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Research Article

Sequential Therapy for *Helicobacter pylori* Eradication with or without Bismuth Subcitrate

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Abstract

Background: *Helicobacter pylori* (*H. pylori*) is one of the most common infections worldwide, can lead to several upper gastrointestinal (GI) tract conditions. Recent reports have shown that *H. pylori* is gaining resistance to several antibiotic agents. This prompted the clinicians to prescribe various combined therapies, including, Bismuth-based therapies to overcome the drug resistance. In this study we aimed to compare *H. pylori* eradication rates in sequential therapy consisted of Amoxicillin, Tinidazole, Clarithromycin with and without Bismuth Sub-citrate.

Methods: In this randomized clinical trial, 106 symptomatic *H. pylori* positive patients were randomly assigned to two groups. Group A was treated with Amoxicillin, Pantoprazole, Tinidazole, and Clarithromycin; group B was treated with Bismuth Subcitrate added to the same regimen administered to group A. At the end of treatment, urease breath test was done for the participants, and reported as positive or negative. T-test and Chi-square test were used for evaluation of the the results, and P-value < 0.05 was considered as significant.

Results: The overall *H. pylori* eradication rate was 71.7% (76/106). Eradication rate in group A was 64.15% (34/53) and in group B was 79.2% (42/53). However, no significant difference was observed between the two groups (p = 0.13). Side effects were mild and well-tolerated in both groups.

Conclusion: In this study, adding Bismuth Subcitrate to sequential therapy did not make any significant change with regard to the statistical analysis results. However, further studies with greater sample size might change this conclusion and are needed to find out the most effective eradication therapy regimen with higher compliance and lower adverse effects.

Keywords: *Helicobacter pylori; Sequential Therapy; Eradication; Bismuth*

Introduction

Helicobacter pylori (*H. pylori*) is one of the most common infections worldwide involving the gastrointestinal (GI) system. *H. pylori* infection can lead to several upper gastrointestinal (GI) tract conditions such as duodenal ulcers, gastritis, and gastric marginal zone lym-

phomas, specifically mucosa-associated lymphoid tissue cancers (MALToma) [1,2]. The prevalence of *H. pylori* infection is tended to be declining in developed countries while the prevalence is still concerning in countries with limited resources or expertise [3]. For example, in Iran the prevalence was estimated to be about 90% in patients with upper GI problems, and 50% in asymptomatic individuals [4-7].

The *H. pylori* treatment regimens that are effective in a specific region or population were found to have unsatisfactory results in other populations [8]. Moreover, some regimens that have being used in different regions of the country seem not be working any more, mainly because of the drug resistance [9]. Hence, several combined therapy were examined aiming to overcome drug resistance, and find a more cost-effective treatment for *H. pylori* eradication.

For many years a standard triple therapy consisted of a proton pomp inhibitor agent (PPI), Clarithromycin, and Amoxicillin or Metronidazole has been used as the first-line regimen for treatment of *H. pylori* infection [10]. But recent reports have shown that *H. pylori* is gaining resistance to Clarithromycin and Metronidazole rendering this regimen less effective in this regard [11].

Another proposed approach for *H. pylori* eradication is sequential therapy, that includes PPI plus amoxicillin for the first 5 days, then PPI, Clarithromycin, and Tinidazole for 5 days [12-14]. Eradication rates with sequential therapy in Latin America and Asia were reported to be lower compared to triple therapy; whereas, the efficacy of sequential therapy was higher in Europe [15-19]. Several studies mentioned that this method could be recommended as a first-line treatment for *H. pylori* eradication [15,20].

Bismuth-containing therapies have also been suggested for *H. pylori* eradication, which showed desirable effects in many cases [21-24]. A prior investigation showed that a quadruple therapy consisting of Bismuth compound had been well-tolerated and had eradicated nearly 90% *H. pylori* infections in duodenal ulcer patients [25,26]. It has been proposed that the quadruple therapy could be also considered as first-line treatment, because it provides higher eradication rates [27].

The efficacy of current standard triple therapy is extremely challenged in many regions of the world, because of the increasing rates of antibiotic resistance [28]. The *H. pylori* resistance to Clarithromycin, and Levofloxacin has prompted the clinicians to prescribe a combination of drugs to circumvent the problem [28]. According to the available evidence, a Bismuth-based quadruple therapy could be a promising alternative treatment for *H. pylori* infection [28]. In the present study we aimed to investigate whether the addition of Bismuth Subcitrate to the sequential therapy could increase the *H. pylori* infection eradication rate.

Materials and Methods

Design and population

This randomized clinical trial was performed between April 2018 and April 2019, in patients with GI symptoms who underwent endoscopy because of different indications [29]. After obtaining informed consent, patients were recruited according to the following inclusion criteria: 1) Not being treated with *H. pylori* eradication regimens before, 2) Not used the antibiotics up to one month prior to the study, 3) Had a positive *H. pylori* test that was confirmed by pathology lab, 4) 18 < Age < 70 years old. The exclusion criteria were 1) patients' unwillingness to continue the study and/or the treatment, 2) Loss of medical records or being out of reach, 3) having any other diseases affecting the treatment process. An expert gastroenterologist performed the endoscopic evaluation by using video endoscopic device (ED-3490TK, PENTAX Medical, Tokyo, Japan), after obtaining informed consent and checkups for any contraindications for endoscopy including advanced heart and lung diseases [29]. Three biopsy samples were taken from their antrum and corpus, and the endoscopic findings were recorded [30]. The samples were sent to the pathology laboratory to be evaluated for infection with *H. pylori*. Overall, 106 patients were recruited and were randomly divided into two treatment groups, group A and B (n = 53). The sample size was estimated using the formula for estimation of sample size considering the level of confidence interval (CI) as 95% and test power as 80%.

Group A was treated with Pantoprazole 40mg (Capsule, Abidi Pharma™, Iran), and Amoxicillin 1000 mg (two 500 mg Capsule, Daana Pharma™, Iran) twice a day for 5 days, then Tinidazole 500 mg (Tablet, Abidi Pharma™, Iran), and Clarithromycin 500 mg (Tablet, Daana Pharma™, Iran) twice a day and for 5 days aftermath. Group B received the same regimen plus Bismuth Subcitrate 120 mg (Tablet, Chemiedarou™, Iran), every 6 hours, for the 10 days.

During the study and at the end of the treatments, the participants were visited by a gastroenterologist to evaluate the process of treatment or any possible complications. One week after the last dose of Pantoprazole, the urease breath test (UBT) was performed on the patients by using HELIPROPE® device (Kibion™, Uppsala, Sweden) and the result of UBT test was reported as positive or negative [30].

The study protocol was approved by ethics committee of Najafabad Medical Branch, Islamic Azad University, Isfahan, Iran (IRB number: Reg. No: ir.iau.najafabad.rec.1396.79).

Statistical analysis

Data were gathered and analyzed using SPSS Software version 21.0 (IBM, USA). Continuous and categorical data were presented as means ± SD and frequency. Demographic variables were analyzed by using Chi-square or t-test. The paired t-test and one-sample t-test were used to compare variables between and within groups, respectively. P-values less than 0.05 were considered as statistically significant.

Results

Demographic data of the participants are summarized in table 1. There was no association between the eradication rate of *H. pylori* and the participants' gender (p = 0.69) or age (p = 0.29). The overall *H. pylori* eradication rate in all patients was 71.7% (76/106). In group A, the eradication rate was 64.1% (34/53), and in group B it was 79.2% (42/53). However, the difference between the response to the regimens was not significant (p = 0.13) (Figure 1).

Variables		Groups		
		B	A	P value*
Gender	Male	43.4% (23)	39.6% (21)	0.69
	Female	56.6% (30)	60.4% (32)	
Age (year)		38.623 ± 16.13	35.491 ± 14.15	0.29

Table 1: *Demographic features of the participants.*
**Results of Chi-square test.*

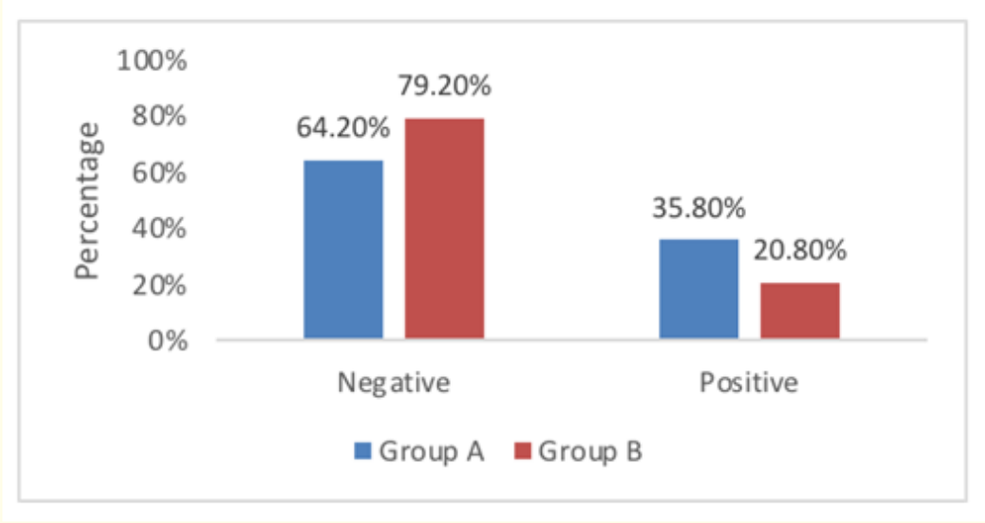

Figure 1: *H. pylori Eradication Rate in Group A (sequentioal therapy) and Group B (Sequential therapy plus Bismuth Sub-citrate).*

Considering the side effects of the treatment regimens, 33 (62.2 %) individuals in group A and 38 (71.6%) in group B reported no complication and drug adverse effects during the study (Table 2). The major complaints among the patients were headache, dizziness, bad taste, itching, abdominal discomfort, anorexia, bloating, fatigue, nausea, and constipation. However, these complaints were tolerated well by the participants and all of them were able to complete the treatment courses. There was no significant difference between the two groups encountering these adverse effects based on Chi-square test results ($\chi^2 = 2.090$, $P > 0.05$).

Groups	No adverse reactions	Headache	Dizziness	Bad taste	Itching	Epigastric pain	Anorexia	Bloating	Fatigue	Rash	Nausea and vomiting	Constipation
Group A	33	2	1	6	1	0	1	2	2	1	4	0
Group B	38	0	1	4	1	3	0	1	0	0	4	1
Total	71	2	2	10	2	3	1	3	2	1	8	1

Table 2: *Drug adverse effects.*

**: According to Chi-square test the difference between the two groups was statistically insignificant ($\chi^2 = 2.090$, $p > 0.05$)*

Discussion

The aim of this study was to evaluate the effect of adding Bismuth Subcitrate to sequential therapy for the eradication of *H. pylori*. The outcome showed that adding Bismuth Subcitrate to the sequential therapy regimen did not lead to a significant increase in *H. pylori* eradication compared to conventional sequential therapy (79.3% vs. 64.15%, p = 0.13). An acceptable regimen for *H. pylori* eradication is assumed to be based on the intention-to-treat success rate of 85 - 90%, must be low risk (adverse effects of less than 50%), cost-effective [5]. Thus, none of the regimens that have been evaluated in the current study could be considered an appropriate treatment.

Different factors such as the efficacy of regimens and, drug tolerance, costs, and antibiotic resistance should be considered for the selection of therapy [3]. The most common problem that can hinder the eradication of *H. pylori* is drug resistance in many regions of the world, especially in third world countries. For example, about 37.5% and 28% of *H. pylori* strains are resistant to Metronidazole and Clarithromycin, respectively, in Iran [31]. As the quadruple regimen of Bismuth Subcitrate, PPI, Amoxicillin, and Metronidazole showed less than 70% intention-to-treat eradication rate in the Iranian population [32], whereas the same regimen had resulted in 92% *H. pylori* eradication in the Netherlands [33]. Hence over, novel therapeutic guidelines are needed in the regions that have high antibiotic resistance and more investigations should be done in this regard.

Bismuth Subcitrate is prescribed as a part of *H. pylori* eradication regimen in China [34,35]. Adding Bismuth compounds to the *H. pylori* eradication regimens could be beneficial since it previously showed an increased response rate in the infected patients [35-37]. Multiple studies also reported that the addition of Bismuth Subcitrate could significantly increase *H. pylori* eradication after two weeks [38,39]. Moreover, ten days of quadruple therapy with Omeprazole, Clarithromycin, Amoxicillin, and Bismuth Subcitrate was found to be more effective than triple therapy by Omeprazole, Clarithromycin, and Amoxicillin in patients with *H. pylori*-induced chronic gastritis [40]. Consistently, the outcome of the present study also showed an improved response to the treatment in patients with *H. pylori* infection after the addition of Bismuth Subcitrate.

A previous investigation by Fakheri., *et al.* showed that both sequential and modified Bismuth-based quadruple therapies have acceptable outcomes for *H. pylori* infection treatments [41]. Moreover, it has been mentioned that modified Bismuth-containing quadruple therapy could be prescribed for patients with refractory *H. pylori* infection [42]. Besides, a modified Bismuth-included quadruple was found to be more effective in Chinese patients [43]. Accordingly, we believe that the low *H. pylori* eradication rate which was found in the present study could be because of the small sample size or some other confounding factors making further investigations with greater populations necessary.

Evaluating the statistical analyzes revealed that if the population of this study was doubled (confidence interval = 95%, power = 95%) the difference between the Urea breath test between the two groups would become more significant. Thus, a relatively small sample size can be considered as one of the limitations of the

present study. Another limitation is that the results may not apply to other countries and populations and further investigations on the effectiveness of these regimens should be performed on similar populations in different regions.

Conclusion

The results of the present investigation showed that adding Bismuth Subcitrate to sequential therapy did not lead to any significant increase in *H. pylori* eradication rate. We suggest further high-population studies to determine the best regimen in terms of treatment success, compliance, costs, and adverse effects.

Ethics Approval and Consent to Participate

Informed consent was obtained from all participants, their anonymity was guaranteed, and the study protocol was approved by the institutional research board (IRB) of Islamic Azad University of Najafabad, Isfahan, Iran (Reg. No: ir.iau.najafabad.rec.1396.79).

Consent for Publication

All authors of this article have been involved with the investigation and have approved the paper and agree to its submission and publishing in this journal.

Availability of Data and Material

The datasets used during the current study are available from the corresponding author on reasonable request.

Competing Interest

The authors have no competing interest to declare.

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Author Contributions

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