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The Effectiveness of a Sequential Helicobacter Pylori Eradication Regimen on the Severity of Clinical Symptoms in Children with Chronic Gastritis: A Randomized Clinical Trial

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Abstract

Background: The effectiveness of eradicating Helicobacter pylori infection in improving the symptoms of chronic gastritis has been examined; however, the results of the studies have been contradictory, especially in childhood. This study aimed to compare the clinical effectiveness of sequential Helicobacter pylori eradication treatment and proton pump inhibitor alone in children with chronic Helicobacter pylori-positive gastritis.

Methods: This randomized double-blinded clinical trial was conducted on 84 children aged 5 to 15 years suffering from Helicobacter pylori-associated active chronic gastritis. The patients in the experimental group received sequential therapy including omeprazole, amoxicillin, clarithromycin, and metronidazole; and those in the control group only received omeprazole. Before the intervention, and 2 and 4 months after it, the severity of clinical symptoms was assessed.

Results: After therapeutic regimens, the intervention group was found to have a significantly higher decrease in the severity grades of some symptoms including heartburn, gastroesophageal reflux, and abdominal pain in the epigastric area as compared to the control group ($P<0.05$). The assessment of the frequency of clinical symptoms in the intervention and control groups also indicated a greater reduction in epigastric pain in the group treated with Helicobacter pylori eradication as compared to the control group ($P<0.05$).

Conclusion: Prescribing a sequential Helicobacter pylori eradication regimen can lead to reducing the severity of clinical symptoms in children suffering from chronic gastritis.

Key Words: Abdominal Pain, Children, Chronic Gastritis, Epigastric Pain, Gastroesophageal Reflux, Helicobacter Pylori, Heartburn.

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1- INTRODUCTION

Chronic gastritis is a multi-stage, progressive, and lifelong inflammation of the gastric mucosa, which may lead to structural changes in the gastric glands (1). Chronic gastritis usually begins in childhood as a simple chronic superficial inflammation with the simultaneous presence of acute neutrophilic inflammation of varying degrees (2). Gastritis gradually progresses over years and decades to atrophic gastritis, characterized by the loss of normal mucosal glands (3). Chronic gastritis has been known and studied since the early decades of the 20th century, but it gained more attention in 1982 after the discovery of Helicobacter pylori by Warren and Marshall (4). This bacterium has been found to be the cause of gastritis in the vast majority of cases, a possible exception being gastritis of autoimmune origin (5). As a result, chronic gastritis can be treated by eradicating Helicobacter pylori, which even leads to the normalization of gastric mucosa (6).

Infection with Helicobacter pylori is widespread throughout the world and it reaches more than 80% in developing countries and more than 50% in developed countries; however, diseases related to this bacterium are observed in only 10-20% of these populations (7). Researchers consider this difference in pathogenicity to be related to two factors including those factors that depend on the host (the genetic and immunological characteristics of people, smoking, and non-steroidal anti-inflammatory drugs which they call the risk of contracting the disease) and the factors that depend on bacteria (different strains and types of bacterium) (8). Up to 90% of people infected with Helicobacter pylori never experience symptoms or complications. However, infected people have a 10-20% lifetime risk of developing peptic ulcers (4). Acute Helicobacter pylori infection may present as acute gastritis, however, in some cases, it may turn into chronic gastritis (9).

Adopting appropriate treatments in digestive tract diseases is very helpful in formulating treatment strategies because of preventing other disorders and obtaining the best results (10, 11). Until now, several clinical studies have been conducted to investigate the effectiveness of the eradication treatment of Helicobacter pylori infection in improving the symptoms of patients with gastritis; however, the results of the studies have been contradictory. In adults, treatment of Helicobacter pylori infection is recommended only for patients with active gastric or duodenal ulcers (12, 13). According to this guideline, Helicobacter pylori treatment is recommended in children with duodenal or gastric ulcers, mucosa-associated lymphoid tissue (MALT) lymphoma, and atrophic gastritis with metaplasia. Treatment of Helicobacter pylori-associated gastritis is also left to the physician's judgment because there is insufficient evidence to support the initiation or withholding of eradication therapy in this setting (14).

In general, eradication therapy has not yet been approved in children with chronic active gastritis associated with Helicobacter pylori, and studies have reported conflicting results regarding its effectiveness in improving gastritis symptoms. Therefore, the present study was conducted with the aim of comparing the clinical effectiveness of Sequential Helicobacter pylori eradication treatment and proton pump inhibitor alone in children with chronic Helicobacter pylori-positive gastritis in order to be a guide to identify patients who clinically benefit from Helicobacter pylori treatment.

2- MATERIALS AND METHODS

2-1. Design and participants

This randomized double-blinded clinical trial was conducted on 84 children

aged 5 to 15 years suffering from Helicobacter pylori-associated active chronic gastritis referred to Hajar Hospital in Shahrekord, Iran in 2021 and 2022.

2-1.1. Inclusion and exclusion criteria

The main criteria for including the subjects in the study was the rapid urease test (RUT) positivity and its matching with the results of clinical examination, endoscopic report, and pathological findings on gastric tissue samples. Those with the following criteria were not included in the study: the evidence of ulcers or any pathology other than chronic gastritis in the stomach, esophagus, and duodenum, functional abdominal pain, the evidence of Mallet's lymphoma, sideroblastic anemia, immune thrombocytopenia, hiatal hernia, the history of stomach cancer in first degree relatives, parents' lack of consent for the patient's participation in the study, or abandoning drug treatment and lack of follow-up.

2-2. Procedure

In the initial assessment, the baseline characteristics including demographic information (age and gender), history of antibiotic use, duration of abdominal pain, location of abdominal pain, family history of Helicobacter pylori infection, clinical manifestations (the frequency and severity of heartburn, reflux, vague, diffuse abdominal pain, epigastric area and around the navel, vomiting, and indigestion) were determined by interviewing along with physical examinations by a single children's gastroenterologist. The severity of symptoms was graded according to grade zero (no symptoms), grade 1 (mild symptoms with spontaneous improvement and no interference with usual activity and sleep), and grade 2 (severe symptoms without spontaneous improvement and interference with usual activity and sleep). The frequency of symptoms was also graded as zero (no symptoms), grade 1 (occasionally, presence of symptoms less than 2 days per week), grade 2 (common, presence of symptoms 2 days per week), and grade 3 (very common, presence of symptoms 3 days or more per week). The score of each symptom was calculated by multiplying the intensity score and its frequency score; the total score of symptoms was in the range of 0-36 and the score of 0-11 indicated mild symptoms, 12-23 moderate, and 24-36 severe involvement. The results related to endoscopic assessment and pathological findings were also collected by reviewing the patients' hospital-recorded files. Wright-Giemsa staining was used to investigate Helicobacter pylori and hematoxylin and eosin staining was used for histology.

After the initial assessment, patients were divided into two groups using a simple random allocation method. The way of randomization was that 2 cards with letters A and B were placed in front of the patient's parents and they chose one, each letter corresponding to one of the two groups. 1) Group A was treated sequentially for 10 days using omeprazole (Dr. Obidi Pharmaceutical Company, Iran) with the dose of 2 mg/kg/day in two divided doses for 10 days, amoxicillin (Farabi Pharmaceutical Company, Iran) with the dose of 50 mg/kg/day in two divided doses for the first 5 days and then Clarithromycin (Elixir Pharmaceutical Company, Iran) with the dose of 15 mg/kg/day in two divided doses for the second 5 days and Metronidazole (Alborz Pharmaceutical Company, Iran) with the dosage of mg/kg/day in two divided doses for 10 days. The patients then received omeprazole (1 mg/kg/day) in a daily dose alone for 50 days. 2) Group B received only omeprazole (Dr. Obidi Pharmaceutical Company, Iran) with a dosage of 1 mg/kg/day for 60 days. Helicobacter pylori antigen in stool was checked 4-8 weeks after the eradication treatment to ensure the treatment. The

clinical symptoms and endoscopic findings of the patients were re-evaluated after the end of the treatment period. It should be noted that the drugs used and the dosage of the drugs for children were safe and without complications according to the latest children's reference and did not have drug interactions. Also, the children who abandoned drug treatment and did not return for follow-up were excluded from the study. The patient's information form was also kept by the medical secretary and was not disclosed to the physician or researchers.

2-3. Data analysis

The collected data were entered into the statistical software SPSS version 26 and analyzed. Descriptive statistics were presented in the form of mean and standard deviation (for quantitative variables), frequency, and percentage (for categorical variables). Data were analyzed using Chi-square test to compare qualitative variables, and Mann-Whitney test to compare quantitative variables with non-normal distribution or independent t-test for quantitative variables with normal distribution. The level of statistical significance in this study was considered as $p<0.05$.

3- RESULTS

Initially, 84 children were included in the study and were randomly assigned into intervention (n 42) and control (n = 42) groups (**Fig. 1**).

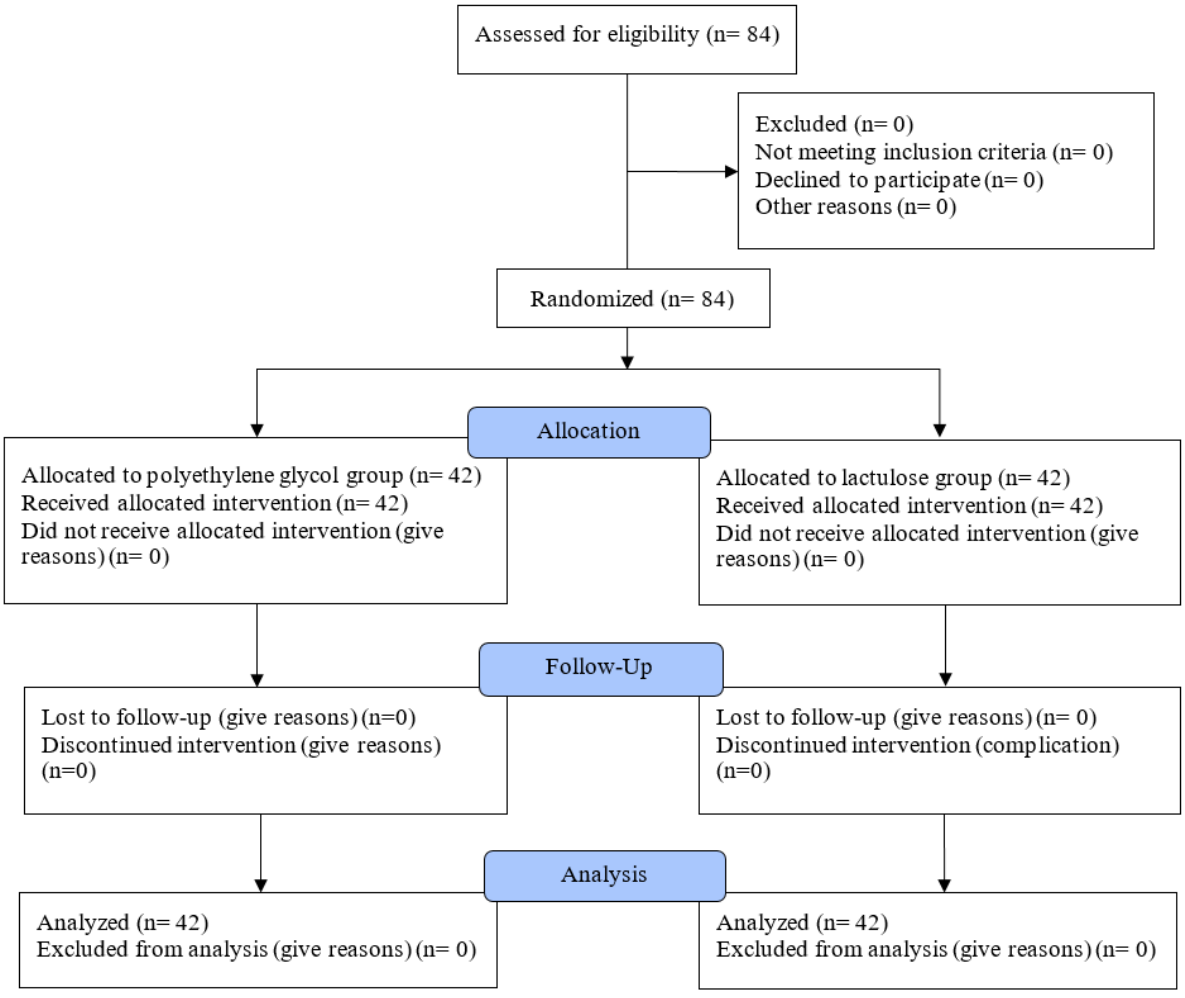

Fig. 1: CONSORT flow diagram of the study population

Of those, all children in the first group completed their treatment protocols, while 4 of the control subjects refused to continue participating in the study or could not be followed up with treatment and therefore were excluded from the study. The patients were assessed before as well as 2 and 4 months after that. As shown in **Table 1**, the two groups were similar in baseline information including gender (p = 0.83), average age (p = 0.68), family history of Helicobacter pylori infection (p = 0.82), history of antibiotic use (p = 0.98) and the duration of gastric pain (p = 0.11).

Table-1: Baseline characteristics of the study population

Characteristics		Intervention group	Control group	P-value
Gender	Male %	20 (47.6)	19 (50.0)	0.83
	Female %	22 (52.4)	19 (50.0)	
History of Helicobacter pylori positivity %		32 (76.2)	29 (78.4)	0.82
History of recent antibiotic use %		33 (76.6)	29 (78.4)	0.98
Mean age (year)	Mean±SD	9.14±2.94	8.87±3.08	0.68
Mean duration of pain (month)	Mean±SD	6.75±4.33	5.42±2.77	0.11

Assessing the clinical manifestations between intervention and control groups before and after therapeutic regimens (**Table 2**) showed significantly lower severity grades of some symptoms including heartburn, gastroesophageal reflux, and abdominal pain in the epigastric area in the former group. The assessment of the frequency of appearing clinical symptoms in the intervention and control groups (**Table 3**) also indicated a greater reduction in epigastric pain in the group treated with Helicobacter pylori eradication as compared to the control group.

4- DISCUSSION

The present study was conducted with the aim of comparing the effect of Helicobacter pylori eradication treatment with no eradication treatment in improving the symptoms of chronic gastritis in children. Children with chronic gastritis with Helicobacter pylori infection were treated in two groups; A (Sequential eradication treatment for 10 days along with omeprazole for 50 days) and B (omeprazole for 50 days alone). The two groups were similar in terms of confounding variables such as age, gender, duration of pain, family history of Helicobacter pylori infection, and history of antibiotic use; and there were no significant differences. The findings showed that after 2 and 4 months of treatment, in the intervention group receiving Helicobacter pylori eradication treatment along with omeprazole, the severity of symptoms, except for diffuse abdominal pain, had a significant improvement as compared to the group that only received omeprazole. Also, there was a significant improvement in the severity of symptoms, except for indigestion and diffuse and vague abdominal pain. The results also showed that the improvement rate of heartburn intensity, reflux intensity, indigestion intensity, and frequency and intensity of epigastric and vague abdominal pain was higher in the group treated with Helicobacter pylori eradication.

The effectiveness of Helicobacter pylori eradication treatment in improving the symptoms of chronic gastritis in children has been evaluated in several studies. In a study by Uc et al., children with indigestion symptoms related to

Helicobacter pylori infection were treated with clarithromycin, amoxicillin, and a proton pump inhibitor regimen for 2 weeks. Finally, it was observed that the average score of the total symptoms of indigestion decreased significantly in 2 to 4 weeks after treatment and 9 months' follow-up (15).

In another study by Ozgenc et al., children with Helicobacter pylori-related chronic gastritis were treated with omeprazole for 2 weeks and clarithromycin and amoxicillin for 1 week.

Their results showed that the pointed treatment led to the eradication of bacteria in 29 children (87.9%). In addition, the symptoms disappeared completely in 27 cases (93.1%) that responded positively to eradication treatment; and there was 1 resistant case (16).

Table-2: Comparing the severity of symptoms before and after the intervention

Characteristics		Intervention group (Mean±SD)	Control group (Mean±SD)	P- value
Heartburn	Before	1.10±1.23	0.50±0.89	0.02
	Two months later	0.00±0.00	0.05±0.23	0.04
	Four months later	0.00±0.00	0.11±0.39	0.02
P-value (Intergroup)		<0.001	0.002	-
Reflux	Before	0.90±1.21	0.39±0.79	0.03
	Two months later	0.00±0.00	0.11±0.38	0.02
	Four months later	0.00±0.00	0.13±0.47	0.02
P-value (Intergroup)		<0.001	0.02	-
Nausea	Before	0.38±0.54	0.21±0.41	0.12
	Two months later	0.05±0.22	0.05±0.23	0.51
	Four months later	0.02±0.15	0.05±0.23	0.24
P-value (Intergroup)		<0.001	0.010	-
Dyspepsia	Before	0.33±0.85	0.03±0.16	0.03
	Two months later	0.00±0.00	0.00±0.00	-
	Four months later	0.00±0.00	0.00±0.00	-
P-value (Intergroup)		0.01	0.37	-
Epigastric pain	Before	1.67±0.87	1.89±0.56	0.17
	Two months later	0.05±0.22	0.34±0.63	0.01
	Four months later	0.05±0.22	0.43±0.80	0.01
P-value (Intergroup)		<0.001	<0.001	
Diffuse abdominal pain	Before	0.05±0.31	0.08±0.36	0.68
	Two months later	0.00±0.00	0.03±0.16	0.31
	Four months later	0.00±0.00	0.05±0.32	0.31
P-value (Intergroup)		0.32	0.23	-
Vague abdominal pain	Before	0.32±0.79	0.03±0.16	0.03
	Two months later	0.00±0.00	0.00±0.00	-
	Four months later	0.00±0.00	0.00±0.00	-
P-value (Intergroup)		0.01	0.32	-
Periumbilical pain	Before	1.32±1.06	1.05±0.97	0.33
	Two months later	0.05±0.23	0.10±0.44	0.56
	Four months later	0.08±0.28	0.10±0.44	0.77
P-value (Intergroup)		<0.001	<0.001	-

Table-3: Comparing the number of symptoms before and after the intervention

Characteristics	Time point	Frequency	Intervention group	Control group	P-value (Intergroup)
Heartburn	Before	0	22 (52.4)	28 (73.7)	0.09
		1	17 (40.5)	7 (18.4)	
		2	3 (7.1)	3 (7.9)	
	2 months	0	42 (100)	36 (94.7)	0.22
		1	0 (0.0)	2 (5.3)	
	4 months	0	42 (100)	35 (92.1)	0.10
		1	0 (0.0)	3 (7.9)	
Reflux	Before	0	25 (59.5)	31 (81.6)	0.09
		1	9 (21.4)	3 (7.9)	
		2	8 (19.0)	4 (10.5)	
	2 months	0	42 (100)	35 (92.1)	0.10
		1	0 (0.0)	3 (7.9)	
	4 months	0	42 (100)	35 (92.1)	0.10
		1	0 (0.0)	3 (7.9)	
Nausea	Before	0	27 (64.3)	31 (81.6)	0.08
		1	15 (35.7)	7 (18.4)	
	2 months	0	40 (95.2)	36 (94.7)	0.99
		1	2 (4.8)	2 (5.3)	
	4 months	0	40 (97.6)	36 (94.7)	0.23
		1	0 (0.0)	2 (5.3)	
		2	1 (2.4)	0 (0.0)	
Dyspepsia	Before	0	35 (83.3)	37 (97.4)	0.06
		1	7 (16.7)	1 (2.6)	
	2 months	0	42 (100)	38 (100)	-
	4 months	0	42 (100)	38 (100)	-
Epigastric pain	Before	0	6 (14.3)	2 (5.3)	0.01
		1	26 (61.9)	21 (55.3)	
		2	10 (23.8)	15 (39.5)	
	2 months	0	40 (95.2)	27 (71.1)	0.01
		1	2 (4.8)	10 (26.3)	
		2	0 (0.0)	1 (2.6)	
	4 months	0	40 (95.2)	29 (76.3)	0.01
		1	2 94.8)	9 (23.7)	
Diffuse abdominal pain	Before	0	41 (97.6)	37 (97.4)	0.99
		1	1 (2.4)	1 (2.6)	
	2 months	0	42 (100)	37 (97.4)	0.48
		1	0 (0.0)	1 (2.6)	
	4 months	0	42 (100)	37 (97.4)	0.48
		1	0 (0.0)	1 (2.6)	
Vague abdominal pain	Before	0	36 (85.7)	38 (100)	0.03
		1	6 (14.3)	0 (0.0)	
	2 months	0	42 (100)	38 (100)	-
	4 months	0	42 (100)	38 (100)	-
Periumbilical	Before	0	12 (32.4)	9 (42.9)	0.53

Characteristics	Time point	Frequency	Intervention group	Control group	P-value (Intergroup)
pain		1	16 (43.2)	6 (28.6)	
		2	9 (24.3)	6 (28.6)	
	2 months	0	34 (91.9)	20 (95.2)	0.99
		1	2 (5.4)	1 (4.8)	
		3	1 (2.7)	0 (0.0)	
	4 months	0	34 (91.9)	19 (95.0)	0.99
		1	3 (8.1)	1 (5.0)	
Loss of appetite	Before	No	19 (45.2)	24 (63.2)	0.11
		Yes	23 (54.8)	14 (36.8)	
	2 months	No	33 (78.6)	30 (78.9)	0.97
		Yes	9 (21.4)	8 (21.1)	
Weight loss	Before	Yes	38 (90.5)	34 (89.5)	0.99
		No	4 (9.5)	4 (10.5)	
	2 months	No	42 (100)	38 (100)	-
	4 months	No	42 (100)	38 (100)	-

In a study by Ünlüsoy Aksu et al., in 2018, children with functional dyspepsia with Helicobacter pylori infection underwent eradication treatment. After the intervention, Helicobacter pylori was eradicated in 30 patients (61%), and in the group where the bacterium was eradicated, all dyspepsia symptoms improved, but in the group where the bacterium was not eradicated, only 3 symptoms improved. The total score of symptoms in the eradicated group was significantly lower than that in the non-eradicated group (17). Ganga-Zandzou et al. also showed worsening histological features of gastric mucosa in children with persistent Helicobacter pylori colonization and absence of symptoms in a 2-year follow-up. These patients had not received any eradication therapy because they were asymptomatic, and the researchers observed a progressive inflammatory change in this group, especially between the first and second year (18). In the current study, in line with the above studies, the number of improved symptoms was more in the eradication treatment group, and some symptoms such as heartburn, reflux, indigestion, epigastric, and vague abdominal pain improved more in the eradication treatment group. Therefore, although the diagnosis and treatment of Helicobacter pylori infection imposes some costs, it improves the symptoms of the disease and may even prevent the exacerbation of the disease and inflammation, which is recommended to be investigated in future studies.

4-1. Limitations of the study

Limitations of the study include the relatively small sample size, the short follow-up period, and the lack of endoscopic and histological examinations after the treatment period; so, it is recommended that more studies with larger sample sizes and follow-up periods of 1 or 2 years and endoscopic and histological evaluations be done to investigate the macroscopic and inflammatory changes of the gastrointestinal tract.

5- CONCLUSION

According to the results, a significant decrease was observed in the severity of symptoms among the patients receiving Helicobacter pylori eradication treatment along with routine medication (omeprazole). In this regard, the

improvement rates in heartburn intensity, reflux intensity, indigestion intensity, and the frequency and intensity of epigastric and vague abdominal pain were higher in the group treated with Helicobacter pylori eradication.

6- ACKNOWLEDGMENTS

This work was approved by Shahrekord University of Medical Sciences, Shahrekord, Iran. The researchers gratefully thank the patients who participated in this study.

7- ETHICAL CONSIDERATIONS

The study protocol was ethically approved by the ethical committee at Shahrekord University of Medical Sciences with the approval code of IR.SKUMS.MED.REC.1402.015. Before starting the intervention, comprehensive and sufficient explanations regarding the objectives of the research were given to the parents of the patients and their consent and willingness to participate in the research was obtained. The protocol of the study was also registered and approved by the Iranian Registry of Clinical Trials with code: IRCT20230612058464N1.

8- CONFLICT OF INTERESTS

None.

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