The Interaction of *H. pylori* and Non-Steroidal Anti-Inflammatory Drugs and Their Effect on Induction of Peptic Ulcer

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Abstract

***Objective*:** To study the interaction of non steroidal anti-inflammatory drugs (NSAIDs) and *Helicobacter pylori* infection in induction peptic ulcer.

***Methods*:** Fifty patients with dyspepsia (28 males and 22 females) attended to Endoscopic Units in Ramadi Teaching Hospital during the period from May 2009- March 2010. Endoscopic was done for them and findings varied from gastritis, peptic ulcer to duodenitis. Biopsy specimens from the antrum and the corpus of the stomach were taken and then were prepared for detection of *H. pylori* using the rapid urease test and culture. Anti-*H. pylori* antibody was measured by enzyme-linked immunosorbent assay (ELISA).

***Results*:** Out of the fifty patients with dyspepsia, 23 (46%) patients were found to have peptic ulcer. Fifty percent of the patients were NSAIDS users and the other half were NSAIDs non users. Among NSAIDs users, nine patients (36%) had *H. pylori* infection; while 17(68%) of the NSAIDs non users had *H. pylori* infection.

Conclusion: NSAIDs appeared to be a risk factor for gastric ulcer, further *H. pylori* infection play a role in decreasing the rate of gastric ulcer among NSAIDs.

***Key word*:** NSAIDs**,** *H. pylori*, peptic ulcer.

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Introduction:

It is well realized that both *H. pylori* and NSAIDs can cause peptic ulcers but by different mechanisms. The effect of both of these risk factors together is not a synergistic enhancement of injury, ulceration or rates of complications. Indeed, there are circumstances under which patients infected with *H. pylori* are less prone to NSAID-induced ulcers than those who are not infected or who have undergone eradication treatment [(1)]. This may be because of opposite effects on gastric mucosal prostaglandin synthesis [(1, 2, 3)]. Some studies have shown harmful effects of *H. pylori* in patients given NSAIDs [(4, 5, 6)]. The role played by the interaction of NSAIDs and *H. pylori* infection in the induction of gastroduodenal ulcers is controversial. Some investigators reported a deleterious effect of *H. pylori* in the development of gastroduodenal ulcers among NSAID users [(7- 9)], whereas other investigators found no such untoward effects of *H. pylori* on NSAID gastropathy [(10- 15)]. There are many reasons for these controversies, including differences in the characteristics of subjects, differences in methods of approach, relatively small sample sizes, etc. *H. pylori*-infected gastric tissue have upregulated cyclooxygenese-2 (COX-2) expression and increased prostaglandin E2 (PGE2) production, which may be important for cell proliferation [(16, 17)]. In the case of NSAID-induced gastric injury, the most important mucosal injury factor appears to be the decrease in mucosal PG production by COX inhibition and apoptosis induction [(18, 19).] The aim of study was carried out to evaluate the role of *H. pylori* and NSAIDs and their interaction in the induction of peptic ulcer.

Patients and Methods:

Fifty patients with dyspepsia who attended the Endoscopy Unit in Ramadi Teaching Hospital from the period of (May 2009- March 2010). These were NSAIDs users with dyspepsia underwent gastrofibrescopic examination with special reference to the detection of gastro-duodenal ulcers and *H. pylori* infection. Patients ages ranged from 13- 70 years with SD of 36.6 ± 13.4 years. Questionnaire form was filled by direct interview with each patient which included general demographic characteristics (age , sex, occupation, residence, medical history, type of treatment).

Five gastric mucosal biopsy specimens from the antrum and the corpus were obtained from each patient and divided into two parts. These specimens were used for culture and rapid urease test .

The culture was performed according to the criteria mention by Hazell *et al* [20] with modification. Briefly each antral and corpus biopsy specimen was immediately placed in transport media and brought to the laboratory within 2 hours, and stored under cold conditions. The biopsy specimens were cultured on compylobacter media, the plates were incubated at 37C^{o} under microaerophilic conditions (5% O2, 10% CO2, 85% N2) and examined after 4 and 7 days of incubation. Characteristic colonies of *H. pylori* were confirmed by Gram staining, oxidase, catalase and urease tests.

Rapid ureae test (RUT): one antral and one corpus biopsy specimen were directly inoculated onto the commercial RUT broth. The results were observed and recorded within 2 hours: a positive result was indicated when the color changed from yellow to pink [(21)] .

Regarding to ELISA technique, serum samples taken from those dyspeptic patients were assayed for IgG antibodies against *H. pylori* .The tests were performed according to commercial ELISA kits (Determiner; Kyowa Medex, Tokyo, Japan).

Results:

Fifty patients with dyspepsia were exposed to endoscopic examination. Half of them were NSAIDs users and the other half were non- NSAIDs users . Among those who used NSAIDs , 9 patients (36%) were infected with *H. pylori*(six of nine NSAID users with peptic ulcer were infected by *H. pylori)* and the other 16 patients (64%) were free from *H. pylori* infection while those patients with non NSAIDs users 17(68%) patients infected with *H. pylori* and the other 8 (32%) patients were non infected by *H. pylori*. This difference was found to be statistically of significance ($p<0.05$) (table 1). Among the 25 NSAID users with dyspepsia, endoscopic findings revealed that 7 of them (28%) had gastric ulcer(GU), 6 (24%) had duodenal ulcer (DU), 3 (12%) had duodenitis and 9 (36%) had gastritis without ulcer formation.

Among the17 non –NSAIDs users, 3 of them had GU (17.6%), 7 (41.1%) had DU, 4 (23.5%) had duodenitis, 2 (11.7%) had gastritis and Gastric carcinoma was detected in one patient (6%). Twenty three out of 50 patients (46%) had peptic ulcer [13/25 (52%) had NSAID-related peptic ulcer and 10/25(40%)patients had non-NSAID related peptic ulcer] (table 1). In NSAID related peptic ulcer there were 8/13 (62%) males and 5/13 (38%) females, while in non- NSAIDs related peptic ulcer disease 7/10 (70%) were males and 3/10 (30%) were females, these differences was statistically significant ($p<0.5$)(Table 2). RUT showed positive in 19/26 (73.1%) with peptic ulcer and in 9/25(36%) of NSAID- related peptic ulcers, while among patients with non-NSAID related peptic ulcers, *H. pylori* was positive in 10/17 (59%) and Culture showed positive in 14/26 (53.8%). Serological analysis using ELISA for detection of anti- *H. pylori* IgG revealed that *H. pylori* was seropositive in 23/26 patients (88.5%), these findings indicated that the sensitivity of ELISA test was significantly higher in comparison to the other two tests (table 3) .

Table (1) : Distribution of dyspeptic patients in relation to history of using NSAIDs according to gastroendoscopic findings.

Site of peptic ulcer	NSAIDs user			Non – NSAIDs user		
	H. pylori Positive n (9)	*H. pylori* Negative n (16)	P value	*H. pylori* Positive N (17)	*H. pylori* Negative n (8)	P value
Gastric ulcer	2	5	P> 0.05	3 (17.6%)	0	p< 0.05
Duodenal ulcer	4	2	P< 0.05	7 (41%)	0	P<0.05
Gastritis	2	7	P< o.o5	4 (23.5%)	4	p> 0.05
Duodenitis	1	2	P< o.05	2 (11.7%)	4	
Gastric carcinoma	0	0		1	0	

Table(2**) :** Distribution of patients with peptic ulcer in relation to history of NSAIDs using according to gender

Gender	Total No. of patients with peptic ulcer	NSAIDs users with *H.pylori*		NSAIDs users without *H. pylori*		Non NSAIDs users with *H .pylori*	
		No.	%	No.	%	No.	%
Males	15	4	66.6	4	57.1	7	70
Females	8	2	33.4	3	42.9	3	30
Total	23	6		7		10	

Table (3): Sensitivity of tests used for diagnosis of *H. pylori* among patients with peptic ulcer.

Type of test	Total no. tested	Positive no.	%
ELISA	26	23	88.5
RUT	26	19	73.1
Culture	26	14	53.6

Discussion:

It is well recognized that NSAIDs and *H. pylori* infection are the two most important independent factors in peptic ulcer disease. In our study, among the NSAIDs uses, 9 patients were *H. pylori* positive; 6 of them (66%) were having peptic ulcer. *H. pylori* infection may not increase the prevalence of GU formation in NSAID users. If we accept the idea that GU can be induced by damage additional to that produced by established gastritis, *H. pylori* might play a partially protective role in preventing GU induced by NSAIDs. The NSAIDs induced gastrointestinal injury, is primarily due to inhibition of gastric mucosal prostaglandin synthesis, which subsequently impairs the cytoprotective factors. Development of highly selective cyclo-oxygenase (COX)-2 inhibitors has followed better understanding of the mechanisms involved in NSAIDs mediated damage of the stomach [22], in addition to that, the shortage of prostaglandin, NSAIDs damage the gastric mucosa by hyperacidity and direct toxicity against such cells.

The ability of *H. pylori* to protect against mucosal damage is probably related to the secretion of *H. pylori* urease, which can neutralize gastric acid and thus protect against mucosal injury caused by hyperacidity or direct toxicity. Moreover, *H. pylori* induces prostaglandin secretion, which is blocked by NSAIDs [23]. Also, *H. pylori* induces IL-1 and some growth factors that accelerate the proliferation of mucosal cells, although there are some discrepancies in the data concerning this finding among previous results. Overall, the presence of *H. pylori* in the stomach does not constitute supporting evidence of ulcer formation among NSAID users, although *H. pylori* is likely to be associated with gastritis.

This finding was also similar to other studies conducted by Mizokami Y, Narushima K,et al and Ng TM, *et al* who also found a lower prevalence of *H. pylori* in GU patients receiving NSAIDs than in those not receiving them[24, 25]. Their relative frequency as the cause of peptic ulcer varies and is partly related to the use of NSAIDs and frequency of *H. pylori* infection in a population. The use of NSAIDs and *H. pylori* infection is both common in elderly population[26].

In another study those taking a relatively higher dose of aspirin (300mg) or soluble aspirin complained of more symptoms. However, endoscopy did not show a corresponding rise in mucosal injury in them.[25] NSAID related-peptic ulcers were associated with *H. pylori* infection in 34% of our cases. Also, *H. pylori* infection was more commonly associated with NSAIDs related duodenal ulcer than gastric ulcer in our study. This may be consistent with an increased incidence of *H. pylori* infection in our part of the world. NSAID related peptic ulcer disease was found to be common with or without concomitant *H. pylori* infection in our study. There was a statistically significant higher association of *H. pylori* infection in duodenal ulcer than those observed in gastric ulcer, gastritis and duodenitis. *H. pylori* have been implicated by the damaging effect of this bacteria on the gastric and duodenal mucosa, the most important being cytotoxins released by *H. pylori* strains expressing vacuolating cytotoxin A (*vacA*) and cytotoxin-associated gene A (*cagA*) proteins, *H. pylori*-derived lipopolysaccharides and the enhanced generation of free oxygen radicals and ammonia, the product of germ urease [27,28].

H. pylori infection induces a substantial inflammatory reaction in the gastric mucosa with recruitment of leukocytes and overexpression and release of proinflammatory cytokines. Interestingly, this infection causes overexpression of COX-2 mRNA leading to enhanced biosynthesis of endogenous PG in the gastric mucosa [28,29].

Our findings also indicated that the rate of male patients among NSAIDs related peptic ulcer was significantly higher than in females, this may be due to the fact that the life style factors of males differ from that in females which presented by alcohol drinking, smoking, eating habits, stress and other social factors that may play role as a risk factors for peptic ulcer acceleration. In the present study also we found the laboratory investigation of *H. pylori* positive patients revealed 14/26 (53%), 23/26 (88%)and 19/26 (73%) included culture, ELISA and RUT respectively. The lower isolation rate comparing to other lab investigation may be due to patchy distribution in gastric mucosa, fastidious nature, mucosal trophy,[30] intestinal metaplasia (in stomach), administration of antibiotics [31].

The results of biopsy based rapid urease test in our study were comparable with earlier studies. Significant IgG titers were detected in 88% cases in this study which is consistent with other authors[32]. Results of positive serology were also comparable with biopsy based rapid urease test which at present is most commonly used test for diagnosis of *H.pylori* infection. This may be due to past infection or patchy distribution of organism in the stomach which was responsible for negative rapid urease test. Serology also will become an established procedure for monitoring the therapeutic effect of antimicrobial treatment for the eradication of *H.pylori* as well as screening sera in epidemiological studies.

The ELISA has high sensitivity and good negative predictive value, thus making an excellent screening test, but cannot be used as a confirmatory test, because of low specificity and positive predictive value. However when combined with urease test it is useful for the diagnosis especially in those patients where history of prior antimicrobial treatment.

Our findings can be explained by the fact that serology assays the systemic response to entire stomach, therefore serological tests may be better in already established (chronic) infections where the organism may not be detected bacteriologically. [32]The study concluded that NSAIDs appeared to be risk factor for gastric ulcer, further *H. pylori* infection play a role in decreasing the rate of gastric ulcer among NSAIDs.

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