ARTIGO ORIGINAL/ORIGINAL ARTICLE

TRIPLE THERAPY WITH CLARITHROMYCIN, AMOXICILLIN AND OMEPRAZOLE FOR *Helicobacter pylori* ERADICATION IN CHILDREN AND ADOLESCENTS

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ABSTRACT *– Background – Helicobacter pylori infection presents high prevalence in developing countries, but there are few pediatric assays evaluating antimicrobial treatment. Objective - The aim of this study was to investigate Helicobacter pylori eradication rate using a short regimen (7 and 10 days) of triple therapy with clarithromycin, amoxicillin and omeprazole. Patients and methods - Twenty-five Hp positive patients who presented severe epigastralgia, were submitted to antimicrobial treatment with amoxicillin (50 mg/kg/day - maximum dose 1g bid), clarithromycin (30 mg/kg/day - maximum dose 500 mg bid) and omeprazole (0.6 mg/kg/day - maximum dose 20 mg bid) during 7 or 10 days. After 2 months, clinical symptoms were evaluated and gastric biopsies were taken to test Hp eradication. Results - Overall eradication rate was achieved in 16/25 patients (64% - IC(95%) = 45-83%), in 11/15 (73% - IC(95%) = 51-95%) patients who used 10 days therapy course and in 5/10 (50% - IC(95%) = 19-81%) who used 7 days therapy course. Eradication drugs were well accepted and adverse effects were reported in two patients (8%). Conclusions - This triple therapy regimen had moderate efficacy (64%). The data suggests that 10 days therapy course achieves better eradication rate (73%) than 7 days course (50%) to treat Hp infection in our population.*

HEADINGS – *Clarithromycin. Amoxicillin. Omeprazole. Helicobacter infections. Child. Adolescence.*

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Helicobacter pylori (Hp) eradication results in healing and prevents recurrence of peptic ulcer disease as in adult patients[9, 25] but children rarely have peptic ulcer (4-6 patients/year)[4] and Hp positive gastritis without peptic ulcer is so far the most common diagnosis. A meta-analysis of a large number of controlled studies indicated that the presence of Hp gastritis in the absence of peptic ulcer may be a risk factor in non-ulcer dyspepsia (odds ratio 1.6, IC(95%) = 1.4-1.8) and symptoms improve when the organism is successfully eradicated (1.9, IC(95%) = 1.3-2.6)[10]. In children a positive correlation between Hp gastritis without peptic ulcer and dyspeptic symptoms or recurrent abdominal pain[17] has not been well established[8, 14, 22]. Two pediatric consensus on Hp infection recommended not to treat all Hp positive children with recurrent abdominal pain[6, 28]. In dyspeptic children of developing countries, we could overtreat these children due to the high prevalence of Hp infection. Recently, refractory iron deficiency anemia that respond to the Hp eradication have been described[3, 16].

Current treatment protocols suggest triple therapy as first line therapy, proton pump inhibitor plus two antibiotics (amoxycillin, clarithromycin or metronidazole) two times daily[7]. Clinical assays have shown proton pump inhibitors in combination with clarithromycin and amoxicillin (CAO) to be effective in clinical trials with eradication rate in more than 80%[15]. In children, the same treatment has presented similar rate although rate of 75% has been obtained[26, 29]. Advantages of this therapy, widely used in adult patients, involves the exclusion of nitroimidazole, that presented high bacterial resistance, ranging from 40% to 98%[2, 18] with higher prevalence in developing countries[18, 24].

The aim of this study was to evaluate the Hp eradication rate following 7-days and 10-days CAO course in treatment of Hp associated gastritis with or without primary peptic ulcer in children.

PATIENTS AND METHODS

Twenty-five Hp positive dyspeptic patients were included in the analysis. The infected patients without peptic ulcer were selected for Hp treatment if they fulfilled the following entry criteria: (1). severe epigastric pain with recurrent dyspeptic symptoms or refractory to treatment (prokinetics, H2 receptor antagonist and changes in life style); (2). severe epigastric pain and peptic disease or gastric carcinoma related in the relatives. Patients with chronic digestive or extra digestive disease, with previous anti-Hp treatment or with non-steroidal anti-inflammatory drugs or aspirin were also excluded. Clinical symptoms were recorded.

Patients were submitted to antimicrobial treatment with amoxicillin (50 mg/kg/day - maximum dose 1 g bid), clarithromycin (30 mg/kg/day - maximum dose 500 mg bid) and omeprazole (0.6 mg/kg/day - maximum dose 20 mg bid) during 7 or 10 days. Follow-up visits were scheduled at the day after finishing the treatment period to assess adverse effects and to check treatment compliance. Patients were asked to return the unused medication, and pill counting to assess compliance. After 2-month, patients were reassessed clinically and submitted to endoscopic biopsies for Hp status.

Endoscopic biopsies were taken to determine Hp status by rapid urease test (homemade solution: 1 mL distilled water, 0.1 g urea and 2 drops 1% red phenol) and by histology (hematoxylin-eosin and Giemsa stains). The pathologist was unaware in all cases that the patient was being included in the study. To assess Hp eradication, four antral and four body biopsies were taken: antral mucosa (two) and body mucosa (two) for rapid urease test and histology respectively. Hp was positive if both histology and rapid urease test were positive and Hp negative if rapid urease test and histology were both negative. ^{13}C urea breath test (non dispersive infrared spectrometer) was performed if rapid urease test was positive and histology was negative. Values more than 40% were considered positive. The Ethics Committee of our institution approved this study. The parents of the patients gave their informed consent on recruitment of the children to the study.

RESULTS

The age of 25 patients ranged from 5y9mo to 18y (median = 11y10mo), 12 (48%) were male and 13 (52%) female. All patients reported peptic disease in first or second degree relatives, except one who presented primary duodenal ulcer. Endoscopy was normal in 9/25 patients (36%) and abnormal in 16/25 patients (64%); 9/16 (56%) presents gastritis, 6/16 (38%) erosive duodenitis and 1/16 (6%) duodenal ulcer. Antimicrobial treatment was well accepted with total compliance; side effects (metallic and bitter taste) were reported in two patients (8%).

Overall eradication rate was 64% ($IC^{(95\%)}$ = 45-83%). Fifteen patients used 10 days antimicrobial treatment regimen and Hp infection was eradicated in 11 patients (73% - $IC^{(95\%)}$ = 51-95%). Endoscopic diagnosis was nodular gastritis in four, erosive duodenitis in three, normal in three, and duodenal ulcer in one; 7/11 (64%) presented total remission of symptoms, but symptoms persisted in four (36%), 2/4 with erosive duodenitis, one with gastritis and one with normal exam; 2/4 who remained infected became asymptomatic, both with normal endoscopy. Ten patients used 7 days antimicrobial treatment regimen and Hp was eradicated in five (50% - $IC^{(95\%)}$ = 19-81%). Endoscopic diagnosis was nodular gastritis in three and normal endoscopy in two; only 1/3 patient with normal endoscopy became asymptomatic; 2/5 patients with gastritis who remained infected, became asymptomatic.

The results of rapid urease test and histology agreed in all patients except in three (88%); 2/3 had positive histology and were considered Hp positive and another had a positive rapid urease test and negative histology. ^{13}C urea breath test was positive in this last patient and morphologic examination of the antral mucosa showed chronic inflammatory cells with neutrophilic infiltrate. Then, the patient was considered Hp infected.

DISCUSSION

This therapy with CAO eradicated Hp from the gastric mucosa with an overall eradication rate of 64%. Ten days course of antimicrobial treatment achieves 73% eradication rate and 7 days course achieves 50%. Our small sample could be a big one due to higher prevalence of Hp infection in our dyspeptic children. We really selected only children who routinely have Hp treatment indicated in our institution. All of them present severe epigastric symptoms or peptic disease in their relatives.

This eradication rate was higher than previous triple therapy used in our institution: colloidal bismuth subcitrate, amoxicillin and nitroimidazole compounds (metronidazole or tinidazole) during 1 week (35%) and during 2 weeks (40%)[13] and triple therapy with omeprazole, clarithromycin and nitroimidazole (metronidazole or tinidazole) during 2 weeks (25%)[21]. Thus, the non-inclusion of nitroimidazole seems very important on account of prior low rates of Hp eradication in children of our country. Clarithromycin resistance ranges from 5% to 15%, in European studies[23, 30] and is increasing in children because of the widespread use in pediatric practice, mainly in developed countries.

The poor compliance could be another important reason for this low rate of eradication. The problems associated with poor compliance, such as treatment failure, development of drug resistance and the expenses and inconvenience of further investigation and therapy, make it imperative to find a short course, highly effective and well tolerated regimen. Side effects, a factor contributing to non-compliance, occurred in only two patients (8%), less than that reported by KATO et al.[12] (33%). Clarithromycin can cause metallic taste, nausea, vomiting or diarrhea. The patients must be advised to continue the treatment even if these symptoms occur. KATO et al.[12] noted a high eradication rate (92%) using CAO therapy for Hp ulcer disease and nodular gastritis in a smaller sample (12 children), but our result was similar to other two studies using CAO therapy: in 32 Swedish children for 2 weeks (75%)[29] and in 45 Italian children (78%)[20].

A long-term study is important to determine the effect of Hp eradication on remission or recurrence of symptoms in children with Hp positive gastritis without peptic ulcer. Similar studies have shown resolution of symptoms in non-eradicated infection like we observed in this study[5, 9, 12].

^{13}C urea breath test is considered the best test to assess Hp eradication in children and adults, but in developing countries, endoscopy is more accessible than this high-cost non-invasive method. In this study we used this test only in selected children because ^{13}C urea breath test is not routinely available in our institution.

The long-term eradication in children of low socioeconomic level in developing countries has to be determined. There are no studies evaluating the reinfection rate. In developed countries, although rare, reinfection is most common in children younger than 5 years old[27] Hp infection is common among relatives[19]. Treatment of relatives of Hp infected children promoted good compliance to antimicrobial treatment[11, 19] and could act by lowering the reinfection. In our institution, we always submitted the relatives to Hp treatment if they presented peptic ulcer. We approach the symptomatic relatives of duodenal ulcer children regarding Hp investigation, although different strains can be identified in the same family and more than one strain can be present in the same individual[1].

In summary, a 10-day course of CAO resulted in 73% eradication of Hp infection and 7-days course resulted in 50%. Further studies with a bigger sample and search for a better Hp treatment regimen are needed.

Kawakami E, Ogata SK, Portorreal ACM, Magni AM, Pardo MLE, Patrício FRS. Terapia tríplice com claritromicina, amoxicilina e omeprazol para erradicação do Helicobacter pylori em crianças e adolescentes. Arq Gastroenterol 2001;38(3):203-206.

RESUMO – *Racional – Apesar da alta prevalência da infecção por Helicobacter pylori em países em desenvolvimento, existem poucos ensaios pediátricos avaliando o tratamento antimicrobiano para erradicação. Objetivo - Avaliar a eficácia de esquema tríplice contendo claritromicina, amoxicilina e omeprazol para erradicação da infecção por Helicobacter pylori durante 7 e 10 dias. Pacientes e Métodos - Vinte e cinco crianças e adolescentes Helicobacter pylori positivo com queixas dispépticas de forte intensidade foram submetidas a tratamento com amoxicilina (50 mg/kg/dia - dose máxima 1 g bid), claritromicina (30 mg/kg/dia - dose máxima 500 mg bid) e omeprazol (0,6 mg/kg/dia - dose máxima 20 mg bid), durante 7 e 10 dias. Após 2 meses, realizou-se controle clínico e biopsia gástrica para avaliar erradicação do Helicobacter pylori. Resultados - Helicobacter pylori foi erradicado em 16/25 pacientes (64% - IC(95%) = 45-83%), em 11/15 (73% - IC(95%) - 51-95%) que utilizaram esquema antimicrobiano por 10 dias e em 5/10 (50% - IC(95%) = 19-81%) que utilizaram o esquema por 7 dias. Houve boa aceitação do tratamento antimicrobiano e efeitos colaterais ocorreram em dois pacientes (8%). Conclusões - O índice de erradicação obtido (64%) foi de eficácia moderada. Os dados da presente série sugerem que o esquema antimicrobiano por 10 dias (73%) seja mais eficaz que o esquema por 7 dias (50%) para tratamento da infecção por Helicobacter pylori em nossa população, embora seja necessária amostragem maior.*

DESCRITORES – *Claritromicina. Amoxicilina. Omeprazol. Infecções por helicobacter. Criança. Adolescência.*

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Recebido em 30/10/2000.
Aprovado em 17/7/2001.