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Effect of *Helicobacter pylori* eradication on ulcer recurrence after simple closure of perforated duodenal ulcer☆

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ABSTRACT

Background: This study was conducted to elucidate the prevalence of *Helicobacter pylori* in patients with a perforated duodenal ulcer and to determine whether eradication of *H. pylori* prevent ulcer recurrence following simple repair of the perforation.

Patients and method: Eighty-three patients with perforated duodenal ulcer (68 males); mean age was 47.8 years ± 7.2. Antral mucosal biopsies (to determine the status of HP by rapid urease test, culture and histological examination/staining) were obtained during laparotomy by passing a biopsy forceps through the perforation site. *H. pylori* positive patients who had undergone patch repair were randomized into the eradication group who received amoxicillin, metranidazole plus omperazole and the control group was given omeprazole alone. Follow-up endoscopy and antral biopsies were performed at 8 weeks, 16 weeks and 1 year to show ulcer healing and determine *H. pylori* state.

Results: Of 77 patients in the study, 65 patients (84.8%) had *H. pylori*. These patients were randomly divided into the triple therapy group (34 patients) and the control group (31 patients). Eradication of *H. pylori* was significantly higher in the triple therapy group than the control group and initial ulcer healing was significantly better in the eradication group. After 1 year, ulcer recurrence was (6.1%) in the eradication group vs. (29.6%) in the control group ($P = 0.001$).

Conclusion: H. pylori was present in a high proportion of patients with duodenal ulcer perforation. Eradication of *H. pylori* after simple closure of a perforated duodenal ulcer reduced the incidence of recurrent ulcer.

1. Introduction

Perforation is a serious and potentially fatal complication of duodenal ulcer. The incidence of perforated duodenal ulcer has not decreased despite advances in medical treatment.[1] Simple closure was initially and remains one of the treatments of perforated duodenal ulcer. However, the long-term results of omental patch repair for perforated duodenal ulcer are unsatisfactory; a high incidence of ulcer recurrence has been reported, reaching 40–50% in some series.[2–4] Use of acid suppressing agents to reduce ulcer recurrence after simple patch closure produced debatable results.[5–7] Immediate definite surgery although is effective with low recurrence rate, is associated with long-term side effects.[5]

Helicobacter pylori (*H. pylori*) has been described as an opportunistic pathogen attracted by changes in the gastric mucosa caused by inflammation and ulcer.[11] However, its role in duodenal perforation has been investigated extensively and the results are conflicting.[6–10] Eradication of *H. pylori* heals most uncomplicated duodenal ulcers and prevent relapse.[8–12]

The aim of this study was to elucidate the prevalence of *H. pylori* in patients with a perforated duodenal ulcer and to determine whether eradication of *H. pylori* prevent ulcer recurrence following simple repair of the perforation.

2. Patients and methods

Of the 83 patients admitted with perforated duodenal ulcer between March 2005 and January 2007 at the Emergency Mansoura University Hospital, 77 patients were treated by simple closure and they were included in our study. Exclusion criteria were

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age younger than 16 or older than 75 years, history of recent intake of antibiotics, H2 antagonists or proton pump inhibitors within 4 weeks before admission, sealed off perforation, previous gastrectomy or vagotomy or patients with perforated gastric ulcers. Demographic data, history of dyspepsia for more than 3 months, smoking and the use of non-steroidal anti-inflammatory drug (NSAIDs) were recorded at time of admission.

All patients were resuscitated before surgery. Informed consent was obtained from every patient for surgical exploration and inclusion in the study. Intravenous cefuroxime (1.5 gm) was administered during induction of anesthesia; no other antibiotics or acid suppressing treatment was prescribed before the operation.

When duodenal ulcer perforation was confirmed at laparotomy, multiple antral mucosal biopsies were obtained by passing a biopsy forceps through the perforation site. Antral biopsies were examined as follows:- one piece for a rapid urease test (Campylobacter-like organism CLO, Delta West, West Australia); three pieces transported in brain–heart solution at room temperature for subsequent culture (Columbia agar supplemented with 5% horse blood at 37 °C for 5 days under microaerophilic conditions) and the presence of *H. pylori* was confirmed by Gram stain and biochemical tests (for oxidase, catalase and urease); and three pieces were fixed with 10% buffered formalin for histological examination after Haematoxylin and Eosin (H & E) staining. Patients were considered to be *H. pylori* positive when two of three tests showed presence of the bacteria.[14]

Omental patch repair was then commenced unless there were indications for definitive acid reduction surgery (large perforation >1 cm in diameter not amenable to simple closure or perforation concomitant with obstruction). Patients who underwent immediate definitive surgery were excluded from the study. Peritoneal lavage was performed before closure of the abdominal incision. Intravenous cefuroxime was continued every 8 h for 3 days after surgery.

H. pylori positive patients who had undergone patch repair were eligible for randomization. After resuming an oral diet, patients were randomly assigned to one of the two treatment options by opening a sealed envelop. Patients in group I: eradication group (triple therapy) received 1 week of oral amoxicillin 750 three times daily, metranidazole 500 mg twice daily for 10 days and omeprazole 40 mg for 4 weeks. Patients in group II (control group) were given omeprazole alone 40 mg daily for 4 weeks.

All patients were called back for personal interview and follow-up endoscopy at 8 weeks and after 1 year. At each endoscopy, mucosal ulceration of 5 mm or more in the duodenum was considered as persistent or recurrent ulcer.[13] Ulcer healing was defined as either complete re-epithelialization of the duodenal mucosa or presence of a scar.[14] Endoscopic antral biopsies were obtained to reevaluate the *H. pylori* status. Additional biopsies were taken from the body of the stomach to avoid false negative results secondary to proximal gastric migration of the bacterium after therapy.

All patients with complete ulcer healing on the scheduled endoscopy were then interviewed every 6 months. Maintenance acid suppression agents were not prescribed during follow up period. Repeated endoscopic examination was performed whenever the patients were symptomatic.

For patients who had ulcers which was not healed at 8 weeks, another 4 weeks course of omeprazole 20 mg twice daily was prescribed and a second endoscopy was scheduled at 16 weeks. Primary treatment failure was considered to be present if the patients had persistent non-healing ulcer at 16 weeks.

Statistical analysis of data was performed using SPSS version 10. For continuous variables, descriptive statistics were calculated and were reported as mean $\pm$ SD. Categorical variables were described using frequency distributions. The Student's *t*-test for paired samples was used to detect differences in the means of continuous variables and Chi-square test was used in cases with low expected frequencies (P-value <0.05 was considered to be significant).

3. Results

From March 2005 to January 2007 at the Emergency Mansoura University Hospital, 83 patients (68 male and 15 female) with a mean age of 47.8 years $\pm$ 7.2 were found to have perforated duodenal ulcer at laparotomy. Six patients were excluded: two were older than 75 years and four required definitive operation. Of the remaining 77 patients, 65 (84.8%) were infected with *H. pylori* (Table 1). Patients with positive *H. pylori* were randomly assigned to one of the two treatment options by opening sealed envelops:- 34 patients were assigned to triple therapy (the eradication group) and 31 patients to omeprazole alone (the control group). The two groups were comparable in age, sex, smoking habit, use of NSAID, size of perforation, severity of peritonitis and postoperative complications (Table 2).

H. pylori eradication was significantly higher in the triple therapy group than the omeprazole alone group (at 8 weeks 91.2% vs. 22.6% and at 16 weeks 97.6% vs. 51.6%). Initial healing of ulcers at 8 weeks follow-up endoscopy was significantly better in the eradication group. There were 85.3% healed ulcers in the triple therapy group and 48.4% in the omeprazole alone group ($P<0.05$). At 16 weeks endoscopy the healed ulcer rates increased to 97.6% in the triple therapy group and 87.1% in the omeprazole group ($P=0.48$) (Table 3). Patients with documented ulcer healing were scheduled for follow up visits following the study protocol.

After 1 year, three patients in the triple therapy group and another four patients in the omeprazole group were lost to follow up. They reported no significant dyspeptic symptoms and refused to undergo further endoscopic examination. Of the remaining 58 patients who followed the study protocol, 10 patients had ulcer recurrence (Table 4). Two patients in the triple therapy group had ulcer relapse: one patient was asymptomatic and had recurrent ulcer diagnosed at the scheduled 1-year endoscopy, the other had melena 7 months after the repair operation and was found to have recurrent *H. pylori* infection. Of the eight patients with ulcer recurrence in the omeprazole alone group, five were symptomatic

Table 1
Demographic data of the all patients (83 patients) with perforated duodenal ulcer.

Variables	No (%)
Age	47.8 $\pm$ 7.2
Sex	
Male	68 (81.9%)
Female	15 (18.1%)
Smoking	
Yes	56 (67.5%)
No	27 (32.5%)
NSAID intake	
Yes	21 (25.3%)
No	62 (74.7%)
Exclusion	6
Age above 75 years	2
Definite surgery	4
Patients in the study	77
Age (mean $\pm$ SD)	46.7 $\pm$ 10.2
Sex	
Male	64 (83.1%)
Female	13 (17.9%)
H. pylori status	
Positive	65 (84.4%)
Negative	12 (15.6%)

NSAID: non-steroidal anti-inflammatory drug, and *H. pylori*: *Helicobacter pylori*.