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Ornidazole-based sequential therapy is not effective in *Helicobacter pylori* eradication in children

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Background/aims: *Sequential therapy is one of the recent answers given to the problem of increasing antibiotic resistance and decreasing eradication rates of Helicobacter pylori infection. The aim of this study is to compare the ornidazole-based sequential therapy with the standard triple therapy in Helicobacter pylori eradication.* ***Materials and Methods:*** *Children aged 4-18 years diagnosed with Helicobacter pylori infection based on histology and at least one of ^{13}C urea breath test and rapid urease test positivity were included in the study. Children were randomized to standard triple therapy with amoxicillin, clarithromycin, and lansoprazole for 14 days and sequential therapy with amoxicillin and lansoprazole for the first 5 days and clarithromycin, ornidazole and lansoprazole for another 5 days in 2:3 randomization. At the end of the treatment, families were contacted by phone, and side effects of and the compliance to the treatment were noted. Patients were requested to do ^{13}C urea breath test 6-8 weeks after the treatment.* ***Results:*** *Sixty-one children were included for the final analysis. Per-protocol eradication rates were 48.6% for sequential therapy group and 54.2% for standard triple therapy group. Intention to treat eradication rates were 40.9% and 46.0%, respectively. There were no differences between eradication rates in the two study groups. Side effect rates were also similar between the two groups.* ***Conclusions:*** *Ornidazole-based sequential therapy did not show any superiority compared to the standard triple treatment in children with Helicobacter pylori infection.*

Key words: *Helicobacter pylori,* sequential therapy, children, eradication

Ornidazol temelli ardışık tedavi çocuklarda *Helicobacter pylori* eradikasyonunda etkili değildir

Giriş ve Amaç: *Ardışık tedavi, Helicobacter pylori eradikasyon oranlarındaki azalma ve artan antibiyotik direnci sorununa karşı verilen güncel bir yanıttır. Bu çalışmanın amacı, Helicobacter pylori eradikasyonunda ornidazol temelli ardışık tedaviyle standart üçlü tedaviyi karşılaştırmaktır.* ***Gereç ve Yöntem:*** *Histoloji ve ^{13}C üre nefes testi ya da hızlı üreaz testi pozitifliğinden en az birisinin varlığıyla Helicobacter pylori infeksiyonu tanısı konulan 4-18 yaş arası çocuklar çalışmaya dahil edilmiştir. Çocuklar 14 gün boyunca standart üçlü tedavi (amoksisilin, klaritromisin ve lansoprazol) ya da 10 gün ardışık tedavi (ilk 5 gün amoksisilin ve lansoprazol, ikinci 5 gün klaritromisin, ornidazol ve lansoprazol) alacak şekilde 2:3 oranında iki gruba randomize edilmiştir. Tedavi tamamlandıktan sonra ailelere telefonla ulaşılarak ilaç yan etkileri ve tedavi uyumu sorgulanmıştır. Tedaviden 6-8 hafta sonra ^{13}C üre nefes testi tekrarlanarak eradikasyon değerlendirilmiştir.* ***Bulgular:*** *Çalışmanın son analizine 61 çocuk dahil edilmiştir. Per-protokol eradikasyon oranları ardışık tedavi için %48.6 ve standart tedavi için %54.2 olarak bulunmuştur. Tedavi amacına yönelik analizde eradikasyon oranları sırasıyla %40.9 ve %46.0 olarak bulunmuştur. Çalışma grupları arasında anlamlı fark saptanmamıştır. Yan etki oranları iki grupta da benzer bulunmuştur.* ***Sonuç:*** *Ornidazol temelli ardışık tedavi Helicobacter pylori eradikasyonunda, standart üçlü tedaviyle benzer biçimde etkili bulunmamıştır.*

Anahtar kelimeler: *Helicobacter pylori,* ardışık tedavi, çocuk, eradikasyon

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INTRODUCTION

Decreasing efficiency of *Helicobacter pylori (H. pylori)* eradication treatments has been well documented (1). This decrease is especially clear in countries with high clarithromycin resistance like Mediterranean countries such as Spain, France, Italy, and Turkey. Increasing antibiotic resistance of *H. pylori* necessitates novel treatments. One of the recent answers given to this problem is the sequential therapy.

Sequential therapy consists of a proton-pump inhibitor and amoxicillin for the first 5 days and proton pump inhibitor, clarithromycin and a nitroimidazole (mainly tinidazole) for another 5 days. The goal of this therapy is to overcome the clarithromycin resistance (2). Sequential therapy shows higher eradication compared to the standard triple therapy in both adults and children (3). Whether the same results are valid for other nitroimidazoles is not known.

The aim of this study is to compare the efficacy of standard triple therapy and ornidazole-based sequential therapy in children with *H. pylori* infection.

MATERIALS and METHODS

This study was carried out in pediatric gastroenterology unit between October 2008 and March 2010. Children aged 4-18 years with gastrointestinal symptoms who were diagnosed with *H. pylori* infection based on histology and at least one of ^{13}C urea breath test (^{13}C UBT) and rapid urease test positivity were included in the study. Children who were previously treated for *H. pylori* and had taken any antibiotic or any gastric acid inhibitory treatment within one month prior to the study were excluded. Children with the diagnosis of any condition that might affect the absorption of drugs such as celiac disease or Crohn's disease were also excluded.

Upper gastrointestinal endoscopy was performed with Olympus GIF Q260 videoendoscope (Olympus Optical, Tokyo, Japan) after informed consent was obtained. During gastroscopy, morphological endoscopic findings were noted. In each patient, two biopsies were obtained from antrum for the rapid urease test (CLOtest; Kimberly-Clark, Draper, UT, USA) and histological examination. Corpus, esophagus, and duodenal biopsies were also obtained. Gastric biopsy specimens were stained with hematoxylin and eosin and modified Giemsa and were examined for the presence of *H. pylori*. Gastritis was graded according to the updated Sydney histological scoring system (4).

Children were randomized to standard triple therapy (STT) and sequential therapy (ST) groups in 2:3 randomization. STT consisted of amoxicillin (50 mg/kg/day), clarithromycin (15 mg/kg/day), and lansoprazole (1 mg/kg/day) for 14 days. Sequential therapy consisted of amoxicillin (50 mg/kg/day) and lansoprazole (1 mg/kg/day) for the first 5 days and clarithromycin (15 mg/kg/day), ornidazole (30 mg/kg/day) and lansoprazole (1 mg/kg/day) for another 5 days. At the end of the treatment, families were contacted by phone and side effects of and the compliance to the treatment were noted. Patients not taking more than 90% of the prescribed drugs were accepted as non-compliant. In order to detect eradication, the patients were requested to do ^{13}C UBT 6-8 weeks after the treatment (5).

Informed consent was obtained from the parents. This study was approved by the ethics committee of Hacettepe University. Chi-square test was used to compare the demographic variables, eradication rates, and side effects of both treatments.

RESULTS

Seventy-two children were included in the study. Celiac disease was diagnosed in three children (two in ST, and one in STT group) and they were excluded. Eight children (five in ST and three in STT) were lost to follow-up so repeat UBT was not performed.

Sixty-one children (30 female, 31 male) were included for the final analysis. Twenty-four children were randomized to STT and 37 children were randomized to ST groups. Demographic features, endoscopic and histopathological findings were compared between the two groups (Table 1). There were no differences between the two groups in terms of gender and age. Endoscopic and histopathological findings were similar between two groups except antral nodularity which was more common in ST group (p=0.02).

Per-protocol eradication rates were 48,6% (18/37) for ST group and 54,2% (13/24) for STT group. Intention to treat eradication rates were 40,9% (18/44) for ST group and 46,0% (13/28) for STT group. There were no significant differences in eradication rates between the two study groups.

Twenty-eight side effects were noted in 18 patients (Table 2). Number and type of side effects we-

Table 1. Comparison of study groups in terms of demographic variables, endoscopic and histopathological findings

	Standard triple therapy (n=24)	Sequential therapy (n=37)	P value
Gender (F/M)	11/13	19/18	0,6
Age	12,6±3,2	12,2±2,8	0,6
Antral nodularity	13 (54,2%)	31 (83,8)	0,02
Antral hyperemia	6 (25,0%)	10 (27,0%)	0,8
Corpus hyperemia	4 (16,7%)	9 (24,3%)	0,4
Duodenal ulcer	5 (20,8%)	8 (21,6%)	0,9
Duodenogastric reflux	3 (12,5%)	3 (8,1)%	0,5
Esophagitis	1 (4,2%)	3 (8,1%)	0,5
Pangastritis	3 (12,5%)	3 (8,1%)	0,5
Mildgastritis	8 (33,3%)	16 (43,2%)	0,7
Moderate gastritis	13 (54,2%)	17 (45,9%)	
Severe gastritis	3 (12,5%)	4 (10,8%)	

F: Female. M: Male

Table 2. Side effect profile of different treatment protocols

Side effect	Standard treatment (n, %)	Sequential treatment (n, %)	P value
Metallic taste	1 (4,2)	2 (5,4)	NS
Abdominal pain	4 (16,7)	6 (16,2)	NS
Dirrhea	3 (12,5)	2 (5,4)	NS
Nausea	1 (4,2)	6 (16,2)	NS
Vomiting	0 (0)	1 (2,7)	NS
Rash	0 (0)	1 (2,7)	NS
Itching	0 (0)	1 (2,7)	NS
Total number of patients experiencing side effects	11 (29,7)	7 (29,1)	NS

NS: Non significant

re not different between the two groups. The number of patients with side effects did not differ between the groups; there were 7/24 (29,1%) children in STT and 11/36 (29,7%) children in ST groups with side effects. Most frequent side effects were abdominal pain and diarrhea in the STT and abdominal pain and nausea in the ST groups.

DISCUSSION

H. pylori treatment has become a greater challenge over time largely because of increasing antibiotic, especially clarithromycin, resistance (1). Although clarithromycin resistance is increasing, standard triple therapy with amoxicillin, clarithromycin, and proton-pump inhibitor remains the most commonly chosen treatment method (1, 6). Eradication rates decrease as clarithromycin resistance increases. In PERTH trial, the eradication rate was 60,5% in 157 children treated with standard triple therapy. Eradication rate in the presence of a clarithromycin-resistant strain drops to 48%, while it remains 70,5% in the presence of a clarithromycin-sensitive strain (6). Dramatic decrease in eradication rates led the investigators search for new therapies. Sequential therapy seemed to be promising, and results from adult studies have shown that it was superior to other standard triple therapy (7). Three studies from our center, including the current one, strikingly showed that the eradication rate with standard triple therapy has dropped from 75,5% in 2001 to 54,2% in 2009. In the study by Özçay et al. performed between 2001 and 2002, the eradication rate for standard triple therapy was 75,5% (8). Between 2003 and 2006, Usta et al. (9) compared the short-duration (7 days) and long-duration (14

days) standard triple therapies. They found 55,8% and 60,5% eradication rates, respectively.

It has been suggested that ST might have two separate way of action; first, in the initial five days of therapy proton-pump inhibitor and amoxicillin lowers the bacterial load which improves the efficacy of antibiotics in the second part of therapy. Second, by disrupting the cell wall of *H. pylori,* amoxicillin prevents the development of efflux channels for clarithromycin (2).

Although it seems attractive to use sequential therapy in order to increase eradication rates, there are some limitations greatly acknowledged by Gisbert et. al (3). There are a few studies performed in children investigating the role of sequential therapy. Francavilla et al. (10) demonstrated that the eradication rate of *H. pylori* infection was significantly higher in sequential therapy (97,3%) versus standard triple therapy (75,7%) in 87 children. Lionetti et al. (11) found an overall eradication rate of 82,5% in 40 children. Lerro et al. (12) compared sequential therapy to amoxicillin, omeprazole and tinidazole combination therapy in *H. pylori* eradication. They randomly assigned 50 children into two therapy groups. Eradication rate with sequential therapy was 92%, whereas it was 80% in the second therapy group. The difference between the two groups was not significant. Kalach et al. (13) showed that the eradication rates were similar in standard (80%) and sequential therapy (84.6%) groups in children infected with *H. pylori.* In a recent study from Poland, sequential therapy resulted in higher eradication rates compared to standard triple therapy (14). However, Yang and Sheu (15), using metronidazole instead of tinidazole in sequential therapy, did not show superiority in terms of eradication rates compared to standard triple therapy. Apart from Kalach and Yang's studies, tinidazole was the primary antibiotic used in sequential therapy, and in Lerro's study tinidazole was included in the standard triple therapy. Various treatment protocols of these studies make the comparison difficult. Most studies were performed in Southern European countries like Italy and France where the clarithromycin resistance is as high as in Turkey. The main reason for the difference in the eradication rates might be the use of ornidazole in our study instead of tinidazole which is not found in our country. Ornidazole has the same antibacterial activity spectrum as metronidazole and tinidazole, however, it has much longer half life which makes the two daily dosage possible (16). In vitro studies have shown that MIC values of ornidazole against anaerobic bacteria are either similar or slightly higher than tinidazole and similar or slightly lower than metronidazole. Of these three drugs, tinidazole seems to have better pharmacokinetic and pharmacodynamic profile (17).

A small study from Turkey indicated that sequential treatment with metronidazole-based regimen might be effective in children, especially in those who are sensitive to clarithromycin (18). However, by using the same regimen, a novel study from Turkey including 113 children, did not show any superiority of sequential treatment over standard therapy (19). Although both studies have found clarithromycin resistance rate to be 25%, Ertem et al. did not find any advantage of the sequential treatment. Eradication rate reached only 60,5% in this study. In the former study, eradication rate with sequential regimen was 93,7% (18). Bontems et al. showed that sequential treatment is effective for eradicating *H. pylori* in children except for clarithromycin-resistant strains. They stated that sequential treatment could be used as a first-line therapy only in areas with a low clarithromycin resistance rate (i.e. <20%) (20).

In this current study, the eradication rate for standard therapy was 54,2%. The ornidazole-based sequential therapy has just reached an eradication rate of 48,6%. In view of these findings, sequential therapy with ornidazole has no superiority over the standard therapy and cannot be accepted as alternative.

Small patient number is an important limitation of our study; however, this is due to an interim analysis demonstrating that the eradication rates were not different between the two groups. For this reason, the study was discontinued. Lack of antibiotic resistance data is another drawback of the study.

In conclusion, effectiveness of sequential therapy with amoxicillin plus lansoprazole for the first five days and lansoprazole, clarithromycin, and ornidazole for the second five days is similar to the standard triple therapy for eradicating *H. pylori* in treatment-naive children and should not be used in *H. pylori* treatment.

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