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Original Article

Levofloxacin+Tetracycline Quadruple Regimen for Eradication of *Helicobacter pylori*: A Multicenter Multinational Randomized Controlled Trial

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Abstract

Background: The ideal combination regimen for *Helicobacter pylori* (HP) eradication has not yet been determined and the success rate of HP eradication has been extensively reduced worldwide due to increasing antibiotic resistance. So this multinational multi-center randomized controlled trial was designed to evaluate the efficacy of tetracycline +levofloxacin for HP eradication.

Methods: During a 6-month period, all of the cases with HP infection in eight referral tertiary centers of three countries were included and randomly allocated to receive either tetracycline + levofloxacin or clarithromycin plus amoxicillin quadruple regimen for two weeks. For all of the participants, pantoprazole was continued for 4 more weeks and after one to two weeks of off-therapy, they underwent urea breath test C13 to prove eradication.

Results: Overall 788 patients were included (358 male (45.4%), average age 44.2 years). They were diagnosed as having non-ulcer dyspepsia (516 cases, 65.5%), peptic ulcer disease (PUD) (234 cases, 29.69%), and intestinal metaplasia (38 cases, 4.8%). Racially 63.1% were Caucasian, 14.5% Arab, 15.6% African, and 6.1% Asian. The participants were randomly allocated to groups A and B to receive either tetracycline + levofloxacin or clarithromycin. Among groups A and B in intention to treat (ITT) and per protocol (PP) analysis, 75.2% & 82.1% (285 cases) and 67.5% & 70.1% (276 cases) of participants achieved eradication, respectively ($P=0.0001$). The complete compliance rate in groups A and B were 84.4% and 83.6%, respectively. During the study, 33.5% of the participants in group A (127 cases) reported side effects while the complication rate among group B was 27.9% (114 cases, $P=0.041$). The most common complaints among groups A and B were nausea and vomiting (12.6% & 9.3%) and abdominal pain (4.48% & 2.68%), respectively. The rate of severe complications that caused discontinuation of medication in groups A and B were 2.1% and 1.46%, respectively ($P=679$). In subgroup analysis, the eradication rates of tetracycline+levofloxacin among patients with non-ulcer dyspepsia, PUD, and intestinal metaplasia were 79.4%, 88.1%, and 73.9%, respectively. These figures in group B (clarithromycin base) were 71.3%, 67.6%, and 61.5% respectively ($P=0.0001$, 0.0001, and 0.043).

Conclusion: Overall, the combination of tetracycline+levofloxacin is more efficient for HP eradication in comparison with clarithromycin+amoxicillin despite more complication rate. In areas with a high rate of resistance to clarithromycin, this therapeutic regimen could be an ideal choice for HP eradication, especially among those who were diagnosed with PUD.

Keywords: *Helicobacter pylori*, Eradication, Dyspepsia, Tetracycline, Levofloxacin

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Introduction

Helicobacter pylori (HP) is the most common chronic bacterial infection of the human gastrointestinal system worldwide.[1-3] While HP is an important cause of not only peptic diseases such as peptic ulcers, precancerous lesions, and gastric cancer but also morbidity in several organs.[4-8]

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the optimal therapeutic regimen for eradication of this infection is a challenge since 30 years ago and the subject of controversy and debates.[9,10] The clarithromycin-based quadruple therapeutic regimen is one of the first-line protocols for the eradication of HP and is recommended by the current guidelines.[10-13] However, primary resistance against clarithromycin is augmented in recent years and has been supposed as the main factor in decreasing the efficacy of HP eradication.[14-16]

Levofloxacin-based quadruple therapy and metronidazole are used widely as a second-line treatment of HP infection or as a salvage treatment[17-19] but increasingly, resistance is detected against not only levofloxacin but also metronidazole and outreaching this resistance is currently a clinical challenge.[20-25] The majority of levofloxacin-resistant clones have been identified to be linked to mutations in the fluoroquinolone resistance-determining region within the gyrA gene: Asn87 and Asp91.[26-28] Resistance to metronidazole in HP primarily involves the inactivation of the RdxA and FrxA genes.[29-31] But these mechanisms of resistance could be ignored for tetracycline, and quadruple-diets containing tetracycline seem to be a good choice to recommend as first-line treatment for HP eradication.[32] So this multicenter multinational randomized controlled trial was designed to evaluate the efficacy of levofloxacin + tetracycline quadruple regimen in comparison with clarithromycin plus amoxicillin for eradication of HP, which is challenging despite many available guidelines and different choices based on the current antibiotics resistance and HP infection status in each region.

Materials and Methods

During a 6-month period, all of the subjects who attended outpatients clinics of eight referral tertiary centers in three countries (Egypt, Iran, and Vietnam) with the complaint of dyspepsia whose HP infections were diagnosed based on tissue biopsy specimens were included and allocated randomly into groups A & B to receive either tetracycline + levofloxacin base quadruple regimen (pantoprazole 40 mg twice a day, tetracycline 500 mg twice a day, levofloxacin 500 mg daily, and bismuth sub salicylate 240 mg twice a day, group A) or clarithromycin plus amoxicillin quadruple regimen (pantoprazole 40 mg twice a day, clarithromycin 500 mg twice a day, amoxicillin 1gr twice a day, and bismuth sub salicylate 240 mg twice a day, group B) for 2 weeks. Randomization performed by allocation of computer generated random numbers to each participant and they were unaware of their therapeutic regimen. For all of the participants, pantoprazole 40 mg twice a day was continued for 4 more weeks and after 1 to 2 weeks of off therapy (week 7 or 8), they underwent a urea breath test to prove eradication (Heli FAN plus 13C, Germany & Sercon's ABCA2, UK). The rate of eradication and complication between the 2 groups was determined and compared.

Inclusion criteria were confirmation of HP infection by endoscopic biopsy or rapid urease test , age range between 18 to 95 years, and clinical and endoscopic diagnosis of peptic ulcer disease (PUD), non-ulcer dyspepsia or pathologic diagnosis of intestinal metaplasia. Exclusion criteria were severe heart failure, chronic renal failure, pulmonary insufficiency, advanced chronic liver diseases including viral hepatitis, active malignancy in the last 3 years, history of surgery on upper gastrointestinal (GI) tract, consumption of antibiotics in recent 4 weeks or HP eradication in the last six months, uncontrolled diabetes mellitus, any organ transplantation, allergy to any of the medications used in HP eradication regimen, any history of esophageal varices, pregnancy, or breastfeeding for women and warfarin or clopidogrel consumption.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, so this study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.HGOLESTAN.REC.1399.102) and registered in Iranian Registry of Clinical Trials (identifier: IRCT20200707048038N1). Before participation, the method of study was explained to all of the participants and they were requested to sign a consent form. They were in touch with the clinician by phone call and requested to report any potential complication or side effect.

We used SPSS software version 22.0 for data analysis. The data is described as mean, SD, and percent. Proportions of the patients were compared between the two treatment groups with the χ^2 and Fisher's exact tests. Two independent sample *t* test was used to compare two quantitative variables. Efficacy, number needed to treat (NNT), and number needed to harm (NNH) were calculated to assess the effects of the intervention. Analyses declared significant for *P* values < 0.05.

Results

Overall 788 patients were included (358 male (45.4%), average age 44.2 years). The demographic characteristics of the participants are mentioned in Table 1. They were diagnosed as having non-ulcer dyspepsia (516 cases, 65.5%), PUD (234 cases, 29.69%), and intestinal metaplasia (38 cases, 4.8%). Racially 63.1% were Caucasian, 14.5% Arab, 15.6% African, and 6.1% Asian

Table 1. The demographic characteristics of participants

Characteristic	Group A (LTBP)	Group B (CABP)	*P* value
M/F ratio	173/206	185/224	0.96
Age average (range)	44.2 (18-82)	44.2 (18-94)	0.94
Diagnosis			
PUD (GU + DU)	130 (59 + 71)	103 (39 + 64)	0.006
NUD	225	291	0.001
IM	24	14	0.057

LTBP: Levofloxacin, tetracycline, bismuth, pantoprazole; CABP: Clarithromycin, amoxicillin, bismuth, pantoprazole; M/F ratio: male to female ratio; PUD: Peptic ulcer disease; GU: Gastric ulcer; DU: Duodenal ulcer; NUD: Non-ulcer dyspepsia; IM: Intestinal metaplasia.

(Table 2). The participants were randomly allocated to groups A and B to receive either tetracycline + levofloxacin or clarithromycin (Figure 1).

Among groups A and B in intention to treat (ITT) and per protocol (PP) analysis, 75.2% and 82.1% (285 cases) and 67.5% and 70.1% (276 cases) of participants achieved eradication, respectively ($P=0.0001$). The complete compliance rate in groups A and B were 84.4% and 83.6%, respectively. During the study, 33.5% of the participants in group A (127 cases) reported side effects while the side effects rate among group B was 27.9% (114 cases, $P=0.041$). The rate of severe complications, which caused discontinuation of medication in groups A and B were 2.1% and 1.46%, respectively ($P=0.679$). The most common complaints among groups A and B were nausea and vomiting (12.6% and 9.3%) and abdominal pain (4.48% and 2.68%), respectively (Table 3). In subgroup analysis, the eradication rates of tetracycline + levofloxacin among patients with non-ulcer dyspepsia, PUD, and intestinal metaplasia were 79.4%, 88.1%, and 73.9%, respectively. These figures in group B (clarithromycin base) were 71.3%, 67.6% & 61.5% respectively (P = 0.001, 0.001 & 0.043).

Apart from cases with Turk and Afghan races (too few cases to have a meaningful comparison), the most effective results for the tetracycline + levofloxacin combination were seen among those of African descent (Table 2). The NNT and NNH of this combination in comparison with the clarithromycin base quadruple regimen were 8 and 17 respectively and its efficacy was 15% more.

Table 2. Eradication rate based on race of participants

Race	Eradication Rate		*P* value
	Group A (LTBP)	Group B (CABP)	
Caucasian	81% (162/200)	74.9% (197/263)	0.002
Arab	74.6% (44/59)	59.5% (25/42)	0.314
African	90% (54/60)	55% (33/60)	0.001
Asian	87.5% (21/24)	70.8% (17/24)	0.155
Turk	100% (3/3)	66.6% (2/3)	0.27
Afghan	100% (1/1)	100% (2/2)	0.84

LTBP: Levofloxacin, tetracycline, bismuth, pantoprazole; CABP: Clarithromycin, amoxicillin, bismuth, pantoprazole.

Discussion

Despite the importance of effective HP eradication, the success rate has decreased significantly in recent years mostly due to the widespread consumption of antibiotics around the world, especially in developing countries. While the eradication rate with standard triple therapy has been around 80% just 3 decades ago, the rate declined to 45-60%, which could be an alarming sign of antibiotic resistance and treatment failure.[33-36]

Besides resistance, antibiotics' side effects are another issue that can affect compliance and acceptance of any therapeutic regimen and encourage researchers and clinicians to seek shorter courses of effective therapy with fewer antibiotics and minimal doses as much as possible.[37-39]

In recent years, the resistance to levofloxacin was reported to be more than 30% with an ascending slope.[36,40] This high rate of resistance has been also true for clarithromycin (>30%) but one of the lowest resistance rates has been reported about tetracycline (15%), which probably could be explained by less interest in the participation of this antibiotic for HP eradication.[36,41,42] On the other hand, there has been no resistance in vitro to both levofloxacin and tetracycline and even resistant strains to levofloxacin have been susceptible to tetracycline.[43,44] So the current

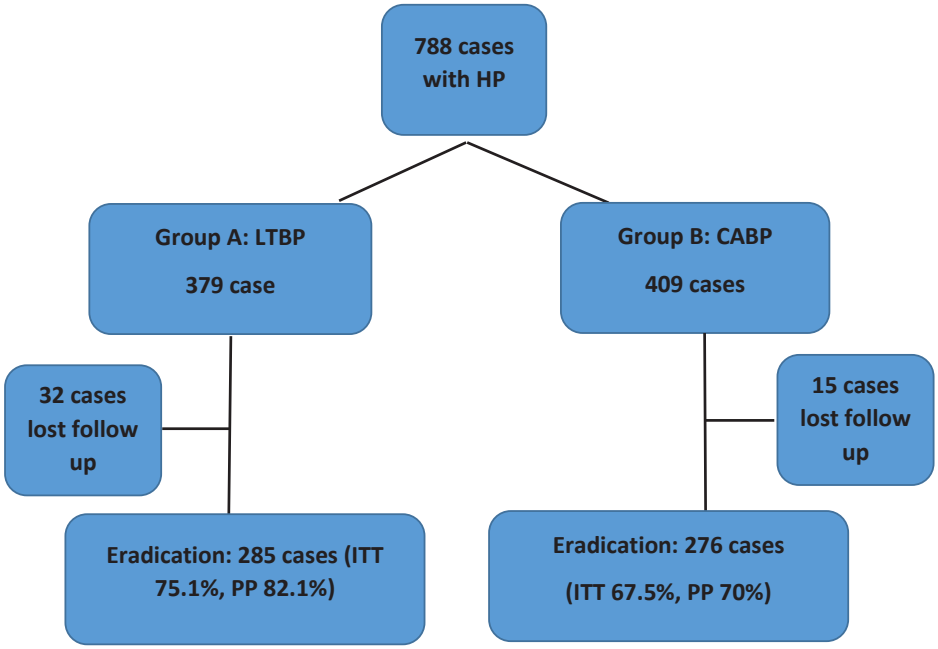

Figure 1. Flow chart of study. HP: *Helicobacter pylori*; LTBP: Levofloxacin, tetracycline, bismuth, pantoprazole; CABP: Clarithromycin, amoxicillin, bismuth, pantoprazole; ITT: Intention to treat; PP: Per protocol.

Table 3. Reported complaints during HP eradication, some of the participants had more than one complaint

Complaint	Group A (LTBP)	Group B (CABP)
Nausea & vomiting	48 (12.6%)	38 (9.3%)
Abdominal pain	17 (4.48%)	11 (2.68%)
Headache	14 (3.6%)	12 (2.93%)
Diarrhea	10 (2.6%)	12 (2.93%)
Constipation	8 (2.1%)	3 (0.73%)
Arthralgia	6 (1.6%)	1 (0.24%)
Fatigue	5 (1.3%)	5 (1.2%)
Bloating	5 (1.3%)	0 (0%)
Bitter taste	4 (1%)	8 (1.95%)
Loss of appetite	3 (0.79%)	2 (0.48%)
Body pain	3 (0.79%)	2 (0.48%)
insomnia	2 (0.52%)	0 (0%)
Dark urine	2 (0.52%)	0 (0%)
Palpitation	1 (0.26%)	0 (0%)
Mouth ulcer	1 (0.26%)	0 (0%)
Leg pain	1 (0.26%)	0 (0%)
Hypersensitivity reaction	1 (0.26%)	1 (0.24%)
Gastrointestinal upset	1 (0.26%)	0 (0%)
Eructation	1 (0.26%)	0 (0%)
Heartburn	0 (0%)	9 (2.2%)
Vertigo	0 (0%)	5 (1.2%)
Dysgeusia	0 (0%)	4 (0.97%)
Paresthesia	0 (0%)	1 (0.24%)
Itching	0 (0%)	1 (0.24%)
Hematemesis	0 (0%)	1 (0.24%)
Dry mouth	0 (0%)	1 (0.24%)

LTBP: Levofloxacin, tetracycline, bismuth, pantoprazole; CABP: Clarithromycin, amoxicillin, bismuth, pantoprazole.

study which was performed as a multinational multicenter controlled trial, compared the efficacy of levofloxacin plus tetracycline quadruple therapy to find if there is any role for an almost old medicine in the eradication of HP and this combination is capable to overcome levofloxacin resistance or not.

The findings of this study (82.1% eradication rate by levofloxacin plus tetracycline quadruple therapy) were similar to a study by Hsu and colleagues in 2017 who found this combination to be highly effective (98% success rate) and suggested a 10-day proton pump inhibitor (PPI)-bismuth-tetracycline-levofloxacin quadruple therapy as a good option for rescue treatment of HP infection following the failure of standard triple or non-bismuth quadruple therapy.[45] But the mentioned study was a single center with the participation of 100 cases. Similar results were reported by a multi-center study about 10-day quadruple therapy comprising PPI, bismuth, tetracycline, and levofloxacin that achieved a very high eradication rate for HP infection after failure of sequential therapy. They reported well tolerance and suggested this protocol to have great potential to become a good choice of rescue treatment following non-bismuth-containing quadruple therapy in regions with high clarithromycin resistance.[46] But this study included just 24 cases and few numbers of participants could interpret as an important limitation.

Another study in 2015, found that the resistance rate to levofloxacin in comparison with tetracycline was 40.2% vs. 1.1% and concluded increasing fluoroquinolone resistance has made tetracycline quadruple therapy a better choice for empiric second-line therapy for HP infection. However, compliance was significantly higher with levofloxacin-bismuth quadruple therapy.[47] A systemic review and meta-analysis in 2016 reported the efficacies of levofloxacin triple therapy before 2008, between 2009 and 2011, and after 2012 were 77.4%, 79.6%, and 74.8% respectively[48] which is lower than our findings (82.1%), which proves the importance of combining levofloxacin with tetracycline. They also reported that the eradication rate was higher when levofloxacin was given once daily (80.6%, 95% CI: 77.1-83.7) than twice daily (73.6%, 95% CI: 69.7-77.2) and this suggested dose is similar to the current study. The possible explanation was that levofloxacin is a concentration-dependent anti-microbial agent and unlike time-dependent antibiotics, the therapeutic effect is mostly correlated with the ratio of the area under the concentration-time curve to minimal inhibitory concentration.[49]

In the literature review, there are a lot of studies that used levofloxacin for HP eradication as sequential therapy with contradictory results.[34,50] These differences could be explained by regional patterns of bacterial resistance and the popularity of specific antibiotic prescriptions in any defined region.[51,52]

The complications and side effects of the levofloxacin-based regimen were more than quadruple standard clarithromycin-based regimen (35.5% vs. 27.9%, $P=0.041$) and in contrast to the study of Alsaadi and colleagues who found the side effect with clarithromycin more than with levofloxacin[53] and also the multicentric Spanish study on 300 cases, which reported minor complications such as nausea and myalgia in up to 20% of cases without any major side effect.[18] Despite the high rate of complaints especially nausea and vomiting (12.6%) and abdominal pain (4.48%), most of them were mild and did not interfere with continuing medications and therapeutic regimen success rate.

In subgroup analysis, the highest rate of eradication was seen among those suffering from PUD (gastric ulcer 88.1%, deudenal ulcer 86.7%) and similar to previous experiences with clarithromycin- and furazolidone-based regimens.[54] A possible explanation for this superiority could be better compliance and commitment to medication among those who were diagnosed as having PUD due to fear of bleeding or catastrophic events. One of the distinctive features of the current study is the participation of patients from different geographic regions with different races and subgroup analysis based on descent. During this study, the best results with the combination of levofloxacin + tetracycline

were seen among those of African and Asian descent (90% & 87.5% respectively, Table 2), which probably could be explained based on regional differences of resistance pattern and could offer this combination as an ideal first line choice for HP eradication in North Africa and East Asia. The advantage of the current study is to be multi-centric with a considerable number of participants and the inclusion of different races. As we performed this study during COVID-19 pandemic, there were some limitations in case collection and some of the centers were unable to complete the exact requested number of participants or achieve their follow-up due to social restrictions. Another limitation of our study is that we did not separate those who experienced HP eradication more than 6 months before the study from naïve patients.

Conclusion

Overall, the combination of tetracycline + levofloxacin is more efficient for HP eradication in comparison with clarithromycin + amoxicillin despite more side effects. In areas with a high rate of resistance to clarithromycin, this therapeutic regimen could be an ideal choice for HP eradication, especially among those who diagnose with PUD or those of African or Asian descent.

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Competing Interests

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

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