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Clarithromycin versus Gemifloxacin in Quadruple Therapeutic Regimens for *Helicobacter Pylori* Infection Eradication

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ABSTRACT

BACKGROUND

Helicobacter pylori (*H. pylori*) infection is a major casual factor in any peptic diseases. Clarithromycin as one of the drugs recommended for the infection eradication regimen has shown different levels of resistance. The present study is comparing the effectiveness of clarithromycin- and gemifloxacin - based quadruple regimens in *H. pylori* eradication.

METHODS

This was a prospective double blind randomized clinical trial on patients with clear indication of *H. pylori* eradication. The patients were randomly divided into two groups: "BPAC group" treated with bismuth subcitrate (240 mg), pantoprazole (20 mg), amoxicillin (1 gr), and clarithromycin (500 mg), all twice daily, and the "BPAG group" treated with bismuth subcitrate, pantoprazole, and amoxicillin with same doses as "BPAC group" and gemifloxacin (320 mg daily) all for 10 days. Three months after the end of therapy, 14C-Urea breath test was performed to confirm the eradication. All the patients were assessed for compliance and drug side effects. Based on per-protocol (PP) and intention-to-treat (ITT) methods, data were analyzed and a *P* value<0.05 was considered as statistically significant. This project has been registered in the Iranian registry of clinical trials (IRCT).

RESULTS

Three patients were excluded from the survey and finally, 179 patients (89 patients in BPAC group and 90 patients in BPAG group) including 71(39.66%) men with the mean age of 46.4±12.3 years completed the treatment period. The incidence of side effects between the two study groups did not differ significantly. The success rate of BPAC regimen eradication was remarkably greater than BPAG regimen (ITT analysis; 89% vs 77%, respectively; CI 95%: 1.072-5.507, *P*<0.015 and PP analysis; 91% vs 77.8% respectively; CI 95%: *P*<0.015). There was no significant relationship between the demographic features and the eradication results.

CONCLUSION

The results showed that gemifloxacin is not a good alternative for clarithromycin in *H. pylori* eradication regimens in our region.

KEYWORDS:
Helicobacter pylori infection; Eradication regimens, Clarithromycin, Gemifloxacin.

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INTRODUCTION

On the basis of the fact that there is a wide range of *Helicobacter pylori* (*H. pylori*) infection prevalence rate among the world's populations (50-70%)[1] , it seems that it is the most common human infection worldwide. Also, some

epidemiological surveys have reported that the infection has affected about 20-50% of the population in Western countries and up to 80% in developing countries.[2,3]

Currently, the strong relationship between *H. pylori* infection and chronic gastritis, peptic ulcer disease, and gastric cancers is well demonstrated.[2-4] On the other hand, eradication of the infection is associated with ulcer healing[4], regression of mucosa associated tissue lymphoma[5], and decreased cancer risk.[6] Therefore, the eradication of the pathogen is of great importance to reduce *H.pylori* related complications.

The most approved *H. pylori* infection eradication regimen, with a success rate of around 80%[7], is a quadruple combination of an acid suppressor (usually a proton pump inhibitor), and bismuth subcitrate with two antibiotics (amoxicillin, metronidazole, tetracycline, or clarithromycin).[8]

Currently, due to the high level of antimicrobial resistance, patients' poor compliance, and drugs side effects, the treatment failure rate is increasing.[9] Considering this worldwide problem, there has been a search for an alternative drug that is effective, safe, easy to use, inexpensive, and with a low propensity to induce the development of resistant strains.[8,9]

One of the drugs that show such a high level of resistance is clarithromycin.[9] In a recent study, Camargo and colleagues[10], reported 12% resistance for clarithromycin. Also, some Iranian surveys such as those performed by Farshad[11], Abadi[12], and their colleagues showed a resistance rate of 5-45.2% for this macrolid. Based on these findings and the fact that Iran is one of the developing countries with high prevalence of *H. pylori* infection (83.5%)[13], the importance of *H. pylori* eradication and replacing clarithromycin with other antibiotics becomes more evident.

The present study is evaluating the *H. pylori* eradication rate of gemifloxacin in comparison with clarithromycin in quadruple regimen combined with bismuth subcitrate, pantoprazole, and amoxicillin.

MATERIALS AND METHODS

This was a prospective double blind randomized clinical trial, designed by Gastrointestinal and Liver Diseases Research Center of Guilan University of Medical Sciences, in Rasht the capital of Guilan province, northern Iran, from October 2013 to August 2014.

We included the consecutive patients (aged between 18 to 80 years) with dyspepsia and no history of previous *H. pylori* treatment, referred to internal medicine and gastroenterology clinics. If the presence of *H. pylori* infection was established and there was a clear indication for the eradication therapy, the patient would be enrolled to the study. *H. pylori* infection defined as positive 14C-Urea breath test (UBT) or positive pathology of the endoscopic biopsy samples. The samples were analyzed by a pathologist who was blind to the study protocol. Dyspepsia is a general term that refers to symptoms originating from the upper gastrointestinal tract. As such, it may encompass a variety of symptoms. Typically, the affected patients describe epigastric pain but may also complain of heartburn, nausea, vomiting, abdominal distention, heartburn, early satiety, and anorexia.[14]

Exclusion criteria: Pregnant and breast feeding women, and patients with gastric and esophageal malignancies or surgeries, pyloric stenosis, liver cirrhosis, opium addiction, consumption of cholestyramine, chronic renal failure, congestive heart failure, history of seizure and hematologic disorders were excluded from the study.

Study protocol: At the first step, the demographic features were recorded and then all the patients were randomly divided into two groups. Randomization was done using the simple randomization method. The two study groups were: "BPAC group" (n=91) treated with bismuth subcitrate 240 mg, pantoprazole 20 mg, amoxicillin 1 gr, and clarithromycin 500 mg, all twice a day and the "BPAG group" (n=91) treated with bismuth subcitrate, pantoprazole, and amoxicillin with the same dose as the first group and gemifloxacin 320 mg daily, all for 10 days.

12 weeks after the end of the treatment, 14C-UBT was performed to confirm the eradication. All the patients were assessed for compliance and side effects. The severity of any side effects was classified as "mild" with no limitation of the usual daily activities, "moderate" with mild limitation, and "severe" with impossible daily activities. Also, compliance was acceptable when over 80% of the total medications were taken. The patients with severe side effects and no good compliance were excluded from the study. This study was reviewed and approved by the Ethics Committee of Guilan University of Medical Science, and written informed consent was

Table 1: Comparison of demographic features between the two study groups

Demographic features		BPAG (%) n=90	BPAC (%) n=89	*P* value
Gender	Male	31 (34.45)	40 (56.3)	NS
	Female	59 (65.55)	49 (2.05)	
Age group	20>	1 (1.1)	0 (0)	NS
	20-39	32 (35.56)	31 (34.83)	
	40-59	47 (52.23)	47 (52.81)	
	60<	10 (11.11)	11 (12.36)	
Smoking	Yes	8 (8.88)	6 (6.74)	NS
	No	82 (91.12)	83 (93.26)	
NSAIDs usage	Yes	29 (32.22)	23 (25.84)	NS
	No	61 (67.78)	66 (74.16)	
Duration of Symptoms	< 1 month	75 (83.33)	72 (80.9)	NS
	> 1 month	15 (16.64)	17 (19.1)	

BPAG: Bismuth subcitrate, Pantoprazole, Amoxicillin, Gemifloxacin; BPAC: Bismuth subcitrate, Pantoprazol, Amoxicillin, Clarythromycin; NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; p- value<0.05 considered as statistically significant

obtained from all the participants. Also, this project has been registered in the Iranian registry of clinical trials (IRCT registration number: IRCT201310221155N17).

Statistical analysis: All data were statistically analyzed using SPSS software for windows version 21.0 (SPSS Inc., Chicago, IL, USA). Using Chi-square test, the gender distribution and the efficacy and frequency of side effects were analyzed. Based on per-protocol (PP) and intention-to-treat (ITT) methods, the data were assessed and a *P* value<0.05 was considered as statistically significant.

RESULTS

Due to severe drug side effects, three patients were excluded from the survey; two patients in BPAC group (a man with severe diarrhea and a woman with severe nausea and vomiting) and one patient in BPAG group (a woman with severe nausea and no compliance). Finally, 179 patients (89 patients in BPAC group and 90 patients in BPAG group) including 71 (39.66%) men and 108 women (60.34%) with the mean age of 46.4±12.3 years completed the treatment period. Table 1 shows the demographic characteristics of the patients in both study groups.

The incidence of side effects between the two study groups did not differ significantly. The most frequent drug side effect was mild abdominal pain (15 cases in BPAC group vs 14 cases in BPAG group, table 2).

Table 3 shows the success rate of the two regimens based on two analyses; PP and ITT. Both analyses nearly showed similar results. Based on ITT analysis, the eradication rate achieved by the BPAC regimen was remarkably greater than that obtained by BPAG regimen (89% vs 77%, respectively; CI 95%: 1.072-5.507, OR=2.43, p<0.015). Also, based on PP analysis, the eradication rate achieved by the BPAC regimen was remarkably greater than that obtained by BPAG regimen (91% vs 77.8%, respectively; CI 95%: 1.2-6.975, OR=2.89, p <0.015). There was no significant relationship between the demographic features and the eradication results.

DISCUSSION

Currently, the treatment failure of *H. pylori* infection is increasing worldwide and an ideal therapeutic regimen has not yet been identified.[15] There are several theories for this medical limitation such as antibiotic resistance with changing the bacterial morphology as antibiotic exposure happens from spiral to coccoid appearance, patients' poor compliance, high gastric acidity, high bacterial load, and cytochrome P450 2C19 (CYP2C19) polymorphism.[15-17]

There are several studies declared that clarithromycin is an strong macrolide for *H.pylori* eradication, but this antibiotic shows a high level of resistant and is expensive and unavailable for every patient especially in some developing countries.[17,18] A possible cross resistance be-

Table 2: Drugs side effects

Table 2 Drugs side effects Drugs Side Effects	BAPG n=90 (%)		BAPC n=89 (%)		P value
	Mild	Moderate	Mild	Moderate	
Diarrhea	3 (3.33)	9 (10)	4 (4.5)	3 (3.37)	NS
Nausea	7 (7.77)	6 (6.67)	2 (2.25)	9 (10.11)	NS
Vomiting	3 (3.33)	0 (0)	1 (1.12)	3 (3.37)	NS
Heartburn	10 (11.11)	3 (3.33)	9 (10.11)	0 (0)	NS
Abdominal pain	8 (8.88)	7 (7.77)	9 (10.11)	5 (5.62)	NS
Loss of appetite	4 (4.45)	3 (3.33)	4 (4.5)	1 (1.12)	NS
Cramps	3 (3.33)	0 (0)	2 (2.25)	3 (3.37)	NS
Headache	4 (4.45)	5 (5.56)	6 (6.75)	4 (4.5)	NS
Dizziness	4 (4.45)	6 (6.67)	7 (7.86)	5 (5.62)	NS
Back pain	2 (2.22)	2 (2.22)	4 (4.5)	0 (0)	NS
Dry mouth	5 (5.56)	6 (6.67)	7 (7.86)	3 (3.37)	NS

CLD, chronic liver disease: EHPVO, extrahepatic portal vein obstruction; ESRD, endstage renal disease; HTN, hypertension; SMA, superior mesenteric artery; IBD, inflammatory bowel disease, NASH, non-alcoholic steatohepatitis; TB, tuberculosis; VA, villous atrophy

Table 3: ***H. pylori*** **eradication rate based on two analysis method**

	PP Analysis			P value	ITT Analysis			P value
	Eradicated	Not eradicated	Success rate		Eradicated	Not eradicated	Success rate	
BPAC	81	8	91 %	0.015	81	10	89%	0.03
BPAC	70	20	77.8 %		70	21	77%	

PP: Per Protocol; ITT: Intention to treat; BPAG: Bismuth subcitrate, Pantoprazole, Amoxicillin, Gemifloxacin; BPAC: Bismuth subcitrate, Pantoprazol, Amoxicillin, Clarythromycin; p-value<0.05 considered as statistically significant

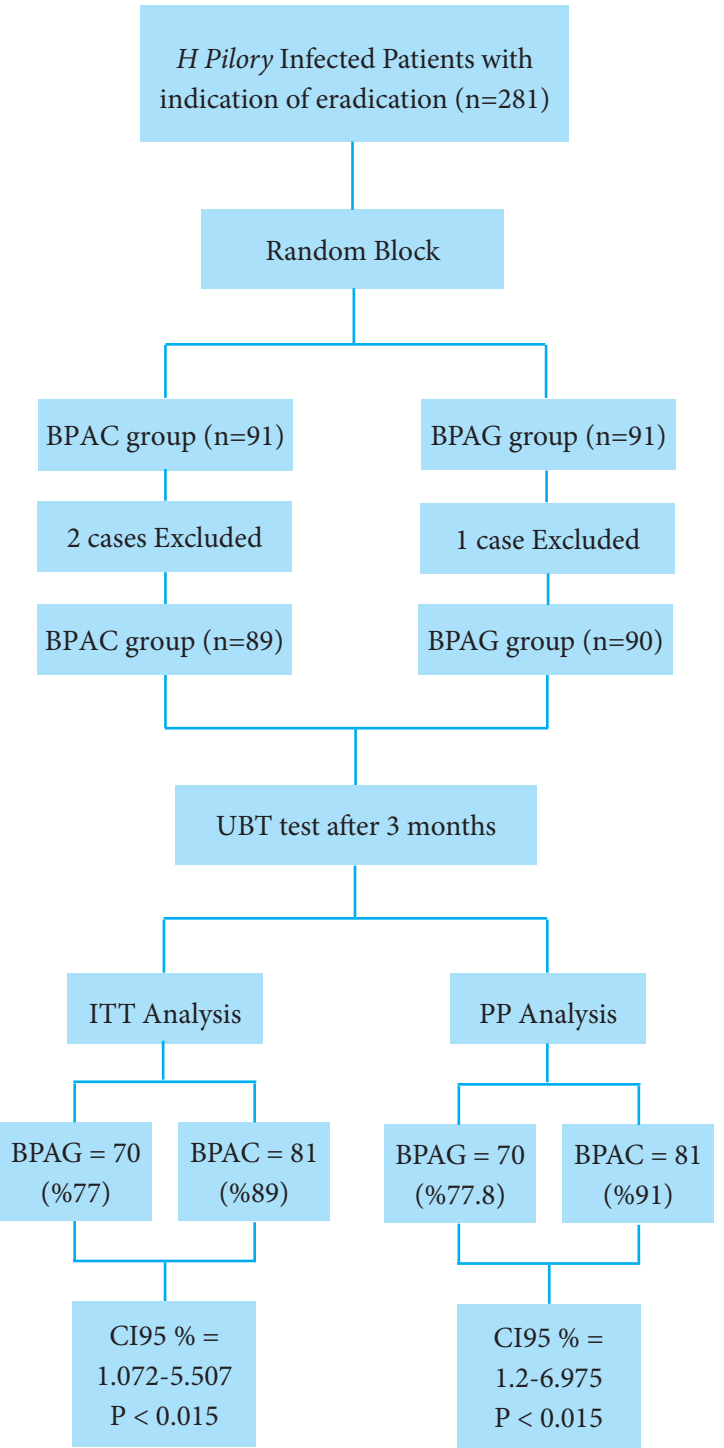
tween clarithromycin and erythromycin, an antibiotic that has been widely prescribed for various infections in Iran for many years, may partially explain the unexpectedly high resistance rate of clarithromycin.[18]

Fluoroquinolone-containing regimens are of other measures with good results for *H. pylori* infection treatment. One of these antibiotics is gemifloxacin, which inhibits DNA-gyrase and topoisomerase. Gemifloxacin prevents the cellular replication of gram-positive and gram-negative bacteria.[19]

There are a handful of studies in the literature on gemifloxacin, which claimed that in comparison with clarithromycin, gemifloxacin showed a higher treatment success rate in different infections.[20-23] Here we tried to compare the treatment results of two quadruple regimens based on clarithromycin and gemifloxacin in *H.pylori* infection eradication. Figure 1 shows a summary of this survey's method and results.

Our results presented a success rate of 77% for gemifloxacin with the ITT and 89% with clarithromycin, respectively. Clinical success in the PP was 77.8% with gemifloxacin and 91% with clarithromycin, respectively. Since the eradication rate of *H. pylori* infection by BPAC regimen was higher than 80%, it can be considered as an effective regimen in eradicating the infection. But, on the other hand, the BPAG regimen failed to achieve the eradication rate of 80%, so it cannot be used as an effective regimen for the eradication of *H. pylori* infection in our geographic region.

Our findings were similar to some other surveys presented the high power of clarithromycin in *H. pylori* infection treatment.[18, 24, 25] For example, Fakheri and colleagues[18], reported an eradication rate of 84% by ITT analysis for clarithromycin in quadruple therapy regimen. On the other hand, in contrast to our findings, there are several surveys declared that gemifloxacin was an effective antibiotic for *H. pylori* eradication.[26-28] In a randomized clinical trial, Masoodi and co-workers[27], presented that gemifloxacin containing regimen was at least as effective as clarithromycin regimen and this new treatment could



BPAC: Bismuth subcitrate, pantoprazole, amoxicillin, clarithromycin; BPAG: Bismuth subcitrate, pantoprazole, amoxicillin, gemifloxacin; UBT: 14C-Urea breath test; ITT: Intention to treat; PP: Per Protocol

Fig.1: Flow diagram of clarithromycin versus gemifloxacin therapy

be considered as an alternative for the patients who cannot tolerate clarithromycin. Also, Chang WL and colleagues[26], concluded that, comparing to fluoroquinolones, gemifloxacin had a more effective anti-bacterial activity on clinical types of *H.pylori*. In the present study the effect of clarithromycin was lower among the new cases without previous first-line treatment while in our last study[3], the patients were resistant to clarithromycin. In contrast to our results, in another recent study that was conducted among patients with first-line standard quadruple therapy (clarithromycin–amoxicillin–bismuth–omeprazole) failure, it was revealed that gemifloxacin-containing quadruple therapy provided high *H. pylori* eradication rate.[29] It seems that the first-line status of the patients affects the treatment results.

A limitation of our study was the lack of regional estimates of eradication rates with regard to antibiotic resistance. As these studies require personal-based evaluations and the drug resistance rate should be determined in each comparative study the expression of the adverse results obtained in this study highlights the consideration of the other factors such as gastric microbiota in the study population.[30]

Furthermore, the results of this study may not be applicable to patients who failed other treatments. Although the incidence of drug side-effects was similar between the two antibiotics, our findings showed that gemifloxacin was not a good alternative for clarithromycin. Because of the overt usage of macrolids in Iran, the drug resistance has been increased, so this study recommended reducing the over-prescription of such antibiotics by physicians. Also, other fluoroquinolone-containing regimens such as levofloxacine or ofloxacin would be good alternatives for clarithromycin, but it should be noted that in order to avoid a further rapid increase in *H. pylori* resistance to such alternative antibiotics, the usage of quinolones-based regimens should be confined to rescue therapy only.

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CONFLICT OF INTEREST

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

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