Comparison of Ciprofloxacin-Based Triple Therapy with Conventional Triple Regimen for *Helicobacter pylori* Eradication in Children

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Abstract- *Helicobacter pylori* infection is a prevalent disease among Iranian children. The purpose of this study was to compare the effect of ciprofloxacin and furazolidone on eradicating *helicobacter pylori* in Iranian children in combination with amoxicillin and omeprazole. In this cohort study, *helicobacter pylori* infection was confirmed by gastroscopy, rapid urease test or pathologic assessments. A total of 66 children were randomly enrolled; based on the random number table, and were divided into two groups; first, a combination regimen consisting of ciprofloxacin, amoxicillin, and omeprazole; second, a three-medication regimen consisting of amoxicillin, furazolidone, and omeprazole. The effect of both medical regimens on the successful eradication of *helicobacter pylori* infection was assessed and compared. Chi-square test was used for evaluating the association between quantitative variables. All comparisons were made at the significance of $P<0.05$. Endoscopic tests prior to initiating treatments showed that 66.7% of the patients had a degree of nodularity while peptic ulcer was only observed in one patient. One month after the end of the treatments, eradication of the *helicobacter pylori* infection was reported 87.9% (29/33) in the first group (CAO) and 60.6% (20.33) in the second group (FAO) ($P=0.011$). It appears that a major advantage of our proposed regimen over others is a lack of wide use of fluoroquinolones for treating children's diseases. Given FDA's recommendation about the possibility of prescribing ciprofloxacin for infected patients with multidrug resistance, we can use the regimen proposed in this study in patients with resistance to standard treatments.

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Keywords: *Helicobacter pylori*; Children; Eradication; Ciprofloxacin; Furazolidone

Introduction

Helicobacter pylori (HP) is a gram-negative bacterium responsible for the most prevalent type of chronic bacterial infection observed in all ages across the globe (1-2). In 1983, Warren and Marshal discovered *helicobacter pylori*. Further studies showed that gastrointestinal infection with HP is the main causing agent for peptic ulcer. This organism contributes to the development of chronic gastritis, MALT lymphoma and gastric adenocarcinoma (3-7).

Based on various studies, the prevalence of HP infection is 30-40% in Iran and 80% in children with chronic abdominal pain related to peptic diseases (8). Infliction of the disease occurs at a young age and is less prevalent in developed countries compared to the developing ones.

In children, HP might cause malnutrition, anemia, and gastrointestinal disorders and therefore delay in physical growth (9).

Despite the progress in antimicrobial treatments, a proper regimen for eradicating HP has not yet been introduced. In fact, a proper medical regimen depends on numerous different variables, including age at contracting the infection, household population, socioeconomic status, ethnicity, immigration from regions with high prevalence and also the infection status of other family members (10). Therefore, we should also be a prospect for treatment failures (11). The selected medical regimen varies in different regions

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based on the drug resistance of each region's HP; therefore, it is advised that each region is attributed its own medical regimen based on local studies (8). Evidently, the presence of drug resistance prior to the start of HP treatments affects results of the treatment in a negative way (12). If medical regimen consisting of metronidazole fails, the alternative medical regimen consists of clarithromycin; however, this medication is expensive, and resistance against it is rising (13). Ciprofloxacin and furazolidone are easily available inexpensive medications that are highly effective in eradicating the bacteria. New studies have shown that HP is much less resistant to ciprofloxacin than to metronidazole and clarithromycin (14-15). Given that HP resistance to metronidazole and clarithromycin is rising, researchers have also considered alternative medical regimens such as the one containing fluoroquinolones (16-17). Nowadays, various studies have reported the safety of prescribing this medication to infants and children (18-19).

Given the high costs of medical care and the probable recurrence of the infection or development of resistance to medication, finding a proper medical diet to eradicate the organism would be a major step in helping patients. We thus intend to compare two medical treatments in this study; first, a regimen consisting of ciprofloxacin, amoxicillin, and omeprazole and second, a three-medication regimen consisting of amoxicillin, furazolidone, and omeprazole; our study population is comprised of children between the ages of 7 and 15 infected with *helicobacter pylori* admitted to the children's medical center in 2011-12; we intend to evaluate the effect of replacing furazolidone with ciprofloxacin in treating these children.

Materials and Methods

The present study was conducted after approval of the ethics committee of Tehran University of Medical Sciences.

The study population is comprised of the patients admitted to the gastroenterology clinic of the children's medical health center from March 2012 until February 2014. Inclusion criteria consisted of having undergone endoscopy to assess chronic abdominal pain and the possibility of a peptic disease and having HP infection diagnosis confirmed through a rapid urease test in the gastric mucosa sample or a pathology test. Exclusion criteria included having a history of the gastroduodenal disease or being previously treated with proton-pump inhibitors or receiving empirical anti-HP treatments and not having the parents' consent for participating in the study. Sixty-six patients were ultimately included in the study and were divided into two groups based on the random number table; first, the group receiving ciprofloxacin, amoxicillin, and omeprazole; second, the group receiving amoxicillin, furazolidone, and omeprazole. In the first group, ciprofloxacin was used in two divided 30 mg/Kg/day doses over a period of one week, amoxicillin in two divided 50 mg/Kg/day doses over one week and omeprazole in two divided 1 mg/Kg/day doses over a four-week period; in the second group under treatment, furazolidone was used in a 6 mg/Kg/day single-dose over a period of one week, amoxicillin in two divided 50 mg/Kg/day doses over one week and omeprazole in two divided 1 mg/Kg/day doses over a four-week period. Within one month of completing the treatments, the patients were assessed with regard to their medical responses by stool antigen test. The parents of the children who participated in this study and the laboratory director who conducted the stool antigen test were blind to children's grouping. Cases with a negative stool antigen test result were considered to have given the proper medical response. Patients were randomly selected.

The data of each patient was collected in a questionnaire for personal information such as children's age, sex, clinical symptoms of the disease, laboratory test results, endoscopic findings, pathological findings and response rate to treatment.

Once the questionnaires were collected, data were analyzed using the statistical software SPSS version 19. Quantitative data were reported in the form of Mean±Standard Deviation while qualitative data were reported as frequencies. In these cases, the Chi-squared test was used for evaluating the association between the qualitative data. Comparisons were made at a significance level of $P<0.05$.

Results

This study showed that HP infection is observed 1.9 times more in boys than in girls given that 43 of the patients (65.2%) were boys.

The mean age was 9.69±2.91 years for female patients, 9.51±2.82 years for males and 9.57±2.83 years overall. Nevertheless, no significant statistical difference was observed between the patients' mean age in the two groups ($P=0.804$).

As the patients were randomly divided into the two groups, out of 43 patients, 69.7% (23) of those treated with furazolidone and 60.6% (20) of those treated with

ciprofloxacin were males; however, the gender difference between the two groups was not statistically significant (*P*=0.606).

Table 1 shows a comparison of the frequency of clinical and endoscopic findings in patients. Stool antigen test was used to verify the outcome of the treatment; in other words, a positive result showed failed treatment and a negative result showed eradication of the HP infection.

Table 1. Clinical and endoscopic findings in each of the groups post-treatment

	Ciprofloxacin-based triple therapy	Furazolidone-based triple therapy	Total	*P*-Value
Vomiting	6 (18.2%)	5 (15.2%)	11 (16.7%)	1.000
Abdominal pain	21 (63.6%)	19 (57.6%)	40 (60.6%)	0.614
Iron deficiency anemia	3 (9.1%)	2 (6.1%)	5 (7.6%)	1.000
GI bleeding	2 (6.1%)	4 (12.1%)	6 (9.1%)	0.672
Positive Urease test	25 (75.8%)	22 (66.7%)	47 (71.2%)	0.415
H.Pilory in histology	19 (57.6%)	24 (72.7%)	43 (65.2%)	0.196
Doudonal ulcer	7 (21.2%)	8 (24.2%)	15 (22.7%)	1.000
Nodularity	18 (54.5%)	26 (78.8%)	44 (66.7%)	0.37

One month after the treatment had ended, results of the stool antigen test reported 87.9% of the group treated with ciprofloxacin and 60.6% of the group treated with furazolidone negative, i.e. they were considered to have recovered from this infection; these differences were statistically significant (*P*=0.011).

Table 2 compares the incidence of stool antigen with respect to positive *helicobacter pylori* in each of the groups post-treatment.

Table 2. The incidence of stool antigen with respect to positive *helicobacter pylori* in each of the groups post-treatment

			Treatment group		Total
			Furazolidone-based triple therapy	Ciprofloxacin-based triple therapy	
stool antigen test for HP infection	**Negative**	**N**	20	29	49
		(%)	60.6%	87.9%	74.2%
	Positive	**N**	13	4	17
		(%)	39.4%	12.1%	25.8%
Total		**N**	N	33	66
		(%)	(%)	100.0%	100.0%

Discussion

The present study was conducted on patients admitted to the gastroenterology ward and clinic of Tehran's children's medical center. Endoscopy, rapid urease testing of a sample of gastric mucosa and evaluation of the pathology reports were used for the definite diagnosis of the infection. Sixty-six patients whose diagnosis of HP infection was confirmed were randomly enrolled in two groups of treatments with ciprofloxacin, amoxicillin, and omeprazole, or amoxicillin, furazolidone and omeprazole. Review of the literature indicated that even though amoxicillin, furazolidone, and omeprazole are routine medications for treating HP infection in children, no studies have been conducted until now on the use of ciprofloxacin, amoxicillin, and omeprazole in treating this infection in children. Studies conducted on adults, on the other hand, indicate the effectiveness of fluoroquinolones on the eradicating this infection (20-22). According to prescription guidelines, ciprofloxacin is recommended for children and adolescents between 5 and 17 years old at two oral divided doses of 10-30 mg/Kg/day (maximum dose allowed 5.1 grams/day); several studies have demonstrated its safety for children and infants (18,19,23,24).

This study indicated that HP infection is observed 1.9 times more in boys than in girls given that from among all the patients, 43 (65.2%) were boys, and 23 (34.8%) were girls. This finding is in line with results of the studies by Sykora (25) and Mahalanabis (26). The mean age was 9.69±2.91 years for female patients,

9.51±2.82 years for males and 9.57±2.83 overall. This rate was relatively similar to the mean age reported by Najafi (17); however, it is lower than the mean age reported by Francavilla (27) and Lionetti (28) and higher than the one reported by Haghi-Ashtiani (29). It is important to keep in mind that we only evaluated a few patients and thus the mean age reported might be different from the real statistics.

In the present study, distribution of male patients infected with HP in the group treated with furazolidone was approximately 1.15 times more than that in the group treated with ciprofloxacin even though HP infection was distributed equally in both groups. This difference can be attributed to the random inclusion of 3 more male patients in the group treated with furazolidone; however, the gender difference between the two groups was not statistically significant and thus does not negatively affect the study results.

Endoscopic tests conducted on the patients prior to treatment indicated the presence of nodularity in 66.7% of the patients. In the studies conducted by Luzza (30) and Prasad (31), however, the presence of nodularity was observed in less than 50% of the patients infected with HP. The delay in admission to the hospital and diagnosis of patients under study might have caused high incidence of this infection in the present study compared to other studies; however, given the unavailability of health information and medical records of the patients prior to admission to the children's medical center, this hypothesis cannot be verified.

Based on clinical findings of the tests conducted on the patients, abdominal pain occurred in 60.6% of the patients, persistent nausea in 16.7%, gastrointestinal bleeding in 9.1% and iron deficiency anemia in 7.6%. According to the studies by Tindberg (32) and Cherian (33), abdominal pain was reported among the most prevalent symptoms ranging from 63% to 82.4%.

According to the study conducted by Cherian (33), nausea was reported in 14.1% of the cases. In the study by Doroudian (34), on the other hand, gastrointestinal bleeding occurred in 9.8% of the patients with HP infection and iron deficiency anemia in 3.4%.

Based on the patients' endoscopic test results, gastrointestinal bleeding reportedly occurred in only one case in our study population. In the study by Luzza (30), ulcer occurred in only 1% of the patients.

Based on the results of the stool antigen test one month after treatment, 87.9% of the group treated with ciprofloxacin and 60.6% of the group treated with furazolidone were reported negative (P=0.011). A study by Kazemi (35) showed that stool antigen test had a sensitivity of 96%, specificity of 83%, positive predictive value of 98%, and negative predictive value of 96% for HP infection; therefore, we can consider the cases that were reported negative in the stool antigen test as recovered from this infection.

A review of the literature indicates that this study is the first report on regimens containing ciprofloxacin for treating children with HP infection. In Amini's study (36), ciprofloxacin regimen's rate of success in eradicating HP infection in adults was reported 67.1%. Dresner's study (37) conducted in the USA demonstrated that using a combination regimen of ciprofloxacin, omeprazole, and bismuth increased eradication rate of HP to 76%; the study conducted by Finizio (21) and Wong (22) demonstrated that the 10-day-long regimen of levofloxacin, amoxicillin, and PPI led to successful eradication of HP in over 90% of adults; meanwhile, the four-medication regimen consisting of tetracycline, furazolidone, bismuth and a proton-pump inhibitor could only successfully eradicate less than 75% of HP infections.

In their comparison between the three-medication regimen consisting of ciprofloxacin and a low dose of furazolidone and the usual four-medication regimen consisting of tetracycline, metronidazole, bismuth and omeprazole for eradicating HP infection in adults, Hashemi *et al*., (20) demonstrated that 18.8% of patients treated with ciprofloxacin developed side-effects, particularly nausea and vomiting. The HP eradication rate was 72.5% for the three-medication group (CFO) and 80% for the four-medication group (TMBO).

Not using fluoroquinolones for treating children's diseases might be the major advantage of our regimen of ciprofloxacin; nevertheless, this hypothesis cannot be explained by findings of reports on microbial resistance in Iran. According to Rafeei (38) and Kohantab (39), among Iranian patients, the rate of ciprofloxacin resistance was reported 7% and 4.7% and the rate of furazolidone resistance 9% and 9.4%, respectively. Learning about the medication resistance rate can significantly contribute to the selection of empirical treatment for patients resistant to treatments. Fock (40) reported that the rate of eradication of infections was 87% in the three-medication treatment containing omeprazole, amoxicillin, clarithromycin, 80% in the one containing omeprazole, amoxicillin and metronidazole, and 85% in the one containing omeprazole, metronidazole, and clarithromycin. This study indicated that metronidazole resistance existed in 34% of the patients prior to initiating the treatment, which was identified as a major cause of treatment failure in the

group receiving omeprazole, amoxicillin, and metronidazole, but it did not affect the failure of the two other medical regimens. However, in the study conducted by Khademi *et al*., (41), resistance to clarithromycin, metronidazole and erythromycin were 15.3%, 55.1% and 6.4% in patients with *helicobacter pylori* infection.

Given FDA's recommendation about the possibility of prescribing ciprofloxacin for infections in children with multidrug resistance, we can use the regimen introduced in the present study for patients who are resistant to standard treatments.

Given the resistance of HP to antibiotics, which is caused by the non-indicated use of antibacterial medications in our society, it is crucial to culturally educate and inform the general public about the risks associated with indiscriminate use of these medications.

The three-medication regimen consisting of furazolidone, amoxicillin, and omeprazole is an approved medical treatment with a high success rate for eradicating HP infection in children. Nevertheless, this study shows that consuming the antibiotics ciprofloxacin and amoxicillin alongside omeprazole is highly valuable as HP is not yet resistant to it. Therefore, these antibiotics alongside omeprazole are recommended for successful eradication of HP in regions where the resistant infection is suspected.

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