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Eradication of Helicobacter pylori with triple therapy regimen (Omeprazole, Clarithromycin and Amoxicillin) in children for seven days (A Pilot Study)

Mehri Najafi[1]

Fariba Seighali[2*]

[1]Children Medical Center Hospital, Tehran University of Medical Sciences, Tehran-Iran

[2]Maternal, Fetal and Neonatal Research Center, Tehran University of Medical Sciences & Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine, Tehran, Iran

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Abstract

Background and purpose: Successful treatment of Helicobacter pylori infection causes not only eradication of pathogen, but also prevents the associated diseases such as peptic ulcer, gastric carcinoma and lymphoma. The aim of this study was to evaluate the efficacy of 7 days triple therapy as a lowest drug resistance, shortest duration and fewer numbers of drugs in children.

Materials and Method: The target population was 22 children <15 years with peptic disease complaints. The inclusion criteria were: positive endoscopic finding, inflammatory evidence in gastric biopsy and presence of Helicobacter pylori in gastric mucosa. Two pieces from incisura and body of gastric mucosa were taken and stained with Gimsa. Helicobacter pylori positive patients were treated with omeprazole, clarithromycin and amoxicillin for 7 days. One month later, all cases were evaluated by repeated endoscopy or Urea Breath Test and H pylori eradication were assessed. Data was gathered and analyzed with SPSS software, and McNamara's and Chi-Square test were performed. **Results**: Nineteen patients were studied including twelve boys, 26.3% 2-6 years and the rest older than 6 years. The most common clinical presentations and endoscopic findings were chronic abdominal pain (74%) and nodularity (47.4%), respectively. The per-protocol and intention-to-treat H. pylori eradication rates were 84.2% and 76%, respectively in seven days triple therapy regimen.

Conclusion: Seven days triple therapy successfully eradicated H pylori in children.

**Corresponding Author: Fariba Seighali MD; Assistant Professor of Pediatric Gastroenterology, Maternal, Fetal and Neonatal Research Center, Tehran University of Medical Sciences & Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine, Tehran-Iran*
Mailing Address: Valiasr Hospital, Imam Khomeini Hospital Complex, Keshavarz Blvd. Tehran- Iran
Tel: +98 21-66924545
Fax: +98 21 66924545
Email: fseighali@yahoo.com

Introduction

Helicobacter pylori (H. pylori) is acquired during childhood and has a long life in the absence of treatment. Infection could be acquired at any age; however, the incidence is higher in children. The prevalence of H pylori in childhood (<10 years) was reported 80% in developing countries.[1-3] The infection rate among children has reached to 50-60% in Bangladesh, 48% in Ethiopia and 50% in Egypt.[4] H. pylori infection is prevalent in Iran, and the estimated prevalence of H. pylori infection is reported 65%.[5] H. pylori cure rates are reported different in different geographical regions because of hosts as well as in H. pylori strains. Successful treatment of H pylori infection causes not only eradication of pathogen but also cures and prevents the associated diseases such as peptic ulcer, gastric carcinoma and lymphoma.[6,7]

The most successful eradication therapy includes combination treatment regimen in which the number, the frequency and the duration of medications and therapy should be considered. Recommended initial treatment consists of a gastric acid suppression agent and two antibiotics for one to two weeks.[3] Triple therapy has been indicated as an effective method for H. pylori eradication in children.[8] Treatment with three or four drugs achieves efficacy in more than 80% of infected patients.[4]

According to the standard 10-14 days triple therapy recommendations for treatment of H. pylori infection formulated at the Maastricht III Consensus Conference (2005) using a PPI with clarithromycin and amoxicillin or metronidazole twice daily remains the first choice treatment.[9] In some studies from all over the world, the efficacy of eradication schemes has failed by drug resistance and poor compliance.[4, 10]Many children do not complete therapy because of long duration of drug consumption. The most effective regimen for H pylori eradication especially in children needs to be determined. In our country, helicobacter resistance to metronidazole has reduced the successful eradication rate.[11] On the other hand ten days to two weeks classic regimen with clarithromycin constrains a great budget. So we applied this standard regimen for a shorter period to evaluate the regimen efficacy in children. The primary objective of the present study was to assess the efficacy of 7days triple therapy regimen consisting of omeprazole, amoxicillin and clarithromycin in children <15 years in a public hospital. The secondary objective was to investigate the association between clinical manifestation, age, sex, endoscopic findings and H pylori eradication.

Materials and Methods

A before- after, One sample, clinical trial study was carried out in the endoscopy ward of Children's Medical Center (Tehran-Iran) from January 2011 to January 2012. Ethics approval for the study was obtained from the institutional review board of Tehran University of Medical Sciences. The target population was 22 children younger than 15 years of age with complaints related to peptic disease. The inclusion criteria were positive endoscopic findings (nodular gastritis, duodenal or gastric ulcer), inflammatory evidence in gastric biopsy and presence of H. pylori in gastric mucosa. Exclusion criteria were positive history of allergy to each drugs used in our study, previous history of H. pylori eradication and recent antibiotic therapy. All participants and or their parents gave informed consent before participating in the study.

Endoscopy with some biopsies is a reliable diagnostic test for H pylori and related gastro duodenal diseases. Urea breathe test with or without nonradioactive isotope is another sensitive and specific test.[3]

An expert pediatric gastroenterologist took two pieces from incisura and body of gastric mucosa for RUT (Rapid Urease Test) and histology. The gastric specimen was fixed in 10% formalin and stained with Hematoxillin-Gimsa and reported by a pathologist expert in pediatric GI pathology blindly. H.P. positive patients were treated with omeprazole (0.7-3.3mg/kg/day) single dose in the morning, Amoxicillin (50mg/kg/day) and clarithromycin (15mg/kg/day) all in two divided doses for one week. One month after completion of therapy, all cases were evaluated by repeated endoscopy and gastric biopsy or qualitative Urea breathe test (C-UBT).[13] These procedures were selected based on patients' willingness, ability to breathe test or endoscopic findings. Re-endoscopy was done in patients with hemorrhagic ulcer, history of GI bleeding and those who could not do the breathe test.

All data were gathered and coded. The software package SPSS version 19 and McNamara's test were used to perform the statistical analysis. P-value < .05 was considered significant.

Results

Of 22 patients, three were excluded from the study because of drug intolerance in two cases and failure to return in one case. One month after completion of treatment, endoscopic procedure was performed for 16 cases and three cases went for urea breathe test.

Among 19 patients, five (26.3%) were 2-6 years and the rest (73.7%) were older than 6 years old. There were twelve boys (63%) in the study. The most common clinical presentations were chronic abdominal pain, hematemesis and melena and both chronic abdominal pain and GI bleeding which are illustrated in table 1. The most endoscopic findings included nodularity and duodenal ulcer, no gastric ulcer was seen. Most endoscopic findings are shown in table 2.

Based on histopathology evidences, inflammatory cells and H. pylori were observed in lamina properia of stomach in all biopsy specimens. Sixteen cases (72.8%) responded to triple therapy regimen whereas 3 cases did not. Male/Female ratio was 10/6 and 2/1 in responsive and non-responsive groups, respectively. Seven days triple therapy regimen eradicated H. pylori 84.2% per protocol and 76% intention to treat. No significant differences were seen between H. pylori eradication and sex, age and endoscopic finding, Table 3.

Discussion

Although it seems that effective treatments in adult will also effective in children, however the most efficient treatment for H pylori eradication in children needs to be determined.[3] Drug resistance, side effects of drugs, intolerance due to long time therapy and high cost of treatment are amongst the causes of treatment failure. In this study we applied a regimen with lowest drug resistance, shortest duration of therapy and fewer numbers of drugs that more acceptable by children. It should be mentioned that regimen with less than 3 drugs is not effective enough and increases the acquired antibiotic resistance.[3]

Triple therapy is the most frequently used treatment regimen in children, but different eradication rates in different regions of the world were reported because of different host factors, different characteristics of the

Table 1: The most common clinical presentations

clinical presentations	Number (%)
Chronic abdominal pain	74%
hematemesis and melena	21%
chronic abdominal pain and GI bleeding	5%
total	100%

Table 2: Endoscopic biopsy findings in patients

endoscopic finding	Number (%)
nodularity	9 (47.4)
duodenal ulcer	5 (26.3)
nodularity and	5 (26.3)
duodenal ulcer	-
total	19 (100)

Table 3: The relation between H.pylori eradication and different variables

Variables	H.pylori eradication(P Value)
Age	.065
Sex	.061
Endoscopy finding	.070

infecting strains and antimicrobial resistance acquired during the treatment.[11]

Standard 7-14 days triple therapy recommendations for treatment of H pylori infection formulated at the Maastricht III Consensus Conference (2005) using a PPI with clarithromycin and amoxicillin or metronidazol twice daily remains the first choice treatment.9In our country resistance to metronidazol and sensitivity to clarithromycin were reported in some studies.[13,14] Mirzaei et al. in 2013 indicated 37.5% H pylori resistance to metronidazol in 15-58- year- old Iranian patients.[5] A study carried out in Poland (2012,) children resistance rates of H pylori to Amoxicillin, clarithromycin and metronidazol were reported 0%, 29% and 40%, respectively.[4]

In addition, shorter therapy duration with clarithromycin may not only prevent a great burden on family's economy but also decrease poor patient's compliance and drugs adverse effects. Bontems et al. found (in 165 children, median age 10. 4 years) 17% abdominal pain, 5% nausea and 0% vomiting with triple therapy group in contrast to 24%, 8% and 4% respectively, in sequential therapy group.[12] Uygun et al. in a study in 2008 compared 14 days sequential and 7days standard triple drug regimen for H pylori eradication in patients older than 18 years of age and found no significant difference between the two groups regarding side effects (diarrhea, nausea/vomiting, abdominal discomfort and headache). All adverse effects resolved after completion treatment course.[15] Less side effects and better compliance may guarantee completion of treatment particularly, in children.

Based on our study, seven days triple therapy regimen eradicated H pylori 84.2% per protocol and 76% intention to treat. An acceptable minimum success rate for H pylori eradication is 80% which was achieved in our study.[15] Our findings was compatible with some previous studies which showed eradication rates >85 and 90% with triple therapy.[17,9] In a study carried out in Iran, Najafi et al. confirmed the efficacy of 7 days triple therapy for H pylori eradication in children (84.2% and 72.8% per protocol and intention to treat respectively).[17] On the other hand, rate of eradication with proton pump inhibitors, Amoxicillin and clarithromycin was lower than 80% in the USA, Europe, Japan, Korea and China in contrast to Hong Kong and Singapore (more than 80%).[4] Kato et al. in 2004 found triple therapy including metronidazol more effective as the first line therapy in H pylori infected children in

compared to triple therapy with clarithromycin (87.5% vs77.4%) due to increasing resistance to clarithromycin in Japanese population.[8] The most common clinical presentations in our study were chronic abdominal pain, hematoemesis/ melena, both chronic abdominal pain and GI bleeding (74%, 21%, and5% respectively). Saadah also showed abdominal pain as the most frequent clinical presentation in 230 Saudi children with H pylori infection.[18]

In our study, based on histopathology evidences, inflammatory cells and H. pylori were observed in lamina properia of stomach in all biopsy specimens. We also found nodularity as the most endoscopic findings (47.4%) followed by duodenal ulcer. Same results were also observed in another study among 2.7-16-year-old children by Najafi et al. 17 Similarly, nodularity also was the most common finding in a cohort children study that can associate with increased density of H pylori organism and more active inflammation.[18] The degree of mucosal inflammation varies in severity from a minimal inflammatory infiltrate in lamina properia to sever gastritis with different architectures. Gold in 2001 reported an association between nodularity of antral mucosa and children's H. pylori gastritis.[3]

No significant differences were seen between H. pylori eradication and sex, age and endoscopic findings in our study that may be related to small size of our study population. Also, H pylori could be an independent risk factor. However Cutler observed a significant correlation between H. pylori elimination and advanced age ($p = 0.002$), chronic inflammation on baseline antral biopsy ($p = 0.024$). Eradication was also inversely related to the presence of a gastric ulcer ($p = 0.008$) and lack of medication compliance ($p = 0.030$). Sotirios et al. among some influencing factors on H pylori eradication (sex, smoking, endoscopic findings, compliance with therapy) found that only absence of lymphoid follicles in routine gastric biopsies and coexistence of antral and body gastritis, significantly increased H. pylori eradication rate.[19]

Limitation: our findings should be interpreted with caution because of small size of the study population. Peptic disease in children is not as common as in adults and only 22 patients were feasible and available through our study.

Suggestion: A multicenter study with control group in large sample size is suggested.

Conclusion

In conclusion, our results showed that 7 days triple therapy was greatly efficient for eradication of H pylori in children. We also found no significant differences between H. pylori eradication and sex, age and endoscopic finding.

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Conflict of Interest

The authors declare that there is no conflict of interests.

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