IS ERADICATION OF HELICOBACTER PYLORI PREVENTS RECURRENCE OF ULCER AFTER SIMPLE CLOSURE OF DUODENAL ULCER PERFORATION?

By
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Background: most patients with chronic peptic ulcer disease have helicobacter pylori (h.Pylori) infection. In the past, immediate acid reduction surgery has been strongly advocated for perforated peptic ulcer because of the high incidence of ulcer relapse after simple closure. Although H. Pylori eradication is now the standard treatment of uncomplicated and bleeding peptic ulcers, it's role in perforation remains controversial.

Study aim: The aim of this randomized study, is to determine whether eradication of H. Pylori could reduce the risk of ulcer recurrence after simple closure of perforated duodenal ulcer or not

Patients and methods: Of 80 patients suffering from acute peptic ulcer perforation, 65 (81%) were shown to be infected by H. Pylori (CLO test). Sixty-five positive patents were randomized to receive a course of triple anti-helicobacter therapy or a 4-week course of omeprazole alone. Follow-up endoscopy was performed 8 weeks, 16 weeks (if the ulcer did not heal at 8 weeks), and 1 year after hospital discharge for surveillance of ulcer healing and determination of H. Pylori status. The endpoints were initial ulcer healing and ulcer relapse rate after 1 year.

Results: Of 58 patients who did undergo follow- up endoscopy, 31 of the 32 patients in the first group (anti- Helicobacter group) and 4 of the 26 patients in the second group (omeprazole alone group) had H. Pylori eradicated, initial ulcer healing rates were similar in the two groups (90.6% versus 88.4%). After 1 year, ulcer relapse was significantly less common in patients treated with anti-Helicobacter therapy than these who received omeprazole alone (6.2% versus 34.6%).

Conclusions: We have found a high prevalence of H. Pylori infection in patients with perforated peptic ulcer. An immediate and appropriate H. Pylori eradication therapy for perforated peptic ulcers reduces the relapse rate after simple closure. Response rate to triple eradication protocol was excellent in hospital setting. Immediate acid- reduction surgery in the presence of generalized peritonitis is unnecessary.

Key words: Helicobacter pylori Duodenal ulcer Omeprazole Endoscopy Anti-Helicobacter pylori

INTRODUCTION

The long-term results of omental patch repair for perforated duodenal ulcer are unsatisfactory; a high incidence of ulcer recurrence has been repeatedly reported [1-5]. Some advocate immediate acid-reduction procedures in addition to repar of the ulcer as a preventive measure against subsequent ulcer relapse [6,7]. Immediate definitive surgery in selected patients is safe, without increasing the rate of perioperative complications or death [8]. However with recent advances in antiulcer medical therapy, fewer surgeons have acquired sufficient expertise in performing

the definitive operation. Because perforated peptic ulcer is often an emergency a simpler life-saving procedure suth as simple oversewing procedures either by an open or laparoscopic approach is an attractive option in many centers [9].

The recent rediscovery of Helicobacter Pylori has revolutionized the therapeutic approach to peptic ulcer disease. Eradication of H. Pylori heals most uncomplicated peptic ulcer and prevents relapse [10-12].

In the case of bleeding peptic ulcers, a short course of antibiotics eradicating H. Pylori is efficacious as maintenance acid-reduction medication in preventing recurrent ulcer haemorrhage [13]. Meeting of the European Helicobacter Pylori Study Group have recommended eradicatin of H. Pylori as the standard treatment for uncomplicated and bleeding peptic ulcers [14-15].

However, the association between H. Pylori and perforated duodenal ulcer is less well defined. The reported infection rates range widely, from 47% by serologic testing [16] to more than 80% in two recent biopsy-based studies [17-18]. Whether there is a causal relation between the bacterium and duodenal ulcer perforation is contraversial. We therefore performed a prospective randomized trial to determine whether eradication of H. Pylori could lead to sustained ulcer remission in patients who underwent only simple repair for doudenal ulcer perforation.

PATIENTS AND METHODS

Of eighty patients with clinical or radiologic sign of perforated peptic ulcer, 65 (81%) were shown to be infected by H. Pylori.

Another 7 patients were excluded from this study for several reasons (as 3 failed endoscopic examination, 2 patients refused to undergo intraoperative endoscopy, 2 patients do not follow up by endoscopy). So our study including 58 patients, and done in Sohag University Hospital from March 1999 to March 2001. Informed consent was obtained for surgical exploration, intraoperative per oral gastroscopy, and possible enrollment into the study if infected with H. Pylori.

Exclusion criteria were age older than 75% or younger than 16y, use of antibiotic or acid-suppressing medications within 4 weeks before admission, previous vagotomy or gastrectomy, pregnancy.

All patients received fluid resuscitation; intravenous cefobid 1 gram was administered during induction of anesthesia. No other antibiotics or acid suppressing medication were prescribed before surgery. When duodenal ulcer perforated was confirmed by laparotomy, intraoperative flexible gastroscopy was performed to obtain biopsy samples of gastric antrum several samples were obtained one for urease test (campylobacter- like organism test "CLO test") 2 for gram stain and culture, and 2 in 10% buffered formalin for histologic examination.

Patients were considered to be H. Pylori positive if any one of the following results was found a positive CLO test plus gram-negative helical bacteria in the smear or positive CLO test result plus helical microorganism in histologic section of gastric biopsy samples

Gastrectomy or other definitive acid reduction procedures were considered only if patients had large perforation (more than 1 cm in diameter) not suitable for simple over-sewing of the perforation or perforation associated with hemorrhage or obstruction, and such patients not included in our study.

Perforation less than 1 cm in diameters were repaired by simple omental patch repair. After closure of the perforation, thorough peritoneal lavage with worm saline was performed before closure of the abdominal incision. After surgery, intravenous cefobid (1 gram) was continued every 12 hours for 3 days and intravenous omeprazole 40 mg/day was given until the patient resumed eating on oral diet. Only H. Pylori- positive patients who had undergone patch repair were eligible for randomization trial. After resuming an oral diet, patients were randomly assigned to one of the two treatment options

First group or eradication group in which patients receiving triple eradication protocol, or 1 week course of oral antibacterial treatment (metranidazole 500 mg two times daily, amoxicillin 500 mg three times daily) plus 4 weeks of omeprazole (20 mg twice daily) was prescribed. Second group or control group in which patients were given a 4-week course of omeprazole alone.

Endoscopy was scheduled 8 weeks after randomization. Biopsy samples were again obtained from the gastric antrum to determine the patient's H. Pylori status (Fig. 1).

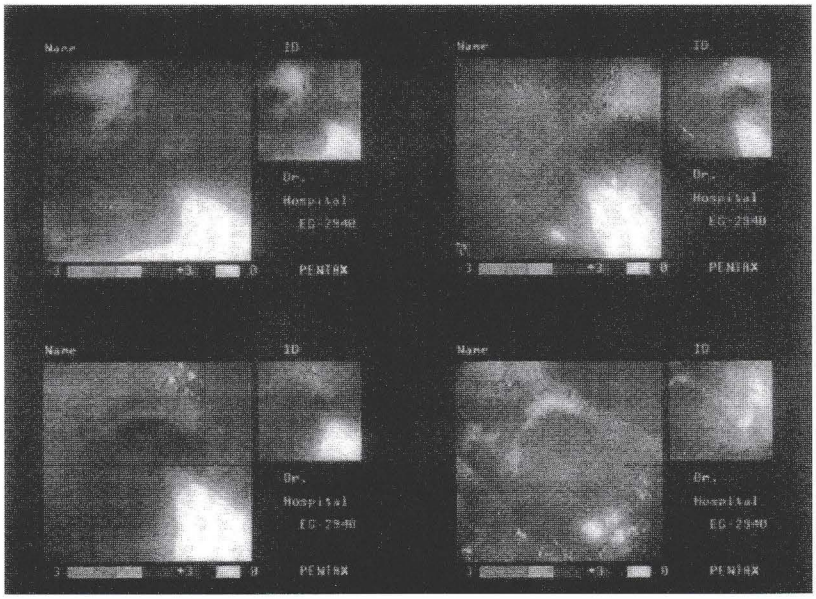

Fig. (1): Biopsy samples obtained from gastric antrum.

All patients with complete ulcer healing confirmed on scheduled endoscopy were then interviewed every 3 months for symptomatology. Maintenance acid-suppression agents were not prescribed during the follow up period. Repeated endoscopic examination was performed whenever patients were symptomatic. All patients were invited for follow up endoscopy at 1 year for ulcer surveillance and determination of H. Pylori status.

RESULTS

From March 1999 to March 2002, 80 patients (66 men and 14 woman), mean age of 49.3 years (SD=16.2) were confirmed to have duodenal ulcer perforation by laparotomy. Sixty-five patients (81%), out of 80 patients were infected with H. Pylori. So this 15 patients were excluded from our study, other 7 patients were excluded for different reasons as 3 cases failed endoscopic examination, 2 patients refused to undergo intraoperative endoscopy, last 2 patients excluded also as long term follow up was not possible for them. Of the remaining 58 patients, 32 were allocated to anti- Helicobacter therapy and 26 to omeprazole alone.

The two groups were evaluated in age, sex, ratio, smoking habit, use of non-steroidal anti-inflammatory drugs, severity of peritoneal contamination and method of repair (Table 1).

Table (1): *Characteristics of patients.*

	Triple therapy N=32	*Omeprazole therapy N=26*
Age (years)	45±13	43±14
Sex:		
• Female	6	5
• Male	26	21
Cigarette smoking:		
• Not smoker or ex-smoker	12	11
• 4-8 packs/week	18	13
• > 8 packs/week	2	2
Dyspepsia >3 months	14	9
Previous ulcer	3	1
Severity of peritonitis:		
• Mild	8	6
• Moderate	21	19
• Sever	3	1
Size of perforation (mm)	4.4±1.5	4.6±1.5
Type of repair:		
• Open method	32	26
NSAIDs intake	13	9

- NSAIDs=Non-steroidal anti-inflammatory drugs
- Previous ulcer signifies a history of peptic ulcer disease confirmed by either barium meal or endoscopy.

As expected, the H. Pylori eradication rate of the anti-Helicobacter treatment group was significantly higher than that of omeprazole alone group (87.5% versus 15%, p<0.001). Four patients in the omeprazole alone group had complete eradication of H. Pylori (Table 2). When case records were reviewed, 3 out of 4 patients had received extra antibiotics, including ampicillin or metranidazole in the early postoperative period (both are effective antibiotics for eradication of H. Pylori).

Table (2): ***Early outcomes.***

	Triple therapy N=36	*Omeprazole therapy N=29*
Patents who underwent initial follow up endoscopy	32 (88.8%)	26 (89.6%)
H.Pylori eradicated	28 (87.5%)	4 (15%), P<0.001
Complete ulcer healing	29 (90.6%)	23 (88.4%)

Initial healing of ulcers was comparable between the two groups (Table 2). There were six non-healing ulcers despite repeated courses of omeprazole, three in the anti-helicobacter group and three in the omeprazole group. Complete ulcer healing was found and documented in 29, 23 patient respectively. Patients with complete ulcer healing were examined by upper endoscopy according to the study protocol (Fig. 2).

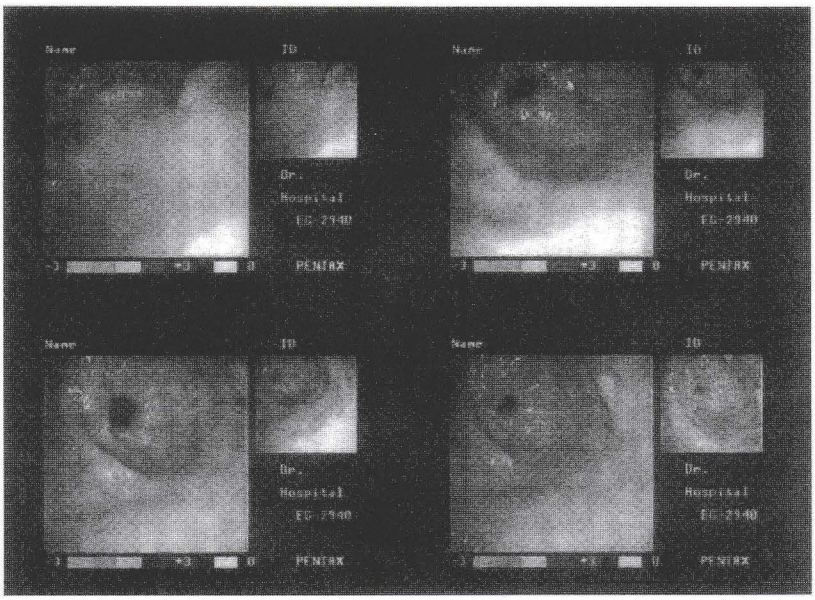

Fig. (2): Follow-up upper endoscopy according to study protocol.

After 1 year, one patient in the anti-helicobacter group and one patient in the omeprazole group were lost to follow-up (Table 3).

Table (3): *Outcomes of patients at 1-year follow-up.*

	Triple therapy	*Omeprazole therapy*
Patients with complete ulcer healing on initial endoscopy	29	23
All ulcer recurrence:	2 (6.2%)	9 (34.6%)
• Duodenal	2	7
• Gastric	0	2
• Gastric +duodenal	0	0
Symptomatic ulcer recurrence:	0 (0%)	6 (26%)
• Pain	-	4
• Bleeding	-	1
• Obstruction	-	1

Two patients in the anti-helicobacter group had ulcer relapse. They were asymptomatic and had recurrent ulcer diagnosed at scheduled 1-year endoscopy six out of 9 patients with ulcer recurrence in the omeprazole alone group; were symptomatic four patients showing severe ulcer pain one with bleeding, and last one with gastric outlet obstruction. The difference in ulcer recurrence between the anti-helicobacter group and the control group was statistically significant (6.2% versus 34.6%, P=0.0001, intention to treat). Ten out of eleven ulcer recurrence were associated with persistent H. Pylori infection; 9 in the omeprazole group and 1 in the anti-helicobacter group.

DISCUSSION

The most perfect surgical treatment for perforated duodenal ulcer has been controversial. Simple repair has been the most commonly performed procedure since its popularization by Graham in 1937 [19]. However, long-term follow up of the patients who underwent simple repair reveals in a high incidence of ulcer relapse [1-4]. In

prospective series by Bornman et al [20], forty-eight of 131 patients (42.5%) had recurrent ulcer disease after simple closure of duodenal perforation over a median follow-up of 42 months. 30% of them required further surgery for intractable symptoms or recurrent ulcer complications. Because of the unsatisfactory results of simple repair, immediate acid- reduction procedures have been strongly advocated

In the 1980, several prospective randomized studies reported significantly fewer ulcer recurrence by adding immediate proximal gastric vagotomy to patch repair of ulcer perforation [8,21-23]. The recent rapid development in laparoscopic surgery has complicated the issue. Since the first successful laparoscopic repair performed by Mouret et al [24] in 1990. Nevertheless, reservations about the use of laparoscopic repair still exist.

Our study was designed to determine whether perforated duodenal ulcer is causally related to H. Pylori infection or not. Anti-helicobacter therapy would be a more desirable option than definitive surgery if eradication of the bacterium confers prolonged ulcer remission after simple closure of the perforation.

In our study, patients with perforated duodenal ulcer, H. Pylori infection rates 81%. This figure is much higher than that reported by Reinbach et al [16] but is consistent with that of Metzger et al [5], Sebastian et al [17] and Matsukura et al [18] Ng et al [25], Ng et al [26]. Suggesting as association between H. Pylori infection and duodenal ulcer perforation

Our study showing high consumption rate of NSAIDs 22 out of 58 patients 38% and this cancer with the results other authors as Thompson et al [27], Collier et al [28]. Although perforated peptic ulcers have been related to the use of NSAIDs, our results showing that association was shown mainly in the elderly patients who took these drugs on a long-term basis and this agree with the result of Walt et al [29]. H. Pylori infection, as a risk factor, appears to be more relevant in younger patients, in whom acid-reduction surgery with its attendant complications is most undesirable.

After H. Pylori eradication and without maintenance acid-suppression agents 90 of patients remained ulcer free at 1- year follow up and this results of our study agree with the results of Graham et al [10], Vander et al [11], Ng et al[26].

In this study, there were high prevalence of H. Pylori infection and a few recurrences after eradication. The bacterium is likely to be causally related to the strong ulcer diathesis in patients with duodenal ulcer perforation and this is cancer with the results of Ng et al [26].

Conclusions

There is high prevalence of H. Pylori infection in patients with perforated peptic ulcer. Conventional simple repair is the procedure of choice for duodenal ulcer perforation, H. Pylori status should be determined by either endoscopic biopsy or serology, and bacterium should be eradicated in those who were infected, as an immediate and appropriate H. Pylori eradication therapy for perforated peptic ulcers reduces the relapse rate after simple closure. Response rate to triple eradication protocol was excellent more than omeprazole alone in the hospital setting. Immediate acid reduction surgery is unnecessary unless there are other concurrent ulcer complications, such as obstruction or hemorrhage.

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