Original Article

Clarithromycin vs. Gemifloxacin in Quadruple Therapy Regimens for Empiric Primary Treatment of *Helicobacter pylori* Infection: A Randomized Clinical Trial

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ABSTRACT

BACKGROUND

Eradication of *Helicobacter pylori* infection plays a crucial role in the treatment of peptic ulcer. Clarithromycin resistance is a major cause of treatment failure. This randomized clinical trial aimed at evaluating the efficacy of a clarithromycin versus gemifloxacin containing quadruple therapy regimen in eradication of *H.pylori* infection.

METHODS

In this randomized double blind clinical trial (RCT 2012102011054N2), a total of 120 patients were randomized to two groups of 60 patients each. Patients with proven *H.pylori* infection were consecutively assigned into two groups to receive OBAG or OBAC in gastroenterology clinic in Rasoul-e-Akram General Hospital in Tehran, Iran. The patients in the OBAG group received omeprazole (20 mg) twice daily, bismuth subcitrate (240 mg) twice daily, amoxicillin (1 gr) twice daily, and gemifloxacin (320 mg) once daily, and those in the OBAC group received omeprazole (20 mg) twice daily, 240 mg of bismuth subcitrate twice daily, amoxicillin (1 gr) twice daily, and clarithromycin (500 mg) twice daily for 10 days.

RESULTS

Five patients from each group were excluded from the study because of poor compliance, so 110 patients completed the study. The intention-to-treat eradication rate was 61.6% and 66.6% for the OBAC and OBAG groups, respectively. According to the per protocol analysis, the success rates of eradication of *H.pylori* infection were 67.2% and 72.7% for OBAC and OBAG groups, respectively (p=0.568).

CONCLUSION

The results of this study suggest that gemifloxacin containing regimen is at least as effective as clarithromycin regimen; hence, this new treatment could be considered as an alternative for the patients who cannot tolerate clarithromycin.

KEYWORDS
H.pylori; Gemifloxacin; Clarithromycin; Iran

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INTRODUCTION

Helicobacter pylori infection is not only a major cause of gastritis,

peptic ulcer, gastric cancer, and MALT (mucosa-associated lymphoid tissue) lymphoma but also plays a leading role in creation of iron deficiency anemia, vitamin B12 deficiency, and idiopathic thrombocytopenic purpura.[1]

Eradication rates in the first-line *H.pylori* therapy have been declining over the years, essentially due to increasing resistance against the recommended antibiotics of metronidazole and clarithromycin. Resistance of *H.pylori* to clarithromycin is an important reason for the treatment failure.[2,3]

Fluoroquinolones are active against gram–negative bacteria such as *H.pylori* and have a synergistic effect with proton pump inhibitors (PPIs).[4,5] Some data showed that levofloxacin-based therapy was an effective treatment with 70-80% eradication rate.[6,7] Minehart evaluated the susceptibility of *H.pylori* to fluoroquinolones, and found that gemifloxacin was the most active agent followed by gatifloxacin, ciprofloxacin, levofloxacin, and moxifloxacin.[8]

Some studies in Iran showed that the resistance rate to clarithromycin was in the range of 5% to 45.2%.[9,10] Shokrzadeh and colleagues reported the resistance rates to metronidazole, ciprofloxacin, clarithromycin, and tetracycline as 40.5%, 2.4%, 14.3%, and 4.8%, respectively.[11] This alarming finding indicates an urgent need for introduction of new antibiotics in Iran.

The present study aimed at evaluating the efficacy of a clarithromycin versus gemifloxacin containing quadruple therapy regimen in eradication of *H.pylori* infection.

MATERIALS AND METHODS

This double blind randomized clinical trial (RCT 2012102011054N2) was conducted in Rasoul-e-Akram Medical University Hospital (Tehran, Iran) during 2012-2013. The participants were chosen from those patients with the complaint of dyspepsia who referred to the Gastroenterology Clinic of the hospital. They were enrolled for this study after giving informed consent.

A total of 120 patients were included to make two groups of 60 patients. The sample size was calculated assuming eradication of *H.pylori* in at least 85% of treated patients, aiming to detect a difference of 10% based on a 0.80 power to detect significant difference (p=0.05).

Exclusion criteria were: receiving *H.pylori* treatment, pregnancy, age lower than 18 years, history of chronic renal failure, congestive heart failure, decompensated liver cirrhosis, and gastric surgery.

The presence of *H.pylori* was defined as positive ^{13}C-urea breath test (UBT), positive pathology and/or rapid urease test (RUT). All biopsy samples were stained with hematoxylin & eosin and giemsa in Pathology Department by a pathologist, who was blinded to the treatment arm. The result of RUT was defined positive if the color of the gel turned pink or red 6 hours after examination. Of the 120 patients, 77 underwent endoscopy and were diagnosed by using RUT and/or histological evaluation (64.1%), and 43 were diagnosed by UBT (35.9%). Endoscopy was performed by the discretion of the managing physician.

A trained interviewer obtained demographic data and filled a standardized questionnaire. The participants were randomly assigned into two groups to receive OBAG or OBAC. The former group received omeprazole (20 mg) twice daily, bismuth subcitrate (240 mg) twice daily, amoxicillin (1 gr) twice daily, and gemifloxacin (320 mg) once daily for 10 days, and the latter group received omeprazole (20 mg) twice daily, bismuth subcitrate (240 mg) twice daily, amoxicillin (1 gr) twice daily, and clarithromycin (500 mg) twice daily for 10 days.

The participants were requested to refer again to the clinic during the second week to evaluate their compliance, as well as adverse drug effects. Compliance was acceptable when over 80% of the total medications were taken. The adverse effects included anorexia, nausea, vomiting, headache, skin rash, and bitter mouth. All the participants underwent UBT 8 weeks after completion of treatment to confirm *H.pylori* eradication.

Gender distribution as well as the efficacy and frequency of side effects in the two groups were compared by Chi-square test. Data analysis was performed on both per protocol (PP) and intention-to-treat (ITT) bases. A p-value<0.05 was considered

as statistically significant. Statistical analyses were performed using the SPSS software (version18; SPSS Inc.).

This study was approved by both the Deputy Research of Iran University of Medical Sciences and Colorectal Research Center at Rasoul-e-Akram General Hospital, Tehran, Iran.

RESULTS

A total of 120 patients were enrolled in the study, and randomly assigned into OBAG (n=60) or OBAC (n=60) groups. Five patients from each group were excluded from the study because of poor compliance. Both groups had similar compliance according to the number of pills used (OBAG=98.3%, OBAC=97.1%, p=0.903).

Finally, 110 patients completed their treatment and follow-up. They had a mean age of 40.57±12.74 years (range, 19-81 years). Fifty four (49.09%) patients were men. ITT and PP analyses showed similar eradication rate in both groups. According to the PP analysis, the success rates of eradication of *H.pylori* infection were 67.2% and 72.7% for OBAC and OBAG groups, respectively (p=0.568, table 1).

There was significant statistical difference in the eradication rate of *H.pylori* infection according to the pathological findings between the two groups (p=0.001, table 2). In logistic regression analysis, after adjusting for endoscopic and pathological findings, there was no significant difference between the two groups in response to the treatment (p=0.732).

Adverse drug effects were reported in 37 (61.66%) and 19 (31.66%) patients in the clarithromycin and gemifloxacin groups, respectively. Among those, only bitter mouth was significantly more common in the clarithromycin group (p=0.001, table 3).

DISCUSSION

Our findings in the present study showed that gemifloxacin is as effective as clarithromycin in eradication of *H.pylori* infection. 5-45% of *H.pylori* isolates from Iran show some degrees of resistance to clarithromycin.[9,10] To tackle this problem, an alternative drug that is effective, safe, and easy to use has been searched.

The eradication rate has got a decreasing trend by using clarithromycin from 2000 to 2012 in Iran. Fakheri and colleagues showed that the ITT eradication rate was 85% for clarithromycin in quadruple therapy regimens in 2000.[12] However, similar to the present study, Minakari and co-workers found the eradication rates of ITT and PP as 64.5% and 74.7%, respectively, by using amoxicillin, clarithromycin, bismuth and omeprazole as the second-line therapy.[13]

The main risk factor for clarithromycin resistance is previous consumption of macrolides. Although clarithromycin had not been introduced in Iran, some studies has shown 17% resistance rate to this drug. Erythromycin was used instead of it in Iran.[14,15]

Several authors have reported an increasing trend in clarithromycin resistance rates in other areas of the world such as Latin America and Turkey.[16,17] In contrast, there was no change in the trend of *H.pylori* eradication rate by using PPI, clarithromycin and amoxicillin over the recent 11 years in Korea.[18]

Unfortunately, inappropriate use of antibiotics, especially macrolides in Iran has led to the emergence and spread of resistant bacteria, and plans to reduce the over-prescription of antibiotics by physicians should be arranged.

It is important to keep in mind that clarithromycin containing triple therapy is not an appropriate regimen when resistance is between 7% and 10%.[19] So identifying alternative treatments that are more effective than clarithromycin against *H.pylori* is crucial.

Some randomized trials have shown that a levofloxacin containing therapy is more effective compared with a clarithromycin containing regimen.[6,20] There are reports showing that levofloxacin had significant activity against *H.pylori* in vitro but no cross-resistance to B-lactams and macrolides. Moreover, it had a synergistic effect with PPIs.[4-5]

The eradication rate of levofloxacin-containing triple therapy ranged from 72% to 96%. Some

Table 1: **Demographic data and treatment results in patients receiving OBAC and/or OBAG**

Variables		Gemifloxacin	Clarithromycin	*p*-value
Mean age		41.20±14.00	39.93±11.98	0.646
Male		22 (40%)	34 (58.3%)	0.028
Smoking		6 (13.3%)	6 (13.3%)	0.990
Endoscopy		38(69.09%)	39(70.90%)	0.890
Endoscopy	Non-erosive gastritis	3	2	0.870
	Erosive gastritis	14	14	
	Peptic ulcer	21	23	
Treatment result	ITT[1](n=60)	40 (66.6%)	37 (61.6%)	0.568
	PP[2](n=55)	40 (72.7%)	37 (67.2%)	

[1]ITT= intention to treat,
[2]PP=per protocol

Table 2: **Eradication rate of *H. pylori* infection in the two groups receiving OBAC and/or OBAG tratment**

Endoscopic findings OBAC group	n	Eradication rate(%)	*p*-value
PUD[1]	23	16 (73.91)	0.001
Erosive gastritis	14	8 (57.14)	
Non-erosive gastritis	2	2 (100)	
Endoscopic findings OBAG group			
PUD[1]	21	11 (52.38)	
Erosive gastritis	14	10 (71.42)	
Non-erosive gastritis	3	1 (33.33)	

[1]Peptic ulcer disease

Table 3: **Adverse effects reported by the patients during the treatment**

Adverse effect	OBAC (n=55)	OBAG (n=55)
Nausea	3	2
Vomiting	1	1
Diarrhea	3	3
Abdominal pain	2	3
Headache	2	2
Skin rash	1	6
Bitter mouth*	25	2

*$p<0.001$

authors suggest that this regimen is reasonable in populations with clarithromycin resistance greater than 15-20% and fluoroquinolones resistance less than 10%.[21] But it might not be as the first-line therapy because over-consumption of fluoroquinolones would likely lead to the emergence of more quinolone-resistant pathogens responsible for other organs infections.[19]

A first-line eradication regimen should be based on the prevalence of antimicrobial resistance in Iran. Primary resistance of *H.pylori* isolates in Iran was to clarithromycin (34%), levofloxacin (5.3%), and moxifloxacin (4.6%).[22] So we need more studies to identify the best regimen for *H.pylori* infection therapy.

Gemifloxacin has shown an spectrum of activity against Gram-positive and Gram-negative bacteria. Its mechanism of action focuses on inhibiting DNA gyrase and topoisomerase, thus preventing cellular replication.[23] Some studies have shown that gemifloxacin is superior to levofloxacin in antimicrobial activity against *H. pylori*, and even overcomes some levofloxacin resistance.[8,24]

Graham suggested that in empiric therapies that did not reliably yield 90% or greater cure, ITT should not be prescribed.[25] It has been reported that standard triple therapy is not a suitable regimen in the areas with clarithromycin resistance over 20% because the PP eradication rate of that regimen is often less than 85%, and the ITT eradication rate is usually less than 80%.[26]

To overcome the problem of the growing clarithromycin resistance in the Middle East, several methods of treatment have been proposed, including the extension of the treatment duration to 14 days, and using bismuth-containing quadruple, sequential, and concomitant treatments.[19] Nasa and colleagues reported that sequential therapy was

better than standard therapy for eradicating *H.pylori* infection.[27] More studies are needed to find the best regimen for eradication of *H.pylori* in Iran.

The results of this study suggest that gemifloxacin containing regimen is at least as effective as clarithromycin regimen; hence, this new treatment could be considered as an alternative choice for the patients who cannot tolerate clarithromycin. Non-optimal result of the two regimens may be due to the emergence of resistant strains of *H.pylori* in Iran. So empirical use of these regimens without susceptibility testing may not be appropriate.

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CONFLICT OF INTEREST

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

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