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Addition of Clidinium-C to the 14-Day Proton Pump Inhibitor Based Triple Therapy for *Helicobacter pylori* Eradication

Mohammadreza Seyyedmajidi[1], Saba Homapoor[1], Elahe Zanganeh[1], Mohammad Dadjou[1], Shahab Eskandari Nejad[1], Mohammad Hadi Tajik Galayeri[1] and Jamshid Vafaeimanesh[2*]

[1]Golestan Research Center of Gastroenterology and Hepatology-GRCGH, Gorgan, Iran.
[2]Clinical Research Development Center, Qom University of Medical Sciences, Qom, Iran.

Authors' contributions

This work was carried out in collaboration between all authors. Authors MS and JV designed the study, performed the statistical analysis, wrote the protocol. Authors SH and MD managed the analyses of the study. Authors SEN, EZ and MHTG managed the literature searches and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aims: To assess the effect of clidinium-C on *H. pylori* eradication with a triple therapy including omeprazole, clarithromycin and amoxicillin (OCA) in patients with peptic ulcer disease (PUD). Also, to investigate the efficacy and safety of clidinium-C in prevention of drugs' side effects.
Study Design: Prospective double-blinded randomized clinical trial study.
Place and Duration of Study: Department of Internal Medicine, Golestan University of Medical Sciences, from March 2011 to November 2012.
Methodology: A total of 200 histopathologically proven *H. pylori* positive patients with PUD enrolled in this study were randomly assigned to participate in two groups: Group A: a 14-day OCA triple therapy with 20 mg omeprazole bid, 1000 mg amoxicillin bid and 500 mg clarithromycin bid; Group B: a 14-day clidinium-C bid plus OCA triple therapy. Subjects were asked to report any side effects of therapy during the treatment period. A13C-urea breath test was performed for eradication assessment 6 weeks after

**Corresponding author: Email: j.vafaeemanesh@muq.ac.ir;*

completion of the treatment.
Results: Totally 184 of 200 patients (90 in group A and 94 in group B) could continue the treatment protocols. *H. pylori* eradication was achieved in 71.1% in Group A (OCA without clidinium-C) and in 72.3% in Group B (OCA with clidinium-C), (p=0.73). The frequencies of abdominal pain and stool abnormality, among the side effects recorded during the therapy period, were significantly lower in group B (OCA with clidinium-C) than in group A (p=0.01 and p=0.001, respectively).
Conclusion: Addition of clidinium-C to OCA triple therapy does not increase the *H. pylori* eradication rates; however, it significantly decreases the frequency of abdominal pain and stool abnormality. This suggests a possibility that the addition of clidinium-C might be an option for increasing the patient's compliance.

Keywords: Clidinium-C; Helicobacter pylori; eradication; triple therapy; proton pump inhibitor.

1. INTRODUCTION

Helicobacter pylori (*H. pylori*) is a Gram-negative, spiral-shaped, motile micro-organism that infects approximately half of the world population and the prevalence of the disease in asymptomatic patients appears to be age-related [1]. The human is its reservoir and the transmission of this micro-organism involves oral‑oral and fecal‑oral routes. The infection takes place usually in childhood, within one's own family (between parents and children or between siblings) [2]. Gastric infection by *H. pylori* is actually considered to be the most relevant cause of chronic gastritis and peptic ulcer disease (PUD). It is also associated with an increased risk of mucosa associated lymphoid tissue (MALT) lymphoma and gastric cancer [3]. Selection of the best drug regimens for effective eradication of *H. pylori* infection is already challenging. Some recent studies suggested that the effectiveness, compliance and side-effects of quadruple regimen containing a gastric acid inhibitor, a bismuth compound and two antibiotics might be comparable with PPI-based triple therapy when administered as first-line treatment for *H. pylori* infection [4-6]. However, some others could show slight differences in effectiveness, usually in favor of quadruple therapy [7].

Antibiotic resistance due to frequent and uncontrolled use and the high prevalence of antibiotic side effects are the most common causes for treatment failure. To increase the eradication rates, as defined in the Maastricht IV report [8], several clinical trials have been initiated involving extended treatment duration, the use of new antibiotics or the addition of probiotics or other drugs to therapy [9]. Clidinium bromide is an anticholinergic drug which may help symptoms of cramping and abdominal stomach pain by decreasing stomach acid and slowing the intestines. Chlordiazepoxide is used as an anxiolytic, sedative, hypnotic, anticonvulsant and skeletal muscle relaxant. The drug may inhibit monosynaptic and polysynaptic reflexes by acting as an inhibitory neuronal transmitter or by blocking excitatory synaptic transmission. This drug may also directly depress motor nerve and muscle function. Clidinium bromide is commonly prescribed in combination with chlordiazepoxide by the name of clidinium-C [10].

The aim of this study was to assess the effect of clidinium-C on *H. pylori* eradication with a triple therapy including omeprazole, clarithromycin and amoxicillin (OCA) in patients with peptic ulcer disease (PUD). In areas of low clarithromycin resistance, clarithromycin-containing treatments are recommended for first-line empirical treatment and bismuth-containing quadruple treatment is also an alternative [8]. The secondary aim of the study

was to investigate the efficacy and safety of clidinium-C in the prevention of side-effects related to *H. pylori* eradication.

2. METHODOLOGY

2.1 Patients

This prospective, randomized, clinical trial study was conducted on 200 consecutive *H. pylori* infected patients with PUD from March 2011 to November 2012. Subjects were excluded if they were taking non-steroid anti-inflammatory drugs (NSAIDs), PPI, bismuth preparations or antibiotics during the previous eight weeks. Pregnant women, age fewer than 18, patients with renal and/or liver function test abnormalities or with previous gastric surgery were not enrolled. Gastroscopy was done using a videoscope (Olympus GIF-XQ260, Japan) and two specimens were obtained from the antrum. *H. pylori* infection was diagnosed by histopathological examination. This research was approved by the Ethical Committee in Golestan University of Medical Sciences. Informed consent was obtained from all patients.

Patients were randomly assigned to one of the two treatment protocols; Group A (Control group, n=100): the patients were received a 14-day standard OCA triple therapy for *H. pylori* infection eradication with 20 mg Omeprazole bid, 1000 mg Amoxicillin bid and 500 mg Clarithromycin bid; Group B (Case group, n=100): in this group the patients were received a 14-day clidinium-C bid plus OCA triple therapy. Patients were asked to return at the end of the treatment to assess the compliance with therapy that was defined as consumption of greater than 80% of the prescribed drugs. Subjects reported any side effects were given a possible side effect list, such as epigastric pain, taste disturbance and abnormal bowel habit. Medications were discontinued if any intolerable adverse events occurred. A13C-urea breath test was performed for eradication assessment 6 weeks after completion of the treatment.

Statistical analysis was performed with Chi-square test as well as Fisher's exact test, and one-way analysis of variance (ANOVA) test. P values of 0.05 or less were considered statistically significant. All the data were analyzed using SPSS 16 for Windows (SPSS Inc., Chicago, IL, USA) and the values were expressed as mean ± standard deviation (SD) for continuous variables and percentages for categorical variables.

3. RESULTS AND DISCUSSION

One hundred eighty four of 200 patients (42.9% males, between 19-72 years with mean age of 42.3±11.3 years) could continue the treatment protocols and underwent 13C-urea breath testing: 90 in group A and 94 in group B. There were no statistically significant differences between the two groups regarding age, gender and body mass index (Table 1). *H. pylori* eradication was achieved in 64 of the 90 (71.1%) patients in group A (OCA without clidinium-C) and in 68 of the 94 (72.3%) patients in group B (OCA with clidinium-C). The difference was not statistically significant (*P*= .73) (Table 2).

The side effects are shown in Table 3. The frequencies of abdominal pain or cramp and stool abnormality, among the side effects recorded during the therapy period, were significantly lower in group B (OCA with clidinium-C) than in group A (*P*= .01 and *P*= .001, respectively). The differences between the remaining side effects in both groups demonstrated no statistical significance.

Table 1. Baseline characteristics of the study subjects in different groups

Character	Group A (OCA) n=90	Group B (CC+OCA) n=94	Total (n=184)	P value
Age (years)	42.7±11.9	41.9±10.7	42.3±11.3	.62
Gender (M/F)	38/52	41/53	79/105	.81
BMI (Kg/m^2)	23.6±4.7	24.2±4.5	23.9±4.6	.43

OCA = Omeprazole, Amoxicillin and Clarithromycin
CC = Clidinium-C

Table 2. *Helicobacter pylori* eradication rates of study subjects in different groups

***H. pylori* eradication regimens**	***H. pylori* eradication rate**	**P Value**
Group A (OCA) n=90	64 (71.1%)	.73
Group B (CC + OCA) n=94	68 (72.3%)	

OCA = Omeprazole, Amoxicillin and Clarithromycin
CC = Clidinium-C

Table 3. Drug side effects in different groups

Characteristics	Group A (OCA)	Group B (CC+OCA)	P value
Dyspepsia	13 (14.4%)	7 (7.4%)	.21
Nausea	13 (14.4%)	6 (6.3%)	.12
Abdominal pain or cramp	9 (10%)	1 (1.1%)	.01
Diarrhea and/or constipation	14 (15.5%)	3 (3.1%)	.001
Dizziness	4 (4.4%)	5 (5.3%)	.83
Headache	6 (6.6%)	5 (5.3%)	.76
Bad taste	18 (20%)	19 (20.2%)	.91

OCA = Omeprazole, Amoxicillin and Clarithromycin
CC = Clidinium-C

According to the Maastricht IV Consensus Report about patients with *H. pylori* infection, in areas of low clarithromycin resistance, clarithromycin-containing treatments are recommended for first-line empirical treatment and bismuth-containing quadruple treatment is also an alternative. In areas of high clarithromycin resistance, bismuth-containing quadruple treatments are recommended for first-line empirical treatment. If this regimen is not available sequential treatment or a non-bismuth quadruple treatment is recommended. Extending the duration of PPI-clarithromycin-containing triple treatment from 7 to 10-14 days improves the eradication success and may be considered [8].

Antibiotic related side effects during *H. pylori* eradication are common and usually affect the gastrointestinal system. Poor patient compliance due to the side effects and discontinuation of the therapy impair the efficiency of the therapy and increase the possibility of resistance development against the antibiotics [11-12]. On the other hand, with clarithromycin containing treatments the eradication rates are falling due to a combination of antibiotic resistance and a poor compliance with therapy, which is primarily due to the side effects of the antibiotics [13]. In countries in which frequent and uncontrolled antibiotic utilization is common, as in Iran, the *H. pylori* eradication rates are decreasing. In this study, we selected the use of clidinium-C, because this is an anticholinergic drug which may help symptoms of cramping and abdominal pain by decreasing stomach acid and slowing the intestines. In literature reviews, we did not find any eradication study using clidinium-C.

In the present study, the success rate of *H. pylori* eradication with OCA first-line triple therapy was 71.1% and it was 72.3% with the addition of clidinium-C (p=0.73). In the studies published in western countries, the success rate of *H. pylori* eradication therapy was reported as approximately 70%, which is near the ideal values [14]. Thus, the addition of clidinium-C to the *H. pylori* eradication therapy could not increase the success rates.

Another goal of our study was to investigate the efficacy of clidinium-C for the prevention of the side effects related to the therapy. Because of the higher antibiotic resistance rates, developing countries prefer 14-day treatment regimens. This increased duration of therapy carries the burden of increased side effects. It has been shown that the large doses of antibiotics used in the triple therapy change the normal bowel flora. This may account for the adverse events in the gastrointestinal tract [15]. In our study, we did not observe addition of clidinium-C to OCA regimen to have any effect on the dyspepsia, nausea, dizziness, headache and bad taste. However, abdominal pain and stool abnormality were significantly lower in the clidinium-C arm than in control group. This effect is important for those countries in which *H. pylori* eradication regimens are applied for longer periods (10-14 day).

4. CONCLUSION

The study suggests that the addition of clidinium-C to OCA triple therapy does not increase the *H. pylori* eradication rates; however, it significantly decreases the frequency of abdominal pain and stool abnormality. This suggests a possibility that the addition of clidinium-C might be an option for increasing the patient's compliance, thus encouraging more research in this field.

CONSENT

All authors declare that ‘written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Correa P, Houghton J. Carcinogenesis of *Helicobacter pylori*. Gastroenterology. 2007;133(2):659-72.
2. Rowland M, Daly L, Vaughan M, Higgins A, Bourke B, Drumm B. Age-specific incidence of *Helicobacter pylori*. Gastroenterology. 2006;130(1):65-72.
3. Amieva MR, El-Omar EM. Host-bacterial interactions in *Helicobacter pylori* infection. Gastroenterology. 2008;134(1):306-23.

4. Gené E, Calvet X, Azagra R, Gisbert JP. Triple vs. quadruple therapy for treating *Helicobacter pylori* infection: A meta-analysis. Aliment Pharmacol Ther. 2003;17(9):1137-43.
5. Katelaris PH, Forbes GM, Talley NJ, Crotty B. A randomized comparison of quadruple and triple therapies for *Helicobacter pylori* eradication: The quadrate study. Gastroenterology. 2002;123(6):1763-9.
6. Laine L, Hunt R, El-Zimaity H, Nguyen B, Osato M, Spénard J. Bismuth-based quadruple therapy using a single capsule of bismuth, metronidazole and tetracycline given with omeprazole versus omeprazole, amoxicillin and clarithromycin for eradication of *Helicobacter pylori* in duodenal ulcer patients: A prospective, randomized, multicenter, North American trial. Am J Gastroenterol. 2003;98(3):562-7.
7. Seyedmajidi S, Mirsattari D, Zojaji H, Zanganeh E, Seyyedmajidi M, Almasi S, et al. Penbactam for *Helicobacter pylori* eradication: A randomized comparison of quadruple and triple treatment schedules in an Iranian population. Arab J Gastroenterol. 2013;14(1):1-5.
8. Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, et al. European *Helicobacter* study group: Management of *Helicobacter pylori* infection-the Maastricht IV/ Florence consensus report. Gut. 2012;61(5):646-64.
9. Yaşar B, Abut E, Kayadıbı H, Toros B, Sezıklı M, Akkan Z, et al. Efficacy of probiotics in *Helicobacter pylori* eradication therapy. Turk J Gastroenterol. 2010;21(3):212-7.
10. Pathak A, Rai P, Rajput SJ. Stability-indicating HPLC method for simultaneous determination of clidinium bromide and chlordiazepoxide in combined dosage forms. J Chromatogr Sci. 2010;48(3):235-9.
11. Baglan PH, Bozdayi G, Ozkan M, Ahmed K, Bozdayi AM, Ozden A. Clarithromycin resistance prevalence and Icea gene status in *Helicobacter pylori* clinical isolates in Turkish patients with duodenal ulcer and functional dyspepsia. J Microbiol. 2006;44(4):409-16.
12. Kearney DJ. Retreatment of *Helicobacter pylori* infection after initial treatment failure. Am J Gastroenterol. 2001;96(5):1335-9.
13. Reid G, Anukam K, Koyama T. Probiotic products in Canada with clinical evidence: What can gastroenterologists recommend? Can J Gastroenterol. 2008;22(2):169–75.
14. Fontham ET, Ruiz B, Perez A, Hunter F, Correa P. Determinants of *Helicobacter pylori* infection and chronic gastritis. Am J Gastroenterol. 1995;90(7):1094-101.
15. Lewis SJ, Freedman AR. Review article: The use of bio-therapeutic agents in the prevention and treatment of gastrointestinal disease. Aliment Pharmacol Ther. 1998;12(9):807-22.

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