



## Comparing the Effect of Two Low-dose and High-dose Four-drug Regimens of Furazolidone in Eradicating *Helicobacter Pylori*

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### ABSTRACT

#### BACKGROUND

Antibiotic resistance is a major cause of *Helicobacter pylori* (*H. pylori*) treatment failures. The increased resistance to clarithromycin and metronidazole has reduced the ability of this therapeutic regimen and prompted researchers to look for other drugs. One of the antibiotics of interest in this regard is furazolidone because of its low drug resistance. The aim of this study is compare two-drug regimens including low-dose and high-dose furazolidone in the treatment of *H. pylori*.

#### METHODS

This study is a clinical trial in which the studied subjects were categorized into two groups. The first group underwent treatment with amoxicillin 1000 mg-BD, furazolidone 100 mg-BD, omeprazole 20 mg-BD, and bismuth subcitrate 240 mg-BD for two weeks (low-dose OFAB). The second group received furazolidone 200 mg-BD (high-dose OFAB). Then eight weeks after completion of the treatment, they were examined in terms of eradication via the UBT test.

#### RESULTS

85 participants completed the study in each group. The response to treatment was 76% and 83% in the low and high-dose groups, respectively, based on intention to treat analysis. Based on per protocol analysis the response to treatment was 78% and 84%, respectively, if excluded patients had completed their protocol and had response to treatment, and 72% and 79%, respectively, if excluded patients had completed their protocol and did not have response to treatment ( $p = 0.298$ ). In the low-dose and high-dose groups, 16.5% and 24.7% of the participants suffered the complications of treatment with furazolidone ( $p = 0.18$ ), respectively. Three patients in the high-dose group and one in the low-dose group did not complete the treatment because of the medication's bad taste ( $p = 0.03$ ).

#### CONCLUSION

Low doses of furazolidone had a comparable therapeutic effect compared with high doses, but patients experienced significantly lower levels of bad taste, which was a major cause of reluctance to continue treatment. Therefore, we think four-drug low-dose furazolidone treatment is a good choice in eradicating *H. pylori*.

#### KEYWORDS:

*Helicobacter pylori*, Furazolidone, Low-dose, High-dose

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Received: 11 Sep. 2020  
Accepted: 07 Feb. 2021

Please cite this paper as:

Seyedmajidi M, Hosseini SA, Vafaeimanesh J. Comparing the Effect of Two Low-dose and High-dose Four-drug Regimens of Furazolidone in Eradicating *Helicobacter Pylori*. *Middle East J Dig Dis* 2021;13:131-138. doi: 10.34172/mejdd.2021.216.



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## INTRODUCTION

*H. pylorus* is a gram-negative bacterium whose specific microbiological characteristic is having urease enzyme, allowing it to live in the stomach and colonize in the antrum of the stomach.<sup>1</sup> Different studies have suggested that *H. pylori* infection can cause some complications including chronic gastritis, peptic ulcer disease, functional dyspepsia, and stomach cancer.<sup>2</sup> *H. pylori* has involved around 50% of the adult population, while only 20% of these patients are symptomatic.<sup>3</sup> Experts have emphasized the importance of *H. pylori* in the pathogenesis of gastric diseases and recommended the eradication of *H. pylori* for preventing gastric cancer.<sup>4</sup> Additionally, *H. pylori* eradication decrease active inflammation in the gastric mucosa,<sup>5</sup> and reverse gastric atrophy and intestinal metaplasia.<sup>6</sup> The prevalence of *H. pylori* has remained high in some areas despite its decreasing trend over time. Additionally, the *H. pylori* reinfection rate has varied in different countries because to socioeconomic and hygienic conditions.

Although reduction of *H. pylori* infection has occurred in response to improved healthcare with anti-*H. pylori* treatments, gradual increase in its treatment failure has also been observed.<sup>7</sup> During recent decades, the rate of antibiotic resistance (particularly to clarithromycin) has rapidly increased in most countries around the world.<sup>8</sup> Currently, *H. pylori* treatment success has decreased from 90% in 1990 to less than 60%.<sup>9</sup>

The main reason for treatment failure of this bacterium is antimicrobial resistance especially to clarithromycin,<sup>10</sup> which has most probably been related to its excessive use in upper respiratory tract infections.<sup>7,11</sup> Currently, it has been found that the bacterium can develop external channels across its cellular wall for clarithromycin, which rapidly drives clarithromycin outside the bacterium, thereby preventing its attachment to the ribosome.<sup>12</sup> The resistance rate of clarithromycin is relatively high (13.9–52.6%),<sup>13</sup> and similar resistance rates have also been observed for metronidazole (41.6–99.5%). However, the resistance rates for amoxicillin (0–6.8%),<sup>14</sup> tetracycline (0–7.3%)<sup>15</sup> and furazolidone (0–0.1%)<sup>14</sup> were relatively low.

In Iran, in 2003-2011, resistance to clarithromycin and metronidazole increased considerably from 1.2% to 30-34% and from 32% to 78%, respectively, while only a slight increase has been observed in resistance to furazolidone (0-4.5%).<sup>16-17</sup>

Because *H. pylori* infection and reinfection present serious challenges and because *H. pylori* resistance to clarithromycin, metronidazole or levofloxacin remains high in most countries, the selection of an efficient regimen to eradicate *H. pylori* is critical. Currently, bismuth-containing quadruple therapies still achieve high eradication rates.

In Iran, various studies have been done on the therapeutic effect of furazolidone in the treatment of *H. pylori*. Based on these studies, it has been recommended that in developing countries such as Iran, furazolidone-based regimens can replace clarithromycin-based regimens for *H. pylori* eradication. The reason is that in addition to a very low level of drug resistance, it is also inexpensive and highly effective.<sup>18</sup> However, in some studies, the furazolidone-based regimen has usually had a low eradication rate and only a high dose furazolidone regimen can offer an acceptable extent of eradication.<sup>19</sup>

Nevertheless, there is a concern that high doses of this drug might be associated with higher rates of side effects. Accordingly, we designed this study to compare two-drug regimens including low-dose and high-dose furazolidone in the treatment of *H. pylori*.

## MATERIALS AND METHODS

This study was a randomized clinical trial Ethics code: (IR.IR.GOUMS.REC.1394.135) conducted during 2018-2019 on patients with peptic ulcer disease referred to Shahid SayadShirazi's educational healthcare Center in Gorgan City. In this clinical trial, the participants were chosen randomly from among patients with peptic ulcer referred to the mentioned healthcare center based on endoscopic examination of the upper digestive system and rapid urease test (RUT). Upon diagnosis of *H. pylori* infection, they were included as every other person in one of the groups. After obtaining their written informed consent, 180 patients were enrolled. First, 90 patients were included in each group. During the study, five were excluded from each group and at the time of analysis, 85 patients were analyzed. Two patients in the high-dose treatment group and four in the low-dose treatment group did not return for being examined for *Helicobacter pylori* eradication. Three patients in the high-dose group and one in the low-dose group did not complete

the treatment because of its bad taste. The sample size was chosen based on a previous study considering 95% confidence level and 80% power using the following formula. The sample size required for each group was calculated to be 76 and considering a 10% drop-out rate, the final study population was 90 individuals.<sup>20</sup>

The inclusion criteria were having peptic ulcer with endoscopic diagnosis and confirmed *H. pylori* infection through RUT, and consent to cooperate. On the other hand, the exclusion criteria were pregnancy, having cancer or renal or hepatic failure, diabetes mellitus, history of smoking and alcohol consumption, and history of drug allergy.

First, the demographic characteristics of patients including age and gender were recorded. Then their height and weight were measured. The weight was measured with minimum clothing and bare feet with standard scale Seca with an accuracy of 0.1 kg. Also, the height of the individuals was measured in standing position such that the back of the head, shoulders, hip, and heel were tangential to the wall from the back. The instrument utilized was the Seca standard wall stadiometer with an accuracy of 0.1 cm. Based on the data obtained from the weight and height measurement of patients, body mass index (BMI) was calculated for each of them. Next, the study samples were divided into two 90-subject groups (in the form of a lottery):

A) low-dose 4-drug regimen (OFAB): amoxicillin 1000 mg-BD, furazolidone 100 mg-BD, omeprazole 20 mg-BD, and bismuth subcitrate 240 mg-BD for 2 weeks

B) high-dose 4-drug regimen (OFAB): amoxicillin 1000 mg-BD, furazolidone 200 mg-BD, omeprazole 20 mg-BD, and bismuth subcitrate 240 mg-BD for 2 weeks

The drugs were not known by the other physician who was the study's co-author, and the study participants did not know the type of drug until the end of the study. Eight weeks after completion of the treatment course, UBT with a radiocarbon C13 test was performed on all the studied subjects to prove the eradication of *H. pylori*. Then the obtained results were compared with each other between the two groups. After collection and coding, the data were analyzed using SPSS software, version 18. For describing the data, frequency, percentage, mean, and standard deviation were used. To compare age, sex, height, weight, and BMI between the two groups, Chi-square and t tests were used. To compare the extent of

the eradication of *H. pylori* and the result of the UBT test between the two groups, Chi-square was used. The significance level across all tests was less than 0.05. If side effects induced the person not to continue taking the medication or a sustainable increase in aminotransferase or creatinine was seen, it was considered severe.

## RESULTS

The mean  $\pm$  SD age of the participants was  $44.96 \pm 11.83$  years with a range of 17-84 years.

In the low-dose and high-dose groups, the mean  $\pm$  SD ages of the participants was  $44.11 \pm 6.87$  and  $45.11 \pm 32.85$  years, respectively ( $p = 0.694$ ). Moreover, the two groups did not differ significantly in terms of gender and BMI (table 1). In both groups, more than 50% of the participants were overweight in terms of BMI (BMI > 25 kg/m<sup>2</sup>).

The extent of response to the treatment was assessed between the two groups (Figure 1).

The treatment response was positive in 71 (83.5%) and 65 (76.5%) patients in the high-dose and low-dose groups, respectively. Chi-square test showed that the two groups did not differ significantly concerning the extent of treatment response ( $p = 0.25$ , table 2)

With respect to the fact that 10 participants were excluded (5 patients in each group), to assess the difference in response to treatment between the groups, analysis was performed by intention to treat and per protocol. There was no significant difference between the responses to treatment in the groups in both analyses. More than 70% of the patients in all groups responded to treatment. The response to treatment based on intention to treat analysis in the low-dose and high-dose groups was 76% and 83%, respectively, and based on per protocol analysis it was 78% and 84%, respectively.

Assessment of the extent of the response to the treatment in the two groups was also performed in terms of sex. The results showed that 78.3% and 86.4% men in the low-dose and high-dose group had positive treatment response to furazolidone. Chi-square test suggested that the difference between the two groups was not statistically significant ( $p = 0.31$ ).

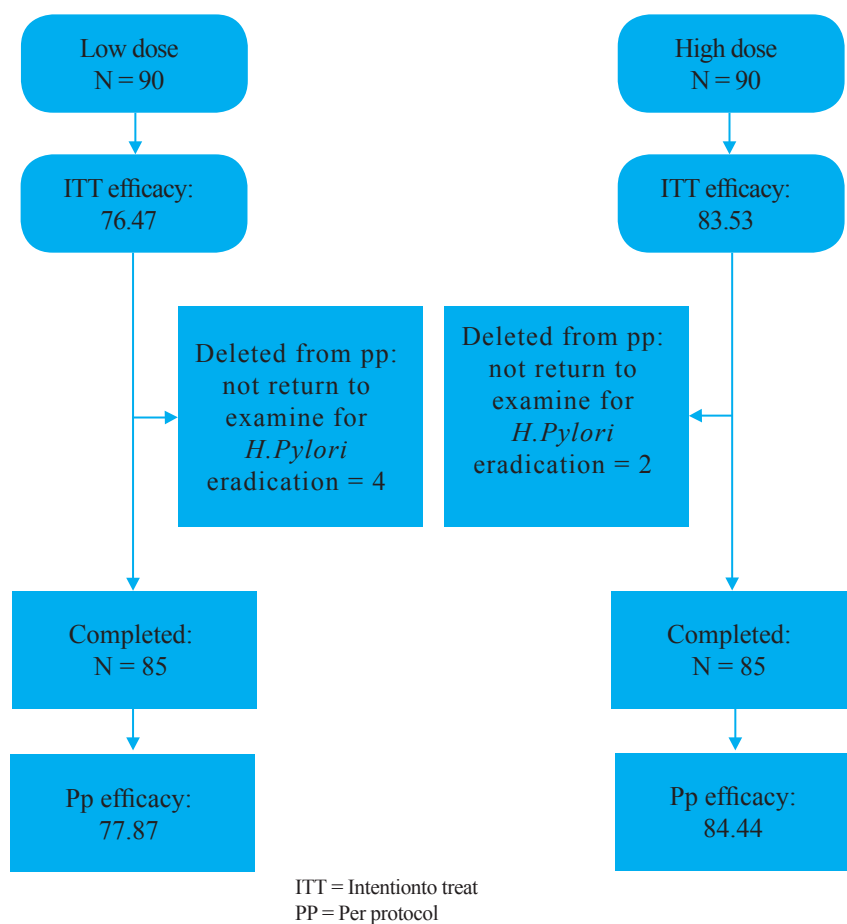
On the other hand, the extent of response treatment in women in the low-dose and high-dose groups was positive in 74.4% and 80.5% for furazolidone, while the others had

**Table 1: Demographic Characteristics of the Participants**

Variables	Total (N = 180)	Low dose	High dose	p value
Age (mean ± SD)	44.86 ± 11.8	44.9 ± 6.6	45.16 ± 32.4	0.68
Sex (male [%])	93 (51.66%)	46 (57.5%)	47 (58.75%)	0.78
BMI (mean ± SD)	25.24 ± 3.5	25.19 ± 4.47	25.2 ± 3.4	0.630

**Table 2: The value of variables before and after treatment**

Variables	Total	Low dose	High dose	p value
Age	44/96 ± 11/83	87/11 ± 6/44	85/11 ± 32/45	0.694
Sex(male)	90(52/9)	46(54/1)	44(51/8)	0.76
Sex(female)	80(47/1)	41(48/2)	39(45/8)	0.65
BMI	25/26 ± 3/51	25/2 ± 4/48	25/3 ± 3/54	0.63
Response		71(83/5)	65(76/5)	0.25
Side effect		14(16/5)	21(24/7)	0.18



**Fig.1: Response rate to treatment by intention to treat and per protocol analysis**

**Table 3: The details of the side effects of treatment in both groups**

Side Effect	Low dose	High dose	<i>p</i> value
Weakness	0	0	0.38
Dyspepsia	0	0	0.34
Abdominal cramp	1	1	0.78
Urine orange discoloration	0	1	0.75
Nausea	2	3	0.23
Vomiting	0	1	0.16
Glossitis	1	2	0.45
Heartburn	2	3	0.23
Diarrhea	2	3	0.21
Constipation	2	1	0.28
Bad taste	3	5	0.02
Drug fever	0	0	0.29
Anorexia	1	1	0.74
Total	14	21	0.18

no treatment response and this difference was not statistically significant ( $p = 0.51$ ). The extent of treatment response in the two groups was also tested in terms of age. Chi-square test results revealed that in both groups, age did not affect response to treatment ( $p = 0.52$ ). Investigation of the relationship between the extent of treatment response and BMI was not statistically significant either ( $p = 0.52$ ).

The results of frequency distribution indicated that in the low-dose group, 14 (16.5%) patients and in the high-dose group 21 (24.7%) patients experienced furazolidone side effects ( $p = 0.18$ ). Note that, Three patients in the high-dose group and one in the low dose group did not complete the treatment because of its bad taste ( $p = 0.03$ ), while other side effects did not inhibit the continuation of treatment (table 3).

## DISCUSSION

Although various regimens have been introduced for the treatment of *H. pylori*, no single suitable treatment regimen has been found to date. The most common drug regimen which has been recommended and consumed in recent years is the triple-drug regimen for two weeks based on clarithromycin. However, in recent years the impact of the triple regimens has been challenged, and their rates of efficacy have diminished<sup>21</sup> and its extent of eradication in developed countries has reached 75-80.5%.<sup>22, 23</sup> This level is lower in developing countries. For example, in

Iran, the extent of eradication through the triple-drug regimen is less than 60%.<sup>24</sup>

Therefore, alternative drug regimens with high efficacy and safety should be designed and tested in different regions depending on the pattern of endemic resistance. Treatment strategies should reduce the unnecessary use of antibiotics, prevent the spread of resistance to other organisms, and decrease the cost of *H. pylori* treatment.<sup>25</sup>

A sequential treatment regimen based on clarithromycin is one of the regimens that has also been introduced as an effective alternative treatment for the classic triple-drug regimen in developed countries. However, in Asian countries, the results of this treatment regimen have not been very satisfactory,<sup>23</sup> which can be related to increased resistance to clarithromycin.<sup>26-27</sup> In another study, 78.6% of patients with *H. pylori* infection have resistance to metronidazole, 34% to clarithromycin, 10% to amoxicillin, and 4.5% to furazolidone.<sup>16</sup>

Because of the increasing resistance to clarithromycin and other families of antibiotics, it seems that furazolidone is a good option for the treatment of this infection in Iran.<sup>28</sup> Furazolidone is one of the drugs that has been used successfully in eradication regimens.<sup>25</sup> It is a nitrofurantoin antibacterial agent and monoamine oxidase inhibitor (MAOI). It is effective on both gram-negative and gram-positive bacteria.<sup>29</sup>

Furazolidone is a low-risk drug and the carcinogenicity of furazolidone was listed as Class III. It should be noted that metronidazole, is classified as a Class I (definite) human carcinogen.<sup>30</sup> Also, furazolidone is inexpensive and available in both countries.<sup>17-31</sup> Furazolidone-based quadruple therapy for *H. pylori* infection in an area with a high prevalence of clarithromycin resistance showed high eradication rates.<sup>32</sup>

Despite this advantage, the main limitation for the common use of furazolidone is related to its gastrointestinal side effects such as nausea, anorexia, abdominal discomfort and etc., which usually occur in the second week of treatment and lead to interruption of the treatment in many instances.<sup>33</sup> In addition, doses and duration of use of furazolidone also affect the incidence of side effects.<sup>29, 31</sup>

Also, some articles have reported that with a higher dose of furazolidone (> 200 mg per day), the incidence of some side effects such as fever and anorexia has

increased compared to the control group, but the overall incidence of total side effects has not increased.<sup>29</sup> Using a lower dose may have lesser side effects, but some believe the eradication rate is unacceptable. However, researchers have tried a triple-drug regimen to eradicate *H. pylori*.<sup>31</sup> In contrast to some investigators, the eradication rate in treatment with low-dose furazolidone drug was significantly higher than the standard drug containing clarithromycin.<sup>20</sup> Another group of researchers reported that even in people who had a history of failure in previous *H. pylori* eradication therapy One- or two-week furazolidone and amoxicillin-based quadruple rescue therapy with low-dose furazolidone (100 mg bid) was effective for the eradication of *H. pylori*. Extending the antibiotic course to 14 days could improve eradication rates.<sup>34</sup>

In our study, the assessment of the extent of response to treatment was done for the groups. *H. pylori* eradication was achieved in 71 (83.5%) patients in the high-dose group (200 mg BID) and in 65 (76.5%) patients in the low-dose group (100 mg BID). Due to the fact that an acceptable therapy is reaching 85-89% cure rate, the results in both groups are less than this rare. No significant difference was observed between the two groups in terms of the extent of response to treatment. Another study similar to ours did not consider increasing the dose of furazolidone to increase eradication rates and only attributed the failure to treatment.<sup>33</sup> In one study, the resistance rates to amoxicillin and furazolidone were 27.1% and 23.9%, respectively.<sup>18</sup>

Note that the best therapeutic outcome for the four-drug furazolidone treatment in a small-scale study (55 subjects) was obtained through tetracycline and furazolidone 100 mg QID. Alongside bismuth (QID) and omeprazole twice per day. In this study, *H. pylori* eradication was 94.5%.<sup>33</sup> Of course, many factors may lead to a reduction in the rate of *H. pylori* eradication, including various aspects including antibiotic resistance, bacterial viral factors, drug pharmacodynamics and pharmacokinetic effects, drug interactions, and poor patient tolerance.<sup>29</sup>

In this study, the results of frequency distribution showed that in the group receiving low-dose treatment, 14 (16.5%) patients and in the high-dose group 21 (24.7%) patients experienced the side effects of furazolidone; but this difference was not significant ( $p = 0.18$ ). Three

patients in the high dose group and one in the low dose group did not complete the treatment because of bad taste ( $p = 0.03$ ), while other side effects did not inhibit the continuation of treatment. Therefore, low-dose furazolidone was safe and tolerable for use in *H. pylori* eradication in our study.

Another study showed that side effects occurred in 17% of patients; in 2.8% it caused early discontinuation. The common side effects were abdominal discomfort, dizziness, nausea, fatigue, anorexia, rash, and pruritus). All of the side effects were resolved after completion or discontinuation of treatment without any occurring of severe hepatotoxicity or nephrotoxicity.<sup>35</sup> Based on our study and other studies, although the side effects of *H. pylori* treatment regimens containing furazolidone are common which is reportedly around 18-33%,<sup>36</sup> in our previous study, the extent of side effects in a four-drug regimen containing furazolidone 400 mg/day was greater compared to that of the triple-drug regimen containing levofloxacin.<sup>37</sup> In another study, to optimize the eradication of *H. pylori*, the recommendation was made for this containing alcohol throughout the treatment course and carefully adhering to the consumption of medications and controlling other drugs to reduce drug interactions.<sup>17</sup>

One of the limitations of this study is that it is the single-center study with its relatively small sample size, and most of the patients lived in areas near Gorgan. However, as a pilot experiment, the results could be useful for future research including large sample sizes and multi-center trials.

## CONCLUSION

Considering the high extent of resistance to clarithromycin and metronidazole in Iran, and given the availability and inexpensiveness of furazolidone, it can be used for the treatment of *H. pylori*. In our study, both regimens did not reach acceptable therapeutic levels, however low doses of Furazolidone had a comparable therapeutic effect to high doses, but patients experienced significantly lower levels of bad taste, which was a major cause of reluctance to continue treatment.

## ACKNOWLEDGMENT

This study has been an outcome of a clinical trial (Ethics code: IR.IR.GOUMS.REC.1394.135) in Golestan University of Medical Sciences and was supported by the Clinical Research Development Center in Shahid Beheshti Hospital of Qom University of Medical Sciences. We wish to thank Dr. Abidi Pharmaceutical Company who took part in this research project, especially Miss Shiva Sotoudeh.

### ETHICAL APPROVAL

There is nothing to be declared.

### CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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