

Protective Effect of *H pylori* Infection in Non-Steroidal Anti-Inflammatory Drug Users

B. Heidari, Sh. Savadkouhi

Abstract

Background: Non-steroidal anti-inflammatory drug (NSAID) use and *H pylori* infection are two major causes of peptic ulcers. This study investigates the effect of *H pylori* infection and NSAIDs on gastroduodenal damages and bleeding (GIB).

Methods: 104 patients with acute gastrointestinal bleeding (GIB) and 102 patients with dyspepsia without bleeding were studied. Duodenal (DU) and gastric ulcers (GU) were identified by endoscopy and *H pylori* infection by histologic examination of biopsy samples. Association of NSAID and *H pylori* with DU, GU and/or GIB was determined by calculation of odds ratio.

Results: The percentages of NSAID-users in patients with and without GIB were 50% and 34% respectively. DU and GU were more frequent in patients with GIB than those without bleeding ($P < 0.001$). In NSAID-users, the percentages of DU as well as GIB were significantly higher as compared with non-users ($P < 0.02$). Concerning *H pylori*-infected as compared to non-infected patients, the prevalence of DU was significantly higher ($P < 0.000$). The percentage of GU was significantly lower ($P < 0.02$). DU was significantly higher in NSAID-users who were infected with *H pylori* than those of non-infected ($P < 0.001$), but such a relationship was reversed with respect to GU ($P < 0.015$). However, the rate of GIB in this group was not decreased significantly.

Conclusion: *H pylori* infection increased the risk of DU in NSAID users, whereas, it decreased the risks of GU and GIB in NSAID and GU in non users.

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Keywords • NSAID • *H pylori* • Peptic ulcer • Bleeding

Introduction

Widespread use of non-steroidal anti-inflammatory drugs (NSAID) among patients with musculoskeletal pain, particularly in the elderly, has put a large population at risk of ulcer complications.¹ NSAID and *H pylori* infection are two major causes of peptic ulcers among general population.²⁻⁶ In contrast to NSAID that inhibit prostaglandin (PG) synthesis, *H pylori* induces mucosal PG production.⁷ NSAID toxicity to gastro-duodenal mucosa is linked to their ability in suppressing PG synthesis.⁷ *H pylori* eradication therapy restores PG levels and thus may resolve associated symptoms.⁸ Precise mechanism by which *H pylori* infection

Department of Internal medicine,
Shaheed Beheshti hospital,
Babul University of Medical Sciences,
Babul, Iran.

Correspondence:

Behzad Heidari MD,
Department of Internal medicine,
Shaheed Beheshti hospital,
Babul University of Medical Sciences,
Babul, Iran.
Tel: +98 111 2256001
Fax: +98 111 2251664
E-mail: beheidari@yahoo.com

contributes to Peptic ulcers formation has not been defined.^{8,9}

However, *H pylori* interfere mucosal defense mechanisms and immune response through secretion of cytokines and influence on gastric mucosal blood flow.¹⁰

The relation between *H pylori* infection and use of NSADs in the pathogenesis of peptic ulcer disease is controversial.¹¹

The results of some studies have shown that *H pylori* infection potentiates the development of NSAID-induced ulcers and bleeding from gastric or duodenal ulcers.¹¹⁻¹⁵ On the other hand some studies have shown a protective effect from developing mucosal damages, bleeding from ulcers or promoting the healing of gastric ulcers (GU).¹⁶⁻¹⁹ Data from other studies suggest that both *H pylori* and NSAID are independent risk factors for ulcers disease or peptic ulcer hemorrhage.²⁰⁻²¹ However, on the basis of the available data there are no firm conclusions on the role of *H pylori* infection in patients taking NSAID.

Different pathogenic mechanisms operate in the development of duodenal ulcer (DU) or GU. Furthermore, *H pylori* and NSAID exert different pathological effects on gastric and duodenal mucosa. Therefore, the relationship between pathogenic effects of either *H pylori* infection or NSAID and the development of DU and GU should be investigated separately. The present case-control study was thus designed to examine the association of *H pylori* and NSAID with DU, GU and GIB.

Patients and Methods

The study comprised patients referring to Shaheed Beheshti hospital, Babul, Iran, for GIB or dyspepsia between September 2001 and April 2002. They were subjected to upper endoscopy for detection of gastro-duodenal mucosal lesion particularly DU or GU. Data were obtained from clinical examination, taking history with respect to regular NSAID usage defined as regular utilization of NSAID for one week or longer as well as the presence of *H pylori*. GIB was confirmed on the basis of history, clinical examination, and gastric lavage. DU and GU were identified when endoscopic examination showed an open crater of more than 5 mm in diameter or length in the gastric or duodenal mucosa. *H pylori* were verified by histologic examination of gastric biopsy samples taken from the gastric antrum. At least three biopsy samples were prepared by Geimsa staining.

Exclusion criteria entailed the presence of malignancy, prior acid suppressive therapy or *H pylori* eradication treatment, esophageal

varicosis and esophagitis as well as patients with a history of occasional NSAID consumption for less than one week.

The patients under study were stratified into four groups according to *H pylori* status and NSAID usage. They included *H pylori* infected NSAID users; *H pylori* infected non NSAID-users; non *H pylori* infected NSAID-users groups. The fourth group consisted healthy individuals non *H pylori* infected non NSAID-users, who had been matched for sex and age with the patients as control group.

Statistical analysis

In statistical analysis the frequency of DU, GU, and GIB in NSAID users, *H pylori* infection in NSAID users, and *H pylori* infection in non-NSAID users were compared with healthy subjects as control group. A comparison was also made between *H pylori* infection and non *H pylori* infection in NSAID users. The association between NSAID and *H pylori* with DU, GU, and GIB were also determined by calculation of odd ratios (OR) with 95% confidence interval (95%CI) using Chi-square and Fisher exact tests.

Results

The study comprised of 104 patients with acute GIB and 102 patients with dyspepsia without bleeding. The mean ages of the two groups (48±20 and 44±18 yrs) were not significantly different. The respective proportion of patients receiving NSAID users in the two groups were 50% and 34% (P<0.025). DU and GU were found in 67% of patients with GIB and 19.5% of patients without GIB (P<0.0001). Tables 1 and 2 show the characterization of patients enrolled in the study.

Compared to the control group, the percentage of DU was significantly higher in non *H pylori* infected NSAID-users (19.3% vs. 5.2%; P<0.021). Likewise, the percentage of GIB was also higher in NSAID users (64.9% vs. 42.1%; P<0.012). Compared with control, the proportion of patients with GU was also higher in non-infected NSAID-users, but the difference was not statistically significant (21% vs. 15.8%; P<0.08). In *H pylori* infected non NSAID users as compared to control group, the percentage of DU was significantly higher (56.4% vs. 5.2%; P<0.0001). This was in contrast to the percentage of GU, which was significantly lower than control ones (3.2% vs. 15.8%, P<0.02). However, the difference in frequency of GIB was not significant (45.1% vs. 42.1%, P>0.05). In *H pylori* infected NSAID-users compared with control group, the percentage of DU was significantly higher (53.3% vs. 5.2%; P< 0.0001), whereas in re-

Table 1: Number of patients with duodenal (DU) or gastric (GU) ulcers, with (+) or without (-) gastrointestinal bleeding (GIB) in NSAID-users (+NSAID) and *H pylori* infected (+HP) compared to healthy individuals not infected with *H pylori* (-HP) and not using NSAID (-NSAID).

Patients	GIB status	DU	GU
		(n=65)	(n=25)
+ NSAID	Bleeding (24)	1	8
- HP	Not bleeding (33)	2	1
Total n(%)	57	3(5)	9(16)
+NSAID	Bleeding (15)	12	2
+ HP	Not bleeding (15)	4	0
Total n(%)	30	16(53)	2(7)
+ NSAID	Bleeding (37)	10	11
- HP	Not bleeding (20)	1	1
Total n (%)	57	11(19)	12(21)
- NSAID	Bleeding (28)	25	1
+ HP	Not bleeding (34)	10	1
Total n(%)	62	35(56)	2(3)

gard to GU, the corresponding frequency was lower but not significant (6.6% vs. 15.8%; P = 0.19). However, the percentage of GIB was also not significantly higher (50% vs. 42.1%). As compared to non-infected NSAID-users, the percentage of DU in *H pylori* infected NSAID-users was increased significantly (53.3% vs.19.3%; P<0.001), but the percentage of GU was decreased significantly (6.6% vs. 21%; P<0.015). In this group the decrease in frequency of GIB was not significant (50% vs. 64.9%).

Discussion

The results of the present study indicated that, NSAIDs have a deleterious effect on both gastric and duodenal mucosa by increasing the risk of DU, GU, and GIB. However, *H pylori* infection in both NSAID- and non NSAID-users decreases the risk of GU and GIB and as a consequence; it has a gastroprotective effect. Several studies concerning *H pylori* and NSAID, have shown the beneficial effects of *H pylori* in patients receiving NSAID.¹⁷⁻¹⁹ However, others have shown the deleterious effects of *H pylori* in NSAID users.¹²⁻¹⁶

Consistent with the results of this study, Hawkey showed that eradication of *H pylori* in long-term NSAID-users having past or current history of ulcer or dyspepsia led to impaired healing of GU.¹⁷ Santaloria also found a protective effect of *H pylori* on bleeding from GU but not against bleeding from DU in NSAID-users.¹⁹ The presence of *H pylori* was not associated with increased risk of gastro-duodenal damages in long-term NSAID-users.²² Bianchi-Porro reported that *H pylori* eradication did not confer any significant advantage on the healing of GU and DU associated with long-term consumption of NSAID.²³ Matsukawa also showed that the prevalence of *H pylori* infec-

Table 2: Number of patients with GU or DU & with or without gastrointestinal bleeding (+ or - GIB) taking non-steroidal anti-inflammatory drugs (+NSAID) infected (+HP) or not infected (-HP) with *H pylori*.

	Duodenal ulcer		Gastric ulcer	
	+ GIB	- GIB	+ GIB	- GIB
+NSAID +HP	12	4	2	0
+NSAID -HP	10	1	11	1
-NSAID +HP	25	10	1	1
Total	47	15	14	2

tion in GU patients treated with NSAID was lower than those who did not receive the drugs. Furthermore, *H pylori* infection did not increase the prevalence of GU formation in NSAID-users, but in contrast it showed a protective role by reducing the risk of GU in NSAID users.²⁴ Therefore, it is too soon to correlate the beneficial or harmful effects of *H pylori* infection on bleeding from GU and DU.

There is no confirmed evidence showing that *H pylori* infection increases the risk of GIB in chronic NSAID-users. In agreement with the results of our study, Pilotto found an increased prevalence of NSAID-related DU and GU in elderly infected with *H pylori*, but not a higher prevalence of upper GIB.¹⁸ A case-control study showed that, NSAID usage and *H pylori* infection increase ulcer bleeding, but *H pylori* infection does not increase the risk of NSAID.²⁵ Wu described *H pylori* infection and NSAID-users as two independent risk factors for ulcer bleeding without having any synergistic effect on each other.²⁶

In the contrary they found a protective role for *H pylori* in NSAID-users.²⁶ Stack showed that Cag A positive type of *H pylori* was associated with an increased risk of ulcer bleeding but in the presence of *H pylori* this risk was reduced in NSAID-users but not in aspirin users.²⁷ In another case-control study, *H pylori* infection was more associated with non-bleeding peptic ulcer than in those with bleeding peptic ulcer, when compared with the control.²⁸

In contrast, other studies have shown an increasing risk of bleeding in *H pylori* infected NSAID-users. Aalykke reported an almost two-fold increase in the risk of bleeding peptic ulcer in NSAID-users infected with *H pylori* compared with non-infected NSAID users.¹² Reports have indicated that patients receiving NSAID and were infected with *H pylori* had an almost doubled risk of bleeding peptic ulcers compared with non *H pylori* infected NSAID-users.¹¹ Hsu also found that *H pylori* related ulcer patients who use NSAID were more prone to upper gastrointestinal hemorrhage.¹⁵

In the present study we have shown different effects of *H pylori* infection on gastric-, as well as on duodenal mucosa. Regarding the

findings of this study, *H pylori* infection seems to increase the risk of DU, but decrease the risk of GU in both NSAID- and non NSAID - users. Moreover, it has no protective effect on GIB in NSAID-users.

The role of NSAID in the pathogenesis of peptic ulcer is less understood and the interaction between NSAID and *H pylori* infection in relation to ulcer development pathogenically is controversial.¹¹ *H pylori* increases the synthesis of prostaglandins and restricts tissue damage by mucosal production of interleukin-10 and TNF-alpha.^{7,29} It can also influence the rate of epithelial cell proliferation.³⁰ Additionally, in NSAID-users, *H pylori* infection prevents superficial mucosal injuries,³¹ and protects mucosal damage by increasing gastric mucosal blood flow and defense mechanisms.¹⁰ In conclusion, the results of the present study shows that *H pylori* infection confers a beneficial effect on NSAID-users as well as on non-users by decreasing the risk of GU and GIB. Further studies are required to clarify the interaction between NSAID and *H pylori* infection.

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