrence rate of ulcer.

Key words: Peptic ulcer; *Helicobacter pylori*; Killing *H pylori* quadraple therapy

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INTRODUCTION

Helicobacter pylori (*H pylori*) infection is a major pathogenetic factor of peptic ulcer (PU). It is closely associated with refractoriness in the healing quality of ulcer and relapse[1-5]. So far, there has been no satisfactory therapeutic regimen with a high eradication rate of *H pylori* and a high healing quality of PU. This study aimed to investigate the effects of killing *H pylori* quadruple therapy (KHQT - killing *H pylori* capsule plus lansoprazole plus clarithromycin and amoxycillin) in eradication of *H pylori,* healing quality of PU and prevention of ulcer relapse.

MATERIALS AND METHODS

Patients

Selected patients (who provided informed consent) were aged 18 to 65 years, with endoscopically (Olympus JIF-XQ240, Tokyo, Japan) proven PU of diameter 0.5 to 1.5 cm, and presence of *H pylori* infection confirmed by antral biopsy specimens. Patients who had used antibiotics, bismuth or PPI in the preceding two weeks, or had suffered from serious complications of PU and chronic or advanced liver, kidney, heart, or pulmonary diseases were excluded from the study. Seventy-five patients were enrolled for the study conducted from May 1997 to May 2003. Seven of the cases were later excluded for reasons such as not taking the medicine or refusing endoscopic examination; 68 completed the study.

Study design

All cases were randomly allocated to three groups to undergo three kinds of treatment:Group A (new triple therapy): lansoprazole 30 mg qd, clarithromycin 250 mg bid and amoxycillin 500 mg bid for 10 d; Group B (killing *H pylori* quadruple therapy -- KHQT): the three above drugs for ten days and killing *H pylori* capsule 6 capsules bid for 4 wk; Group C (placebo): gastropine, 3 tablets bid for 4 wk. Of the 68 cases, 25 were in group A, 28 in group B and 15 in group C (Table 1). Each case underwent an endoscopic examination three days before start of treatment. Biopsies at 2.0 to 2.5 cm from pylorus were obtained and urease test, Gram staining and Warthin-Starry silver staining were carried out. *H pylori* strains were taken as positive if two or more of the three tests were positive.

Treatment for the study was by the double-blind and

Table 1 Data on enrolled cases (%, mean±SD)

	Group A (n = 25)	Group B (n = 28)	Group C (n = 15)
Sex			
Male	21 (84.0)	23 (82.1)	13 (86.7)
Female	4 (16.0)	5 (17.9)	2 (13.3)
Age (yr)	41.6±11.2	43.2±12.4	38.8±11.8
Height (cm)	169±4.6	166.1±7.9	166.5±7.5
Weight (kg)	64.4±8.1	62.3±9.6	60.2±6.9
Disease course (yr)	4.2±3.8	4.2±4.0	4.2±3.7
Gastric ulcer	5 (20.0)	8 (28.6)	4 (26.7.0)
Duodenal ulcer	20 (80.0)	20 (71.4)	11 (73.3)
Diameters (cm)	1.0±0.5	1.0±0.4	1.0±0.4
Smoking	16 (64.0)	18 (64.3)	9 (60.0)
Alcohol drinking	9 (36.0)	10 (35.7)	5 (33.3)
Upper abdominal pain	23 (92.0)	27 (96.4)	14 (93.3)
Distension	16 (64.0)	16 (57.1)	10 (66.7)
Heart burn or acid reflux	16 (64.0)	16 (57.1)	9 (60.0)
Belch	8 (32.0)	9 (32.1)	5 (33.3)
Inappetence	10 (40.0)	11 (39.3)	6 (40.0)
Constipation	9 (36.0)	10 (35.7)	5 (33.3)

double-simulation method. The medicine, starch or placebo (gastropine) was packed in gelatin capsules of similar appearance. The investigators did not know what medicines were given to the patients, and the patients did not know what medicines they had taken.

After ten days of treatment and again after 4 wk, alterations in symptoms, incidence of side effects and compliance were assessed. In addition, after 4 wk, the condition of healed ulcer and eradication of *H pylori* were assessed through endoscopy and classified as healed (complete epithelialization or scar formation), effective (the size of ulcer reduced by 50% compared to pre-treatment state) and ineffective (not reduced by 50%). Eradication of *H pylori* was affirmed if the three tests (urease test, Gram staining and Warthin-Starry silver staining) were negative. For patients with healed ulcers, the healing quality of ulcers was evaluated.

The healed ulcers were classified as stages S1 (red scar) and S2 (white scar). In patients with healed ulcers at white scar stage, one biopsy specimen was obtained from the center of the scar. The specimen was stained with HE and observed under a light microscope to assess the histological growth of the regenerating mucosa. Histological healing patterns of regenerating mucous membranes were classified[6] as: fine (resembling normal mucosa with well-formed villi or epithelium, well-developed glandular structure and few inflammatory cells); fair (blunt and coarse villi or incomplete epithelia, underdeveloped glandular structures and relatively more inflammatory cells); and poor (a few layers of newly generated cells over the scar, poorly developed or absent glandular structure and dense infiltration of inflammatory cells). Histologic ultrastructure of healed ulcers was observed under an electronmicroscope.

Follow-up

Patients with healed PU were followed up at three-month intervals, by telephone or petition letters, for five years. During the five-year follow-up, most of these patients did not take any drugs. A few took gastropine or Chinese herbs when symptoms relevant to PU occurred. Endoscopy was performed five years after healing of ulcers or earlier if ulcer-like symptoms reappeared. Those cases in which active ulcers reappeared under endoscopic examination were regarded as cases of relapse.

Statistical analysis

Student's t test was used for measurement data, χ^2 test for enumeration data and *Ridit* analysis for ranked data. P values <0.05 were considered statistically significant.

RESULTS

Clinical efficacy

Patients in group B (KHQT) had less upper abdominal pain and distension than those in the other two groups (P<0.05). *H pylori* eradication rate was 92% (23/25) in group A, 96.4% (27/28) in group B and 0.0% (0/15) in group C. There was a significant difference between each of the two therapeutic groups and group C (P<0.005) .The ulcer healing rate was higher in groups A and B than in group C (88% and 100% *vs* 20%, respectively, P<0.005) (Table2). Between groups A and B, there was no significant difference in healing of ulcers and eradication of *H pylori*. In all patients, compliance with taking drugs was excellent and no side-effects were observed except for mild dizziness in one patient.

Table 2 Healing rate of PU

Group	Healed (%)	Improved (%)	Unimproved (%)	Total (%)
A (n = 25)	22 (88.0)[a]	3 (12.0)		100.0
B (n = 28)	28 (100.0)[a]	0		100.0
C (n = 15)	3 (20.0)	4 (26.7)	8 (53.3)	46.7

[a]P<0.005 *vs* group C.

Healing quality

The healing quality was assessed in terms of achievement rate of ulcer healing stage S2 and histological and ultrastructural conditions of regenerating mucosae. The rate of stage S2 in group B (67.9%) was higher than that in groups C (0.0%, P<0.005) and A (32.0%, P<0.01). Degree of histological maturation (Table 3 and Figures 1A-C) and ultrastructural features (Figures 2A-C) of the regenerating mucosa in group B were better than those in groups C and A.

Table 3 Histology of regenerating mucosae of healed ulcers

Group	Good (%)	Fair (%)	Poor (%)
A (n = 17)	7 (41.2)	10 (58.8)	0 (0.0)[a]
B (n = 18)	16 (88.9)	2 (11.1)	0 (0.0)[b,c]
C (n = 3)	0 (0.0)	1 (33.3)	2 (66.7)

[a]P<0.05, [b]P<0.01 *vs* group C; [c]P<0.05 *vs* group A.

Recurrence of PU

Of 53 patients with healed ulcers, 48 patients (20 in group A, 25 in group B and 3 in group C) returned for endoscopy at the end of the five-year follow-up. Five patients were

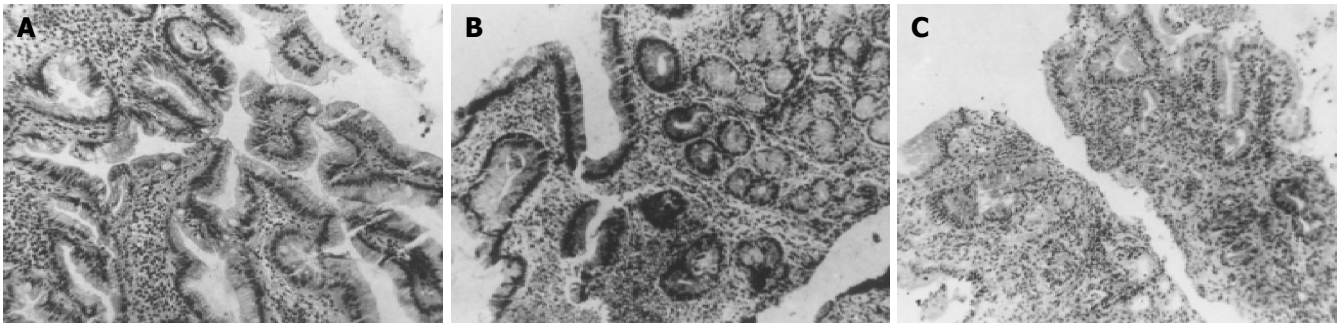

Figure 1 Histological maturation of regenerating mucosa in three groups. A: New triple therapy: incomplete epithelium, poorly developed glandular structure and moderate inflammatory cell infiltration (light microscope 3.3×10); B: Killing Hp quadruple therapy: well-formed epithelia, well-developed glandular structure and fewer inflammatory cells (light microscope 3.3×10); C: Placebo: some layers of newly generated cells over the scar, very poorly developed glandular structure and dense infiltration of inflammatory cells (light microscope 3.3×10).

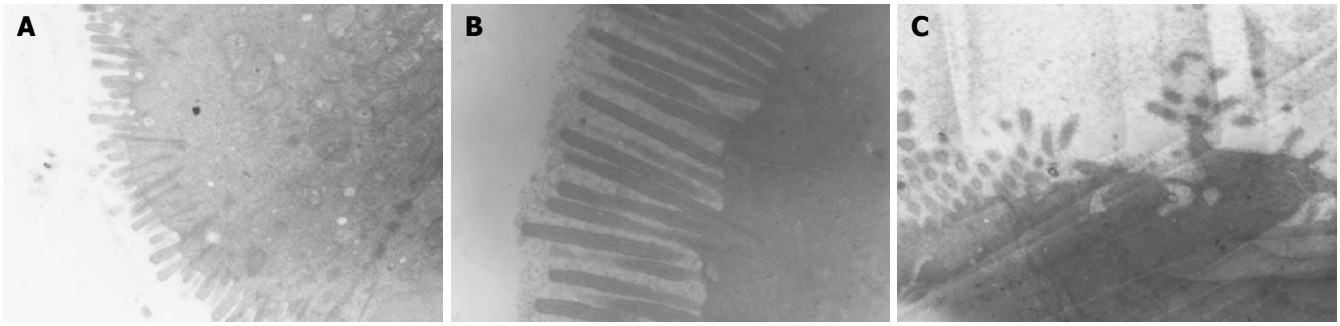

Figure 2 Ultrastructural features of regenerating mucosa in three groups. A: New triple therapy: well-formed epithelia, but short and irregular microvilli, short sugar chains and thin sugar coat of microvilli (electronmicroscope ×15 000); B: Killing Hp quadruple therapy: well-formed epithelia, long and regular microvilli, long sugar chains and thick sugar coat of microvilli (electronmicroscope ×25 000); C: Placebo: shorter and fewer microvilli, shorter sugar chains and thinner sugar coat of microvilli (electromicroscope ×15 000).

withdrawn: three refused endoscopy and for two there was no further follow-up information. Recurrence rate of PU for KHQT patients was 4% (1/25), for new triple therapy patients, 10% (2/20) and for placebo patients, 100% (3/3). There was a significant difference between group B and group C ($P<0.01$). Patients who suffered from ulcer relapse experienced either *H pylori* eradication failure or poor healing quality of ulcers.

DISCUSSION

Eradication of *H pylori* is the key to treating peptic ulcers and to decreasing their relapse[4,5]. Studies[2-9] have shown that relapse is closely related to not only *H pylori* infection but also poor healing quality of ulcers. Clinical trials have also shown that PU has higher healing rates and lower relapses after *H pylori* eradication. The regimen that consisted mainly of metronidazole had a lower rate of *H pylori* eradication, of around 60%[10,11]. So far, *H pylori* has not been found sensitive to some antibiotics which also cause many side effects and poor healing quality. It has been proved that some mucosal protective drugs can improve the healing quality of PU[6,8], and Chinese traditional medicine has attracted attention because of its special efficacy in mucosal protection[12-15].

Killing *H pylori* capsule containing more than ten kinds of Chinese herbs (Radix salviae miltiorrhizae, Poria coccus, Atractylodes macrocephala, Saussurea lappa, Magnolia officinalis, Fructus amomi, Wu mei, *etc.*) has been proved, in animal experiments and clinical trials, to have the efficacy of improving mucosal lesions[16-18]. On the basis of these studies, we used a low-dose triple therapy combined with Killing Hp capsule to study its efficacy on PU.

This combined regimen we named killing *H pylori* quadruple therapy. The results in this study showed that KHQT (group B) had significant effects on abdominal pain and distension, and a high *H pylori* eradication and healing rate commensurate with new triple therapy (group A); and it was significantly superior to controls (group C, gastropine, $P<0.005$). There were no side-effects except for one case of mild dizziness. All cases had good compliance. Our study showed the clinical efficacy was significantly enhanced when KHQT was used in patients with *H pylori* -related PU.

Enhancing the healing quality of PU reduces ulcer recurrence[5-8]. KHQT achieved excellent healing quality of PU with 67.9% ulcer healing stage S2, 88.9% of which were of fine pattern of regenerating mucosa and good ultrastructure, better than those in both group A (32.0 % ulcer healing stage S2, $P<0.01$; fine pattern of 41.2% regenerating mucosa, $P<0.05$) and group C (0.0% and 0.0%, $P<0.01$ respectively). The study indicated KHQT had enhanced the healing quality of PU. It may be related to the cooperative action of antibiotics eradicating *H pylori* infection and Chinese traditional herbs improving the gastric

mucosal barrier[13-15,17-19].

As shown by the five-year follow-up, the recurrence rate in cases treated with KHQT was lower than that in group C (1/25, 4% *vs* 3/3, 100%; $P<0.01$) and in group A (2/20, 10%); but there was no statistical significance perhaps because of the small number of cases. Ulcer recurrence was found in those who had ulcer healing stage S1, poor patterns of regenerating mucosa and failure of *H pylori* eradication. Ulcer recurrence was related to *H pylori* infection and poor healing quality of ulcers.

In conclusion, KHQT can not only improve gastrointestinal symptoms, promote *H pylori* eradication and improve ulcer healing rate significantly, but can also increase the healing quality of PU and reduce recurrence of ulcers. KHQT could be an excellent regimen for treating *H pylori*- related PU.

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