Efficacy of two-week quadruple bismuth treatment versus levofloxacin concomitant Helicobacter Pylori infection regimen as empirical first-line therapy Syrian patients. A randomized controlled trial.

Marouf Muhammad Alhalabi (✉ e.marouf@hotmail.com)

Damascus Hospital <https://orcid.org/0000-0001-5027-2096>

Mohammed Waleed Alassi

Damascus Hospital

Kamal Alaa Eddin

Damascus Hospital

Khaled Cheha

Damascus Hospital

Research Article

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Abstract

Introduction: Antibiotic-resistant reduces the efficacy of conventional triple therapy for *Helicobacter Pylori* infections worldwide, lead to varying treatment protocols according to locations.

Aim: Primary outcome was eradication rates of bismuth quadruple (BQ) and levofloxacin concomitant (LC) as empirical first-line treatment by intention to treat (ITT) in a referral hospital in Syria.

Design: an open-label parallel blind randomized controlled trial.

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

Results: Thirty-nine patients were allocated in each group. In the BQ group, thirty-eight patients completed the follow-up, thirty patients were cured. While in the LC group, thirty-nine completed the follow-up, thirty-two patients were cured. The ITT eradication rates of the BQ and LC groups were 76.92%, and 82.05%, respectively. Odds ratio with 95% confidence interval according to ITT was 1.371 [0.454-4.146]. We didn't report serious adverse effects.

Conclusions:

Both therapy regimens had acceptable rates of eradication. we suggest using both regimens as empirical first-line therapy in the treatment of *Helicobacter Pylori* infection in the Syrian population.

Clinicaltrial.gov, NCT04348786

Introduction

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 the 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 eastern Mediterranean region 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] Tetracycline is unavailable in Syria, we use doxycycline in BQ regimen. [15, 16] We used tinidazole instead of metronidazole in the BQ and LC regimens, as H. pylori had high metronidazole resistant rate. [17] we didn't perform a susceptibility test of H. Pylori to antibiotics, since it's unavailable either in Syria or in neighbouring countries. There is a lack of data about the efficacy of BQ and LC

regimens in Syrian patients, we conducted this trial to evaluate the efficacy and report the eradication rate according to intention to treat analysis (ITT).

Materials And Methods

This was an open-label parallel randomized study performed in the department of gastroenterology at the referral hospital in Damascus, Syria. It was approved by the Ethical Committee of the general assembly of Damascus hospital (Approval No:5-12-19). A proper consent form was collected from the patient. It was clearly stated that only clinical information will be shared in research, without mentioning any personal details at any part of the article.

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.

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.[18] Pathologists confirm H. Pylori infection by microscopic examination after using haematoxylin, eosin, and Giemsa stains.[19] We sent all biopsies to the central pathology laboratory of the same referral hospital. Eligible patients were randomized in a 1:1 ratio to receive two weeks of treatment of either bismuth quadruple (BQ) or concomitant levofloxacin(LC) regimen. The BQ 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 LC group obtained levofloxacin 500 mg q.d, tinidazole 500 mg, amoxicillin 1000 mg, and esomeprazole 20 mg each b.i.d for 14 days. We used Microsoft Excel function called (RANDBETWEEN) to generate a sequence of two randomized numbers, number one refer to the BQ group, and number two refers to the LC 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 in order 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. 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.

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).[20] 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 (ITT).

Sample size and statistical Analysis:

We estimated the sample size based on a recent study on H pylori with the same concomitant levofloxacin-containing therapy, the eradication rate according to ITT was 0.92 %.[21] We assumed that the eradication rate for doxycycline-bismuth-containing therapy was 0.5 which give us the largest sample size (we used tinidazole instead of metronidazole in the doxycycline-bismuth regimen for the first time). [22, 23] we used a power of 99% and a two-sided type 1 error of 5%. Each treatment arm needs thirty-four We added five patients to each group to compensate for the predicted dropout.[24]

Statistical tests to estimate the potential differences in outcomes between the two groups were chi-square test (χ^2 -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 BQ patient 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 bismuth subsalicylate group.

H. Pylori infection was eradicated in thirty patients from the BQ group, and thirty-two patients from the LC group. The ITT eradication rates of the BQ and LC groups were 76.92%, and 82.05%, respectively. Odds ratio with 95% confidence interval according to ITT was 1.371 [0.454-4.146]. 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

SD: standard deviation

Discussion

Researchers worldwide have reported a decrease in the incidence of H pylori eradication following traditional triple therapy, requiring a search for a new regimen. This randomized clinical trial involved 78 patients from a high prevalence (>15%) of clarithromycin and levofloxacin resistant H pylori strains. [12, 14] Both concomitant and bismuth-containing quadruple therapies are recommended as alternate first-line therapies in compliance with the previously mentioned guidelines.[13, 15]

Our findings showed that both regimens had a fair eradicating rate of H pylori. The eradication rate for LC protocol was 82% while the eradication rate for BQ was 76.92%. The average concomitant eradication rate was about 3% higher than that bismuth quadruple therapy but the difference didn't reach statistical significance. The result of the LC regimen can be regarded as Grade D standard, while the result of the BQ regimen can be regarded as Grade F as recently suggested.[25] Our findings are consistent with a Meta-analysis by Essa et al. and similar research by Federico et al., both studies show that concomitant therapy was effective in the eradication of H.Pylori,[21, 26] also using doxycycline in BQ regimen was effective as a meta-analysis by Niv et al. had shown.[16] although we treated patients for a longer period, [27] Our finding didn't show the efficacy mentioned in previous studies. This may be explained by the variety in H. Pylori strains,[28] overusing the antibiotics—especially macrolides and fluoroquinolones—for treatment of respiratory, urinary, and

gynaecological infections, [29, 30] outpatients in compliance to antibiotic regimen [31–33] and using locally produced drugs. [34, 35]

Our study has a few limitations. The only approach to investigate past medication was to interview patients, in consideration of lack of patients' medical records, also we define “naïve” that patient wasn't treated previously for *H. Pylori*. We rely on patients to assess compliance. And we didn't perform a susceptibility test of *H. Pylori* to antibiotics, since it's unavailable either in Syria or in neighbouring countries.

Conclusion

The success rate of the conventional triple therapy with clarithromycin or levofloxacin decreased dramatically due to increasing antimicrobial resistance. In areas with a high prevalence of clarithromycin resistance using bismuth-containing quadruple therapy or non-bismuth concomitant therapy as first-line therapies are highly recommended, we suggest using both regimens as empirical first-line therapy in the treatment of *Helicobacter Pylori* infection in the Syrian population.

Declarations

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>).

Ethics approval and consent to participate:

It was approved by the Ethical Committee of the general assembly of Damascus hospital (Approval No:5-12-19). A proper consent form was collected from the patient. 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:

We transfer, assign, or otherwise convey all copyright ownership, including any rights incidental thereto, exclusively to the journal, if such work is published by the journal.

Availability of data and materials:

The dataset supporting the conclusions of this article is available 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

Competing interests:

The authors declare that there is no conflict of interest.

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Authors' contributions:

Marouf Alhalabi performed the analysis and interpretation. Mohammed Waleed Alassi acquired the data. Kamal Alaa Eddin, Khaled Cheha drafted the manuscript. All authors are responsible for the study concept, design, and critical revision of the manuscript.

all authors have read and approved the manuscript

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Figures

Figure 1

Patient flow chart

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