

Etiology of duodenal ulcers in a Colombian population

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Summary

Introduction: In the last decade the number of duodenal ulcers secondary to *Helicobacter pylori* has decreased in the United States. During the same period there has been an increase in the number reported cases of duodenal ulcers associated with NSAID as well as an increase in the number of reported idiopathic ulcers (*H. pylori* and NSAID/Aspirin negative). Since the prevalence rates of duodenal ulcers secondary to both *H. pylori* and NSAID/Aspirin are to date unknown in Colombia, we decided to undertake this study.

Materials and Methods: This study looks at adult patients who were diagnosed with duodenal ulcers after undergoing esophagogastroduodenoscopies (EGD) in the gastroenterology unit in the Hospital el Tunal and Clínica Fundadores in Bogotá, Colombia.

Results: Between January 2007 and November 2008, 104 patients with duodenal ulcer were recruited to this study. Their mean age was 56 +/- 13 years. 61% were men. *H. pylori* infections were identified in 76 patients (73%), while 12 patients (11.5%) were at risk from NSAID/Aspirin. 31 patients (29.8%) had both risks factors while no risk factors were identified in 12 patients (11.5%).

Conclusions: 14.4% of the duodenal ulcers in our study could not be explained by either *H. pylori* or NSAID/Aspirin. Additional studies are necessary to determine other causes. *H. pylori* was by far the leading cause of duodenal ulcers, while NSAID/Aspirin was a distant second. Given these results, we recommend treatment to eradicate *H. pylori* even in patients whose diagnostic tests have not indicated its presence.

Key words

Helicobacter pylori, NSAID/Aspirin, duodenal ulcer.

INTRODUCTION

Since the discovery of *Helicobacter pylori* (*H. pylori*) in 1982 (1), diverse works have solidly demonstrated that it is the main etiological agent of chronic gastritis (CG) as well as gastric and duodenal peptic ulcers (PUs) (2, 3). It has also been found that the removal of this infection is necessary to cure CG and avoid the reappearance of peptic ulcers (4-8), and it is well documented that the removal of *H. pylori* is more effective than anti-acid secretors to cure duodenal ulcers (DUs) (8). The main causes of DUs are *H. pylori* and non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin (ASA) in antithrombotic doses (9-11); although there are also less common causes such as hypersecretion of acids other than that from Zollinger-Ellison

syndrome (ZE), Crohn's disease, Behçet disease, malignant ulcers, ischemia and cytomegalovirus caused infections (9-13). NSAIDs and *H. pylori* caused infections are considered independent and synergistic risk factors for complicated and non complicated PUs (14). In many previous studies *H. pylori* has been found in more than 90% of the patients with DUs and 70% of the patients with gastric ulcers (15, 16). In other publications the prevalence of the infection is 100% in patients with DUs (17). However, in the last decade it has been documented that in some parts of the world the etiology of PUs has changed. The prevalence of *H. pylori* infections, and consequently *H. pylori* associated ulcers, has declined while the prevalence of NSAID and ASA use, and consequently associated ulcers, has increased (18). In the United States of America (USA) it has been

found that from 20% to 40% of PUs are idiopathic, meaning that they are not associated with *H. pylori* or to NSAIDs (18,19). However, after excluding NSAID related ulcers, *H. pylori* was found in 61% of the patients with PUs (19). In an analysis of six clinical trials that included 2900 patients Ciociola found the infection in 73% of the patients with DUs (20). This contrasts with Japan where idiopathic PUs represent only 1.3% and ulcers associated with *H. pylori* still occur very frequently (21). Treatment guidelines such as those of The American College of Gastroenterology's (22) and the recent *Maastricht III* Consensus (23) recommend that all patients with duodenal ulcers and *H. pylori* infection must undergo treatment with antibiotics and proton pump inhibitors (PPIs) to eradicate the bacteria. Although nearly two decades ago a study using Gram stains and bacterial cultures found *H. pylori* in 80% of the adults studied (24), and in 77% of the patients with DUs studied, the current prevalence of *H. pylori* in the population and among people with ulcers remains unknown. The same can be said about the prevalence of NSAID and ASA use in Colombia, and their association with ulcers. Considering these facts along with the therapeutic impact of eradicating *H. pylori* in patients with duodenal ulcers, we decided undertake the present work. We used upper digestive endoscopy (UDE) to determine the prevalence of *H. pylori* and NSAIDs/ASA in patients with association with peptic ulcers, as well as determining the percentage of ulcers which are not associated with either diagnosis.

MATERIALS AND METHODS

The study included immunocompetent adult patients over 18 years of age who were diagnosed with DU between January 2007 and November 2008 at the gastroenterology units of El Tunal Hospital and Fundadores Clinic. The research protocol and the informed consent procedure were approved by the respective ethics committees of the participating institutions. Even though the Colombian Ministry of Health's Resolution 08430 of 1993 classifies this type of study as non-risk research which does not require written informed consent, written consent was obtained in case the patient was required for an additional interview. The characteristics of each patient were recorded on a form produced specifically for this research project.

EXCLUSION CRITERIA

The following classes of patients were excluded: patients with gastric tumors (adenocarcinoma, lymphoma, sarcoma, carcinoids, etc.), patients with histories of previous gastric surgery, patients with HVI/AIDS, patients undergoing chemotherapy, patients with *Crohn's* disease, patients

with Behçet disease, patients with weight loss over 10% of normal weight, patients with cirrhosis, patients with advanced chronic renal failure (on dialysis), patients with organ transplants, patients with uncontrolled diabetes, patients with malignant disease or coagulopathy, patients who had previously undergone *H. pylori* eradication therapy (or who were undergoing it at the time of the study), patients who were alcoholics, patients who had suffered recent acute myocardial infarct, cerebrovascular disease, congestive heart failure grade 4, severe respiratory failure, patients with suspected perforation of hollow viscera, pregnant women, and patients with any other contraindication for undergoing upper digestive endoscopy. Patients who did not agree to participate in the study, and those who did not sign the informed consent form, were also excluded.

UDEs were performed as usual: with patients in left lateral decubitus position after six or more hours fasting, without sedation, using Olympus Exera CFQ145L or Fujinon 2200 endoscopes. An ulcer was defined as a lesion with loss of mucosal integrity that was 5 mm or more in diameter and which had an apparent depth of 1 mm or more. The lesions diameters were measured using standard gastric biopsy forceps which open 6mm wide. Larger ulcers did not require use of this measure. Depth greater than or equal to 1mm was estimated based on the experience of the gastroenterologists who performed the endoscopies. Four biopsies of the stomach were taken for histology with hematoxylin and eosin: two from the antrum, one each from the greater and lesser curvatures two to three cm from the pylorus; and two from the stomach body, one each from the greater and lesser curvatures taken eight cm from the cardia (24). If the hematoxylin and eosin tests did not identify *H. pylori*, Giemsa stains were used. A biopsy of the antrum was also taken for rapid urease test using a solution of urea and phenol red produced in house according to published recommendations (25). *H. pylori* infections were considered to be present when detected either by rapid urease and/or histology. Data was entered into Excel 2003 and analyzed with Stata 9.0 software. Descriptive statistics were used for the study variables while frequencies and distribution percentages were analyzed with categorical variables. Numeric variables were analyzed with measures of central tendency and dispersion. Statistical tests were evaluated at a significance level of 5% ($p < 0.05$). Continuous variables were reported as frequencies and averages. The differences between averages were determined using the Student's t-test.

RESULTS

Between January 2007 and October 2008 104 patients prospectively recruited. The average age was 56 + / - 13 years. 61% were men. *H. pylori* infection was identified in

76 patients (73%). Consumption of NSAIDs and/or ASA as well as *H. pylori* infection was documented in 31 patients (29.8%). The cause of DU was exclusively NSAIDs (*H. pylori* negative) in 12 patients (11.5%). 15 patients (14.4%) were diagnosed as *H. pylori* negative and had not consumed NSAIDs. Among the different groups there were no statistically significant differences concerning average age or education. Patients' characteristics are shown in table 1.

DISCUSSION

The prevalence of *H. pylori* in patients with duodenal ulcers in this study (73%) is lower than that reported in other countries in the 1990's (> / = 90%) (14.15). However, we have set aside the issue of whether or not our data indicate any change from previous prevalence in Colombia for several reasons. We were unable to find studies on subject except for a work published by the National University group (24). In that study overall prevalence was 80% in people over 30 years of age, and 77% in patients with DUs. Although this date is similar to that found in this study, there is a possibility that the rate of infection was higher than reported in the National University study. That study used Gram staining and bacterial cultures to diagnose *H. pylori*. Both methods tend to under diagnose the presence of the bacteria compared to diagnoses with invasive methods such as the rapid urease test or histology with complementary staining techniques like Giemsa and silver staining used when the microorganism is not found with hematoxylin and eosin (HE) (22). (Gram staining has a lower yield than invasive methods, and bacterial cultures have lower sensitivity than invasive methods.) Considering the drawbacks of the techniques used in the work of the National University, our findings may or may not indicate that DUs are less often associated with *H. pylori* than in the past. In a study by Bravo and colleagues on the prevalence of *H. pylori* in gastric

biopsies (27) the prevalence of the bacteria was found to be 69.1%. This number is also likely to underestimate the true prevalence of the infection in the general population. The patient sample in that study was not screened for previous therapy for *H. pylori* eradication or for use of antisecretory or antimicrobials drugs. All of these factors can influence the detection of the infection (28), even when sensitive testing methods such as the urea breath test are used (28.29). In addition, complementary staining, such as Giemsa, was not used. Neither was specific staining used when hematoxylin and eosin were negative. (26). Finding *H. pylori* in 73% of the DUs in the present study shows that in our environment the prevalence of the infection remains high, although have more accurate and reliable data about the prevalence in the general population would be required for the development of well-designed prevalence studies with suitably calculated sample sizes and samples controlled for the aforementioned variables that can influence the detection of the infection. The prevalence of *H. pylori* found in this study is similar to that found in an analysis of six clinical trials in the USA (73%) a decade ago (20). However, that study included patients who might have taken antimicrobials which could have temporarily suppressed the growth of *H. pylori*. Consequently, the result may have been erroneously high. In contrast, another study during the same period in the same country found a prevalence rate of 61% (18). In this latter study the population was stratified. *H. pylori* prevalence was found 52% in the white population and 78% in the non-white population. The latter number is similar to that found by us, possibly reflecting socio-economic similarities between the two population groups ten years earlier. We believe that the relatively high frequency of the infection, although its accuracy is debatable, could justify empirical eradication treatment in some cases when detection tests are not available.

Table 1. Duodenal ulcer patients' characteristics.

DU Patients N=104	DU patients <i>H. pylori</i> (+) n=76	DU patients NSAID (+) & <i>H. pylori</i> (+) n=31	DU patients, NSAIDs (+), <i>H. pylori</i> (-) n=13	DU patients NSAID (-), <i>H. pylori</i> (-) n=15
Average age: 56 years SD: 13 (21-85)	56 years SD: 12 (21- 84)	55 years SD: 15 (21- 85)	57 years SD: 17 (22-85).	55 years SD: 16 (34-83)
Age Group:				
21 -35 years: 8	21 -35 years: 6	21-35 years: 4	21-35 years: 2	21-35 years: 1
36 -50 years: 32	36-50 years: 22	36-50 years: 8	36- 50 years: 3	36- 50 years: 6
51 -65 years: 39	51- 65 years: 30	51-65 years: 13	51-65 years: 5	51-65 years: 4
> 65 years: 25	> 65 years: 18	> 65 years: 6	> 65 years: 3	> 65 years: 4
Gender:				
Male: 63	Male: 49	Male: 18	Male: 4	Male: 10
Female: 41	Female: 27	Female: 13	Female: 9	Female: 5

The finding that 14% of the duodenal ulcers studies were *H. pylori* negative and NSAIDs/ASA negative is lower than found in U.S., where this percentage has fluctuated between 27% and 40% (18, 20). However, it is 10 times higher than the percentage found in Japan (21) and more than 15 times higher than the one found in Spain where *H. pylori* infection's prevalence is over 95% (17). In Italy, Meucci et al. (30) found that among 409 patients with peptic ulcers, 4.6% had neither *H. pylori* infections nor had consumed NSAIDs/ASA.

Our definition of positive infection combines test results. The tests applied were both highly sensitive and highly specific. They included the rapid urease test with a sensitivity of 88-95% and specificity of 95-100% (28); and histology with 99% sensitivity when three biopsies are taken (31). Although this combination should theoretically be more efficient for identifying infection than separate use of these tests, and therefore our probability of obtaining false negative results should be low, we do not rule out the possibility of some errors. One potential source of errors is in the questioning of patients. If a patient had forgotten to mention a history of using antisecretory drugs, antibiotics or NSAIDs / ASAs, our data would have been affected. The consumption of NSAIDs is considered to be the most common cause of peptic ulcers in *H. pylori* negative patients, with a prevalence of about 50% (32, 33). This contrasts to the 12% we found. One possible explanation for this notable difference could be that the use of NSAIDs may be greater than that reported by patients. Recognition of such drugs may be low in this environment, as has been found in other countries where the use of ASA, for example, has been demonstrated by urine and serum analyses (34). Although it is unlikely that these circumstances have significantly influenced the results, the results of this study suggest that in our environment there could be other causes of DUs which have hitherto been masked by the main causes, *H. pylori* and NSAIDs/ASA. From a practical standpoint it is necessary to start research into this possibility in patients with DUs. We need to look into the use of drugs other than NSAIDs/ASA which might injure the gastroduodenal mucosa. These include bisphosphonates, colchicine, and clopidogrel among others (29). In cases where consumption of all of the possible drugs which might cause DUs are ruled out, and if the patient does not improve with the antisecretory treatment, we believe it is justified to investigate causes of DUs traditionally considered rare. They include ZE (with serum gastrin), biopsies of the angles of the ulcer and adjacent mucosa to exclude malignancy, lymphoma, Crohn's disease and *Helicobacter heilmannii* (29). It has been reported that the latter microorganism can produce DUs which can be treated with quadruple therapy (35). In our environment the prevalence of ZE in patients with pep-

tic ulcers is unknown, although colloquially it is considered to be a very rare entity, as in the USA. There it is thought less than 1% of DUs are caused by ZE (36).

In conclusion, *H. pylori* infection is the main cause of DUs in our population. However DUs which are *H. pylori* negative and NSAIDs/ASA negative represent a relatively large percentage of DUs (greater than NSAIDs alone). Therefore we believe that further studies are needed to determine the underlying etiologies.

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