Medical Journal of the
Islamic Republic of Iran

Volume 19
Number 1
Spring 1384
May 2005

EVALUATION OF TRIPLE AND QUADRUPLE REGIMENS IN ERADICATION OF *HELICOBACTER PYLORI* INFECTION IN PEDIATRIC PATIENTS IN EMAM KHOMEINI HOSPITAL IN 2002-2003: A RANDOMIZED CLINICAL TRIAL

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ABSTRACT

Background: Triple therapy with a proton pump inhibitor, clarithromycin and amoxicillin and quadruple therapy with a proton pump inhibitor, bismuth citrate, metronidazole and amoxicillin have been proposed in Maastricht 2000 as the optimal treatment of *Helicobacter pylori* infection. We aimed to compare these two regimens in Iranian pediatric patients.

Methods: A randomized clinical trial in Emam Khomeini Hospital between 1381 and 1382 was done. Patients with confirmed *H. pylori* infection by histology were divided in to two groups in a randomized 1:1 scheme.

Triple regimen group: Clarithromycin 15 mg/kg/d, Amoxicillin 50 mg/kg/d and Omeprazole 1 mg/kg/day for 10 days.

Quadruple regimen group: Omeprazole 1 mg/kg/d, Amoxicillin 50 mg/kg/day, Metronidazole 20 mg/kg/day and Bismuth citrate 8 mg/kg for 10 days. The eradication was assessed by c-urea breath test 4 weeks after the end of treatment and by perprotocol analysis.

Results: In our study, 100 patients (50 in each group) were found and the eradication rates in the triple and quadruple group were 92% and 84% respectively (p=0.046).

Conclusion: According to our results, we recommend triple therapy as first-line treatment in Iranian pediatric patients and quadruple therapy as a second line regimen.
MJIRI, Vol. 19, No. 1, 29-33, 2005.

Keywords: *H. pylori* infection,pediatrics,triple and quadruple regimen.

INTRODUCTION

Helicobacter pylori is a major etiologic factor in peptic ulcer disease and a risk factor for the development of gastric cancer.[1] The benefits of *H. pylori* eradication include healing of gastritis, enhanced ulcer healing, re-

duction or elimination of ulcer recurrence and prevention of ulcer disease, MALTOMA and gastric cancer.[2] Evaluation and (if positive for *H. pylori*) treatment of patients with active or inactive peptic ulcer disease, hemorrhage, severe gastritis with pathologic features of follicular or chronic active gastritis are now recommended.[3] Many non-invasive tests are now available to diagnose *H. pylori* infection including urea breath test and serologic tests but the gold standard test in diagnosis of *H. pylori* infection is positive culture or compatible histological findings with a positive urease test (sensitivity rate up to 100%),[4,5] however in children because of a lower infection load, the urease test has less sensitivity and only histological findings are reliable in pediatric cases.[6,7]

Despite more than 500 independent clinical studies evaluating eradication therapies, there is no clear consensus on the ideal *H. pylori* eradication regimen. The Maastricht consensus recommended first - line triple therapy with a proton pump inhibitor (PPI), amoxicillin (A) and clarithromycin, and second - line quadruple therapy with a PPI, bismuth, metronidazole and tetracycline for 14 days.[5] Numerous clinical studies specific to *H. pylori* eradication with triple therapy have been published. Recently Pilotto et al.[8] reported an *H. pylori* eradication rate of 94% with triple therapy consisting of PPI, amoxicillin and clarithromycin for 7 days in Italy. Other reports of *H. pylori* eradication triple therapy with a PPI and two antibiotics administered for 5,7,10 or 14 days have shown eradication rates ranging from 67 to 99%, depending in part on the combination of antimicrobials chosen, duration of therapy, geographic region and resistance.[9,10,11,12] The emergence of resistance to antibiotics is predictive of lower cure rates and is related to epidemiologic factors including geography and antibiotic use patterns. Metronidazole resistance is reported significantly in Asian ethnicity, i.e., 46.8%.[13] The predicted rate of clarithromycin resistance was 3.4 to 11.5% and its resistance is predictive of treatment failure, whereas[14] increasing the dose of metronidazole in multidrug-regimens can overcome its resistance and amoxicillin resistance has been reported only rarely.[13] In this study, we aimed to compare *H. pylori* eradication rates of 2 different regimens in Iranian children with confirmed *H. pylori* infection.

PATIENTS AND METHODS

This study was a parallel randomized clinical trial in Emam Khomeini hospital between 2002 and 2003. Patients who were between 1-16 years and had GI symptoms were evaluated by serologic testing (*H. pylori* IgG) as a screening method to identify patients for the prospective study by probability of positive *H. pylori* status. Then highly probable patients underwent endoscopy with biopsy for histology and urease test. Patients with compatible histologic findings, chronic active gastritis, or follicular gastritis with identification of the organism by H&E or immuno-peroxidase staining were invited to the study. Rapid urease test was also performed but not as a diagnostic test. All patients gave their informed consent to participate.

Exclusion criteria were treatment with antibiotics, PPI or bismuth during previous months, regular use of steroids or NSAIDs, allergy to any of the medications of our study, severe renal or hepatic disease and poor compliance status.

Patients were randomly assigned to one of the following regimens with matching age and sex between groups:

1- Triple regimen group: Omeprazole 1mg/kg/day up to 20 mg bid, Clarithromycin 15 mg/ kg/day up to 500 mg bid, and Amoxicillin 50 mg/kg/day up to 1g bid for[2] 10 days and 2- Quadruple regimen group: Omeprazole 1 mg/ kg/day up to 20 mg bid, Amoxicillin 50 mg/kg/day up to 1g bid, Metronidazole 20 mg/kg/day and Bismuth citrate

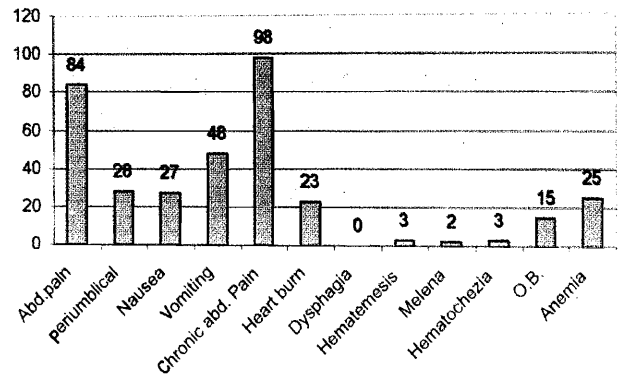

Fig. 1. Signs and symptoms of children with positive *H. pylori* infection in Emam Khomeini Hospital between 2002-2003.

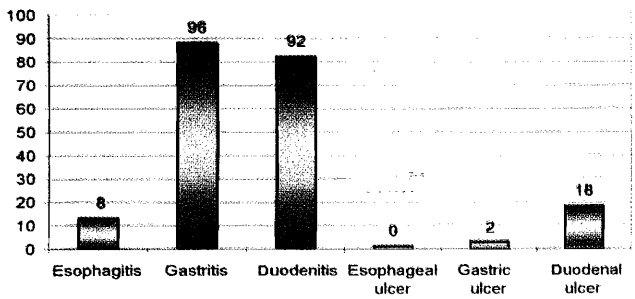

Fig. 2. Endoscopic findings in children with positive *H. pylori* infection in Emam Khomeini Hospital between 2002-2003.

Table I. Demographic characteristics of children with *H. pylori* infection in Emam Khomeini Hospital between 2002-2003.

	Triple Regimen Group No. %	Quadruple Regimen Group No. %	Total No. %
Male/Female	31/19	27/23	58/42
	62%/38%	54%/46%	58% /42%
Mean age±SD	12.4±3.18	12.31±SD	12.36±3.06
(Range,yrs)	(1-16)	(4.5-16)	(1-16)

Table II. Signs and symptoms of children with positive *H. pylori* infection in Emam Khomeini Hospital between 2002-2003.

Signs & Symptoms	Triple Regimen Group No. %	Quadruple Regimen Group No. %	Total No.
Epigastric pain	43 (86)	41 (82)	84
Periumbilical pain	14 (28)	14 (28)	28
Nausea	15 (30)	12 (24)	27
Vomiting	25 (50)	23 (46)	48
Chronic abdominal pain	49 (98)	49 (98)	98
Heartburn	13 (26)	10 (20)	23
Dysphagia	0	0	0
Hematemesis	2 (4)	1 (2)	3
Melena	1 (2)	1 (2)	2
Hematochesia	1 (2)	2 (4)	3
Occult blood	7 (14)	8 (16)	15
Anemia	11 (22)	14 (28)	25

8 mg/kg/day for 10 days.[2]

Follow up evaluation was performed 4 weeks after the last dose of medication. Compliance of patients was considered as a clinical response to therapeutic regimens and also measured by pill-count method in follow up sessions. No major side-effects, requiring discontinuation of responsible drugs, were not seen in our patients. A ^{13}C-urea breath test was performed (which is non-radioactive and safe in children). Breath samples were taken before and 30 minutes after the ingestion of 50 -75 mg ^{13}C-urea in 50 mL of water orally, and the test was considered to be positive if the difference of baseline and 30 min. values was >4% (sensitivity and specificity of ^{13}C-urea breath test by using this cut off point are both 100%).[15] Eradication of *H. pylori* infection was defined as negative urea breath test at 4 weeks after the end of treatment. Evaluation of histologic results and urea breath test was performed by professionals unaware of the goals of our study. The eradication rates were analyzed by per protocol analysis which included only patients who returned for post-treatment urea breath test and were compliant (had taken >80% of prescribed medications). The data were analyzed by chi-square or t-test with statistical significance at a P value of less than 0.05 and by using SPSS software.

RESULTS

During this study, 122 eligible patients were found and assigned to one of the regimens according to a 1:1 randomization scheme. Twenty-two patients (18%) were excluded from the study as they didn't return at the end of treatment or complete their regimens. Only 100 patients (50 patients in each group) entered the final analy-

Table III. Endoscopic findings in children with *H. pylori* infection in Emam Khomeini Hospital between 2002-2003.

	Triple Regimen Group No. %	Quadruple Regimen Group No. %	Total No. %
Esophagitis	4 (8)	4 (8)	8
Gastritis	46 (92)	48 (96)	96
Duodenitis	42 (84)	40 (80)	82
Esophageal ulcer	0	0	0
Gastric ulcer	1 (2)	1 (2)	2
Duodenal ulcer	9 (18)	9 (18)	18

ses. There was no significant difference in demographic and clinical characteristics between the 2 groups. The mean age of patients was 12.36±3.06 (range 1-16 yrs) (12.4 ± 3.18 in triple and 12.31±2.96 in quadruple regimen group). 58% and 42% of patients were respectively girls and boys (62% girls and 38% boys in the triple and 46% boys and 54% girls in the quadruple regimen group) (Table I). Signs and symptoms of patients in both groups didn't differ significantly (Table II, Fig. 1).

Endoscopic findings also didn't have a significant difference between the two groups. The most frequent findings were gastritis (94% of all patients), and duodenitis (82%), duodenal ulcers (18%) (Table III, Fig. 2). In all 100 patients with confirmed *H. pylori* infection by histology, 95 patients also had a positive urease test so the sensitivity of the urease test in our patients was 95%.

Only 4 patients in the triple group and 8 cases in the quadruple group had positive urea breath tests, showing that *H. pylori* infection wasn't eradicated.

The triple regimen and quadruple regimen group achieved eradication rates of 92% (95% CI:83-96%) and 84% (95% CI:74-93%) by per protocol analysis, respectively, which showed a significant difference between the two groups (P: 0.046).

DISCUSSION

H. pylori is a major source of morbidity in infected individuals. Eradication of *H. pylori* has been linked to cure of peptic ulcer disease. Furthermore, while infection with *H. pylori* has been linked to Mucosa-Associated Lymphoid Tissue (MALT) lymphoma, its eradication may also have long-term effects.[2,6]

Antimicrobial - antisecretory drug combination regimens have been found to produce high and consistent cure rates of *H. pylori* infection.

Wieslaw et al[4] found that a triple regimen with a PPI and two antibiotics combination (clarithromycin and amoxicillin) were significantly superior to other regimens. The eradication rate of this regimen has been reported at 87% up to approximately 100%.[4,18] Perri et al[17] evaluated quadruple therapies of *H. pylori* and achieved eradication rates of 83% with bismuth citrate, amoxicillin, metronidazole and a PPI. However they mentioned that tolerability and compliance to a quadruple regimen may represent as a problem for applying them as first line treatments.[17]

In our study, the triple therapy proposed in the Maastricht consensus [Clarithromycin, Amoxicillin, a PPI] achieved a mean per protocol eradication rate of 92% and the quadruple therapy with a PPI, Metronidazole, Amoxicillin, and bismuth citrate achieved a mean per protocol eradication rate of 84% and a significant difference between eradication rates of these two regimens resulted (p: 0.046) which may be due to better compliance with the triple regimen or a lower rate of clarithromycin resistance compared to metronidazole resistance. According to the literature metronidazole resistance (up to 46.8% in Asian ethnicity)[13,14] has been shown as not having a significant impact on treatment failure in multiple drug regimens especially when used in higher doses, but in our study we used the standard dosage so we didn't decrease its resistance effect. Clarithromycin resistance ranged from 3.4 to 11.5 % which is predictive of treatment failure[18,19,20] so because of its main role in the treatment of *H. pylori* we also suggest much more cautiously the use of clarithromycin in other therapeutic fields to keep its low resistance rate.[21,22] According to guidelines of *H. pylori* treatment,[16,4,23] the most appropriate therapy should be based on cost, safety, tolerability and compliance besides local antibiotic resistance rate and it was reported that the lowest cost rates were achieved by regimens associated with cure rates greater than 95%[4,16,24] (such as our triple regimen,

92%).

In conclusion, this study also recommends the triple regimen with Clarithromycin, Amoxicillin and a PPI for first line treatment of *H. pylori* infection and the quadruple regimen with a PPI, bismuth citrate, amoxicillin and metronidazole in whom triple therapy has failed. These results also agree with the Maastricht consensus recommendations.[2,5]

ACKNOWLEDGEMENT

The authors acknowledge the assistance of the attending physicians in the pathology ward and the endoscopy ward of Emam Khomeini Hospital.

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