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An Impact of Helicobacter pylori Eradication after Simple Closure of Perforated Peptic Ulcer: A Prospective Randomized Trial

Petch Kasetsuwan, MD
Somchai Thanasitthichai, MD
Wanchai Krailadsiri, MD
Department of Surgery, Bhumibol Adulyadej Hospital, Phaholyothin Road, Donmeung, Bangkok 10220, Thailand

Abstract

Background: **This study was carried out to evaluate the relationship of *Helicobacter pylori (H. pylori)* infection in perforated peptic ulcer patients and the benefit of *H. pylori* eradication on ulcer healing and ulcer recurrence after simple closure of perforated ulcer.**

Materials and Methods: **Sixty-six patients with perforated peptic ulcer were treated by simple closure with omental patch and intraoperative esophagogastroduodenoscopy (EGD) to assess *H. pylori* infection status. Patients were randomized into two groups; control group (group 1) received Omeprazole regardless of *H. pylori* status whereas the study group (group 2) *H. pylori* positive patients received a course of anti - *H. pylori* therapy. Follow-up EGD was performed at 2 months, and at 1 year after hospital discharge to evaluate ulcer healing and ulcer recurrence respectively.**

Results: ***H. pylori*** **infection rate was 86.3%, 50% and 92.8% in overall perforated ulcer, perforated gastric ulcer and perforated duodenal ulcer respectively. Ten patients did not return at 2 months for endoscopic follow-up. Of fifty-six patients, twenty-nine in group 1 and twenty-seven in group 2 underwent EGD at 2 months follow-up and revealed initial ulcer healing rate of 65.5% and 88.8% respectively (P =0 .038) . At 1 year follow-up, ulcer recurrence rate of patients in group 1 was significantly higher than patients in group2 (36.8% and 5%, P = 0.02).**

Conclusion: **This study confirms a close relationship between *H. pylori* infection and perforated peptic ulcer. *H. pylori* eradication after simple closure and omental patch can promote initial ulcer healing and prevent ulcer recurrence as well. Immediate acid reduction surgery should be reserved only for patients who have obvious risk of gastric outlet obstruction.**

Perforated peptic ulcer is one of the most common surgical emergency conditions especially in low socioeconomic patients. According to the classic work of Byrd et al[1] in 1955, after simple closure and omental patch of perforated peptic ulcer, one-fourth of the patients were cured, one-half had some symptoms that required medication and the remainder had complications and needed acid reduction operation. After that, there were several studies comparing the treatment of perforated peptic ulcer between simple closure with omental patch and immediate acid reduction operation. Some advocated the former combined with long term acid suppression by various kind of drugs which were much improved in their efficacy.[2-4] Others preferred the latter especially in the patients who had a long standing history of ulcer symptoms, had previous treatment of peptic ulcer diseases, or lived in remote area.[5-9] However after the discovery and realizing that *Helicobacter pylori (H. pylori)* was the important cause of peptic ulcer,[10-12] little research has been done about the impact of eradication of this bacteria after surgical management of perforated

peptic ulcer. If *H. pylori* eradication can prevent ulcer recurrence after simple closure of the perforated ulcer, why should we have to perform an acid reduction operation for the treatment of this condition? Therefore we conducted a prospective randomized controlled trial study to compare the clinical outcomes of treating perforated peptic ulcer by conventional simple closure alone and simple closure plus *H. pylori* eradication in the patients who were infected.

Materials and Methods

All patients with perforated peptic ulcer, admitted during January 1998 to April 1999 were included in this study. Exclusion criteria included patients under 15 or over 65 years old, previous gastric surgery, allergy to Penicillin or Erythromycin and operative finding demonstrating a definite risk of gastric outlet obstruction. The patients were resuscitated and given 1 gm of Cefazolin intravenously before operation. After general anesthesia was introduced, exploratory laparotomy was performed and soiling from perforated site was controlled. Then an intraoperative esophagogastro-duodenoscopy (EGD) was performed and the site and size of the ulcer were recorded. Biopsy of the gastric mucosa, 3 pieces from antrum and one piece from the body were taken. One the piece of the antral biopsied specimen was embedded in rapid urease test (CLOR test, Delta West, West Australia) and the rest were sent for histologic examination. Simple closure and omental patch of the perforated ulcer was performed using braided polyglycolic acid 2/0 (Dexon, Davis-Geck, U.S.A.). Postoperatively, intravenous Cefazolin 1 gm every 6 hr. was continued for 4-5 days and also cimethidine 300 mg every 8 hr. was given in all patients until the diet was resumed. Then patients were randomized into two groups by block randomization. In control group (group 1) the patients received Omeprazole (Losec®, Astra, Sweden) 20 mg orally once a day for 2 weeks duration for perforated DU and 4 weeks for perforated GU regardless of *H. pylori* infection status. While in the study group (group 2), the patients who were infected with *H. pylori* (CLO test positive or histological positive for *H. pylori*) received *H. pylori* eradication therapy by using the regimen which included Omeprazole 20 mg twice a day, Amoxycillin 1000 mg twice a day and Clarithromycin (Klacid®, Abbott, U.K.) 500 mg twice a day (OAC regimen) for one week duration. Omeprazole 20 mg. once a day was continued for one week for DU and 3 weeks for GU, non-infected patients were treated the same as in group1 patients (Figure 1).

All patients were invited to undergo an EGD with biosy for *H. pylori* testing at 2 months after discharge. If ulcer did not heal, omeprazole 20 mg once a day was given 2 and 4 more weeks for DU and GU respectively. In group 2, if *H. pylori* was still positive, eradication therapy was repeated using omeprazole, metronidazole and clarithromycin regimen and patients would be rechecked until eradication was succeeded. The patients were then followed every 3 months by using Modified Visick classification and EGD was repeated at

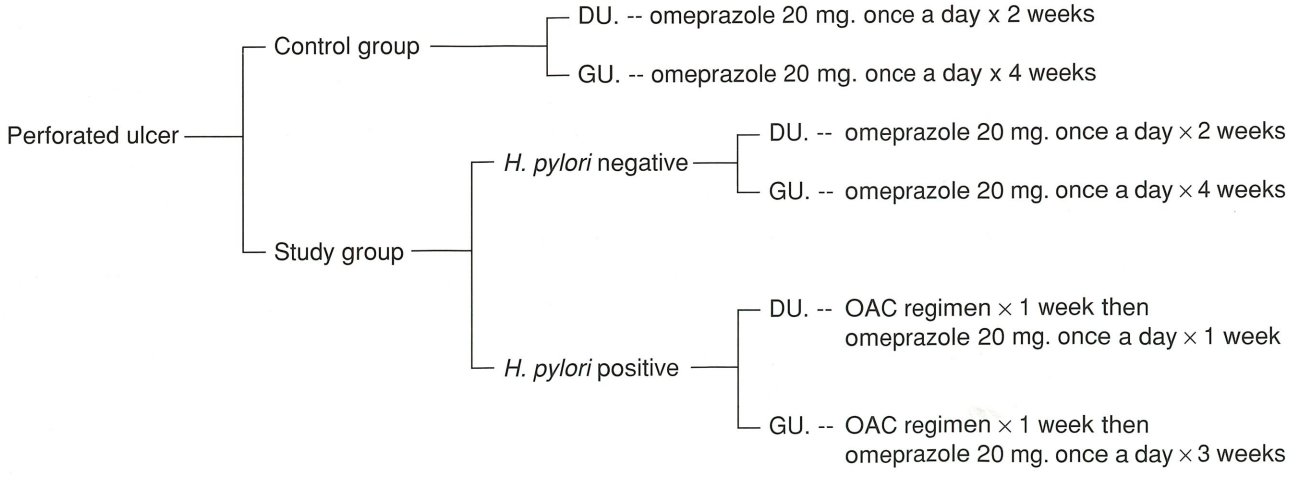

Fig. 1 Management after recovery from the operation

1 year after operation. After that the patients would be periodically interviewed by phone and also advised to come back if the peptic ulcer symptoms recurred.

Statistical Package for Social Science (SPSS) program was used for statistical analysis. Chi-square and Fisher's exact test were used when appropriate. For continuous numeric data, mean and standard deviation were used and compared by the student t-test.

This study was approved by the Ethics Committee of Bhumibol Adulyadej Hospital, Royal Thai Air Force.

Results

From January 1998 to April 1999 there were 66 cases of perforated peptic ulcer patients who were recruited in the study. Fifty-nine cases were men and 7 cases were women. The average age was 43.2 years (ranged from18-65 year). Ten cases were perforated GU and 56 cases were perforated DU. The overall *H. pylori* infected rate was 86.3%. For perforated GU, 5 of 10 cases (50%) had *H. pylori* infection. Meanwhile the infection rate in perforated DU was 92.8% (52 in 56 cases). Interestingly, perforated DU patients without history of NSAIDs usage had 100% infection rate (Figure 2).

In total of sixty-six cases, 10 cases were dropped from the study due to inability to be followed-up by endoscopy at 2 months after discharge. Finally there were 56 remaining cases for follow-up and analysis, 29 cases were the control group (group1) and 27 cases were the study group (group 2). Age, sex, history of peptic ulcer disease, NSAIDs usage, smoking, site and size of the ulcer, *H. pylori* positive rate and postoperative complications of the patients in both groups were comparables (Table 1). At 2 months follow-up, the clinical evaluation using Modified Visick classification in both groups were similar. The majority of the patients in both groups experienced "excellent-good" results (Visick grade1-2). However the initial healing rate of the ulcers, assessed by single endoscopist, in group 2 was significantly higher than in group1 (88.6% vs. 65.5%, P = 0.038) (Table 2). Among group 1, the characters of the patients between healed and unhealed ulcer were compared (Table3). *H. pylori* positive rate and smoking were greater in unhealed ulcer patients even though the difference did not reach statistical significance. While in the unhealed ulcer (3 cases) in group 2, one of them was a patient who failed to succeed in *H. pylori* eradication at the first attempt but after changing the regimen and successful eradication the ulcer healed. The other one was a patient who suffered from severe osteoarthritis and needed long term NSAIDs. The last one was a GU patient who was not infected by *H. pylori*. His ulcer finally healed after the second course of omeprazole . Furthermore in group 2, among the *H. pylori* positive patients, there were 2 cases that the bacteria could not eradicated,

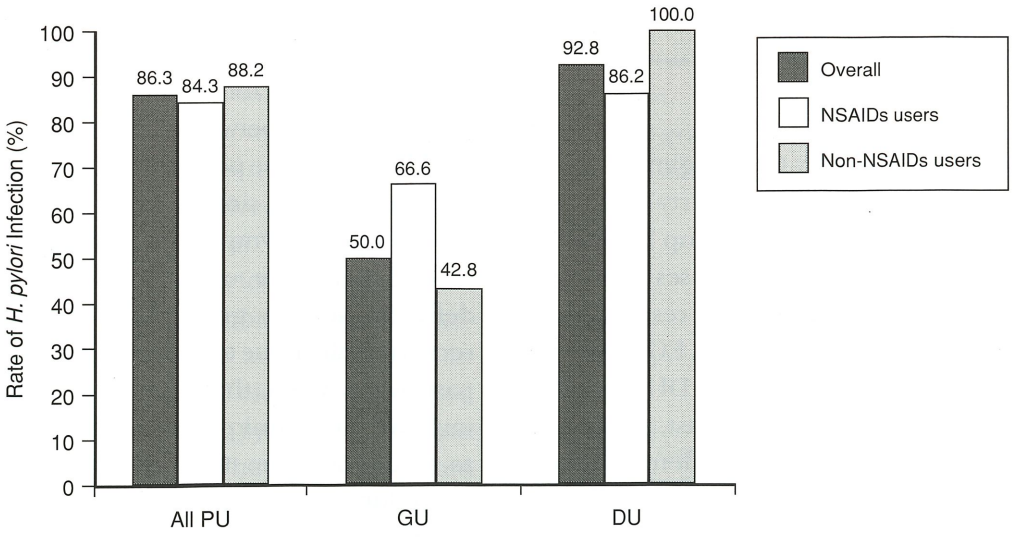

Fig. 2 Prevalence of *Helicobacter pylori* in perforated peptic ulcers.

Table 1 Character of patients compared between both groups

	Control Group (Group 1)	Study Group (Group 2)
No. of patients	29	27
Age (yr.)	43.6 ± 12.3	41.9 ± 13.2
Male:Female	26:3	24:3
History of PUD. (%)	55.1	51.8
NSAIDs users (%)	44.8	44.4
Smoking (%)	72.3	70.3
Site of ulcer (DU:GU)	26:3	22:5
Size of ulcer (mm.)	6.8 ± 3.7	7.1 ± 4.2
H.pylori infection rate (%)	89.6	81.4
Complications (%)	13.7	22.2

Table 2 Result at two months follow- up

	Group 1 (N = 29)	Group 2 (N = 27)	
Initial ulcer healed (%)	19 (65.5)	24 (88.8)	P =.038
Visick's grade			
Excellent - Good	28	27	
Fair - Poor	1	0	
H. pylori eradication rate	-	92.5%	

Table 3 Comparison between Healed and Non-healed ulcer in-group 1

	Healed ulcer N =19	Non-healed ulcer N =10
Male:Female	17:2	9:1
NSAIDs users (%)	47.3	40
Smoking (%)	63.1	90.0
History of PUD. (%)	57.8	50.o
Size of ulcer (mm.)	7.5	5.6
H. pylori infection rate (%)	84.2	100.0

with 92.5% eradication rate by OAC regimen.

At 1 year follow up, there were thirty-nine cases, 19 cases in group 1 and 20 cases in group 2, available for follow-up and EGD. Three of 19 cases of group 1 had Visick grade "fair-poor" (grade 3-4) results, one of them had significant melena. Moreover, EGD revealed 7 of 19 cases (36.8%) had a recurrent DU and all of them were *H. pylori* positive. In contrast, all patients in-group 2 were classified as "good-excellent" (grade 1-2) results and EGD showed only one of them (5%) had recurrent ulcer. These differences reached the statistical significance (Table 4). Additionally there was one

Table 4 Results at one year follow-up

	Group 1 (N = 19)	Group 2 (N = 20)	
Recurrent ulcer (%)	7 (36.8)	1 (5)	P = .02
Visick's grade			
Excellent - Good	16	20	
Fair - Poor	3	0	
Reinfection rate	-	0	

patient in group 1, who did not return for EGD at 1 year follow-up, was re-operated for re-perforated duodenal ulcer sixteen months after the first operation.

Discussion

The treatment of perforated peptic ulcer is still a subject of controversy. Simple closure with omental patch is an easy procedure, which could be performed by any surgical trainee. The only limitation of simple closure is a high recurrence rate of the ulcer disease. Sawyers et al[7] evaluated the outcomes of treating acute perforated DU by simple closure in 184 patients. Thirty-six percent of these patients had been asymptomatic, thirty-seven percent had to have a subsequent definitive surgical procedure for control of their ulcer disease. The remaining twenty-seven percent had recurrent symptoms that were managed by medical therapy. So, many authors advocated an immediate acid reduction surgery to prevent ulcer recurrence. In those reports, either retrospective or prospective, they compared the advantages and disadvantages of the acid reduction procedures after closure of the perforation. Tanphiphat and co-workers[9] demonstrated a superior result of definitive surgery for perforated DU. They reported a prospective trial between simple closure and definitive surgery in sixty-five perforated DU. They found eighty-five percent of simple closure group developed recurrent ulcer symptoms and 33% had already had a second definitive operation, whereas only 8% in definitive surgery group were reoperated upon for recurrent ulcer due to an incomplete vagotomy. In the past twenty years, there have been many attempts to improve the technique of acid reduction surgery such as changing from truncal vagotomy and drainage procedure to proximal gastric vagotomy (PGV) without drainage procedure to avoid postvagotomy and postgastrectomy syndrome.[13-15] Ceneviva et al[8] did a

prospective study comparing PGV plus omental patch suture with the simple omental patch suture for perforated ulcer and they found the recurrence rate was 8% and 62% respectively. They concluded that PGV was a safe operation with a negligible morbidity rate and with a significant rate of effective control of ulcer disease. However simple closure is still recommended by many surgeons especially together with a postoperative "medical" acid control such as H_2 receptor antagonist or proton pump inhibitor.[16,17] A good medical acid control can reduce the ulcer recurrence rate and subsequently reduce reoperation rate. Borman[3] reported only fourteen percent of 113 patients who were treated by simple closure and then required a definitive operation later. At that period of time, "acid" used to be considered the most important cause of peptic ulcer. Therefore a prolonged reduction of gastric acid secretion either surgically or medically had been provided to prevent ulcer recurrence.

Until 1982, Marshall and Warren[10] provided the first insight into another important pathogenic factor in peptic ulcer disease. They isolated a spiral urease-producing organism nestled in the narrow interface between the gastric epithelial cell surface and the overlying mucus gel, which was later named Helicobacter pylori. That discovery had a great impact on the treatment of peptic ulcer, changing a chronic relapsing disease into a curable disease. There is no doubt of the importance of *H. pylori* in uncomplicated peptic ulcer disease. Most of the published data have confirmed significant reduction in ulcer recurrence after eradication of this bacteria.[18-20] NIH Consensus development panel on *H. pylori*[21] concluded that ulcer patients with *H. pylori* infection required treatment with antimicrobial agents in addition to antisecretory drugs. *H. pylori* eradication also shows a positive impact in treating bleeding ulcer. There is now good evidence that recurrent ulceration and bleeding can be prevented by *H. pylori* eradication.[22] However, its importance and correlation in perforated peptic ulcer remains an unsettled issue. Reinbach[23] and Chowdhary[24] reported the lack of such an association. In contrast Sebastian, Ng, Chu and Tokunaga supported a significant relation between *H. pylori* infection and perforated peptic ulcer.[25-28] They recommended eradicating this bacteria to prevent ulcer recurrence.

The present study demonstrates a very high prevalence of *H. pylori* infection (86.3%) in perforated peptic ulcers, either in NSAIDs users or non-NSAIDs users. This confirms a close relationship between *H. pylori* and perforated ulcer especially perforated DU. The initial healing rate of the ulcer after simple closure with omental patch is higher in group 2 which the *H. pylori* was eradicated if infected. In 88.8% of the patients in group 2, their ulcers healed by using a short duration of acid suppression (two weeks for DU and four weeks for GU). While the ulcers healed only in 65.5 percent in-group 1 and all unhealed ulcer were H. pylori positive. Thus, it can be concluded that eradication of *H. pylori* can promote ulcer healing faster than ulcer treatment alone leading to shorter duration of acid suppression. Moreover, the very low rate of ulcer recurrence at 1 year in group 2 (5%) confirms the importance of *H. pylori* eradication as it can prevent an ulcer recurrence and may be better than the result of definitive acid reduction surgery in the past. Therefore we recommend simple closure and omental patch for patients presenting with perforated peptic ulcer. Then identify *H. pylori* status as soon as possible and eradicate if infected. Otherwise in some areas with very high prevalence of *H. pylori* infection, eradication therapy may be given without testing. Then patients should be followed up by endoscopy to confirm healing of the ulcer and completeness of *H. pylori* eradication. Immediate "definitive" acid reduction surgery should be reserved only for patients who have obvious risk of gastric outlet obstruction.

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