

Epidemiological analysis and use of rapid urease test in patients with perforated peptic ulcers

Análise epidemiológica e emprego do teste rápido da urease em pacientes com úlcera péptica perfurada

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A B S T R A C T

Objective: To analyze the epidemiological profile of patients with gastroduodenal ulcer perforation and verify if the presence of *H. pylori* in the peritoneal and intraluminal secretions of these patients can be assessed by rapid urease test. **Methods:** We conducted a prospective, descriptive, cross-sectional study with data from patients in a hospital at a regional level, in patients with peptic ulcer. During surgery, we collected peritoneal fluid samples (in the vicinity of the perforation) and intraluminal secretion, sending them for culture and rapid urease test. **Results:** Fourteen patients were analyzed. The average age was 41.06 years, all men, Whites (71.4%), smokers (57.2%), BMI <30 (85.7%), with a history of dyspepsia (78.6%). Serology for *H. pylori* was positive in 84.6% of cases. The rapid urease test was positive in 78.6% of the samples of the digestive tract and 42.8% of samples from the peritoneal cavity; 41.6% were positive at both sites, 50% only in the digestive cavity and 8.4% only in the peritoneal cavity. Of the 11 patients with positive serology for *H. pylori*, 100% were positive in at least one of the sites surveyed. **Conclusion:** It was found that the incidence was lower than expected. There is significant association between infection with *H. pylori* and the occurrence of perforation. The presence of this pathogen can be assessed both by serology and by the realization of the rapid urease test from fluid collected in the peritoneal cavity and the gastric / duodenal lumen.

Key words: Peptic ulcer. Peptic ulcer perforation. Epidemiology. Urease. *Helicobacter pylori*.

INTRODUCTION

In recent decades the incidence of peptic ulcer disease has declined in the Western world. However, it still ranges from 2 to 10/100.000, remaining a public health problem in modern society. The age range in which the predominant duodenal ulcer occurs is between 20 and 50, while the stomach is a more common site in patients over 50 years¹.

The major complications related to peptic ulcer disease are: bleeding, clinically observed in 15-20% of cases, and perforation, 7%, with an incidence of 7 to 10/100.000 people a year – varying among countries and even between regions of the same country². The annual mortality related to peptic ulcer disease is low, being consequent of the surgical treatment or of complications in patients with comorbidities. Moreover, morbidity rates have been reported from 25% to 89%, with high costs³. Among patients with duodenal ulcer, 6% to 11% present with

perforation, and among those with gastric ulcer, 2% to 5%.

The clinical treatment of peptic ulcer disease has changed greatly since 1970. Enhancements include the introduction of H₂ receptor antagonists, proton pump inhibitors, therapies for eradication of *Helicobacter pylori* and endoscopic approaches for the treatment of bleeding ulcers⁴. In this context, the incidence of elective operations for the treatment of peptic ulcer disease has declined. A study in a university hospital in Tokyo showed that 80% of operations for peptic ulcers were listed in the emergency treatment of duodenal perforation, without noticing the decline of that kind of operation.

The objective of this study was to analyze the epidemiological profile of patients with peptic ulcer treated at the surgical service of a tertiary care hospital, assessing whether the *H. pylori* in the peritoneal and intraluminal secretions can be recognized by the rapid urease test and influence the therapeutic management postoperatively.

Study conducted at the Medical Residency Program in General Surgery of the Miranda Gomes Homer Regional Hospital, in São José county, Santa Catarina State, Brazil.

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METHODS

We conducted a prospective, cross-sectional, descriptive study evaluating data from patients treated at the Emergency Surgery Ward of the Miranda Gomes Homer Regional Hospital of São José (HRHMG), from February 2009 to July 2010, with (visceral) perforating acute abdomen. This study was submitted to the evaluation of the Ethics in Research Committee of the hospital and was approved under protocol 017-09. All patients were informed about the goals and methods of analysis and signed a consent form, even in the preoperative period.

The study included all patients with preoperative or intraoperative diagnosis of gastric ulcer and /or duodenal perforation. Patients with other causes of acute abdomen or pneumoperitoneum were excluded.

The standardization of data collection took place as follows: during surgery, after examination of the cavity, we collected two samples of peritoneal fluid (in the vicinity of the perforation of the ulcer) and two samples of intraluminal fluid, when technically feasible, through the ulcer orifice. A sample of each site (the peritoneal cavity and gastric/duodenal) was sent for culture and Gram staining and the other two immediately injected into vials with a solution of preformed urease (Uretest ®, Laborclin Pharmaceutical Laboratory Inc., Pinhais / PR), duly identified and referred for refrigeration at 2-8 degrees Celsius. Other intraoperatively evaluated data were the location of the ulcer, the surgical technique employed and the performance or not of a biopsy of the ulcer site.

Postoperatively, before hospital discharge, we collected additional information by completing a database, including age, gender, race, smoking, alcohol use, prior use of anti-inflammatory drugs (NSAID), body mass index body, a history of dyspepsia, duration of preoperative

peritonitis (considering the time of onset of pain as a starting point), method of diagnosis that indicated laparotomy, results of urease rapid test (URT) for both samples, culture results of the two samples and serology for *Helicobacter pylori* (by chemiluminescence method).

We used the total number of consultations and laparotomies of that period to calculate the proportions of the disease in question in relation to others. Sydney Jorge Sandin Study Center, HRHMG.

RESULTS

Fourteen patients were included in the study. The average age of patients was 41.0 ± 13.1 years. The age range of 20 to 40 years presented the highest incidence of chloride peptic perforated ulcers, corresponding to 50% of cases (Table 1). Patients who called themselves white predominated over non-whites. There was a balance between the three following evaluated risk factors: history of smoking, alcoholism and chronic use of NSAIDs. The prevalence of smoking among patients was 57.2%, with equal distribution related to the perforation site and alcoholism of 35.7%. Of the patients studied, 42.8% reported chronic use of NSAIDs in the 12 months prior to the outcome.

Patients with BMI <30 with previous dyspeptic complaints predominated, especially those with positive serology for *H. pylori*. In this group of patients, 54.6% reported they were smokers, 45.4% consumed alcohol and 45.4% reported chronic use of NSAIDs. The duration of preoperative peritonitis, defined as the period between the onset of pain and surgery, was less than 24 hours in 85.6% of cases, being equally distributed in the time frames less than 12 hours and between 12 and 24 hours (Table 2).

Table 1 - Epidemiological profile of patients diagnosed with peptic ulcer operated.

Perfil		n	%	Average and Standard Deviation
Age	< 20 years	1	7.1	41.06 (DP = 13.1)
	20-40 years	6	42.9	
	> 40 years	7	50	
Gender	Male	14	100	-
	Female	0	0	-
Color	white	10	71.4	-
	Non-write	4	28.6	-
BMI	< 30	12	85.7	-
	> 30	2	14.3	-
Tobacco use	Present	8	57.2	-
	Absent	6	42.8	-
Alcohol consumption	Present	5	35.7	-
	Absent	9	64.3	-
NSAIDs use	Present	6	42.8	-
	Absent	8	57.2	-

BMI: Body Mass Index; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

In 78.6% of cases, laparotomy was indicated based on clinical data associated with conventional radiography. Computed tomography and clinical examination alone were definitive in this indication in 7.1% and 14.3%, respectively.

Serology for *H. pylori* was positive in 84.6%, considering that one of the patients had no collection made. The TRU was positive in 78.6% of the samples of the digestive tube and only 42.8% of the samples of the peritoneal cavity (table 3). As for cultures, there was no bacterial growth in the duodenal samples and in only one from the peritoneum. Of the patients with antibodies against *H. pylori*, 81.8% were also positive for URT in the gastroduodenal lumen and 54.5% in the free peritoneum.

The assessment in group of patients with positive URT in at least one of the locations (n = 12) showed the following: 41.6% were positive in both sites, 50% only in the digestive cavity sample and 8.4% only in the peritoneal cavity. Considering the 11 patients who had positive serology for *H. pylori*, 100% were also URT positive in at least one of the sites studied (45.5% exclusively in the stomach / duodenum, 9% only in the peritoneal cavity and 45.5% in both).

The most frequent sites of perforation were the pre-pyloric (28.6%) and duodenal (57.2%) regions. The average age of patients with gastric ulcers was 41.6 years and, for those with duodenal ulcer, 43.6 years. It was also noted a positive serology for *H. pylori* in 66.6% of patients with gastric perforation and in 100% of duodenal (Table 4).

DISCUSSION

The annual incidence of perforated peptic ulcers varies between 7 and 10 cases per 100,000 inhabitants¹. Considering the perspective of the Brazilian Institute of Geography and Statistics (IBGE) for the population of the metropolitan region of Florianópolis for 2009-2010 – which points to the amount of approximately one million inhabitants – this study shows an incidence slightly below than the expected for the disease (14 cases in 18 months). However, it is important to note that those patients with the symptoms have other four emergency services in the Greater Florianópolis, which distributes the individuals according to their territoriality. To this must be added the analysis of some of the authors towards the need to reassess

Table 2 - Frequency distribution of the data related to the preoperative period in patients undergoing laparotomy for perforated peptic ulcer.

Preoperative Variables		n	%
Dyspeptic history	Present	11	78.6
	Absent	3	21.4
Time of preoperative peritonitis*	<12h	6	42.8
	12-24h	6	42.8
	>24h	2	14.4
Definite Diagnostic Method**	Conventional Radiography	11	78.6
	Computerized Tomography	1	7.1
	Clinical interview and examination	2	14.3

* Defined as the time between the onset of pain and the beginning of surgery.

** Method that was decisive in indicating the laparotomy.

Table 3 - Results of the investigation for the presence of *Helicobacter pylori* by different methods

<i>Helicobacter pylori</i> test	Result	n	%
URT – peritoneal cavity sample	Positive	6	42.8
	Negative	8	57.2
URT – gastric/duodenal cavity sample	Positive	11	78.6
	Negative	3	21.4
Culture for <i>H.pylori</i> - peritoneal cavity sample	Positive	1	7.1
	Negative	13	92.9
Culture for <i>H.pylori</i> - gastric/ doedenal cavity sample	Positive	0	0
	Negative	14	100
Serology for <i>H. Pylori</i> *	Positive	11	84.6
	Negative	2	15.4

URT = urease rapid test; *missing = 1 (patient who did not have serum collected).

Table 4 - Distribution of data related to the perioperative period and ulcer site.

Variables	Results	n	%	
Ulcer site	Gastric - body	1	7.1	
	Gastric - antrum	1	7.1	
	Gastric - pre-pyloric	4	28.6	
	Duodenal	8	57.2	
Surgical treatment	Graham Omentoplasty	13	92.9	
	Madden Omentoplasty	1	7.1	
	Gastrectomy / Vagotomy	0	0	
Ulcer biopsy	Gastric Ulcer	Performed	4	66.6
		Non-performed	2	33.3
	Duodenal Ulcer	Performed	0	0
		Non-performed	8	100

this established estimate, since the incidence of peptic ulcer disease as a whole is in decline¹⁻⁶.

The average patient age was 41 years, with higher peak incidence in individuals over 40¹. However, the average age of patients with gastric perforation was 41.6 years and 43.6 years for duodenal perforation, which introduces a new element, as it is known that duodenal ulcers affect younger patients, compared to the other sites, however statistically significant.

The exclusive focus on male subjects in this series is a fact not found in other parallel studies or related series, although there is wide predominance of cases in men^{1-3,6,7}. This can be explained by the short period of data collection associated with greater exposure to risk factors, such as smoking and alcoholism. In addition, men with peptic ulcer disease present with complications in early ages, whereas women commonly present it in the sixth and seventh decades of life³.

The association between the occurrence of peptic ulcer disease in skin color is a factor still not known. In this study, there was prevalence in white individuals (71.4%). Whites and blacks in different regions within a country have different incidences⁶. It is noteworthy that Brazil is a country of mixed population, with more than one third of the it composed of mixed races, which frustrates ethnic considerations.

Cigarette smoking, alcohol consumption, history of peptic ulcer and especially the use of anti-inflammatory drugs are considered independent risk factors for complications of ulcer disease⁸. A strong correlation between tobacco use and the occurrence of peptic ulcer and its complications has been shown in other studies^{2,3,7}. It's consumption increases tenfold and the risk of perforation and by three the mortality when perforation ensues^{3,9}. The mechanism of this effect probably occurs by the reduction of gastric mucosal protective factors and delayed healing of already active ulcers. NSAIDs and corticosteroids act in

favor of ulcer disease and perforation, and this risk is independent and directly proportional to the daily dose ingested.

Although no direct link has been found between alcohol consumption and peptic ulcers, it occurs most often in people who have liver cirrhosis, a disease associated with excessive alcohol consumption^{2,5}. Among our patients 35.7% reported they were drinkers, especially those with duodenal ulcers. A perforated peptic ulcer usually presents as a perforated acute abdomen and the peritonitis time is related to the severity^{2,4}. The risk of postoperative death and complications is related to the duration of perforation³. A delay of more than 24 hours in surgery increases mortality by 6.5 times and morbidity by 3.4 times³. There were no death cases in our patients.

Although the role of *H. pylori* in the pathogenesis of uncomplicated peptic ulcer disease has been definitively established, the precise relationship between the microorganism and complicated ulcer has not been sufficiently studied^{8,10}. In an extensive review of the literature on the subject, Gisbert says that the average prevalence of infection by the bacillus in patients with peptic ulcer was 68.1%, considering 19 series around the world, a total of 1169 patients. This study found a prevalence above that average (84.6%)⁸.

The two bacterial genes that have been associated with peptic ulcer are the gene associated with cytotoxin (CagA) and the cytotoxin vacuolizing gene (VacA)¹. The first relates to the increased virulence and the second to the development of a cytotoxin which causes injury to the epithelial cell and the immune system.

The method used by the authors for identification of bacteria varied between serology, the detection of antibodies by ELISA, PCR for DNA and endoscopy in the postoperative mucosal biopsy and implementation of URT. The attempt to identify the presence of *H. pylori* during surgery by means of antral and duodenal biopsy was

unsuccessful because of technical difficulties to obtain the samples⁵. It was thought that the collection of fluid, technically feasible, would overcome this difficulty. The hypothesis is also supported by studies such as Osbek, among others, which clearly showed that the *H. pylori* is an extracellular bacterium, present in gastric mucus¹⁰.

The URT is one of the most widely used tests in outpatient clinical practice due to its convenience, speed (average of 30 minutes for analysis) and low cost^{8,9}. It displays a sensitivity of up to 98% and a specificity of 93% to 98%. Brandi et al. showed in an Italian study that other bacteria such as *Staphylococcus capitis urealiticum* presented an activity similar to the urease of *H. pylori* in hypochloridric patients, deeming false-positive results, which leads to question the test reliability⁹.

In the present study, serology was provided as a standard test to identify infection and benchmark with the URT fluid collected during surgery. All seropositive patients had at least one of the samples positive. This suggests that the use of rapid test during surgery may be useful to define which patients are infected and should receive eradication therapy to prevent relapse, provided that the collection is performed in at least two different sites. But the URT in isolated sites (peritoneal or intragastric) was not equally significant in confirming the infection, although 78% of the gastric/duodenal samples have returned positive. Perhaps the reason for the lower incidence of positive peritoneal URT is the lowest density of bacteria at this site or some other factor such as

omentum blockade, which, given their immunological capacity, would affect the sampling^{11,12}.

The primary closure with interposition of an omental patch over the perforation has been the procedure most frequently performed since its popularization by Graham in 1937^{3,13,14}. In order to reduce the high rate of ulcer recurrence after omentoplasty, eradication of *Helicobacter pylori* was established for these patients postoperatively. The trial of Enders *et al.*, with 104 patients with peptic ulcer treated by the Graham technique, showed that after one year of follow-up 95% of patients treated with eradication of *H. pylori* and free of anti-inflammatory drugs were free of disease recurrence^{7,15}.

This study has important limitations that should be evaluated. Due to the short period of data collection and because of reduced incidence of the disease in recent times in the sample population, the number of cases evaluated is considered small to affect analyzes with greater statistical significance. Nevertheless, the distribution of frequencies and their correlation with studies from trusted sources provide us with important parameters to infer hypotheses and identify the characteristics of the patients. Another factor that was important throughout the study, although not in the design, was the need to correlate epidemiological data with more postoperative outcomes, providing greater power of analysis.

In conclusion, it can be stated that the presence of *H. pylori* should be evaluated in all patients with peptic ulcer and that the bacterium should be eradicated in those infected.

R E S U M O

Objetivo: Analisar o perfil epidemiológico de pacientes com úlcera péptica gastroduodenal perfurada e verificar se a presença do *H. pylori* nas secreções peritoneais e intraluminais desses pacientes pode ser avaliada pelo teste rápido da urease. **Métodos:** Realizou-se estudo prospectivo, transversal, descritivo, com dados de pacientes atendidos em um hospital de abrangência regional, em portadores de úlcera péptica perfurada. Coletou-se, no transoperatório, amostras de líquido peritoneal (na proximidade da perfuração) e da secreção intraluminal, sendo encaminhadas para cultura e teste rápido de urease. **Resultados:** Quatorze pacientes foram analisados. A média etária foi 41,06 anos, todos homens, brancos (71,4%), tabagistas (57,2%), IMC < 30 (85,7%), com história prévia de dispepsia (78,6%). Sorologia para *H. pylori* foi positiva em 84,6% dos casos. O teste rápido da urease foi positivo em 78,6% das amostras do tubo digestivo e em 42,8% das amostras da cavidade peritoneal; 41,6% foram positivos em ambos os locais, 50% somente na cavidade digestiva e 8,4% exclusivamente na cavidade peritoneal. Dos 11 pacientes com sorologia positiva para *H. pylori* 100% apresentaram positividade em pelo menos um dos sítios pesquisados. **Conclusão:** Verificou-se que a incidência foi menor que a esperada. Há associação significativa entre a infecção pelo *H. pylori* e a ocorrência de perfuração. A presença deste patógeno pode ser avaliada tanto pela sorologia quanto pela realização do teste rápido da urease do fluido coletado na cavidade peritoneal e na luz gástrica/duodenal.

Descritores: Úlcera péptica. Úlcera péptica perfurada. Epidemiologia. Urease. *Helicobacter pylori*.

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