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Tailored *Helicobacter pylori* eradication therapy in obese patients undergoing bariatric surgery

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ABSTRACT

Objectives: to compare the efficacy and safety of a tailored quadruple concomitant therapy based on body weight, with the same scheme but with fixed doses in obese patients undergoing bariatric surgery.

Methods: a prospective study was performed of 104 obese patients.
**Results:** the weight-based therapy group achieved significantly higher eradication rates in the intention-to-treat analysis; 86.3% (95% CI: 74.3-93.2) vs 66.1% (95% CI: 52.6-77.3), p < 0.05. Relative risk: 1.31 (95% CI: 1.05-1.63). Discontinuations and adverse events were similar in both groups.

**Conclusions:** a tailored quadruple concomitant therapy based on body weight seems to be more effective than the standard quadruple concomitant therapy in obese patients.

**Keywords:** Helicobacter pylori. Bariatric surgery. Eradication. Obesity.

**INTRODUCTION**
Many guidelines in the field of bariatric surgery recommend routine *Helicobacter pylori* (*H. pylori*) testing and if present, eradication as part of the preoperative workup for bariatric surgery, in particular before Roux-en-Y gastric bypass (1,2). Several studies have shown that obese patients have low eradication rates of *H. pylori* with standard therapy (3-5). The reasons remain unknown but obesity produces physiological changes that could lead to sub-therapeutic concentrations of antibiotics (6). There is a lack of a consensus formula that could be used for dose calculation. However, various ways have been postulated to calculate drug dosing for patients with morbid obesity based on anthropometric measures or formulas like the Cockcroft-Gault’s (7,8).

The aim of our study was to compare the efficacy and safety of a tailored quadruple concomitant therapy based on body weight, with the same scheme but with fixed doses, in obese patients undergoing bariatric surgery.

**PATIENTS AND METHODS**
A prospective, multicenter study was performed from June 2016 to February 2018. A total of 104 consecutive obese patients were included, who were over 18 years, undergoing bariatric surgery. All patients underwent a routine upper gastrointestinal endoscopy as a part of the preoperative evaluation and had a positive histology for *H. pylori*. The indication for bariatric surgery was a body mass index (BMI) ≥ 40 kg/m² (with or without co-morbidities) or BMI ≥ 35 kg/m² and at least one or more obesity-
related co-morbidity. Exclusion criteria were previous attempts at *H. pylori* eradication, intake of antibiotics, proton pump inhibitors or H$_2$-antagonists in the previous four weeks, past history of an allergy to the study drugs and the concomitant use of drugs that might prolong QT interval. The study was approved by the Hospital’s Institutional Ethics Committee. All patients signed an informed consent.

Patients received a quadruple concomitant therapy for 14 days. They were stratified according to BMI (< 40 kg/m$^2$ y ≥ 40 kg/m$^2$) and patients in each stratum were alternatively assigned to one of the treatment schemes. One group received the standard quadruple concomitant treatment with fixed doses of pantoprazole (40 mg every 12 hours), clarithromycin (500 mg every 12 hours), amoxicillin (1,000 mg every 12 hours) and metronidazole (500 mg every 12 hours). The other group received the same quadruple scheme but it was adjusted by body weight for metronidazole and amoxicillin. The metronidazole dose was 7.5 mg/kg every six hours and adjusted by total body weight, until a maximum dose of 4 g/day. The amoxicillin dose was 50 mg/kg/day and adjusted according the adjusted body weight, until a maximum dose of 4 g/day.

Patients were instructed not to drink alcohol or smoke during treatment and probiotics were not included in the treatment. The 13C-urea breath (Tau-Kit, Bacon) test was used to determine the *H. pylori* eradication between 6-8 weeks after treatment completion. Adverse events (AE) and compliance were assessed at the end of treatment via direct interviews and patient self-reports. Adverse events were classified as mild, moderate and severe.

All data were expressed as the mean with the standard deviation for numerical variables and percentages for categorical variables. For group comparisons, the Chi-squared test was implemented with Yates correction or Fisher’s exact test for proportions and the Student’s t test for independent samples for numerical variables. Also, 95% confidence intervals (95% CI) and relative risk (RR) were calculated. A p value < 0.05 was considered as statistically significant. The statistical analysis was performed with the OpenEpi program. The intention-to-treat (ITT) analysis included all patients who received the study medication and took at least one dose of the study medication. The per-protocol (PP) analysis excluded those patients who did not
complete the study or who had major protocol violations.

RESULTS
Data of 51 patients who received a weight-based treatment and 53 patients receiving the fixed dose treatment were analyzed. Both groups were homogeneous in terms of age, sex, smoking proportion, diabetics and obese patients $\geq 40 \text{ kg/m}^2$. The demographic data and clinical characteristics of both groups are shown in table 1. In the intention-to-treat analysis, the $H. pylori$ eradication rate was 86.3% (95% CI: 74.3-93.2) for the weight-based treatment and 66.1% (95% CI: 52.6-77.3) in the group with fixed doses ($p = 0.02890$). RR 1.31 (95% CI: 1.05-1.63).

There were three discontinuations due to vomiting, two patients in the weight-based treatment group and one in the fixed dose treatment group. In the per-protocol analysis, the $H. pylori$ eradication rate was 89.8% (44/49) for the weight-based treatment and 67.3% (35/52) in the group with fixed doses ($p = 0.01259$). RR 1.33 (95% CI: 1.08-1.65). Full compliance with the treatment was 95.9% (47/49) for the weight-based group and 96.1% (50/52) in the group with fixed doses. The percentage of patients reporting AE was 27.4% (14/51) for the weight-based treatment group and 20.7% (11/53) in the group with fixed doses ($p = 0.5691$) (Table 2). The most frequent AE was a metallic taste and all AE disappeared after treatment.

DISCUSSION
There is little evidence-based dosing guidelines for morbidly obese patients. Although the prevalence of obesity is growing, obese patients are excluded or under-represented in clinical trials (9,10). Obesity produces physiological changes that affect drug bioavailability and there is not only an increase of adipose tissue but also of lean tissue. This may affect pharmacokinetics (PK) and pharmacodynamics (PD) of drugs, which could produce a lower gastric mucosa level and explain, at least in part, the lower $H. pylori$ eradication with standard, fixed dose treatments (6,11).

Volume of distribution is the main affected PK parameter and it depends not only on the physicochemical properties of drugs but also on obesity as a disease. Lipophilic drugs will have a large volume of distribution because of adipose-tissue binding, while
the volume of distribution of hydrophilic drugs is related more with the lean weight and depends greatly on liver and renal clearance (12). Regarding pharmacodynamics, the knowledge is even more limited, and obesity affects the affinity and expression of cellular receptors to drugs (13).

Although some authors suggest the need for a tailored \textit{H. pylori} eradication regimen for obese patients based on body weight (6), there are few studies with a weight-based treatment. Pintar et al. (14) increased \textit{H. pylori} eradication with a triple scheme, adjusting the treatment according to the Cockcroft-Gault formula. Patients received a 30\% higher dose.

In the present study, a quadruple concomitant eradication scheme was used for 14 days because it was performed in an area with high resistance to clarithromycin. Without evidence to guide drug dosing in morbid obese patients, drugs were adjusted understanding the physiological changes that obesity produces in the organism and the physico-chemical properties of the antibiotics. We found that obese patients undergoing bariatric surgery have higher \textit{H. pylori} eradication rates when a weight-based regimen was used compared with the standard, fixed dose regimen. Regarding safety, discontinuations, adverse events and severity were similar in both groups.

Our study has limitations that must be taken into consideration. First, this is a non-randomized trial and there is a lack of antimicrobial susceptibility data in a growing antibiotic resistance environment (15).

In conclusion, obese patients undergoing bariatric surgery have a higher eradication rate of \textit{H. pylori} with a weight-based regimen. The actual paradigm “one dose fits all” should be reassessed by an individualized dosing in morbid obese patients.

REFERENCES

Table 1. Baseline characteristics of the total cohort of patients

<table>
<thead>
<tr>
<th></th>
<th>Standard treatment (n = 53)</th>
<th>Weight-based treatment (n = 51)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>43.37 (9.49)</td>
<td>41.76 (8.45)</td>
<td>0.411</td>
</tr>
<tr>
<td>Female gender n (%)</td>
<td>30 (56.6)</td>
<td>28 (54.9)</td>
<td>0.981</td>
</tr>
<tr>
<td>Smoking habits n (%)</td>
<td>10 (18.9)</td>
<td>8 (15.7)</td>
<td>0.865</td>
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<tr>
<td>BMI ≥ 40 kg/m² n (%)</td>
<td>17 (32.1)</td>
<td>19 (37.3)</td>
<td>0.727</td>
</tr>
<tr>
<td>Diabetics n (%)</td>
<td>15 (28)</td>
<td>13 (25)</td>
<td>0.918</td>
</tr>
</tbody>
</table>

SD: standard deviation; BMI: body mass index
Table 2. Adverse events

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Weight-based treatment (n = 51)</th>
<th>Standard treatment (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Severe</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metallic taste</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Headache</td>
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<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>2</td>
<td>1</td>
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