

## Efficacy of standard triple therapy versus Levofloxacin based alternate therapy against *Helicobacter pylori* infection

Shahzad Latif,<sup>1</sup> Noreen Akther,<sup>2</sup> Sameen Amjed,<sup>3</sup> Junaid Jafar,<sup>4</sup> Bushra Saleem,<sup>5</sup> Muhammad Usman,<sup>6</sup> Tuaha Amjad,<sup>7</sup> Waqas Maqsood,<sup>8</sup> Humaira Waseem,<sup>9</sup> Naim Ashraf<sup>10</sup>

### Abstract

**Objective:** To assess the effectiveness of clarithromycin based standard triple therapy versus levofloxacin based first line therapy against *Helicobacter pylori* infection.

**Methods:** This prospective observational study was performed at Akhter Saeed Trust Teaching Hospital, Lahore, from May 2016 to 31st May 2017 and comprised of all patients with positive *H. pylori*, confirmed by gastroscopic biopsy; fulfill the inclusion criteria of this study. Patients were divided into two groups (Group A and Group B). Group A received clarithromycin 500mg, amoxicillin 1g and omeprazole 20mg twice a day for two weeks. In group B levofloxacin 250mg was replaced by clarithromycin whereas rests of medicines remain the same. Patients were followed up at end of first week, second week and at end of treatment to record any adverse effects and cure rate. Data was analyzed by using SPSS version 24.0 and MINITAB V.16.

**Results:** Out of 300 enrolled patients (150 patients in each group), 123 (87.85%) patients cured in group A whereas 134 (92.4%) patients cured in group B. Both treatment regimens were almost equally effective in our population with no statistically significant difference in outcome. Significantly less adverse effects were observed in patients having levofloxacin as compared to standard triple therapy

**Conclusion:** Effectiveness of both standard triple therapy and alternate triple therapy were found satisfactory to be used for treatment in our region. Levofloxacin based alternate therapy is safer to the patients. It can be used in conditions where adverse effects caused by standard therapy are unbearable.

**Keywords:** *Helicobacter pylori*, Clarithromycin standard triple therapy, Levofloxacin, Alternate therapy. (JPMA 68: 1295; 2018)

### Introduction

*Helicobacter pylori* was first reported in early 19th century when its association with gastric carcinoma was suspected. Later Doenges reported that almost 40% of human stomachs were found invaded with a spiral organism when performed an autopsy. Antibiotic effect of bismuth was also reported against spiral bacteria in peptic ulcer patients. In 1982 Barry Marshall and Robin Warren successfully cultured and isolated this spiral bacterium and named it *Campylobacter pylori* later named as *Helicobacter pylori*.<sup>1</sup> Self-ingestion experiments also demonstrated that *H. pylori* colonize human stomach leading to inflammation of gastric mucosa.<sup>2</sup> *Helicobacter pylori* belongs to genus *Helicobacter*. It is a gram negative, urease positive, highly motile bacteria. Its urease activity helps it to survive in low pH environment of stomach whereas motility allows it to move and invade gastric mucosa before acidity harms it.<sup>3</sup>

Most of the individuals infected with *H. pylori* remain

.....  
<sup>1,2,5-7,10</sup>Akhter Saeed Trust Teaching Hospital, Lahore, <sup>3,4,8,9</sup>The University of Lahore, Pakistan.

**Correspondence:** Sameen Amjed. Email: amjedsamenn@gmail.com

asymptomatic for life however it may lead to acute and chronic gastritis, gastric and mucosal ulcers, lymphoma and gastric carcinoma. Distal gastric adenocarcinoma is one of the common malignancies worldwide.<sup>4</sup> Risk of bleeding from ulcer and adenocarcinoma of gastric mucosa makes it a serious health care problem.<sup>2</sup>

The reported prevalence of *H. pylori* is almost 50% worldwide with relatively higher occurrence in developing countries. Pakistan has wide range of reported prevalence ranging between 50-90% in different areas of country.<sup>5,6</sup> Despite its in vitro sensitivity against number of antibiotics, *H. pylori* infection is difficult to treat in vivo with any single antibiotic. This in vivo resistance of *H. pylori* is believed to be because of its habitat at low pH in viscous mucous layer. Clarithromycin with approximately 40% eradication rate when given as mono-therapy is the most effective single drug against *H. pylori*. To improve eradication rate mostly two antibiotics are combined with either a proton pump inhibitor (PPI) or with a bismuth compound.<sup>3</sup> Combination of these medicines is believed to synergies effect of each other resulting in better eradication rate in more than 80% of patients.<sup>2</sup>

Now days, antibiotic resistance is becoming the leading cause of failure to treat *H. pylori* infection. The highest resistance rates are observed against clarithromycin which is believed to be the result of its widespread use against respiratory tract infections. In different geographical areas varying resistance rates are reported. A global review about clarithromycin resistance was done including 11697 cases in 2010. Total 2014 (17.2%) cases were reported resistant to clarithromycin with Europe (11.1%), Asia (18.9%) and America (29.3%).<sup>5</sup> Whereas the threshold of clarithromycin resistance at which this antibiotic should not be used, or clarithromycin susceptibility test should be performed is 15-20%. This increase rate of antibiotic resistance is pushing researchers to search and develop novel interventions and prevention strategies.<sup>3</sup> Recent data shows that new treatment combinations against *H. pylori* infection have been introduced. A lot of studies have been conducted in which levofloxacin was given as first line antibiotic regimen. This replacement of antibiotic from clarithromycin to levofloxacin have been reported to improve eradication rates of *H. pylori*.<sup>7,8</sup> Some of these studies have shown excellent results, with eradication rates ranging from 85% to 92%. In addition levofloxacin presents a good safety profile and is reported to reduce number of side effects.<sup>9-14</sup>

Literature review shows increasing resistance of standard clarithromycin based triple therapy in many parts of world especially developing countries. This study was conducted to determine the efficiency of clarithromycin based standard triple therapy on our local population. Study was also conducted to find out the efficacy of levofloxacin based first line therapy and to compare it with standard triple therapy in terms of efficacy and adverse events.

## Methods

This prospective observational study was conducted at Akhter Saeed Trust Teaching Hospital, Lahore. The study was conducted after taking ethical approval from institutional review board. Akhter Saeed Trust Teaching Hospital afforded all the cost related to patient's examination, diagnostics and medication. Sample size (n = 300) was calculated using following formula.<sup>15</sup>

$$n = z^2 (1 - \alpha/2) pq / e^2$$

$$z (1 - \alpha/2) = 1.96$$

$$p = \text{prevalance} = 0.74$$

$$q = 1 - p = 1 - 0.74 = 0.26$$

$$e = \text{margin of error} = 0.05$$

We used the *H. pylori* prevalence from previous study of Pakistan.<sup>16</sup> The duration of study was one year from May 2016 to 31st May 2017. Purposive sampling technique was used and total 300 newly diagnosed *H. pylori* infected

patients were selected and included in this study after taking written consent. The patients were assured that their information and identity will be kept secret and will not be disclosed and information provided by them will only be used for research purpose. The relevant information including demographic data, lab investigation results, medicine prescribed and adverse effects were documented on a predesigned proforma. Patients aging between 18-60 years, fit for gastroscopy procedure were included in this study. Subjects with active ischaemic heart disease, renal failure, congestive heart failure, history of psychiatric illness or history of use of tranquilizers were excluded from this study. Patients using non-steroidal anti-inflammatory drugs and those refused to go for gastroscopy procedure were also excluded from study.

The baseline blood samples and stool samples of selected patients were collected following standard operating procedures. Complete blood count, *H. pylori* stool antigen, coagulation profile and biochemical tests were performed using standard test protocols with appropriate test controls. Electrocardiogram (ECG) of all patients was performed. Gastric biopsies were taken from all under study patients with normal coagulation profile, normal ECG findings and normal renal function tests. Giemsa stain and gram stain were performed on gastric biopsies for confirmation of *H. pylori* infection.

The selected 300 patients were distributed randomly in two groups (Group A, Group B). Group A received standard triple therapy including clarithromycin 500mg, amoxicillin 1g, and omeprazole 20mg were given twice a day for two weeks. Group B received levofloxacin 250mg twice a day in place of clarithromycin whereas rests of two medicines remain the same. Follow up of these patients was done at the end of first and second week of treatment to record adverse effects of medicine if any. Final follow up was done 8 weeks after completion of therapy and *H. pylori* stool antigen test was performed using ELISA technique to record cure rate of treatment in both understudy groups. Data was analyzed by using SPSS version 24 and MINITAB version 16. We calculated frequencies and percentages of categorical variables whereas mean and  $\pm$  SD of continuous variables were calculated. The Chi-square test was used for the comparison of quantitative data P-value <0.05 was considered as statistically significant. Moreover we apply two proportion Z-test to check the differences of proportions of two groups assuming that difference of proportion of both groups is equal to 0.30 and is not equal to 0.30. For this analysis we use MINTAB V.16.

## Results

Total 300 patients were enrolled in this study, in 2 groups

(Group A, Group B) with 150 patients were included in each group. Flow diagram representing the study groups showing total number of patients enrolled in study in both groups, total number of patients completed therapy, left treatment and loss of follow up is given in Figure.

Out of three hundred enrolled patients 179 were males and 121 were females. A total of (92 males, 58 females) and (87 males, 63 females) were included in group A and group B respectively. Overall mean age of patients was  $49.28 \pm 8.41$  range from 18 to 60 years. The mean age of patients in group A was  $48.93 \pm 8.51$  and mean age of patients enrolled in group B was  $49.61 \pm 8.33$ . Total 100 (33.3%) patients out of 300 patients were smokers, out of which 52 (34.7%) were in group A and 48 (32.0%) belong to Group B. Frequency and percentages of presenting complains, gastroscopy findings and biopsy results are represented in Table-1.

In Group A total 140 patients completed therapy and appeared for final follow up. In group A which was on standard triple therapy 87.85% (123 out of 140) cure rate was observed as per protocol analysis and 82% (123 out of 150) cure rate was observed according to intention to treat whereas 17 (11.3%) patients were not cured. In group B 145 patients completed therapy and appeared for final follow up. The cure rate in group B was 92.4% (134 out of 145) and 89.3% (134 out of 150) according to per protocol analysis and intention to treat respectively, whereas 11 (7.3%) were not cured. Overall better cure rate

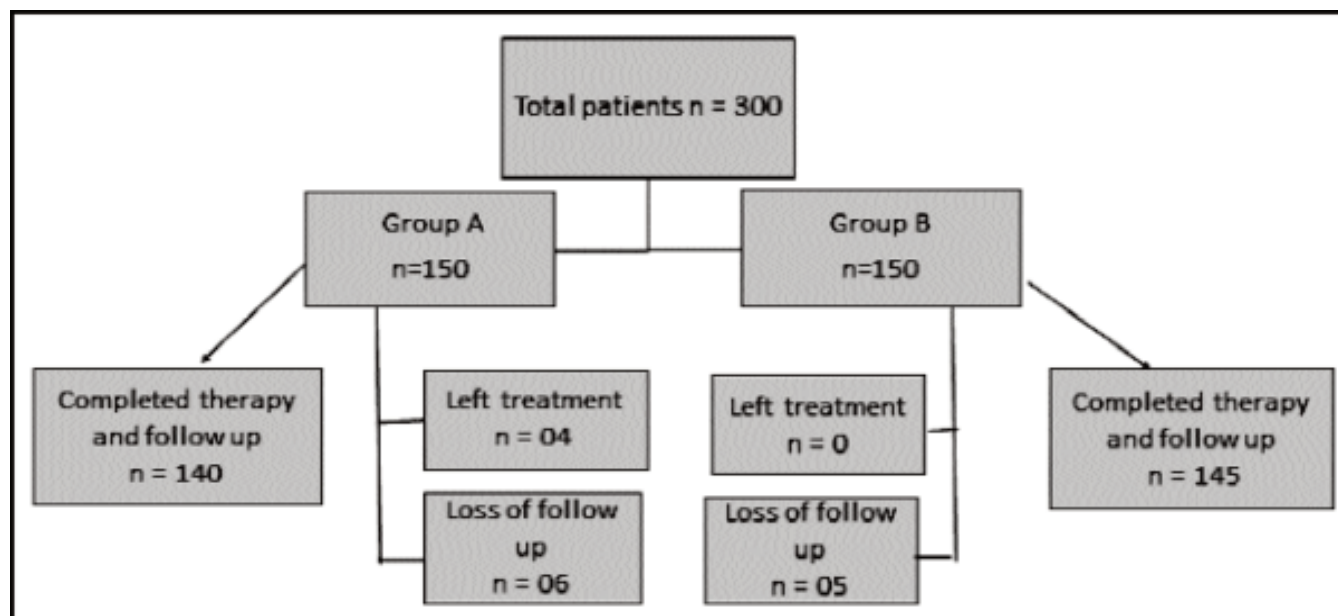
**Table-1:** Clinical characteristics of patients.

	Group A	Group B
<b>Presenting complaints</b>		
Dyspepsia	85 (56.7%)	81 (54.0%)
Pain epigastrium	58 (38.7%)	59 (39.3%)
Hematemesis & melena	7 (4.6%)	10 (6.7%)
<b>EGD* findings</b>		
Mild pangastritis	24 (16.0%)	17 (11.3%)
Moderate pangastritis	43 (28.7%)	40 (26.7%)
Severe pangastritis	43 (28.7%)	56 (37.3%)
Peptic ulcer with sever pangastritis	22 (14.6%)	25 (16.7%)
Multiple erosions & severe pangastritis	18 (12.0%)	12 (8.0%)
<b>Biopsy results</b>		
Mild chronic gastritis with H. pylori seen	76 (50.7%)	56 (37.3%)
Moderate chronic gastritis with H. pylori seen	46 (30.7%)	45 (30.0%)
Severe chronic gastritis with H. pylori seen	28 (18.6%)	49 (32.7%)

EGD: Esophagogastroduodenoscopy.  
H.pylori: *Helicobacter pylori*.

was found in group B but the difference in cure rates of both under study groups (Group A, Group B) was not statistically significant.

Another important finding of this study was that patients in group B receiving alternate therapy (Levofloxacin) experienced much less side effects as compared to patients in Group A receiving standard therapy (clarithromycin). Total 31 (20.7%) patients in Group B experienced different adverse effects whereas 70 (46.7%) patients of Group A



**Diagrammatic representation of under study groups (group A, group B) showing number of patients completed treatment, loss of followup and left treatment.**

**Figure:** Schematic representation of both study groups.

**Table-2:** Adverse effects resulting from antibiotic therapy in patients of both therapeutic groups.

Side effects	Group A	Group B
Skin rash	14 (9.3%)	8 (5.3%)
Diarrhoea	24 (16.0%)	17 (11.3%)
Stomatitis	32 (21.3%)	6 (4.0%)
No side effects	80 (53.4%)	119 (79.4%)

complain of facing different side effects. The difference of proportions of Group A and Group B is approximately 30% statistically insignificant ( $P= 0.678$ ). Frequencies and percentages of different type of adverse effects observed in both groups are presented in Table-2.

## Discussion

The results of present study demonstrate comparatively high resistance rate of clarithromycin based (standard) triple therapy against *H. pylori* whereas Levofloxacin based alternative treatment regimen improved the eradication rate against this infection. The results also suggested levofloxacin based alternative therapy is superior to previously in use clarithromycin based therapy because levofloxacin based therapy is more safe for patients and cause less side effects. Standard triple therapy including clarithromycin, amoxicillin and a proton pump inhibitor was proposed at first in the Maastricht conference, since then it has been adopted worldwide as first line therapy to treat *H. pylori* infection.<sup>17</sup> However in later decades the researchers reported that *H. pylori* infection is becoming resistant to conventional clarithromycin based therapy with eradication rate of 71% in United States, and even more low (60%) in Europe.<sup>18,19</sup> Considering that the acceptable target of cure rate was set at 80%. In regions where *H. pylori* cure rate is reported less than 80%, sensitivity testing must be performed for clarithromycin before prescribing it for treatment purposes or alternate medicinal options must be considered.<sup>20,21</sup>

Reasons behind failure of efficacy varies including resistance to antibiotic, poor compliance, acidity of the stomach, huge bacterial load, and polymorphism of cytochrome P450 2C19 (CYP2C19). Increased body mass index and smoking habit also affects eradication adversely.<sup>7</sup> Worldwide Levofloxacin had been introduced as an alternative antibiotic of clarithromycin during last few years and its efficacy had been tested against *H. pylori* in standard triple therapy, sequential therapy and in quadruple therapy strategies in many studies. According to the research data the cure rate of levofloxacin in standard triple therapy had been reported in range of 72% to 96% in different regions of the world. The studies used quadruple and sequential strategies also demonstrated results

encouraging use of levofloxacin in place of clarithromycin.<sup>7</sup>

In surrounding regions of Pakistan, a recent study conducted on 120 subjects in Iran reported eradication rate of 57.4% with clarithromycin whereas levofloxacin cured 80.4% of the patients according to per protocol analysis, thus encouraging use of levofloxacin in place of clarithromycin.<sup>22</sup> In another study conducted in India on peptic ulcer patients, the eradication rate of clarithromycin was 79% as compared to 87% cure rate of levofloxacin according to per protocol analysis.<sup>23</sup> Almost similar results had been reported by a Chinese study with eradication rate of clarithromycin 78.2% and levofloxacin 83% accordingly to per protocol analysis.<sup>24</sup>

Still not much data is available regarding eradication rate of *H. pylori* in our country. In this study 87.85% cure rate was observed with standard triple therapy according to per protocol analysis whereas 82.0% cure rate was observed according to intention to treat method. The overall cure rate using levofloxacin was superior to control group where 89.3% and 92.4% cure rate was observed according to intention to treat and per protocol analysis respectively. While comparing the overall cure rate in both groups there was no statistical difference. Similar results have been reported previously by Telaku S et al., 2013.<sup>25</sup> However side effects of clarithromycin when compared with levofloxacin were significantly high in the present study. Results of this study also reveals that in local population of studied region both antibiotics can be used to treat *H. pylori* infections since results of this study show sensitivity of both antibiotics above 80% of threshold set by first Maastricht declaration.

So much dissimilarity in results of many studies conducted in various regions of the world may be clarified by the fact that excessive use of certain antibiotic in local population of the area results in development of resistance against that antibiotic. Likewise ethnicity variation, different treatment duration and dosage of the drug used must also be well-thought-out while explaining the variation of results.<sup>22</sup> According to Fischbach and Graham recommendation, clinicians while prescribing medicine should always consider local sensitivity and resistance pattern and disregard statements of consensus and guidelines if they do not match with local results.<sup>20</sup> According to the recommendation of Asian Pacific *Helicobacter pylori* meeting held in 2012 in Singapore: standard triple therapy with clarithromycin should be the first choice in areas where clarithromycin resistance is still low than described threshold.<sup>7</sup>

This study suggested that standard clarithromycin based therapy against *H. pylori* is still effective in our local population. Levofloxacin based alternate therapy can be

given in cases where adverse effects caused by standard therapy are not bearable by the patient or as rescue treatment. The present study also contains several shortcomings as pre-treatment antimicrobial sensitivity testing of both under study drugs was not performed. Patients were not categorized on base of ethnicity, BMI and bacterial load which are reported to affect the cure rate. Genetic polymorphism is also reported to influence the eradication rate. Further studies should be conducted in which the genetic polymorphism of patients showing resistance to therapy should be performed.

## Conclusion

The results of this study shows that both regimens the standard triple therapy with clarithromycin and alternatively levofloxacin in place of clarithromycin can be used in local population of study area keeping in mind the factors including hypersensitivity to either of antibiotics, cost effectiveness and adverse effects. Clinicians must study their local regions to assess resistance pattern and to opt drug of choice.

**Disclaimer:** Unfortunately study was not registered to obtain a clinical trial number.

**Conflict of Interest:** None to declare.

**Source of Funding:** None to declare.

## Reference

1. Marshall B, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *The Lancet*. 1984; 323: 1311-5.
2. Vandenplas Y. Helicobacter pylori infection. *World J Gastroenterol*. 2000; 6: 20.
3. Kusters JG, van Vliet AH, Kuipers EJ. Pathogenesis of Helicobacter pylori infection. *Clin Microbiol Rev*. 2006; 19: 449-90.
4. Gatta L, Vakil N, Vaira D, Scarpignato C. Global eradication rates for Helicobacter pylori infection: systematic review and meta-analysis of sequential therapy. *BMJ*. 2013; 347: f4587.
5. Kuo CH, Hu HM, Kuo FC, Hsu PI, Chen A, Yu FJ, et al. Efficacy of levofloxacin-based rescue therapy for Helicobacter pylori infection after standard triple therapy: a randomized controlled trial. *J Antimicrob Chemother* 2009; 63:1017-24.
6. Mehmood K, Awan AA, Muhammad N, Hasan F, Nadir A. Helicobacter pylori prevalence and histopathological findings in dyspeptic patients. *J Ayub Med Coll Abbottabad*. 2014; 26: 182-5.
7. Kuo CH, Kuo FC, Hu HM, Liu CJ, Wang SS, Chen YH, et al. The optimal first-line therapy of Helicobacter pylori infection in year 2012. *Gastroenterol Res Pract*. 2012;2012: 168361.
8. Malfertheiner P, Megraud F, O'Morain C, Bazzoli F, El-Omar E, Graham D, et al. Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report. *Gut*. 2007; 56: 772-81.
9. Gisbert JP, Bermejo MF, Infante JM, Gallardo BP, Bermejo AB, Rodríguez JM, et al. Levofloxacin, amoxicillin, and omeprazole as first-line triple therapy for Helicobacter pylori eradication. *J Clin Gastroenterol* 2009; 43:384-5.
10. Cammarota G, Cianci R, Cannizzaro O, Cuoco L, Pirozzi G, Gasbarrini A, et al. Efficacy of two one week rabeprazole/levofloxacin based triple therapies for Helicobacter pylori infection. *Aliment Pharmacol Ther* 2000; 14:1339-43.
11. Di Caro S, Zocco MA, Cremonini F, Candelli M, Nista EC, Bartolozzi F, et al. Levofloxacin based regimens for the eradication of Helicobacter pylori. *European journal of gastroenterology & hepatology*. 2002; 14: 1309-12.
12. Marzio L, Coraggio D, Capodicasa S, Grossi L, Cappello G. Role of the preliminary susceptibility testing for initial and after failed therapy of Helicobacter pylori infection with levofloxacin, amoxicillin, and esomeprazole. *Helicobacter*. 2006; 11: 237-42.
13. Antos D, Schneider Brachert W, Bästlein E, Hänel C, Haferland C, Buchner M, et al. 7 Day Triple Therapy of Helicobacter pylori Infection with Levofloxacin, Amoxicillin, and High Dose Esomeprazole in Patients with Known Antimicrobial Sensitivity. *Helicobacter*. 2006; 11: 39-45.
14. Rispo A, Di Girolamo E, Cozzolino A, Bozzi R, Morante A, Pasquale L. Levofloxacin in First-line Treatment of Helicobacter pylori Infection. *Helicobacter*. 2007; 12: 364-5.
15. Pourhoseingholi MA, Vahedi M, Rahimzadeh M. Sample size calculation in medical studies. *Gastroenterol Hepatol Bed Bench*. 2013; 6: 14-7.
16. Naz F, Malik S, Afzal S, Anwar SA. Frequency of seropositivity of helicobacter pylori in patients presenting with dyspepsia. *J Ayub Med Coll Abbottabad*. 2013; 25: 50-4.
17. Malfertheiner P, Megraud F, O'Morain C, Bell D, Bianchi PG, Deltenre M, et al. Current European concepts in the management of Helicobacter pylori infection - the Maastricht consensus report. *Eur J Gastroenterol Hepatol* 1997; 9: 1-2.
18. Malfertheiner P, Bazzoli F, Delchier JC, Celinski K, Giguere M, Riviere M, et al. Helicobacter pylori eradication with a capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline given with omeprazole versus clarithromycin-based triple therapy: a randomised, open-label, non-inferiority, phase 3 trial. *Lancet*. 2011; 377:905-13.
19. Gisbert JP. Sequential or Concomitant Therapy for Helicobacter pylori Eradication? In Response. *J Clin Gastroenterol*. 2010; 44:658-9.
20. Graham DY, Fischbach L. Helicobacter pylori treatment in the era of increasing antibiotic resistance. *Gut*. 2010; 59:1143-53.
21. Graham DY, Lu H, Yamaoka Y. A report card to grade Helicobacter pylori therapy. *Helicobacter*. 2007; 12:275-8.
22. Haji-Aghamohammadi AA, Bastani A, Miroliaee A, Oveisi S, Safarnezhad S. Comparison of levofloxacin versus clarithromycin efficacy in the eradication of Helicobacter pylori infection. *Caspian J Intern Med*. 2016; 7: 267-71.
23. Gopal R, Elamurugan TP, Kate V, Jagdish S, Basu D. Standard triple versus levofloxacin based regimen for eradication of Helicobacter pylori. *World J Gastrointest Pharmacol Ther*. 2013; 4:23-7.
24. Cheng H, Hu FL, Zhang GX, Shi RH, Du YQ, Li ZS, et al. Levofloxacin-based triple therapy for first-line Helicobacter pylori eradication treatment: a multi-central, randomized, controlled clinical study. *Zhonghua Yi Xue Za Zhi*. 2010; 90:79-82.
25. Telaku S, Manxhuka-Kerliu S, Kraja B, Qirjako G, Prifti S, Fejza H. The efficacy of levofloxacin-based triple therapy for first-line helicobacter pylori eradication. *Med Arc*. 2013; 67:348-50.