



Original/*Obesidad*

Helicobacter Pylori (HP) infection in obese patients undergoing Roux-en-Y gastric bypass; efficacy of two different treatment regimens in HP eradication

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Abstract

Introduction: the ultimate cause for the increased incidence of gastric ulcer following Roux-en-Y gastric bypass (RYGB) remains unclear. Treatment of HP infection is recommended before surgery in countries with high prevalence such as Spain in order to diminish the risk. However, the current regimens used might not be adequate in view of the high failure rate for HP eradication.

Methods: we reviewed 243 patients retrospectively undergoing RYGB and found 111 patients (45%) with HP infection. Therefore, we compared the eradication rate between 2 different regimens. Results: 70 patients received OCA (Omeprazole:20 mg/12h, Clarithromycin 500 mg/12h and Amoxicillin 1 gram/12h for 10 days) while 41 patients received OLA (Omeprazole 20 mg/12 hours, Levofloxacin 500 mg/12hours and Amoxicillin 1 gram/12h for 10 days) for HP eradication. In 56/70 (80%) patients receiving OCA therapy HP was eradicated compared to 37/41 (91%) receiving OLA as first line therapy ($p=0.283$). When used as second line therapy, in 13/14 (92%) patients receiving OLA HP was eradicated.

Conclusion: clarithromycin resistance remains a matter of concern in this population while OLA seems to be a good alternative therapy for HP eradication, especially when OCA regimen fails.

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Key words: *Bariatric surgery. Gastric bypass. Helicobacter pylori. Eradication treatment.*

INFECCIÓN POR *HELICOBACTER PYLORI* (HP) EN PACIENTES CON OBESIDAD PREVIO BYPASS EN Y DE ROUX; EFICACIA DE DOS PAUTAS DE ERRADICACIÓN

Resumen

Introducción: las causas implicadas en el aumento de incidencia de úlcera gástrica tras el *bypass* en Y de Roux no son completamente conocidas. El tratamiento de la infección por HP se recomienda antes de la cirugía en países cuya prevalencia sea elevada, como el caso de España, de cara a disminuir dicha complicación. Sin embargo, las pautas actuales de tratamiento pueden no ser adecuadas dados los elevados índices de resistencia.

Pacientes y métodos: análisis retrospectivo de 243 pacientes operados de *bypass* en Y de Roux. De ellos, 111 pacientes (45%) presentaban infección por HP. Objetivo principal: comparación de la eficacia de dos terapias de erradicación de la infección por HP. Resultados: 70 pacientes recibieron OCA (Omeprazol 20 mg/12 h, Claritromicina 500 mg/12 h y Amoxicilina 1 g/12h durante 10 días), mientras que 41 pacientes recibieron OLA (Omeprazol 20 mg/12 h, Levofloxacino 500 mg/12 h y Amoxicilina 1 g/12 h durante 10 días). En 56/70 pacientes (80%) que recibieron OCA HP fue erradicado, comparado con 37/41 (91%) del grupo que recibió OLA como primera terapia ($p=0,283$). La terapia con OLA usada de segunda línea fue eficaz en 13/14 pacientes con HP resistente a la terapia OCA.

Conclusión: la resistencia de HP a Claritromicina es significativa en nuestra serie de pacientes, siendo la terapia con OLA una alternativa adecuada en las cepas resistentes.

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Palabras clave: *Cirugía bariátrica. Bypass gástrico. Helicobacter pylori. Tratamiento erradicador.*

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Abbreviations

HP: Helicobacter Pylori

Introduction

Despite the advances in diet council and drug therapy for obesity treatment, bariatric surgery remains the most effective therapy for long term weight reduction in patients with severe obesity¹. Furthermore, it is effective improving obesity related co-morbidities including different cardiovascular risk factors². Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy are the commonest procedures performed for the management of obesity worldwide, and the number of surgeries performed in specialized centers remains growing. The Spanish register RICIBA (Bariatric Surgery Computerized Register) has previously reported that RYGB is the commonest technique performed in Spain, encountering over 75% of all cases³. However, recent data from the Spanish Society for Bariatric Surgery (Sociedad Española de Cirugía de la Obesidad) reports that RYGB is the technique of choice in 42% of cases. Equally, RYGB is the commonest technique in Europe (38% of all surgeries), whereas Sleeve Gastrectomy is increasingly being performed (37%)⁴.

HP eradication has been proposed prior to RYGB in those with active infection. The proposed reasons are multiple, firstly the endoscopic access to both gastric and duodenum is limited after surgery in the setting of possible complications, when, moreover some complications such ulcers are of particular high risk in this population. Secondly, HP infection is a major risk factor for chronic gastritis and gastric carcinoma.

Furthermore, infection seems to have the potential to cause or aggravate foregut symptoms post RYGB and to predispose to marginal ulcer post-RYGB, even in the absence of ongoing gastric remnant infection⁵. Finally, a recent study also showed that HP infection remains in the excluded stomach for many years and its association with the severity of gastritis suggests that it can play a major role in mucosal change progression increasing even more the gastric cancer risk in patients submitted to RYGB⁶.

The current consensus regarding the need for HP screening before bariatric surgery, stated by the American Association of Clinical Endocrinologists, Obesity Society and American Society for Metabolic & Bariatric Surgery, highlights that well- designed RCTs are necessary to ascertain the specific role of HP screening and eradication in patients undergoing RYGB. However, until then, the evidence does not support routine screening, but aggressive case finding in high-risk patients or in high-prevalence areas may be reasonable⁷. The current HP infection rate in Southern European countries overpasses 50% of adult

population⁸; therefore it seems adequate to screen for HP infection in obese patients prior to RYGB.

The exact prevalence of HP infection in patients undergoing RYGB and the antimicrobial response to different regimens has not been previously evaluated in obese patients in Spain. Our main objective was to evaluate the frequency of HP infection in severe obese patients undergoing RYGB and the different rates of eradication for our two commonest therapeutic regimens used in HP eradication and to assess whether treatment failure rates exceed the recommendations⁹.

Patients and methods

Patients

243 consecutive patients who underwent RYGB were retrospectively reviewed for this study between 2009 and 2013. Patients were potentially eligible for bariatric surgery if they had a BMI >35 and serious comorbidities such as diabetes mellitus or hypertension, or had a BMI >40. A multidisciplinary team including Endocrinologist, Dietitian, Surgeons and Psychiatrist evaluated all patients for its general status, mental condition and expectations. All surgeries were performed by laparoscopy in a single centre. RYGB consisted of the creation of a small vertical gastric pouch of approximately 15-20 ml, a 150-200 cm Roux limb and a 50-100 cm biliopancreatic limb.

Exclusion criteria were previous known history for HP infection, previous eradication treatment, previous bariatric surgery or allergy to Penicillin.

Clinical and biochemical data were obtained from medical charts before surgery. Basal data information included: anthropometric measurements (height, weight, body mass index [BMI], calculated as weight (kg)/height (m²)) and IgG antibodies against HP were measured. All patients signed a written informed consent prior to surgery in which it was specified that clinical and analytical data collected before the bariatric procedure and during follow-up could be potentially used anonymously for investigation and publication. This study was approved by the Ethics Committee of the Hospital Clínico San Carlos and was in compliance with the Helsinki Declaration.

Enzyme-linked Immunosorbent Assay (ELISA)

Blood samples were collected after overnight fasting. After centrifugation serum was separated immediately, protected from light and frozen to -80°C until analysis. IgG antibodies against Helicobacter Pylori were obtained from patients before surgery in order to diagnose HP infection. A commercial ELISA kit was used. Positive antibodies against HP has previously shown to be accurate for HP diagnosis, with correlation rates reported as much as 98%⁹.

Breath Test (Carbon Isotope-urea Breath Test)

In all patients receiving therapy for HP eradication, a subsequent radiolabeled urea breath test was conducted in order to establish HP eradication. Up to 2 weeks before test, all antibiotics, bismuth medicines and proton pump inhibitors were stopped.

The diagnosis of HP infection was made using radiolabeled ¹³C urea breath test. The procedure consists of comparing the increase in ¹³C urea exhaled before and after ingestion of 100 mg ¹³C urea (UB-Test ®, Otsuka Pharmaceutical, España). The samples are analyzed with infrared spectrophotometry (UBiTIR300, Otsuka Pharmaceutical, España). The increase in ¹³C in breath is the result of the difference between the rate ¹³C/¹²C before and 20 minutes after oral radiolabeled urea is ingested. The result is considered positive in the setting of a difference equal to or greater than 2.5%, and the patient is considered to be infected with HP. This method presents a sensitivity of 98.2% (95%CI: 94.8-99.6%) and a specificity of 97.9% (95%CI: 88.9-99.9%).

Treatment regimen for HP infection

All patients with elevated IgG antibodies against HP (>10 mUI/l) or a positive breath test before surgery received treatment either with OCA (Omeprazole 20 mg every 12 hours, Clarithromycin 500 mg every 12 hours and Amoxicillin 1 gram every twelve hours for 10 days) or OLA (Omeprazole 20 mg every 12 hours, levofloxacin 500 mg every 12 hours and Amoxicillin 1 gram/12h, for 10 days) regimens as the first line of treatment.

If the first line treatment failed to eradicate HP after OCA regimen, OLA treatment was used then to treat the infection. Equally, if OLA regimen failed to eradicate HP as the first line treatment, quadruple therapy with ODBM (Omeprazole 20 mg/ 12 hours, Doxycycline 500 mg/6 hours, Bismuth Subcitrate 120 mg/6 hours and Metronidazole 500 mg/8 hours) was then used for eradication.

Statistical Analysis

Descriptive results were expressed as mean ± standard deviation for continuous variables. Categorical variables were summarized as percentages. Statistically significant differences for the main outcome were determined among groups using Chi-Square test. To assess differences in basal characteristics among patients diagnosed from HP infection, and those who don't; age, weight and BMI were compared using T-Student. Differences in gender among groups were assessed using Chi-Square test. The p values were two-sided and statistical significance was considered when p < 0.05. All statistical analyses were performed

using the Statistical Package for Social Sciences, version 15.0 (IBM SPSS Statistics Inc., Chicago, IL, USA).

Results

Patients' characteristics and HP diagnosis

243 patients underwent RYGB and were tested for HP infection before surgery. There were 188/243 (77%) women and 55/243 (23%) men. Mean age was 47 ± 11 years old. Mean weight was 116 ± 18 kg and mean BMI 43 ± 8.5 kg/m².

Elevated IgG antibodies were used initially to diagnose HP infection. Among all patients, 111/243 (45%) had a diagnostic positive test for HP infection.

The differences in patient's characteristics among patients with a positive test and those with a negative test are summarized in table I.

Efficacy for HP eradication among two different treatment regimens (OCA vs OLA treatment)

A total of 70 patients received OCA as first line regimen whereas 42 patients received OLA for HP eradication. Eight weeks after treatment, all patients underwent a subsequent breath test to confirm eradication. Eradication rate was 56/70 (80 %) in OCA regimen while 37/41 (91%) in the group receiving OLA (p=0.283).

When the regimen OCA failed to eradicate HP, second line therapy was used with OLA. In 13/14 (91%) patients receiving OLA as second line regimen, HP was eradicated. Conversely, 2/4 (50%) patients receiving quadruple therapy with ODBM, following failure with OLA, were resistant to eradicate HP and a subsequent HP culture was performed in order to establish antibiotic sensitivity. The final eradication rate after second or third line therapy was 97.2% (108/111). The

Table I
Comparison in basal characteristics among patients diagnosed for *Helicobacter Pylori* and those with a negative diagnostic test

	HP +	HP -	P
Gender (Female/Male) [#]	80/31	108/24	0.12
Age (years)*	46 (10)	48 (11)	0.23
Weight (kg)*	118 (18)	114 (17)	0.15
BMI (kg/m ²)*	43 (6)	43 (10)	0.64

[#]Results expressed as ratio (female/male).

*Results expressed as mean and SD (standard deviation).

treatment algorithm for HP eradication is summarized in figure 1.

On the whole, final eradication rate (including both first and second line treatment) with OCA was 56/70 (80 %) vs 50/55 (90%) in OLA regimen ($p=0.29$).

Discussion

Helicobacter Pylori infection remains an important medical problem regarding the increasing prevalence and potential consequences related to its infection. HP infection is the main factor related to gastritis, gastro duodenal ulcer and gastric cancer¹⁰.

In accordance with the recent consensus for HP screening recommendations in patients undergoing bariatric surgery, and given the lack of prospective randomized controlled clinical trials addressing this specific question, universal screening prior to RYGB is not recommended. However, screening should be considered in countries with high prevalence of infection; such as Spain and other Southern European countries⁶, and in those with symptoms suggesting infection. A previous epidemiological study performed in our population in Madrid reported a prevalence of HP infection of 60.3% in the general population using radiolabeled ¹³C urea breath test¹¹. Therefore, the prevalence in our population (45%) is even lower compared to general population in our area, confirming previous data highlighting that obesity is not a condition predisposing to higher HP infection rates^{12,13}.

The prevalence of elevated antibodies against HP has been reported over 50% in several previous Spanish studies using IgG antibodies as the screening method for HP active infection. Following the Spanish Consensus for the diagnosis of HP infection, the recommended screening method is the radiolabeled urea breath test¹⁴, as the use of antibodies against HP is associated with false positive results. One of the limitations of the present study is that the urea breath test was not available for all patients to confirm infection prior to surgery. In our series, only 35/111 patients

(31%) underwent radiolabeled urea breath test prior to surgery. However, in all cases, elevated IgG levels correlated with positive urea breath test, confirming HP infection in 100% of available cases. Nevertheless, HP IgG antibodies can be useful in cases where the density of HP infection is markedly decreased, such as in extensive intestinal metaplasia, gastric mucous atrophy or diffuse MALT lymphoma. Furthermore, HP IgG antibodies are useful in patients who have received antibiotics recently or in those who cannot stop proton pump inhibitors (PPI). In this context, elevated IgG antibodies can be considered diagnostic of active infection in the absence of previous eradication antibiotic regimen.

On the other hand, there are false negatives to urea breath test, particularly if the patient has taken antibiotics in the previous 4 weeks or PPIs in the last 2 weeks before the test is performed. Moreover, PPIs are frequently used in this population for gastroesophageal reflux symptomatic control, and PPI use is associated with a low HP infection density; potentially undetectable by the radiolabeled urea breath test. We generally prescribed treatment for those patients with elevated HP IgG antibodies in the absence of previous eradication therapy. A biopsy taken with endoscopy can be useful to confirm diagnosis, but can also lead to delay significantly the access to bariatric surgery.

The HP infection rate in obese patients is variable among different populations and previous studies, ranging from 12% in Finland¹⁵, 23.7% in New York¹⁶ and 69% in Portugal¹⁷.

In Spain we only have data from a recent study performed in León reporting HP infection rate in candidates for bariatric surgery. In this study, HP infection rate addressed with oral endoscopy and gastric biopsy was 63.9%. Of notice, the authors did not find relation with BMI¹⁸. Therefore, although with high diagnostic accuracy, biopsy through oral endoscopy is not universally recommended unless specific symptoms are present to justify its use for other diagnostic purposes.

There are different modalities for the treatment of HP infection, but there is agreement that the minimum

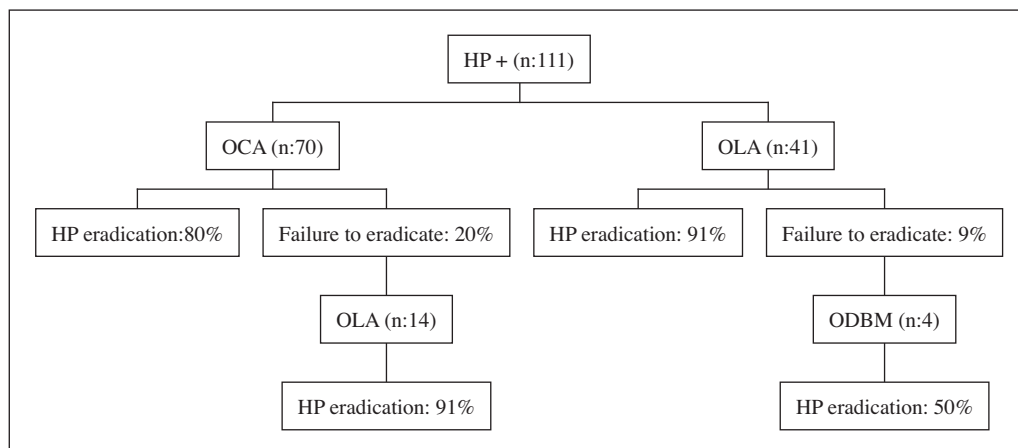


Fig 1.—Treatment algorithm used for HP eradication in our population.

efficacy rate needs to be higher than 80% in each population¹⁴. In view of this, specific eradication rates in patients with different conditions and in different geographic areas need to be assessed in order to establish the best algorithm to treat HP infection.

So far, no studies in obese patients undergoing RYGB have been performed to establish the eradication rate of HP in this specific population in Spain. OCA regimen is generally advised as first line therapy for the vast majority of patients with HP infection. This therapy has good general efficacy rate with 85% patients being cured of the infection in sensitive Clarithromycin bacterial strains and 20% in bacterial strains resistant to Clarithromycin. In Spain, during the last period, the resistance rate has remained stable, with a 10 percent Clarithromycin resistance rate for HP eradication¹⁹, so OCA remains a good first line therapy for general population.

Furthermore, Clarithromycin resistance in Spain has been recently reported to be 12% in a multicenter study, supporting its use as first line therapy²⁰. However, a posterior report by Gisbert et al. over 12 years in a single Spanish center reported only 80% rate of eradication²¹, which is consistent with our results. Accordingly, it seems reasonable that other therapies should be evaluated as first line for HP eradication.

Nevertheless, the eradication rate subsequent to OCA therapy has been proved to be lower in patients with higher BMI, with fewer efficacies being reported in overweight and obese patients compared to controls⁹. However, in our series the eradication rate with OCA is 80%, which is an accepted efficacy rate. Therefore, OCA can still be considered a useful regimen in our population.

One of the most common alternative modalities for patients with allergy to Penicillin is to switch Amoxicillin for Metronidazole 500 mg every 12 hours. In our study, we wanted to evaluate the different efficacy rate between the two most common modalities used in our center (both using amoxicillin), so patients with allergy to penicillin were not eligible for inclusion.

In addition, whether prolonged therapies (over 7 days) associate a higher efficacy rate is a matter of debate. In Europe, prolonged modalities are generally used (usually 10 days), and it seems to be cost-effective in treating functional dyspepsia²², while no differences have been found compared to 7 days of treatment in patients with HP infection and ulcer disease²³. The experience in Europe with OCA therapy (14 days duration) in candidates to RYGB is limited to Portugal, where the prevalence of HP infection is significantly high and the rates of remission following OCA are inadequate (less than 80%)¹⁷.

Failure to eradicate HP infection depends on several factors, such as HP antibiotic resistance, adherence to therapy and different pathogenicity between bacterial strains. For second line therapy, different modalities have been proposed. We generally use OLA as second line therapy given its efficacy, low side effect profile

and better adherence compared to quadruple therapy such as IBP, Bismuth Citrate 120mg/6h, Doxycycline 500mg/6h and Metronidazole 500mg/8h²⁴.

The triple therapy OLA has been proved to be effective both as first line treatment, and after failure of other modalities. Primary eradication rate has been observed to be higher than 90%. In our cohort of patients, a similar failure rate (9%) was observed compared to previous reports. In addition, rescue treatment efficacy after first line treatment failure has been reported between 63-94%²⁵. We have found that OLA is a good therapy with eradication rate of 91% as second line treatment in our obese patients before RYGB. Furthermore, a randomized trial comparing OLA to quadruple therapy showed better efficacy and tolerance in OLA group²⁶. However, resistance to Levofloxacin is increasing rapidly, fact for which it cannot be considered as the first line therapy for HP eradication.

The key question is whether OCA therapy is still a good therapy for obese patients undergoing RYGB. From the 70 patients receiving OCA as primary treatment, 14 (20%) remained with a positive breath test after treatment. 80% is, in fact, the minimum acceptable efficacy rate for therapies used for HP eradication in agreement with Maastrich IV consensus²⁷. Our data suggests that OCA therapy remains an acceptable first line treatment for HP eradication in patients undergoing RYGB in Madrid, although primary treatment failure remains of concern.

In this population, a high failure rate for HP eradication can increase significantly the cost related to investigations and therapies, as well as the cost related to unnecessary frequent follow up in the outpatient clinic. In addition, it can significantly delay the time of surgery and furthermore it can potentially expose patients to unnecessary antibiotic side effects.

Until more data is available supporting the relation between HP infection and subsequent gastric ulcer development after RYGB, HP eradication will continue to be recommended for patients prior to surgery. In order to clarify the specific role of different treatment regimens, further research involving different local hospitals in Spain need to be performed in patients with obesity and HP infection.

In summary, we have found a high prevalence for HP infection in obese patients undergoing RYGB in a single center in Madrid, Spain. In addition, we have shown that resistance to Clarithromycin remains of concern in this population. Finally, treatment with OLA seems to be a good alternative in our patients, especially as second line therapy given the high rate of eradication as rescue regimen.

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