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ORIGINAL ARTICLE

EFFECT OF HELICOBACTER PYLORI ERADICATION ON ULCER HEALING AND RECURRENCE AFTER SIMPLE CLOSURE OF PERFORATED DUODENAL ULCER

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Aim: Helicobacter pylori (H.Pylori) plays a fundamental role in the causation of duodenal ulcer. This study was conducted 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.

Methods: Eighty three patients admitted with perforated duodenal ulcer, only seventy seven patients treated with simple closure included in our study. Sixty five patients (84.4 %) who had H.Pylori infection were randomly divided into triple therapy group (34 patients) and alone group (31 patients). Follow up endoscopy was performed at 8 w, 16 w and 1 year to show the ulcer healing and determine H.Pylori.

Results: The eradication of H.Pylori was significantly higher in triple therapy group than omeprazole alone group (at 8 weeks 91.2% vs. 22.6% respectively). Initial healing of ulcer was significantly better in eradication group and after one year the difference in ulcer recurrence between the two groups was statistically significant (2 (6.1%) in eradication group vs. 8 (29.6%) in omeprazole alone group P=0.001).

Conclusion: H.Pylori was present at a high ratio in patients with duodenal ulcer perforation. Eradication of H.Pylori after simple closure of a perforated duodenal ulcer reduces the incidence of recurrent ulcer.

Keywords: Endoscopic examination, antral biopsies, triple therapy.

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 the treatment 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 has produced debatable results.(5-7) Alternatively immediate definite surgery although is effective with low recurrence rate, but it 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 so, attention as a result has been focused towards the role of H. Pylori in perforated duodenal ulcer.(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.

PATIENTS AND METHODS

Eighty three patients admitted with perforated duodenal ulcer between March 2005 and January 2007 in Emergency Hospital, Mansoura University Hospital, only seventy seven patients who were treated by simple closure included in our studied. Demographic data, history of dyspepsia for more than 3 months, smoking and the use of NSAIDs were recorded at time of admission. Exclusion criteria were age younger than 16 or older than 75 years, 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.

All patients were resuscitated before surgery. Informed consent was obtained from every patient for surgical exploration and possible 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 by laparotomy. Multiple Antral mucosal biopsies were obtained during laparotomy by passing a biopsy forceps (WILSON-COOK,Bathania station road. Winston-Salem) through the perforation site.

Antral biopsies were taken 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 microaerrophilic conditions) hence 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 (Fig. 1). 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 reducing surgery (large perforation > 1cm in diameter not amenable to simple closure or perforation concomitant with obstruction).[13] Patients who underwent immediate definitive surgery were excluded from the study. Peritoneal lavage was performed before closure of the abdominal incision after putting abdominal drains. After surgery intravenous cefuroxime was continued every 8 hours for 3 days.

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 sealed envelops. Patients in group 1: eradication group (triple therapy) received one week course of oral amoxicillin 750 three times daily, metranidazole 500 mg twice daily for 10 days plus omeprazole 40 mg for 4 weeks. Patients in group 11 assigned to control group were given omeprazole alone 40 mg daily for 4 weeks.

All patients were called for personal interview and follow up endoscopy at 8 weeks and after one year. At each endoscopy, mucosal ulceration of 5 mm or more in the duodenum considered as persistent or recurrent ulcer 23. Ulcer healing was defined as either complete re-epithelialization of duodenal mucosa or presence of a scar.[14] Endoscopic antral biopsies were obtained to reevaluate 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 confirmed on 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 patients were symptomatic.

For patients who had ulcers 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 patients had persistent non healing ulcer at 16 weeks.[13]

SPSS 10.0 statistics software was used to establish the data base. Statistical comparison between eradication and control group were made with students T test for continuous normally distributed variables. Chi-square and Fisher's exact test were used to compare proportions when appropriate. Statistical significance was defined as $p < 0.05$.

RESULTS

From March 2005 to January 2007 in Emergency Hospital, Mansoura University Hospital, 83 patients (68 male and 15 female) with a mean age of 47.75 years $\pm$ 7.17 were confirmed to have perforated duodenal ulcer by laparotomy. Six patients were excluded: 2 were older than 75 years and 4 required definitive operation. Of the remaining 77 patients, 65 (84.8%) were infected with H. Pylori as shown in Table 1. Patients with positive H Pylori status were randomly assigned to one of the two treatment options by opening sealed envelops, 34 patients were assigned to triple therapy (eradication group) and 31 patients to omeprazole alone (control group). The two groups were comparable in age, sex, smoking habit, use of NSAID, size of perforation, severity of peritonitis but showed no statistical difference Table 2.

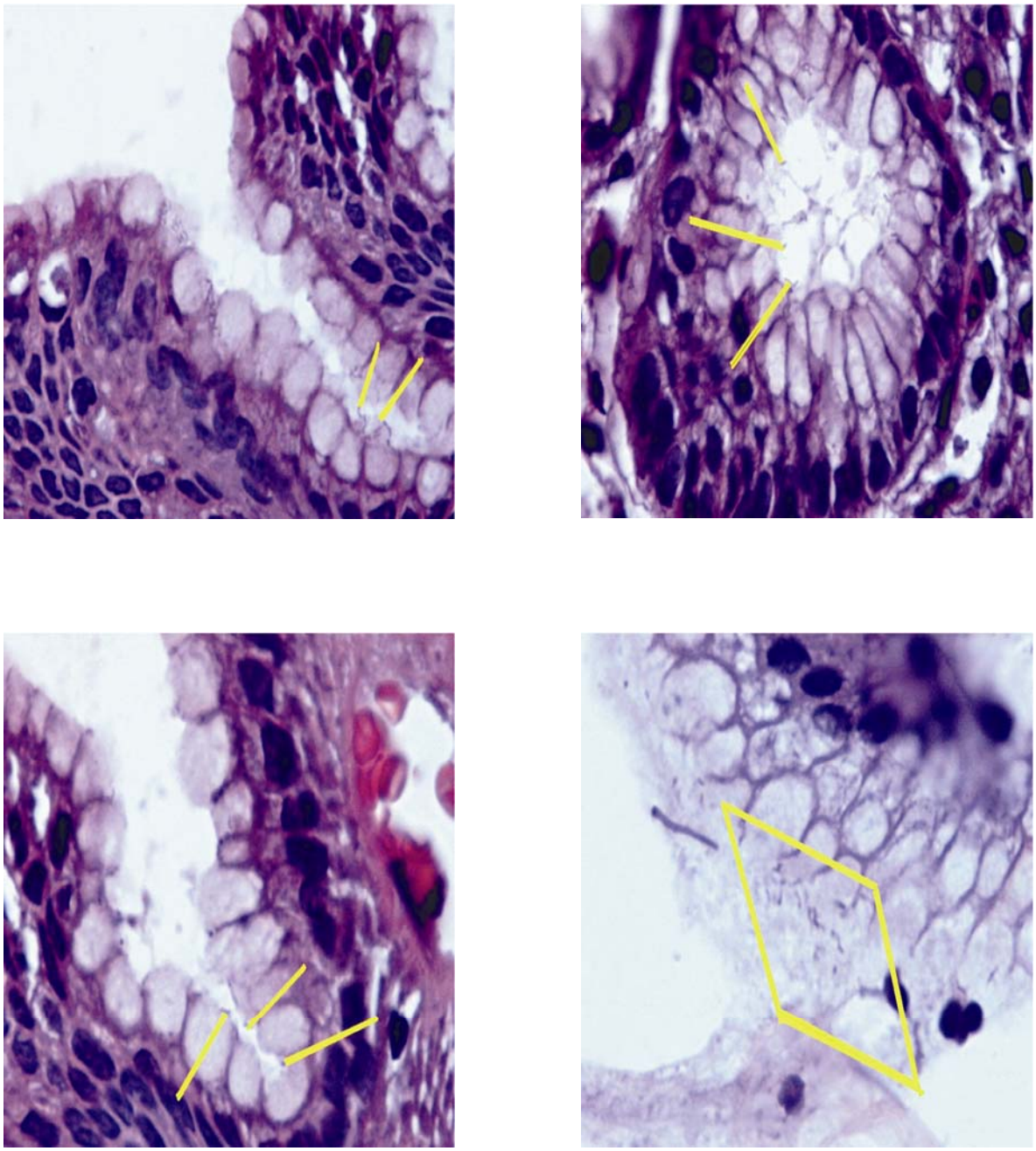

Fig 1. H.Pylori bacilli in antral mucosal biopsies by H & E stain marked by yellow arrows (The magnification X 400).

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

variables		No (%)
Age		47.75±7.17
Sex	male	68
	female	(81.9%)
		15
		(18.1%)
Smoking	yes	56
	no	(67.5%)
		27
		(32.5%)
NSAID intake	yes	21
	no	(25.3%)
		62
		(74.7%)
Excluded cases		6
Character of excluded cases		
Age above 75 years		2
Patients treated with definite surgery		4
Cases included in the study		77
Age		46.65±10.2
Sex	male	64 (83.1%)
	female	13 (16.9%)
H.Pylori status		
	Positive	65 (84.4%)
	negative	12 (15.6%)

Table 2. Patients in triple therapy group and omeprazole alone group.

variables		Triple therapy (34)	Omeprazole alone (31)	P value
age		46±12.9	46.58±10.5	0.6*
Sex	male	32 (94.1%)	27 (87.1%)	0.413**
	female	2 (5.9%)	4 (12.9%)	
Smoking	yes	29 (85.3%)	24 (77.4%)	0.7**
	no	5 (14.7%)	7 (22.6%)	
NSAID	yes	10 (29.4%)	9 (29.1%)	0.06**
	no	24 (70.6%)	22 (70.9 %)	
Dyspepsia>3 m				
	Yes	27 (79.4%)	22 (70.9 %)	0.09**
	no	7 (20.6%)	9 (29.1%)	
Size of perforation (mm)		4.5±1.3	4.6±1.5	0.432*

* Student's T test

* * Chi- square analysis

H. Pylori eradication was significantly higher in triple therapy group than that of the omeprazole alone group (at 8 weeks 91.2% vs. 22.6% and at 16 weeks was 97.6% vs. 51.6%). Also, initial healing of ulcers at 8 weeks follow up endoscopy were significantly better in eradication group, there were 85.3% healed ulcers in triple therapy group and 48.4% in omeprazole alone group ($P < 0.05$), however at 16 weeks endoscopy the healed ulcer increased to 97.6% in triple therapy group and 87.1% in omeprazole group with no statistical difference ($P = 0.48$) as shown in Table 3. Patients with documented ulcer healing were scheduled for follow up according to the study protocol.

Table 3. Early follow up (8w & 16w) in (triple therapy vs. omeprazole alone group).

	Triple therapy	Omeprazole alone	P value
Patients who underwent initial follow up endoscopy	34	31	
H.Pylori eradication			
At 8w	31 (91.2%)	7 (22.6%)	0.001*
At 16 w	33 (97.6%)	16 (51.6%)	<0.05
Complete ulcer healing			
At 8 w	29 (85.3%)	15 (48.4%)	<0.05 *
At 16 w	33 (97.6%)	27 (87.1%)	0.48

*Chi- square analysis

After 1 year, three patients in 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 triple therapy group had ulcer relapse, one patient was asymptomatic and had recurrent ulcer diagnosed at scheduled I year endoscopy, the other had melena 7 months after the operation and was found to have recurrent H.Pylori infection. Of the 8 patients with ulcer recurrence in omeprazole alone group, 5 were symptomatic (three with severe ulcer pain, two with melena) and three patients were asymptomatic and had recurrent ulcer diagnosed at scheduled I year endoscopy. The difference in ulcer recurrence between the two groups was statistically significant 2 (6.1%) in eradication group vs. 8 (29.6%) in omeprazole alone group P=0.001). Eight of these 10 ulcer recurrences were associated with H. Pylori, seven in omeprazole group and one in triple therapy group.

Table 4. One year follow up (triple therapy vs. omeprazole alone group).

	Triple therapy	Omeprazole alone	P value
Patients with complete ulcer healing at the end of 16 w follow up	33	27	
H. pylori eradicated	28 (84.8%)	14 (51.9%)	<0.05*
Ulcer recurrence	2 (6.1%)	8 (29.6%)	0.001*
Symptomatic ulcer recurrence	1 (3.03%)	5 (18.5%)	<0.05*
Pain	0	3	
Bleeding	1	2	
Obstruction	0	0	
reperforation	0	0	
H.Pylori positive in recurrent ulcer	1 (3.03%)	7 (25.9%)	0.01*

* Fisher's exact test

DISCUSSION

Perforated duodenal ulcer is a common surgical emergency. Simple omental patch repair is a rapid procedure but result in recurrent ulceration in up to 42% of patients.[15-18] Because of unsatisfactory result of simple repair, immediate acid-reducing procedures have been strongly advocated. Several prospective randomized studies reported significantly few ulcer recurrences by adding immediate vagotomy to patch repair of ulcer perforation,[13,19] but it requires prolonged operative time also not a practical procedure for most surgical residents, the front line personnel managing patients with duodenal ulcer perforation, and nevertheless accomplished by high incidence of postoperative complication like dumping syndrome, loss of weight, or diarrhea.[13,22]

Although the relationship between H.Pylori infection and peptic ulcer has been well defined, the relationship with perforated ulcer is more controversial 27. In our study, the frequency of H.Pylori infection in patients with perforated duodenal ulcer is 84.4%. This figure is much higher than reported by Reinbach et al (47%) 10 and Chu et al (47%) 20 but is consistent with that of Juan et al (73.9%) 21, Enders et al (80.6%),[13] Sebastian et al (83%),[9] Matsukura et al (95%),[22] Jurg Metzger et al (73.3%)[24] and NG et al (70%),[25] suggesting an association between H.Pylori infection and duodenal ulcer perforation.

Standard triple therapy was used in this study as it is a gold standard for H pylori eradication 24. Omeprazole was given to both groups as it was considered unethical to leave patients with a proven ulcer without antisecretory therapy. Eradication rate were significantly higher after triple therapy than omeprazole alone, at 8 weeks follow up was (91.2% vs. 22.6% P =0.001) and at 16 weeks became (97.6% vs. 51.6% P=0.05). Kate et al reported that the eradication rate was higher in eradication group than with ranitidine alone at 8 weeks was (80% in eradication group vs. 57% in ranitidine group). Enders et al showed that the H.Pylori eradication rate of triple therapy group was significantly higher than that of omeprazole alone group (84.3% vs. 16.7%, P<0.001). Jurg Metzer et al.[24] reported that the eradication rate was 96 % with triple therapy

In the present study, initial healing of ulcers at 8 week follow up endoscopy were significantly better in eradication group, there were 85.3% healed ulcers in triple therapy group and 48.4% in omeprazole alone group. After 1 year, two patients in triple therapy group had ulcer relapse, one patient had melena 7 months after the perforation and was found to have recurrent H.Pylori infection. Of the 8 patients with ulcer recurrence in omeprazole alone group, 5 were symptomatic (three with severe ulcer pain, two with melena). The difference in ulcer recurrence between the two groups was statistically significant 2 (6.1%) in eradication group vs. 8 (29.6%) in omeprazole alone group P =0.001). Eight of these 10 ulcer recurrences were associated with H. Pylori, seven in omeprazole group and one in triple therapy group.

Kate et al[23] from India report a randomized study of 202 patients treated by simple closure and either eradication therapy or ranitidine alone. After routine endoscopy at different follow up intervals, a clear relationship between persistent of H. Pylori infection and ulcer persistence or relapse was established. Some 55%-75% of patients had H. Pylori depend on interval period studied and 4%-28% in those without H. Pylori, which was significantly lower. Ng et al[13] conducted a randomized controlled trial in Hong Kong with 129 patients, 51 of whom were treated by simple suture and eradication therapy. After one year follow up, only 2 patients (4.8%) of latter group had endoscopic relapse, this percentage was significantly lower than that patients without eradication therapy, exclusively treated with omeprazole. In another study, Chu et al[20] reports an endoscopic relapse rate of 41.7%in a series of patients treated mostly by simple closure but with vagotomy in 12.9%, with no eradication therapy. A significant relationship with H. Pylori status was shown.

Therefore, the scanty published experience suggests that H. Pylori is associated with relapse after ulcer perforation treated by simple closure and eradication therapy reduces the relapse rate. In light of the high prevalence of H. Pylori infection and the few recurrence after eradication, the bacterium is likely to be causally related to the strong ulcer diathesis in patients with duodenal ulcer perforation.

We conclude from these results, H. Pylori was present at a high ratio in patients with duodenal ulcer perforation. Eradication of H. Pylori after simple closure of a perforated duodenal ulcer reduces the incidence of recurrent ulcer. So, H. Pylori infection should be assessed at operations and initial endoscopy. If H. Pylori infection is postulated, an appropriate eradication therapy should be started thence.

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