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A randomized clinical trial; comparing levofloxacin based sequential and clarithromycin based sequential versus triple therapy for *Helicobacter pylori* eradication

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General Note

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ABSTRACT

Helicobacter pylori is a major cause of gastric diseases. Some studies in Iran showed that the resistance rate to clarithromycin was in the range of 5% to 45.2%. The present study aimed at evaluating the efficacy of a sequential therapy versus standard triple therapy in eradication of *H.pylori* infection. Patients with positive histopathological *H.pylori* infection were randomly allocated into three groups. All endoscopies were performed with FUJINON by two expert gastroenterologists. The first group received omeprazole 2x20 mg and amoxicillin 2x1 g per day for first week and omeprazole 2x20 mg, metronidazole 2x500 mg and clarithromycin 2x500 mg per day for second week (regimen A). The second group received the same treatment in first week but clarithromycin was replaced by levofloxacin 2x500 mg per day in second week (regimen B). And the last group received omeprazole 2x20 mg, amoxicillin 2x1 g and clarithromycin 2x500 mg per day for two weeks (regimen C) .294 patients completed the study and underwent 13C-UBT at the sixth week. Eradication rates of 87.7% in sequential levofloxacin based (B) and 76.5% were achieved in the clarithromycin-based (A) and 67.3% in standard triple therapy(C). According to this study, only therapeutic intervention in group B has the effect on H pylori eradication. Over the past decade, eradication programs regarding *H. pylori*-related diseases have been based on standard triple therapy worldwide. Present study show sequential levofloxacin based therapy for eradication of helicobacter pylori was more effective than sequential clarithromycin based and standard triple therapy.

Keyword: *Helicobacter pylori*, dyspepsia, Sequential therapy, Standard triple therapy.

1. INTRODUCTION

Helicobacter pylori is a major cause of gastric diseases such as dyspepsia, chronic gastritis, gastroduodenal ulcers, gastric cancer and also plays a leading role in creation of iron deficiency anemia, vitamin B12 deficiency, and idiopathic thrombocytopenic purpura (EHSG, 1997).

WHO has categorized *H. pylori* as a class I carcinogenic agent in humans; therefore, its eradication has been an important step in the treatment of peptic ulcer disease and prevention of gastric malignancy (Van der Hulst, 1996). It acts with various mechanisms and gets resistant to antibacterial agents which make the treatment difficult (Bagheri et al., 2016; Razavi et al., 2015).

The eradication rates of first-line triple therapy, which consists of a proton pump inhibitor (PPI) and two antibiotics (clarithromycin and amoxicillin or metronidazole), have been continuously decreasing (Saberi-Firoozi et al., 1995; Moradniani et al., 2018). Eradication rates in the first-line H. pylori therapy have been declined over the years. Resistance of h.pylori to clarithromycin is an important reason for the treatment failure.

In recent European guidelines recommended triple therapy as the first-line treatment only when the prevalence of clarithromycin resistance is under 20 % (Kashifard et al., 1998). Some studies in Iran showed that the resistance rate to clarithromycin was in the range of 5% to 45.2% (Fakheri et al., 2014; Zendedel et al., 2013).To overcome this unsatisfactory eradication rate, sequential therapy (SQT) and concomitant therapy are currently recommended as an alternative first-line treatment for *H. pylori* infection (Malfertheiner et al., 2012; Greenberg et al., 2011).

However, few studies in Iran have yet demonstrated the efficacy of sequential therapy for *H. pylori* eradication (Sherkatolabbasieh et al., 2017). The present study aimed at evaluating the efficacy of a sequential therapy versus standard triple therapy in eradication of H. pylori infection.

2. PATIENTS AND METHODS

Consenting patients, 18 years or older, with complaint of dyspepsia and endoscopically-proven duodenal ulcer, gastric ulcer, erosive gastritis or erosive duodenitis who attended to our gastrointestinal (GI) clinic in Khorram Abad, Lorestan, Iran were enrolled. All endoscopies were performed with FUJINON by two expert gastroenterologists.

H.pylori infection was proved either by histopathological examination. Patients were excluded if they were pregnant, were nursing a baby, had a history of gastric surgery, had taken antibiotics within the past month, or had allergy to any of the study drugs. They were randomized (computer-generated, block randomization) to receive one of the three anti-*H.pylori* regimens.

The first group received omeprazole 2x20 mg and amoxicillin 2x1 g per day for first week and omeprazole 2x20 mg, metronidazole 2x500 mg and clarithromycin 2x500 mg per day for second week (regimen A).

The second group received the same treatment in first week but clarithromycin was replaced by levofloxacin 2x500 mg per day in second week (regimen B). And the last group received omeprazole 2x20 mg, amoxicillin 2x1 g and clarithromycin 2x500 mg per day for two weeks (regimen C).

Levofloxacin and clarithromycin were packed in similar containers and provided to the patients along with other medications by the caring physician. Each package was identified with a code and the codes were broken at the end of the study.

In addition to demographic data, we recorded the smoking, history of PUD, and previous history of GI bleeding with peptic ulcer source.

The patients were instructed about the use of the medications and probable adverse effect. All patients were contacted one and two weeks after starting the treatment by the same physician.

We checked the patient's compliance by counting the tablets and recorded any adverse effect or newly started medications other than the study medications. Complete compliance was defined when the patients took at least 80% of the given drugs. Severity of adverse symptom was graded from 0 – 3 (0 not present, 1 mild, 2 moderate, and 3 severe or intolerable). Only moderate to severe adverse events were considered for analysis. Medications were discontinued if any intolerable adverse event occurred, any appearance of fever, urticarial rash, or generalized body pain was noticed.

We invited all patients to take a 13C-urea breath test (UBT), six weeks after completing the treatment. UBT was done with 75 mg of 13C-urea in fasting state solved in 100 mL of orange juice. The 13C in the expired air was measured 20 minutes later, using an infrared spectrophotometer (PY test, Kimberly-Clark, USA). The sensitivity and specificity of the 13C-UBT were 90.0% and 95.6%, respectively.

To compensate the patients who could not be evaluated fully, we planned to enroll 101 patients per group.

Chi-square was used for statistical analysis. The protocol was approved by the Ethics Committee of the Lorestan University of Medical Sciences.

3. RESULTS

Three hundred and two patients were enrolled; 5 patients were lost to follow-up and 3 patients were excluded due to adverse effect, 294 patients were followed at the second week. The baseline characteristics of the patients were comparable (Table 1).

Table 1 Characteristics of the patients

	Group A (n=98)	**Group B (n=98)**	**Group C (n=98)**
Male/female(n)	48/50	46/52	47/51
Mean age± SD (years)	40±44	42±32	41±27
Current smokers (%)	6.1	10.2	5.1
HTN(%)	8.2	10.2	4.1
DM(%)	2	2	1

Three patients did not show up for the last follow-up for performing UBT; two, one, and zero patients in groups A, B and C, respectively. Therefore, 294 patients completed the study and underwent 13C-UBT at the sixth week. three patients had to discontinue their medication because of intolerable adverse drug reactions (one, two, and zero patients in groups A-C, respectively) and two patients were non-compliant (took less than 80% of the given medication, two patients in group C). These 8 patients were not included in the per-protocol analysis. Finally, each groups contain 98 patients (Figure 1).

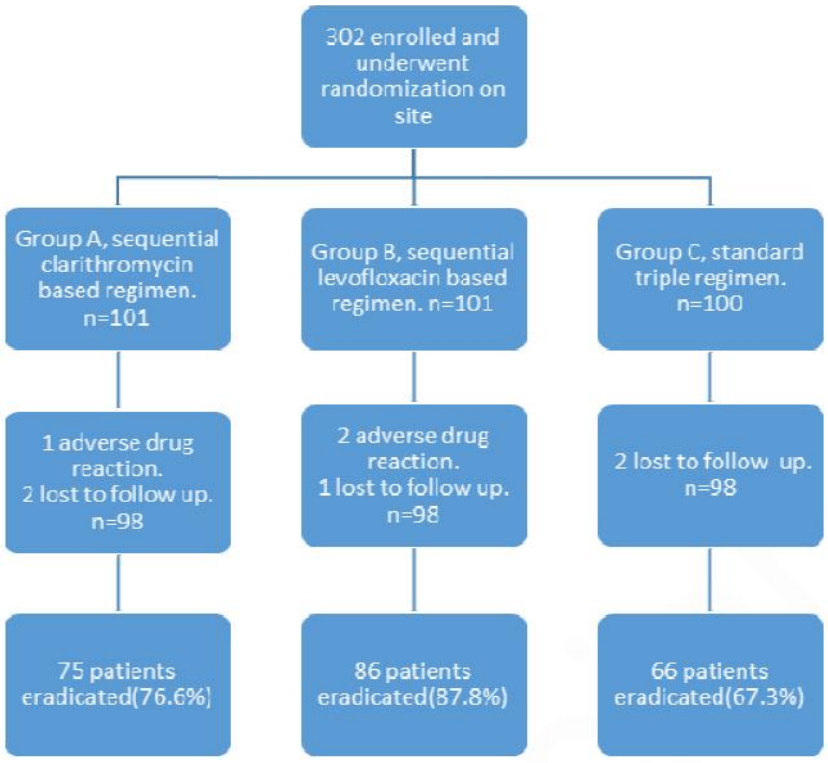

Figure 1 Flow chart of the patients

Adverse events in the three groups are shown in Table 2. Bad taste, nausea, vomiting, dizziness, weakness, abdominal pain, anorexia, and diarrhea were seen in some patients of three groups. Frequency of most adverse events were higher when levofloxacin was administered, but the difference was not significant ($P > 0.05$).

Table 2 Reported adverse drug effects

	Group A (n=98)	Group B (n=98)	Group c (n=98)
Nausea	**8**	**13**	**7**
Vomiting	**2**	**3**	**2**
Diarrhea	**4**	**3**	**6**
Abdominal Pain	**8**	**6**	**10**
Constipation	**3**	**7**	**2**
Anorexia	**9**	**8**	**11**
Skin Rash	**0**	**2**	**0**
Headache	**2**	**6**	**3**
Bad taste	**7**	**6**	**10**

Anorexia (9.2%), nausea (8.2) and abdominal pain were most adverse reaction occurred in group A patients. In group B, nausea (13.3%), anorexia (8.2%), constipation (7.1%) and in group C, anorexia (11.2%), bad taste (10.2%) and abdominal pain (10.2%) were reported.

Eradication rates of h.pylori are shown in Table 3. Eradication rates of 87.7% in sequential levofloxacin based (B) and 76.5% were achieved in the clarithromycin-based (A) and 67.3% in standard triple therapy(C). These were significantly higher than that achieved in the levofloxacin-based group (87.7%).

According to Table (4) and the level of variable significances entered into the Hosmer and Lemeshow model can be said, only therapeutic intervention in group B has the effect on H pylori eradication.

Table 3 Eradication rates of *H. pylori*

	Group A	Group B	Group C
Eradicated (UBT below 200)(%)	**76.5**	**87.8**	**67.3**
Non eradicated (UBT above 200)(%)	**23.5**	**12.2**	**32.7**

Table 4 Level of variable significances entered into the Hosmer and Lemeshow model

	B	S.E.	Wald	df	Sig	Exp(B)	95% C.I.for EXP(B)	
							Upper	Lower
Group			10/972	2	0/004			
Age			3/015	3	0/446			
Smoking	-0/006	0/007	0/0634	1	0/272	0/994	0/980	1/009
HTN	0/353	0/532	0/441	1	0/507	1/423	0/502	4/034
DM	-0/495	1/171	0/179	1	0/627	0/610	0/061	6/051
Education			4/426	6	0/619			

4. DISCUSSION

Over the past decade, eradication programs regarding *H. pylori*-related diseases have been based on standard triple therapy worldwide. However, the eradication rate of the standard triple therapy (PPI + clarithromycin + amoxicillin or PPI + clarithromycin + metronidazole) is lower or far lower than 80% with the increase in drug-resistant *H. pylori*. Increasing the duration of standard triple therapy from 7 to 10 or 14 d could increase the eradication rate by 5% (Kao et al., 2016). The cure rates of *H. pylori* infection are influenced by several factors such as antibiotic susceptibility, insufficient inhibition of acid secretion [e.g., the cytochrome P450 2C19 (CYP2C19) genotype, the environment (e.g., smoking), and protocol compliance (Azadbakht et al., 2017; Chey et al., 2007). Because of the decreased eradication rate, which are due to various factors (Bagheri et al., 2013; Azadegan-Dehkordi et al., 2015), the search for more effective treatment programs or the use of new alternative drugs for *H. pylori* eradication therapy has become imperative. Recently (Bagheri et al., 2015; Albrecht et al., 2011), *H. pylori* treatment with bismuth-containing quadruple therapy or sequential therapy was recommended as the first-line treatment. Choi et al (Cremonini et al., 2001) performed a meta-analysis (8 Italian studies) that showed a trend in preferring sequential therapy to triple therapy. Others have suggested that there is insufficient data to recommend sequential therapy as an alternative first-line therapy for H. pylori therapy in Asia (Moradniani et al., 2017). Our study showed that sequential levofloxacin based and sequential clarithromycin based therapy were satisfactory and safe, and they appear to be well tolerated for initial therapy.

In our study, the overall adverse effects were significantly higher in group B than in group A and C but this difference was not significant. The number of patients who discontinued treatment because of adverse drug reactions were almost similar in groups B, C, and A (two, zero, and one,). Although two weeks clarithromycin-Amoxicillin based regimen had fewer side effects, the lower eradication rate of this regimen makes it unsuitable as the first-line anti Helicobacter pylori regimen.

5. CONCLUSION

Overall, present study showed sequential levofloxacin based therapy for eradication of *Helicobacter pylori* was more effective than sequential clarithromycin based and standard triple therapy. We suggest that in area with high resistance to clarithromycin, physician use sequential levofloxacin in combination of metronidazole for eradication of *Helicobacter pylori* as a first line treatment.

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