Efficacy of Two-Week Therapy with Doxycycline-Based Quadruple Versus Levofloxacin Concomitant for *Helicobacter Pylori* Infection: A Prospective Single-Center Randomized Controlled Trial.

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Research Article

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Abstract

Background: Antibiotic-resistant reduces the efficacy of conventional triple therapy for *Helicobacter Pylori* infections worldwide, lead to varying treatment protocols according to locations. This was an open-label randomized controlled trial. We used two protocols, doxycycline-based quadruple and concomitant levofloxacin regimens. The aim was to compare the eradication rates of previous protocols as empirical first-line treatment to cure *Helicobacter Pylori* infection in intention-to-treat (ITT) and per-protocol analyses (PPA) in Syrian population.

Settings and Design: an open-label parallel randomized controlled trial.

Methods: We randomly assigned seventy-eight naïve who tested positive for *Helicobacter Pylori* gastric infection, with a 1:1 ratio to (D-group) which receive (bismuth subsalicylate 524 mg four times daily, doxycycline 100 mg, tinidazole 500 mg, and esomeprazole 20 mg, each twice per day for two weeks), or (L-group) which receive (levofloxacin 500 mg daily, tinidazole 500 mg, amoxicillin 1000 mg, and esomeprazole 20 mg each twice per day for two weeks). We confirmed *Helicobacter Pylori* eradication by stool antigen test at eight weeks.

Results: Thirty-nine patients were allocated in each group. In the D-group, thirty-eight patients completed the follow-up, thirty patients were cured. While in the L-group, thirty-nine completed the follow-up, thirty-two patients were cured. According to ITT, the eradication rates were 76.92%, and 82.05%, for the D-group and L-group respectively. Odds ratio with 95% confidence interval was 1.371 [0.454-4.146]. According to PPA, the eradication rates were 78.9 %, and 82.05% for the D-group and L-group respectively. The odds ratio with 95% confidence interval was 1.219 [0.394-3.774]. We didn't report serious adverse effects.

Conclusions: The eradication rates in both therapy regimes were fair. Further researches are required to identify the optimum first-line treatment for *Helicobacter-Pylori* Infection in the Syrian population.

Trial registration: We register this study as a standard randomized clinical trial (Clinicaltrial.gov, identifier-NCT04348786, date:29-January-2020, <https://clinicaltrials.gov/ct2/show/NCT04348786>).

Background:

Eastern Mediterranean region countries have a high prevalence rate of *Helicobacter Pylori* (H.Pylori) infection [1]. Chronic infection of H. Pylori contributes to multiple diseases such as peptic ulcer disease and subsequent bleeding [2–4], dyspepsia, gastric adenocarcinoma, [5] mucosa-associated lymphoid tissue (MALT) lymphoma [6], idiopathic thrombocytopenic purpura, [7] unexplained iron deficiency anaemia. [8] World health organization has listed the H.Pylori infection as a class 1 carcinogen.[9] Eradication of H.Pylori cures previous diseases and can decrease the risk of gastric cancer.[10] Globally rate of eradication of H. Pylori infection is decreasing due to increased antibiotic resistance particularly clarithromycin and levofloxacin. [11]. In the eastern Mediterranean area, the resistance to clarithromycin, metronidazole, levofloxacin, amoxicillin, and tetracycline were 29%,61%,23%,14%,10% respectively.[12] Several researchers reviewed many therapy regimens including sequential, concomitant, and hybrid to find the best treatment protocol. [13] The results of conventional triple therapy in Syria were disappointed, [14] Currently tetracycline is unavailable in Syria, we use doxycycline in the bismuth quadruple regimen.[15, 16]Although tinidazole isn't superior to metronidazole in treating *Helicobacter Pylori* infections, [17] we used tinidazole instead of metronidazole in both regimens, as H. pylori had high metronidazole resistant rate. [18] Metronidazole is a very commonly used drug in Syria to treat gynaecological and gastrointestinal complaining with excessive overuse,[19] and tinidazole is more compliant and less confusing to patients with two dosages. There is a lack of data about the efficacy of doxycycline-based quadruple regimen and levofloxacin-containing quadruple concomitant regimen in

Syrian patients, we conducted this trial to evaluate the efficacy and report the eradication rate according to intention to treat analysis (ITT) and per-protocol analysis (PPA).

Methods:

This was a prospective single-center an open-label parallel randomized controlled trial. This study was performed in the department of gastroenterology at Damascus hospital, Syria. We recruited appropriate candidates from patients who visited our clinic for evaluation of dyspeptic symptoms by upper gastrointestinal endoscopy between February 2020 to August 2020. Exclusion criteria were (1) younger than 18 years and older than 80 years, (2) prior eradication treatment for H pylori, (3) documented reactions to any of the studied medications ,(4) recent use of antibiotics, bismuth, or proton pump inhibitors (PPIs) in the preceding month, (5) pregnant or lactating women, (6) previous gastric surgery, (7) alcohol or opioid abuse, or (8) severe concurrent medical illnesses, such as liver failure, renal failure, or terminal malignancy.

H. pylori Detection

All patients have undergone upper gastrointestinal endoscopy. Endoscopists have taken five gastric biopsies, two from the antrum, two from the body, and one from the incisura according to the Sydney system.[20] Pathologists confirm H. Pylori infection by microscopic examination after using haematoxylin, eosin, and Giemsa stains.[21] We sent all biopsies to the central pathology laboratory of the same referral hospital.

Intervention

Eligible patients were randomized in a 1:1 ratio to receive two weeks of treatment of either bismuth quadruple D-group or concomitant levofloxacin L-group. The D-group obtained bismuth subsalicylate 524 mg q.i.d, doxycycline 100 mg, tinidazole 500 mg, esomeprazole 20 mg each b.i.d for 14 days. While The L-group obtained levofloxacin 500 mg q.d, tinidazole 500 mg, amoxicillin 1000 mg, and esomeprazole 20 mg each b.i.d for 14 days. The indication of treatment relied on the American College of gastroenterology guideline and Maastricht V/Florence consensus report [13, 15] including peptic ulcer, chronic gastritis, primary gastric MALT lymphoma, intestinal metaplasia, dyspepsia, and unexplained iron deficiency anaemia.

We used a Microsoft Excel function called (RANDBETWEEN) to generate a sequence of two randomized numbers, number one refer to the D-group, and number two refers to the L-group. We print each code on separate paper and insert it into sealed opaque envelopes in unchanged order, and hold it in a secure locker belonging to an independent medical staff member. After obtaining informed consent, the independent medical staff member took the top envelope to assign the patient to the treatment regimen. We provide written instruction to all patients on how to take the medications. We evaluated compliance by counting the number of unused medications and considered that the patient had a good complaint if he/she had taken at least 90% of the assigned treatment protocol.

At the end of the treatment course, patients revisited the clinic to investigate side effects and evaluate compliance. We reported side effects such as nausea, vomiting, diarrhoea, melena, dysgeusia, and anorexia. After eight weeks, all patients visited the central laboratory of our hospital and performed stool antigen tests by using the enzyme immunoassay method (EIA).[22] Medical laboratory workers were blinded to the treatment arm. a qualified physician collected the data in a questionnaire including (1) participants' demographics, (2) smoking history, (3) medication history, (4) adverse events, and (5) results of stool antigen test. Numerical data were shown as mean, and qualitative data were expressed as a ratio.

Authors report the results of this research according to the CONSORT.

Outcomes:

The primary outcome was the H pylori eradication rates of the initially assigned treatment according to intention to treat analysis (ITT), and per-protocol analysis (PPA).

Sample size and statistical analysis:

Federico et al. Found that the eradication rate based on ITT was 0.922 % in concomitant levofloxacin-containing therapy.[23] While Wang et al. found that the eradication rate based on IIT was 0.6744 in doxycycline-based quadruple.[24] We used a power (1-β) of 80 %, two tails test and Significance level(α) equal to 5%, with a 1:1 allocation ratio. Each treatment arm requires thirty-seven patients in each group. [25, 26] We added two patients to each group to compensate for the predicted dropout. [27, 28]

Statistical tests to estimate the potential differences in outcomes between the two groups were chi-square test (χ² - test) for categorical variables, and t-test for continuous data. We reported the odds ratio with a 95% confidence interval. A P-value of less than 0.05 was considered statistically significant. We performed statistical analyses using SPSS (IBM Corp. Released in 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

Results:

We collected 226 patients diagnosed with H. pylori infection biopsy-confirmed. Seventy-eight treatment-naive patients enrolled in this study (39 patients for each group), only one patient in D-group didn't complete the follow-up. [Figure 1 and Table 1] summarizes the flow chart and baseline characteristics of the patients. The gender, mean age and pharmacological side effects were similar among treatment groups, except for melena, which occurred more frequently in the D-group.

H. Pylori infection was eradicated in thirty patients from the D-group, and thirty-two patients from the L-group. The eradication rates according to ITT and PPA analysis are summarised in table (2). We didn't report serious adverse effects.

Table 1:Baseline characteristics of patients

	Bismuth subsalicylate and doxycycline	levofloxacin and tinidazole	P-value
Gender			
Male	21(55.3%)	20(51.3%)	0.821
Female	17(44.7%)	19(48.7%)	
Age (mean years $\pm$ SD)	41.82 $\pm$ 11.914	45.62 $\pm$ 17.994	0.223
Smoking	16(42.1%)	16(41%)	1.00
Alcoholic	2(5.3%)	0(2.5%)	0.240
Adverse events			
Anorexia	5(13.2%)	11(28.2%)	0.160
Nausea	10(26.3%)	5(12.8%)	0.160
Vomiting	7(18.4%)	4(10.3%)	0.347
Dysgeusia	7(18.4%)	11(28.2%)	0.421
Melena	11(28.9%)	0(0%)	≤ 0.0001
Discoloured Tongue	1(2.6%)	0(0%)	0.494
Diarrhea	6(15.8%)	3(7.7%)	0.310

Table 2: Helicobacter pylori eradication rate in therapy in levofloxacin concomitant and bismuth quadruple therapy groups

	levofloxacin concomitant	bismuth quadruple	Odds Ratio (95% CI)	P-Value
ITT	82.1%	76.9%	1.371(0.454,4.146)	0.78
PPA	82.1%	78.9%	1.219(0.394,3.774)	0.78

CI=confidence interval, ITT=intention to treat analysis, PPA=per-protocol analysis

Discussion:

Researchers globally observed a decline in the rate of H pylori eradication following standard triple therapies, thus requiring a search for new therapeutic approaches. [45–48] This randomized clinical trial included 78 patients from an area of high prevalence (81.5%) of clarithromycin and levofloxacin resistant helicobacter pylori strains. [1, 12, 29–31] Both concomitant and bismuth-containing quadruple therapies are recommended as alternative first-line treatment according to the previously mentioned guidelines, particularly in regions with a high prevalence of clarithromycin resistance.[13, 15]

Our results showed that both regimens had a fair eradicating rate of Helicobacter pylori. The eradication rate for levofloxacin concomitant protocol was 82.05% according to ITT analysis. While Bismuth quadruple therapy had a

PPA eradication rate of 78.94%, and 76.92% according to ITT analysis. The overall eradication rate of concomitant was about 3% higher than bismuth quadruple therapy but the difference didn't reach statistical significance. The result of levofloxacin containing therapy can be regarded as Grade D standard, while the result of bismuth-containing therapy can be regarded as Grade F as proposed recently.[32] the former results are greatly better than our preceding study outcomes regarding the treatment of H. Pylori. [14]Our results are agreeing with a Meta-analysis by Essa et al. and similar research by Federico et al. Both studies showed that concomitant therapy is effective in the eradication of H.Pylori.[23, 33] Similarly Meta-analysis by Niv et al. found that the Doxycycline-based quadruple regimen had good efficacy in the treatment of Helicobacter Pylori infection.[16] Even though this research treated patients for a longer period, [34] Our results didn't show the effectiveness mentioned in previous studies. This may be due to the existence of Helicobacter Pylori resistance strains. [35]Antibiotics are overusing—especially macrolides and fluoroquinolones—for treating respiratory, urinary and gynaecological infections. [36–38] Chokshi et al. reported that the main contributors in emerging antibiotics resistance in developing countries are clinical mismanagement, ease of antibiotics availability, poor quality of available antibiotics, and Insufficiency of surveillance of resistance development. [39] We check compliance by counting remaining pills which raise suspicions about outpatients incompliance to antibiotic regimens.[40–42]

Our study has a few limitations. The only method to investigate past medication was to interrogate patients. Because of the absence of electronic medical records for patients, therefore, authors define “naïve” that patient didn't previously H. Pylori infection treated. We depended on patients to evaluate the compliance. We didn't perform a susceptibility test of H. Pylori to antibiotics, because it's absent in Syria.

This study showed that both regimens had an acceptable rate of eradication, and the difference didn't reach statistical significance. These results were highly promising in treating H. Pylori infection in Syria.

Conclusion:

The success rate of the standard triple therapy with clarithromycin or levofloxacin has declined substantially due to increasing antimicrobial resistance. (ACG) Clinical Guideline and Maastricht Consensus recommended alternative regimens, including bismuth-containing quadruple therapy or non-bismuth concomitant therapy, as first-line therapies, particularly in areas with a high prevalence of clarithromycin resistance like Syria. Both studied regimens had equally reasonable efficacy with no serious adverse. events. Further researches will help select the optimum first-line empirical therapy in the Syrian population for Helicobacter-Pylori Infection.

Abbreviations

PPA: per-protocol analysis

ITT: intention to treat analysis

q.i.d.: four times a day.

b.i.d.: twice a day.

q.d: Once a day.

ACG: American College of Gastroenterology

H. Pylori: Helicobacter Pylori

PPI: proton pump inhibitors

Declarations

Ethics approval and informed consent to participate:

All methods were carried out in accordance with relevant guidelines and regulations.

All experimental protocols were approved by an Ethical Committee of the general assembly of Damascus Hospital (Approval No:5-30-12-19)

Written informed consent was obtained from all patients or their legally authorized representatives.. If the patient is under 18, the informed consent was obtained from a parent and/or legal guardian. It was clearly stated that only clinical information will be shared in research, without mentioning any personal details at any part of the article.

Consent for publication: not applicable

Competing interests:

The authors declare that there is no conflict of interest.

Availability of data and materials:

The dataset supporting the conclusions of this article is Available for free in the [data.mendeley.com] repository, [<https://data.mendeley.com/drafts/fzv77yzshx>], and it will be available after 15 September 2021 to 15 September 2023

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Authors' contributions:

Marouf Alhalabi established the conceptualization and wrote the main manuscript text, as well as prepared tables (1-2) and perform statistics. Khaled Cheha executed supervision, Mohammed Waleed Alassi wrote the main manuscript text, collect data,, Kamal Alaa Eddin prepared Fig. 1, table (1-2). All authors had reviewed and approved the final manuscript.

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Figures

Figure 1

Flow of the study