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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.

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Methods

This prospective study included 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

Abbreviations

Helicobacter pylori: *H pylori*

Body Mass Index: BMI

Relative Risk: RR

95 % Confidence intervals (95 % CI)

Pharmacokinetics: PK

Pharmacodynamics: PD

Adverse Events: EA

INTRODUCTION

Many guidelines in the field of bariatric surgery recommends routine *Helicobacter Pylori* (*H pylori*) testing and, if present, eradication as a 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 a low eradication rates of *H pylori* with standard therapy *(3.4,5)*. The reasons remain unknown but obesity produces

physiological changes that could lead to sub-therapeutic concentrations of antibiotics (6). Even though there is a lack of consensus formula that could be used for dose calculation, 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

This prospective, multicenter study was conducted from June 2016 to February 2018. A total of 104 consecutive obese patients over 18 years undergoing bariatric surgery were included. 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/m^2 (with or without co-morbidities) or BMI ≥ 35 Kg/m^2 and at least one or more obesity-related co-morbidities. Exclusion criteria were previous attempts at *H pylori* eradication, intake of antibiotics, proton pump inhibitors or H_2 antagonists in the previous 4 weeks, past history of 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 informed consent.

Patients received a quadruple concomitant therapy for 14 days. They were stratified according to BMI (<40Kg/m^2 y ≥40 Kg/m^2) and patients in each stratum were alternatively assigned 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 (1000 mg every 12 hours) and metronidazole (500 mg every 12 hours). The other group received the same quadruple scheme but adjusted by body weight for metronidazole and amoxicillin. The metronidazole dose was 7.5 mg/Kg/ every 6 hours and adjusted by Total Body Weight until a maximum dose of 4gr/day. The amoxicillin dose was 50 mg/Kg/day and adjusted according the Adjusted Body Weight until a maximum dose of 4 gr/day.

Patients were instructed not to drink alcohol or smoke during treatment. We did not include probiotics in the treatment.

The ^{13}C-urea breath (Tau-Kit, Bacon) test was used to determine the *H pylori* eradication between 6-8 weeks after completion of treatment. 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 mean with standard deviation in numerical variables and percentage in categorical variables. For group comparison Chi-Square Test was implemented with Yates correction or Fisher's exact test for proportions and the Student test for independent samples for numerical variables. 95 % Confidence intervals (95 % CI) and Relative Risk (RR) were calculated. A p value <0.05 was considered 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 receiving a weight-based treatment and 53 patients receiving the fixed dose treatment were analyzed. Both groups were homogeneous for age, sex, smoking proportion, diabetics and obese patients ≥ 40 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 3 discontinuations due to vomiting, 2 patients in the weight-based treatment and 1 in the fixed dose treatment. 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.

Percentage of patients reporting AE was 27.4 % (14/51) for the weight-based treatment and 20.7 % (11/53) in the group with fixed doses (p=0.5691), Table 2. The most frequent AE was metallic taste. All AE disappeared after treatment.

DISCUSSION

Evidence-based dosing guidelines for morbid obese patients are few. Although the prevalence of obesity is growing, obese patients have been excluded or under-represented in clinical trials (9,10).

Obesity produces physiological changes that affect drug bioavailability. Not only there is 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 PK parameter affected, and it depends not only on the physico-chemical properties of drugs but also by 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, our knowledge is even more limited, obesity affects affinity and expression of cellular receptors to drugs (13)

Although some authors suggest the need of a tailored *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 *H pylori* eradication with a triple schema, 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 produce in the organism and the physico-chemical properties of the antibiotics. We found that obese patients undergoing bariatric surgery have a higher *H pylori* eradication rates when we used a

weight-based regimen 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. Its limitations include the fact that is a non-randomised trial and the 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 *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.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Table 1. Baseline characteristics of the total cohort of patients.

	Standard treatment (n=53)	Weight-based treatment (n=51)	P Value
Age Mean (SD)	43,37 (9,49)	41,76 (8,45)	0,411

Female gender *n (%)*	30 (56,6)	28 (54,9)	0,981
Smoking habits *n (%)*	10 (18,9)	8 (15,7)	0,865
BMI ≥40 Kg/m^2 n (%)	17 (32,1)	19 (37,3)	0,727
Diabetics *n (%)*	15 (28)	13 (25)	0,918

SD=Standard deviation.

Table 2. Adverse events

Adverse events		Weight-based treatment (n=51)	Standard treatment (n=53)
Severity	Mild	9	8
	Moderate	3	2
	Severe	2	1
Type	Metallic taste	10	8
	Diarrhea	8	6
	Headache	3	2
	Abdominal pain	4	2
	Nausea and vomiting	2	1