Original Paper

# A 3-day Anti-*Helicobacter pylori* Therapy is a Good Alternative for Bleeding Peptic Ulcer Patients with *Helicobacter pylori* Infection

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**KEY WORDS:**
*Helicobacter pylori*; Peptic ulcer bleeding; Triple therapy

**ABBREVIATIONS:**
95% Confidence Interval (95% CI); *Helicobacter pylori* (*H. pylori*); Proton-Pump Inhibitor (PPI); Intravenous (IV); Nonsteroidal Anti-Inflammatory Drug (NSAID)

## ABSTRACT

**Background/Aims:** One-week triple therapy has been recommended as a standard regimen for eradicating *Helicobacter pylori* infection. The emergence of antibiotic-resistant strains, adverse drug effects, poor compliance and high cost of therapy add problems to the management of these patients. In this study, we assessed whether a 3-day triple therapy could be effective in eradicating *Helicobacter pylori* infection in bleeding peptic ulcer patients.

**Methodology:** Peptic ulcer patients with *Helicobacter pylori* infection were enrolled in this study. Patients enrolled at the outpatient department (group A) received a 7-day oral regimen: bismuth subcitrate colloid 300mg + amoxicillin 500mg + metronidazole 250mg four times per day. Patients who were admitted to the wards due to peptic ulcer bleeding (group B) received a 3-day regimen including omeprazole 40mg intravenously every 6 hours, amoxicillin 500mg + metronidazole 250mg orally four times daily after hemostasis had been achieved. Patients of both groups received omeprazole 20mg once per day or cimetidine 400mg twice daily per os for at least one month after anti-*Helicobacter pylori* therapy. We followed every patient endoscopically two months after anti-*Helicobacter pylori* therapy.

**Results:** From June 1997 to April 1999, a total of 57 patients (30 in group A and 27 in group B) with gastric or duodenal ulcer and *Helicobacter pylori* infection completed anti-*Helicobacter pylori* therapy. Two months after anti-*Helicobacter pylori* therapy, peptic ulcer was found to be healed with a scar in 26 (86.7%) of group A and 23 (85.2%) of group B ($P>0.1$). The eradication rates of *Helicobacter pylori* in the two groups were not significantly different in an intention-to-treat analysis [group A: 78.8% (26/33), 95% CI: 64.9-92.7%; group B: 80% (24/30), 95% CI: 65.7-94.3%, $P>0.1$] and in a per protocol analysis [group A: 86.7% (26/30), 95% CI: 74.5-98.9%, group B: 88.9%. (24/27), 95% CI: 77.1-100.7%, $P>0.1$]. Fewer side effects occurred in group B (3/30) than those in group A (7/33) ($P>0.1$).

**Conclusions:** In patients with peptic ulcer bleeding a 3-day anti-*Helicobacter pylori* therapy is a good alternative for eradicating *Helicobacter pylori* infection.

## INTRODUCTION

Since the discovery of Marshall and Warren in 1983, the link between *Helicobacter pylori* (*H. pylori*) and gastroduodenal diseases has been clarified in humans (1). It is found to be closely related to peptic ulcer, gastric cancer and low-grade lymphoma (2-4). Therefore, the WHO has classified it as a group I carcinogen (5). An NIH Consensus Conference has recommended that peptic ulcer patients with *H. pylori* infection require eradication of *H. pylori* (6). Current medical treatment of *H. pylori* infection includes triple or quadruple therapy for one or two weeks (6). Although it is highly effective, and the incidence of reinfection is low, the emergence of antibiotic-resistant strains, adverse drug effects, poor patient compliance and high cost of therapy add problems to the management of these patients (7,8).

As compared with a bismuth-based triple therapy, a proton-pump inhibitor (PPI)-based triple therapy has been proved to be highly effective (9-11). In the past few years, shorter anti-*H. pylori* regimens had been tried (7-15). However, the optimal duration of such regimens remains unknown.

In patients with bleeding peptic ulcer who were admitted to our wards, intravenous (IV) PPI was given routinely to prevent rebleeding after successful hemostasis has been obtained (16). A high intragastric pH is obtained soon after IV PPI injection (16,17). We hypothesized that a good anti-*H. pylori* effect might be obtained with a short course of antibiotics while giving IV PPI in these patients. The purpose of this study was to evaluate the anti-*H. pylori* effect of a 3-day triple therapy in patients with bleeding peptic ulcers.

## METHODOLOGY

### Patients

Patients with *H. pylori* infected gastric or duodenal ulcer (either at the outpatient department or

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wards due to bleeding peptic ulcer) were considered for entering this trial after informed consent had been obtained. Ethical approval was given by the Hospital Ethics Committee, Veterans General Hospital, Taipei. Patients were excluded from this study if they had major medical disease (e.g., malignancy, cirrhosis of liver, cerebral vascular accident, uremia, etc.); had pregnancy or lactation, had used any anti-ulcer therapy such as $H_2$-blockers, sucralfate, PPIs, bismuth salt or antibiotics within the past two weeks; had history of surgery for stomach or drugs allergy; had Zollinger-Ellison syndrome; and were unable or unwilling to cooperate.

### Study Protocol

After enrollment, all patients received anti-*H. pylori* therapy within two days. Two months after anti-*H. pylori* therapy, all patients received endoscopic re-evaluation including assessment of the ulcer status and *H. pylori* infection. Side effects related to anti-*H. pylori* therapy was evaluated by patient interview. Side effects were graded as follows: mild discomfort, which was self-limited without discontinuation of all drugs; moderate discomfort, which affected daily activity without discontinuation of all drugs; and severe discomfort, which led to discontinuation of therapy.

A positive history of nonsteroidal anti-inflammatory drug (NSAID) ingestion was defined as >1 tablet/day NSAID ingestion within seven days of enrollment. Positive cigarette smoking was defined as ≥10 cigarettes per day for at least one year. Positive alcohol drinking was defined as ≥40g/day alcohol consumption for at least six months.

### Determination of *H. pylori* Status

We obtained two biopsied specimens from the antrum and two specimens from the low body, greater curvature side of the stomach. For a rapid urease test of *H. pylori*, one specimen from the antrum and one specimen from the body were placed in an Eppendorf vial with a 0.1-mL reagent, which contained urea (2g), 0.5% (w/v) phenol red (10mL), and sodiumazide (20mg) in 100mL of 0.01-M sodium phosphate buffer. The test was positive if the color changed from light yellow to pink. For the pathological examination, one specimen from the antrum and one specimen from the body were placed in a bottle containing 10% neutral buffered formalin immediately after biopsy. The specimens were embedded in paraffin and stained with hematoxylin and eosin and modified Giemsa stain. Each specimen was examined by a senior pathologist who was unaware of the results of the rapid urease test. Patients were defined as positive for *H. pylori* infection if they had positive urease test and pathological examination. Eradication of *H. pylori* infection was defined as negative rapid urease test and negative pathological finding.

### Anti-*H. pylori* Medication

Patients from the outpatient department received a 7-day oral regimen (group A): bismuth subcitrate colloid 300mg + amoxicillin 500mg + metronidazole 250mg four times per day. Another group of patients from the wards received a 3-day regimen (group B) including omeprazole intravenously 40mg every 6 hours, amoxicillin 500mg + metronidazole 250mg orally four times daily.

### Intragastric pH Monitoring

With the permission of patients in group B, a glass pH electrode (Ingold 440-M3, Medical Instruments Corporation, Solothurn, Switzerland) was inserted transnasally and positioned 5cm below the cardia under fluoroscopic guidance after intravenous bolus of omeprazole had been administrated. It was calibrated before and after the pH recording with standard buffer solutions of pH 7.00 and pH 4.01. Electrodes with a pH shift ≥0.2 units were discarded. The pH electrode was connected to a data logger (Gastrograph Mark III, Medical Instruments Corporation, Solothurn, Switzerland). At the end of each recording, the data were transferred to a personal computer, stored, and analyzed with pack-2 software (Medical Instruments Corporation, Solothurn, Switzerland).

### Statistical Tests

The results of treatment were evaluated with the per-protocol analysis and the intention-to-treat analysis. 95% confidence intervals (CI) were also evaluated. Statistical analysis was performed using the unpaired Student's $t$ test or the $\chi^2$ test (or Fisher's exact test) if appropriate. A $P$ value of $<0.05$ was considered statistically significant.

## RESULTS

From June 1997 to April 1999, a total of 33 patients with gastric or duodenal ulcer and *H. pylori* infection were enrolled at the outpatient department (group A). A total of 30 patients with bleeding gastric or duodenal ulcer and *H. pylori* infection were enrolled at the wards after successful hemostasis had been obtained (group B). Age, sex, location of the ulcer and other important clinical parameters were similar between both groups **(Table 1)**. At the end of the study, six patients were excluded (three in the group

**TABLE 1 Clinical Data of the Two Studied Groups**

| | 7-day regimen (group A, n=33) | 3-day regimen (group B, n=30) |
|---|---|---|
| Sex (M/F) | 27/6 | 28/2 |
| Age, median (range) | 69 (33-79) | 71 (21-80) |
| **Location of ulcer** | | |
| Stomach | 16 | 16 |
| Duodenum | 17 | 14 |
| Drop out, No. | 3 | 3 |
| Ulcer size (cm), median | 0.5 | 0.8 |
| Smoking | S | 8 |
| Drinking | 0 | 0 |
| Comorbid illness | 5 | 6 |
| Nonsteroidal anti-inflammatory drugs use | 2 | 3 |

All parameters between both groups, $P>0.05$.

**TABLE 2 Eradication Rates on Intention-to-treat and Per Protocol Analysis in Two Groups**

| Analysis | 7-day regimen (group A) | 3-day regimen (group B) |
|---|---|---|
| Intention-to-treat | 26/33 (78.8%) | 24/30 (80%) |
| (95% CI) | (64.9-92.7%) | (65.1-92.5%) |
| Per protocol | 26/30 (86.7%) | 24/27 (88.9%) |
| (95% CI) | (74.5-98.9%) | (77.1-100.7%) |

$P>0.05$ between both groups.

**TABLE 3 Side Effects Noted During the Treatment in Two Groups**

| Side effects | 7-day (group A) | 3-day (group B) |
|---|---|---|
| Nausea/vomiting | 2 | 0 |
| Anorexia | 1 | 1 |
| Epigastralgia | 2 | 1 |
| Disturbance of taste | 0 | 0 |
| Diarrhea | 2 | 1 |
| Skin rash | 0 | 0 |

A: incomplete therapy in one patient and loss of follow-up in the other two patients; three in the group B: loss of follow-up in two patients and rebleeding in one patient).

Two months after anti-*Helicobacter pylori*, peptic ulcers were found to be healed with a scar in 26 (86.7%) of group A, and 23 (85.2%) of group B ($P>0.1$). The eradication rates of the two groups were not significantly different both with an intention-to-treat analysis [group A: 78.8% (26/33) 95% CI: 64.9-92.7%, group B: 80% (24/30), 95% CI: 65.7-94.3%, $P>0.1$] and a per protocol analysis [group A: 86.7% (26/30), 95% CI: 74.5-98.9%, group B: 88.9% (24/27), 95% CI: 77.1-100.7%, $P>0.1$] **(Table 2)**. At the end of the study, the eradication rate of patients with duodenal ulcer (15/17, 88.2%) was similar to that of patients with gastric ulcer (11/13, 84.6%) in group A ($P>0.1$). In group B, the eradication rate of patients with duodenal ulcer (11/13, 84.6%) was somewhat lower than that of patients with gastric ulcer (13/14, 92.9%) ($P>0.1$).

Eight patients from group B completed 24-hours intragastric pH monitoring. Median pH of these patients was 6.5 (95% CI: 5.81-6.72). Mild side effects were noted in 7 from group A and 3 from group B ($P>0.1$) **(Table 3)**.

## DISCUSSION

An ideal anti-*H. pylori* therapy should be simple, short, effective, well-tolerated and not harmful to the patients. In the past ten years, numerous regimens have been proposed in eradicating *H. pylori*. But, no one therapy has been recommended as the best regimen.

Most of these regimens require a significant number of pills in frequent doses for one to two weeks, making compliance difficult (9,11). An NIH recommending regimen (bismuth-based triple therapy) is associated with poor compliance, frequent side effects and drugs resistance (9,18,19) To avoid side effects and to improve patient compliance, PPI-based triple therapies have been recommended (9,18,19). The eradication rates of PPI-based triple therapies for one week have been reported to be over 90% (9,11).

How is the eradication rate if we shorten the anti-*H. pylori* therapy with fewer tablets? In the past few years, some short-term (<7 days) therapies had been designed with variable results (7,8,12-15). The optimal duration of anti-*H. pylori* therapy remains unknown so far.

Kimura *et al.* conducted a 1-hr topical therapy and obtained a 96% eradication rate (20). However, the method seems to bring suffering to the patients and is rarely used by other authors. One-day high-dose combined therapy has been reported to have a 72% eradication rate (21). In the above two studies, it seems that brief contact with a high concentration of antimicrobials may be enough to kill *H. pylori*. Tucci *et al.* used a weekend (2 days) anti-*H. pylori* therapy and achieved a high (84%) eradication rate (12). The high eradication rate may be explained by the elevation of intragastric pH with omeprazole for five days prior to antimicrobial therapy. Logan *et al.* used a 3-day protocol including tripotassium dicitrate bismuthate, amoxycillin and metronidazole and achieved a poor eradication rate (<50%) (22). De Boer *et al.* used a 4-day quadruple therapy (lansoprazole, bismuth, tetracycline and metronidazole) and obtained an eradication rate of 98% in a per protocol analysis (23). However, the side effects occurred in 79% cases. Trevisani *et al.* used a 4-day therapy including lansoprazole, azithromycin and tinidazile and achieved an 80.8% eradication rate in a per protocol analysis (7). In these short-term anti-*H. pylori* therapies, PPIs seem to play a key role for a higher eradication rate.

PPIs have been proved useful as part of combination therapy with antimicrobial agents to cure *H. pylori* infection. One major cause is related to increased intragastic pH, which may enhance the effectiveness of the local immune response, reduce the washout of antibiotics from the gastric mucosa, and improve the minimal inhibitory concentrations of antimicrobial agents (24).

Omeprazole inhibits $H^+$-$K^+$ adenosine triphosphatase, dose-dependently suppressing basal and stimulated gastric acid secretion (25). It can quickly achieve a high intragastric pH in a short time. In our previous study, a 24-hour median intragastric pH has been achieved as 6.6 (95% CI: 5.9-6.7) by omeprazole 40mg every 6 hours intravenously (16,17). It is thus reasonable to postulate that a successful eradication of *H. pylori* can be obtained with antimicrobials and intravenous omeprazole in a short duration.

In the present study, the 24-hour intragastric pH using a high dose of omeprazole (40mg every 6 hours) was 6.5, 5.81-6.72 (median: 95% CI). Our result was compatible with those of our previous results (16,17). We also proved that a short therapy had a similar effect as a 7-day regimen with fewer side effects. The fewer side effects of the short regimen may be attributed to the fewer tablets of antimicrobials used

in our patients (18,19). By using a fewer tablet regimen, the development of antibiotics resistance would be also reduced (22,23).

In conclusion, the 3-day anti-*H. pylori* regimen is a good alternative for patients with bleeding ulcer in eradicating *H. pylori* infection.

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