

PEPTIC ULCER FREQUENCY DIFFERENCES RELATED TO *H. PYLORI* OR AINES

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ABSTRACT – **Background** – Peptic ulcer etiology has been changing because of *H. pylori* decline. **Objective** – To estimate peptic ulcer prevalence in 10 years-interval and compare the association with *H. pylori* and use of non-steroidal anti-inflammatory drugs. **Methods** – Records assessment in two periods: A (1997-2000) and B (2007-2010), searching for peptic ulcer, *H. pylori* infection and non-steroidal anti-inflammatory drugs use. **Results** – Peptic ulcer occurred in 30.35% in A and in 20.19% in B. *H. pylori* infection occurred in 73.3% cases in A and in 46.4% in B. Non-steroidal anti-inflammatory drugs use was 3.5% in A and 13.3% in B. Neither condition occurred in 10.4% and 20.5% in A and B respectively. Comparing both periods, we observed reduction of peptic ulcer associated to *H. pylori* ($P=0.000$), increase of peptic ulcer related to non-steroidal anti-inflammatory drugs ($P=0.000$) and idiopathic peptic ulcer ($P=0.002$). The concurrent association of *H. pylori* and non-steroidal anti-inflammatory drugs was also higher in B ($P=0.002$). Rates of gastric ulcer were higher and duodenal ulcer lower in the second period. **Conclusions** – After 10 years, the prevalence of peptic ulcer decreased, as well as ulcers related to *H. pylori* whereas ulcers associated to non-steroidal anti-inflammatory drugs increased. There was an inversion in the pattern of gastric and duodenal ulcer and a rise of idiopathic peptic ulcer.

HEADINGS – Peptic ulcer. Helicobacter pylori. Non-steroidal anti-inflammatory agents. Stomach ulcer. Duodenal ulcer.

INTRODUCTION

Until the discovery of the association of peptic ulcer disease (PUD) with *Helicobacter pylori* (*H. pylori*) infection in 1983 by Marshall and Warren⁽¹³⁾, PUD etiology was uncertain. Since there, the literature has shown that *H. pylori* infection and non-steroidal anti-inflammatory drugs (NSAID) were the most common causes of peptic ulcer^(3, 10).

Studies from the 1980s and 1990s, showed the prevalence of *H. pylori* infection was 90% in duodenal ulcer and 70% in the gastric ulcer⁽¹⁰⁾. The prevalence of *H. pylori* infection has been decreasing steadily over the last decades, especially in industrialized countries while the prevalence of peptic ulcer associated with the use of NSAID apparently is increasing^(9, 14, 15). The prevalence of peptic ulcer not related to *H. pylori* nor NSAID – idiopathic PUD - is increasing according to some studies^(4, 9, 24). In North America, it has been reported as 20% to 40%, in Southern Europe as 4.1% to 8% and the Northern Europe as 10% to 15%. Asia and undeveloped countries have low prevalence of idiopathic peptic ulcer⁽¹⁵⁾. Recent data available from Brazil still point out for high prevalence of *H. pylori* infection^(19, 20, 25) and there are mismatched reports on duodenal ulcer prevalence^(12, 21). Therefore, our aim was to assess and compare the prevalence of peptic ulcer

disease and its association with *H. pylori* infection and use of NSAID in a population from the central region of southern Brazil, in two periods with an interval of 10 years.

METHODS

We designed a cross-sectional study to assess the endoscopy records of our Hospital in two periods: period A (1997-2000) and period B (2007-2010). We searched for the diagnosis of uncomplicated gastric and duodenal ulcer. We planned to exclude ulcers with histological diagnosis of malignancy or specific causes as Crohn's disease, Zollinger-Ellison syndrome, cytomegalovirus and other *Helicobacter* infection (e.g. *H. heilmannii*). We also excluded patients under 18 years old, cirrhotic patients with portal hypertension and patients critically ill. *H. pylori* infection was identified by histological examination. Biopsies were taken from each of the five sites listed in the Sydney system criteria⁽⁶⁾. We searched the patients' records for the use of NSAID before upper GI examination. We defined idiopathic ulcer disease when *H. pylori* was absent in the biopsies and there was no prior use of NSAID. We also recorded the patients' demographics (age and gender), tobacco and alcohol consumption and ulcers location. Incomplete records were excluded.

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The statistical analysis compared the frequency of peptic ulcer disease and its association with *H. pylori* infection or NSAID intake in both periods. We also compared the clinical and demographic characteristics of patients. We assessed the means significance by *t* test. With qui-square test followed by adjusted residual analyses, we evaluated the significance of ulcer's location and their association with etiology. The significance level was 0.05. We used SPSS PASW Statistic software for Windows v.18. The Institutional Ethical Committee on Research approved the study with the number 01415912.3.00005346.

RESULTS

We searched examine the records of 2056 patients; 1232 in the period A and 824 in the period B. We identify 393 patients with uncomplicated gastric and duodenal ulcer in period A and 184 patients in period B. We excluded 37 patients because 19 presented malignant ulcers, two patients were infected by *H. heilmannii* and 16 had incomplete records. The final sample was 374 PUD patients in period A and 166 in period B. Age, gender, tobacco, alcohol consumption and ulcers location are described in Table 1. The mean age was higher in the period B. There was no difference related to gender, alcohol and tobacco consumption.

Peptic ulcer prevalence was 30.35% (374/1232 patients) in period A and 20.19% (166/824 patients) in period B. There was a significant statistical decrease in the prevalence of peptic ulcer after 10 years ($P=0.000$). Prevalence of gastric ulcer was higher in period B, 73.30% vs 51.07% ($P=0.000$) while prevalence of duodenal ulcer was lower, 20.48% vs 40.03% ($P=0.000$). There was no difference in the combination of both locations in the two periods ($P=0.072$).

H. pylori infection and the use of NSAID are detailed on Table 2. The NSAID most commonly used in the period

A were aspirin and diclofenac and in the period B were aspirin and ibuprofen. NSAID indication ranged from pain syndromes to prevention of cardiovascular events and many times as self-medication. Comparing both periods (Figure 1), we observed significant reduction of peptic ulcer associated to *H. pylori* infection ($P=0.000$), a significant increase of ulcer related to NSAID and idiopathic ulcer ($P=0.002$). The concurrent association of *H. pylori* and NSAID was also higher in the period B ($P=0.002$).

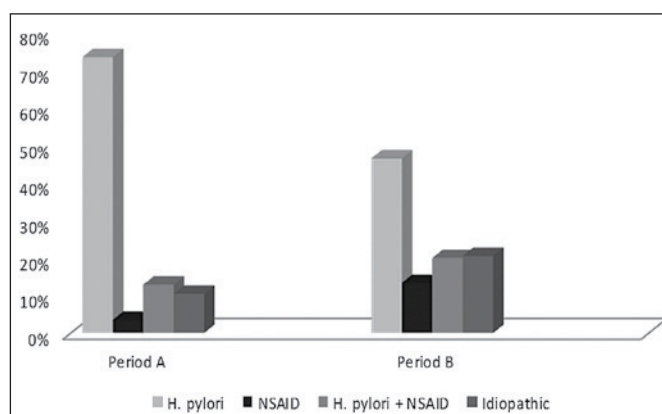


FIGURE 1. Frequency of PUD related to *H. pylori* and/or NSAID in the two periods

PUD: peptic ulcer disease; NSAID: non-steroidal anti-inflammatory drugs

DISCUSSION

Our results showed that the prevalence rate of PUD decreased after 10 years. We also identified the decrease of PUD related to *H. pylori* infection. While *H. pylori* infection became less prevalent, the opposite has occurred with PUD

TABLE 1. Clinical characteristics of patients

| | Period A (1997-2000) n=374 | Period B (2007-2010) n=166 | P value* |
|--------------------------------|-------------------------------|-------------------------------|----------|
| Age (Mean ± DP) | 52.43 (±15.18) | 58.75 (±13.87) | 0.000 |
| Men | 238 (63.60%) | 102 (61.40%) | 0.63 |
| Tobacco | 195 (52.10%) | 79 (47.60%) | 0.40 |
| Alcohol | 79 (21.10%) | 55 (22.30%) | 0.82 |
| Gastric ulcer | 191(51.07%) | 125 (73.30%) | 0.000* |
| Duodenal ulcer | 151(40.03%) | 34(20.48%) | 0.000* |
| Gastric ulcer + Duodenal ulcer | 32 (8.56%) | 7 (4.22%) | 0.072* |

* Adjusted residual analysis

TABLE 2. Peptic ulcer etiology

| | Period A (1997-2000) n=374 | Period B (2007-2010) n=166 | P value* |
|--------------------------|----------------------------|----------------------------|----------|
| | 274 (73.30%) | 77 (46.40%) | 0.000 |
| NSAID | 13 (3.50%) | 22 (13.30%) | 0.000 |
| <i>H. pylori</i> + NSAID | 48 (12.80%) | 33 (19.90%) | 0.034 |
| Idiopathic ulcer | 39 (10.40%) | 34 (20.50%) | 0.002 |

* Adjusted residual analysis; NSAID: non-steroidal anti-inflammatory drugs

related to NSAID intake, which increased in this time, as well as idiopathic PUD. The prevalence of gastric ulcer was higher and duodenal ulcer lower 10 years later.

The fall of prevalence rate of PUD and *H. pylori* infection probably is related to the improvement in social and sanitary conditions over the years⁽¹⁴⁾. We also have to consider that the widespread eradication of *H. pylori* may have a marked effect on the decrease of peptic ulcer associated with *H. pylori* infection⁽⁸⁾. Giving support to our findings there are many studies that identified similar results^(2, 7, 14, 15, 16, 18). On the other hand, it is not a worldwide phenomenon, because in some others studies *H. pylori* still remains highly associated to PUD^(3, 22, 24). Those controversies could be reflecting different ethnics, genetics and environment. Brazil has many inequalities among its regions. *H. pylori* prevalence rates, among adults, have been reported as high as 87% in Northeast region⁽¹⁹⁾ and in South and Southeast regions (that have higher standard of living) those rates, still high, are lower, ranging between 62.9 to 66.5%^(22, 25). A recent study conducted in São Paulo, Brazil, reported high prevalence of duodenal ulcer related to *H. pylori* infection⁽¹²⁾. This study did not assess the use of NSAID and could be also reflecting different type of Brazilian population⁽¹¹⁾ because in Rio Grande do Sul, the most southern Brazilian state, was observed a decrease of duodenal ulcer prevalence along 10 years. This study did not approach *H. pylori* status or NSAID intake⁽²¹⁾.

Brazil has been presenting a new demographic pattern characterized by reduction in the population growth rate and by profound transformation in its age structure, with significant increase of the elderly contingent. Those modifications have caused important changes in the population epidemiological profile⁽²³⁾. NSAID is increasing its potential as a risk factor for peptic ulcer disease because the widespread consumption. NSAID are used under prescription as well as self-medication. Acetylsalicylic acid is widely prescribed for primary and secondary prevention of cardiovascular events and many others clinical conditions. NSAID are easily accessed without medical supervision and largely used for treatment of pain syndromes, such as musculoskeletal diseases^(7, 10, 15). Patients in the period B were older than patients in the period A and were more likely to use NSAID. This could be the explanation for the higher prevalence of NSAID ulcer in period B but it also could due a cohort effect among generations in period B. Moreover, patients in this period could be treated for *H. pylori* eradication in this 10-year period. Furthermore, *H. pylori* infection and NSAID are synergistic risk factors for peptic ulcer. Supporting this evidence there are other studies reporting higher prevalence of peptic ulcer associated to both risk factors in the more recent years^(7, 18).

The changing pattern between duodenal and gastric location identified in our study in this 10-years interval is in agreement with the reduction of *H. pylori* infection and the increase of NSAID use.

There are reports on the increasing prevalence of idiopathic peptic ulcer^(4, 5, 9, 15). In period A, around 10% of our

patients presented idiopathic peptic ulcer, while in period B this diagnosis accounted for more than 20%. This finding suggests that other unknown factors play a role in the pathogenesis of peptic ulcer disease⁽¹⁷⁾. The prevalence of peptic ulcer has decreased as well as *H. pylori* infection, reflecting the improvement of living standards and the widespread treatment for *H. pylori* infection. Our results indicate that the emerging increase of idiopathic ulcer seen in elsewhere, may also be occurring in Brazil. We also need to take in account that the accurate diagnosis of IPUD relies in the exclusion of *H. pylori* infection and the use of NSAIDS⁽⁵⁾. Regarding *H. pylori* diagnosis, the possible bias is minimized by histological diagnosis of *H. pylori* using the five biopsies sites recommended by the Sydney system. The information on NSAID intake searched in the patients is not accurate and spurious use of NSAIDS could be possible. On the other hand, this potential bias may lead to underestimate the use of NSAIDS by those patients.

Other important issue that may affect our results is the use of proton pump inhibitors (PPI). The widespread use of PPI could reduce the number of ulcers and induce false negative results of *H. pylori* tests⁽¹⁾. The ulcer reduction due the use of PPI could interfering in our results, but the effects of PPI in the tests result is minimized by the routine in our hospital to recommend patients avoid PPI 2 weeks before an elective endoscopy.

Our study also has the limitations of its design. It may be biased because of the retrospective data collection, as we state before. To minimize this bias we took care in just include patients with complete record of the study outcomes. Furthermore, the study was restricted to a single reference center from the central region of the most Southern State of Brazil, therefore our results cannot be generalized. Cross sectional studies are not appropriate for the assessment of temporal trends, so we need to be careful regarding these changes along the time. In spite of these limitations, our study brings new information on the behavior of peptic ulcer disease and its major risk factors along an interval of ten years. This trend can be explored with more appropriated design.

CONCLUSION

In two periods with 10 years of interval, we identified a decrease in a prevalence of PUD and *H. pylori* infection. Gastric ulcer became more prevalent and duodenal ulcer had a reduced frequency. Simultaneously, we observed the increase of peptic ulcer associated to NSAID and the rise of idiopathic peptic ulcer.

Author contribution

Fagundes RB and De Carli DM designed the research protocol. De Carli DM conducted the process for IRB permission and coordinated the data collection. Pires RC, Rohde SL and Kavalco CM collected the data. Fagundes RB performed the data analysis and wrote the manuscript. All authors read and approved the manuscript for submission.

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RESUMO – Contexto – A etiologia da úlcera péptica vem apresentando mudanças devido à redução da infecção pelo *H. pylori*. **Objetivo** – Estimar a prevalência da úlcera péptica em dois períodos com intervalo de 10 anos e comparar a associação com a infecção pelo *H. pylori* com o uso de anti-inflamatórios não esteroides. **Método** – Revisão de prontuários em dois períodos: A (1997-2000) e B (2007-2010), com busca por úlcera péptica, *H. pylori* e uso de anti-inflamatórios não esteroides (AINE). **Resultados** – Úlcera péptica apresentou frequência de 30,35% em A e 20,19% em B. Infecção por *H. pylori* ocorreu em 73,3% em A e em 46,4% em B. Uso de anti-inflamatórios não esteroides ocorreu em 3,5% em A e em 13,3% em B. Nenhuma dessas condições esteve associada em 10,4% e 20,5% das úlceras em A e B, respectivamente. Comparando os dois períodos, houve redução da úlcera péptica associada à *H. pylori* ($P=0,000$), aumento das úlceras associadas ao uso de anti-inflamatórios não esteroides ($P=0,000$) e aumento de úlceras idiopáticas ($P=0,002$). A associação concomitante de *H. pylori* e anti-inflamatórios não esteroides foi também mais alta em B ($P=0,002$). Úlceras gástricas aumentaram e úlceras duodenais diminuíram em B. **Conclusões** – No intervalo de 10 anos, a prevalência de úlcera péptica diminuiu assim como as úlceras relacionadas com *H. pylori* e houve um aumento das úlceras associadas ao uso de anti-inflamatórios não esteroides. Houve inversão na frequência das lesões gástricas e duodenais e aumento da prevalência da úlcera idiopática.

DESCRITORES – Úlcera péptica. *Helicobacter pylori*. Anti-inflamatórios não esteroides. Úlcera gástrica. Úlcera duodenal.

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