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Comparison between Hybrid, Reverse Hybrid, and Non-Bismuth Levofloxacin Quadruple Regimens for *Helicobacter Pylori* Infection in Egypt: A Randomized Trial

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ABSTRACT

BACKGROUND

The prevalence of Helicobacter pylori (*H. pylori*) in developing countries is 50.8%, with the highest occurrence presented in Africa (79.1%). It increases the risk of chronic gastritis, peptic ulcer, cancer of the stomach, and lymphoma. The effect of standard treatment for *H. pylori* eradication is below 80%, and evaluation of alternative lines of treatment is needed. We aimed to compare the hybrid, reverse hybrid, and levofloxacin quadruple therapies as first-line therapy in Egypt.

METHODS

This was a randomized interventional trial done in the clinics affiliated with the Internal Medicine Department. 330 individuals were selected according to the inclusion criteria. They were divided into three groups: group 1 (110 subjects who received a reverse hybrid regimen), group 2 (110 subjects who received a hybrid regimen), and group 3 (110 subjects who received a non-bismuth levofloxacin quadruple regimen).

RESULTS

Group 3 had a significantly lower eradication rate of 82.7% versus 92.7% and 91.8% in groups 1 and 2, respectively. There were non-significant differences in the incidence rates of adverse events among the three groups.

CONCLUSION

Both the reverse hybrid and hybrid groups had good eradication rates in the Egyptian population, but non-bismuth levofloxacin quadruple therapy did not obtain a sufficient eradication rate.

KEYWORDS:
Peptic ulcer, Eradication, Helicobacter pylori, Levofloxacin, Omeprazole, Nitazoxanide, Doxycycline

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INTRODUCTION

The frequency of infection by *Helicobacter pylori* (*H. pylori*) in developing countries is high despite its lower prevalence worldwide.[1] *H. pylori* prevalence

in developing countries is 50.8%, with being prominent in Africa (79.1%).[2,3] Unfortunately, details about the extent of this issue in Egypt are still scarce.

The significance of *H. pylori* infection is related to its strong correlation with chronic gastritis, peptic ulcer, adenocarcinoma of the stomach, and gastric mucosa-associated lymphoid tissue lymphoma.[4]

Invasive diagnostic methods for *H. pylori* infection are the most accurate, but they are cumbersome and costly. On the other hand, there are easier and cheaper non-invasive tests, particularly the *H. pylori* stool antigen and urea breath test.[5] The development of resistant strains to antibiotics, particularly clarithromycin, has reduced response to standard triple therapy (STT) (<80%), thus requiring alternative better treatment options with higher safety and compliance.[6]

The treatment option using bismuth-based quadruple treatment gained popularity as an alternative to clarithromycin-based treatment,[7] but it is not a practical option in countries with unavailable bismuth and/or tetracycline.[8] In addition, bismuth-based treatment is more complex and has less safety.[9] This leads to the need for research on other treatment options such as sequential and concomitant non-bismuth (clarithromycin based) quadruple treatments.[10]

A new combined sequential and concomitant therapy named hybrid therapy (HT) has been developed, which is cheaper and more efficient.[11] On the other hand, the obstacle in this therapy is the patients' compliance, as they need to start two additional drugs in the second week of the treatment, causing less adherence to treatment. Thus, a newer therapy called reverse hybrid therapy (RHT) has developed a better understanding of the sequence (quadruple-dual).[12]

An additional alternative option to bismuth-based therapy is levofloxacin quadruple therapy, which is less sophisticated and less harmful than bismuth-based therapy. It includes levofloxacin, omeprazole, nitazoxanide, and doxycycline (LOND), which has a favorable outcome.[13,14]

We aimed to estimate the effectiveness of HT, RHT, and LOND as first-line therapy in the Egyptian population and to find out the most satisfactory and the highest adherence rate regimen in the Egyptians.

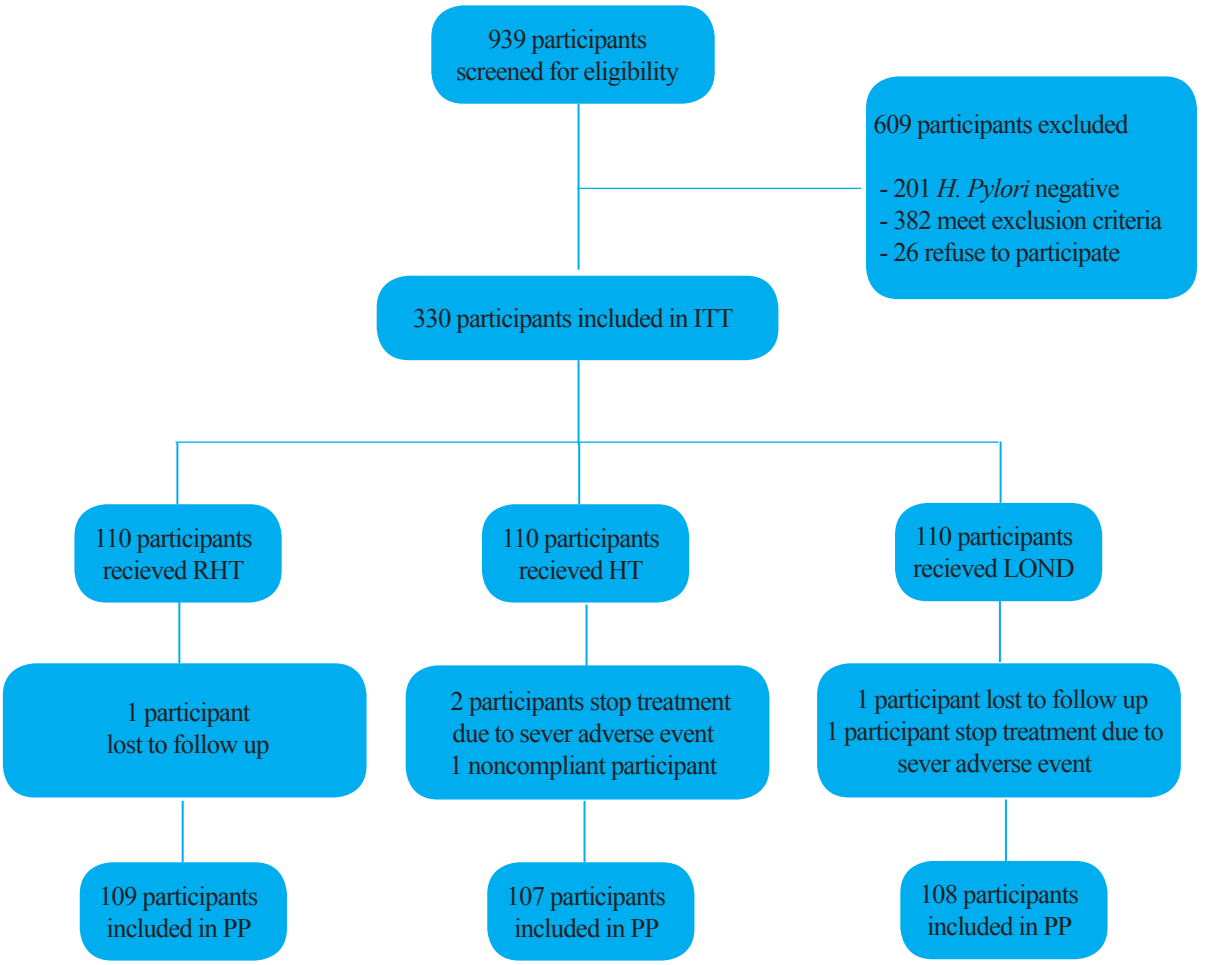
MATERIALS AND METHODS

We conducted an open-label interventional randomized trial. We allocated the participants attending the clinic to stratified randomization method. The randomization was stratified randomization using a computer over the three treatment groups, as illustrated in the flowchart diagram (figure 1).

Figure 1 shows the selection method of the participants in the study from the patients attending the clinic by simple randomization over the three treatment groups. ITT = intention to treat; PP = Per protocol; RHT = Reverse hybrid therapy; HT = hybrid therapy; LOND = Levofloxacin-omeprazole-nitazoxanide-doxycycline.

The sample size was 330 participants, using OPEN EPI (www.OpenEpi.com, updated 2013/04/06. Emory University, Rollins School of Public Health, Atlanta, Georgia, USA) at power: 80% and C.I: 95%. We carried out this research after taking informed written consent from the participants after the approval of the Ethics Committee. We followed the code of ethics for research on humans according to the Declaration of Helsinki guidelines. The study was approved by the Ethics Committee of the Faculty of Medicine, Zagazig University, under the Institutional Review Board number 5089-9-1-2019. We registered the study in the ClinicalTrials.gov with ID number NCT04039412.

We included participants aged 18 years or more, of both sexes, with no history of previous treatment for *H. pylori*. We excluded participants with known hypersensitivity to drugs used in the regimens and those with a history of recent antibiotic use in the previous 3 months. After taking the medical history of the participants and performing a complete clinical examination, we used the fecal antigen test (FAT) to identify *H. pylori* antigen by enzyme immunosorbent assay. The participants with positive FAT were considered for eradication therapy if aged over 45 years with dyspepsia, or age under 45 years with peptic ulcer disease or with dyspepsia and any other risk factors (loss of weight, repeated vomiting, gastric bleeding, or familial history of gastric cancer). Participants were randomly allocated to three treatment groups. Group 1 of 110 participants who received RHT in the form of clarithromycin 500 mg twice daily, omeprazole 20 mg twice daily, amoxicillin 1 g twice daily, and metronidazole 500 mg thrice daily



ITT, intention-to-treat; PP, per protocol; RHT, reverse hybrid therapy; HT, hybrid therapy; LOND, levofloxacin-omeprazole-nitazoxanide-doxycycline.

Fig.1: Study participants' flowchart

for 1 week, followed by omeprazole 20 mg twice daily, and amoxicillin 1 g twice daily in the 2nd week. Group 2 of 110 patients who received HT in the form of omeprazole 20 mg twice daily, and amoxicillin 1 g twice daily in the 1st week, then clarithromycin 500 mg twice daily, omeprazole 20 mg twice daily, amoxicillin 1 g twice daily, and metronidazole 500 mg thrice daily in the 2nd week. Group 3 of 110 patients who received LOND in the form of levofloxacin 250 mg once daily, omeprazole 40 mg once daily, nitazoxanide 500 mg twice daily, and doxycycline 100 mg once daily for 10 days. We followed up on the drug compliance and the occurrence of adverse events after one week and at the end of treatment. We divided the severity of adverse events according to the presence or absence. If it was present, we would subdivide it further, according to the extent of daily activity limitation, into mild, moderate, and severe (no limitation, partial limitation, and profound limitation, respectively). We retested by the FAT one month after finishing the treatment and 14 days after discontinuing the proton pump inhibitors.

Statistical analysis

We used IBM SPSS Statistics for Windows, Version 19.0 (Released 2010, IBM Corp, Armonk, NY). Data were expressed in the form of number and percentage for categorical variables and mean ± standard deviation (SD) for continuous variables that were tested for normality by Shapiro–Wilk test and revealed a normal distribution. Categorical data were analyzed by the Kruskal-Wallis H test, and if results were significant, post hoc analysis by

Table 1: Comparison of the three groups regarding demographic and clinical data

Characteristics	Group 1	Group 2	Group 3	Test	Sig.
Age (years) (Mean ± SD)	32.05 ± 9.772	32.31 ± 9.409	32.44 ± 9.713	0.045	0.956
Sex: no (%) -Male -Female	 53 (48.2) 57 (51.8)	 52 (47.3) 58 (52.7)	 55 (50) 55 (50)	0.169	0.919
Smoking: no (%)	35 (31.8)	34 (30.9)	32 (29.1)	0.199	0.905
Caffeine intake: no (%) -None -Tea -Coffee -Tea and coffee	 29 (26.4) 46 (41.8) 13 (11.8) 22 (20)	 38 (34.5) 40 (36.4) 16 (14.5) 16 (14.5)	 39 (35.5) 47 (42.7) 11 (10) 13 (11.8)	3.722	0.155
NSAID intake: no (%)	23 (20.9)	20 (18.2)	20 (18.2)	0.352	0.839
Comorbidity: no (%) -None -Diabetic -Hypertensive -Both	 94 (85.5) 7 (6.4) 6 (5.5) 3 (2.7)	 88 (80) 10 (9.1) 7 (6.4) 5 (4.5)	 85 (77.3) 10 (9.1) 11 (10) 4 (3.6)	2.462	0.292
GIT bleeding: no (%)	5 (4.5)	4 (3.6)	5 (4.5)	0.149	0.928
BMI (kg/m^2) (Mean ± SD)	27.45 ± 4.609	26.72 ± 4.282	27.29 ± 4.265	0.854	0.426
BMI groups: no (%) -Normal -Overweight -Obese	 30 (27.3) 42 (38.2) 38 (34.5)	 37 (33.6) 40 (36.4) 33 (30)	 32 (29.1) 36 (32.7) 42 (38.2)	1.632	0.442

(Sig): Significance, (NSAID): Non-steroidal anti-inflammatory drugs, (GIT): Gastrointestinal tract, and (BMI): Body mass index.

Table 2: Comparison of the three groups regarding outcomes of treatment

Analysis	Group 1	Group 2	Group 3	Test	*p*-value
Eradication: n (%) ITT 95% CI PP 95% CI	 102 (92.7%) 86.2% to 96.8% 102 (93.6%) 87.2% to 97.4%	 101 (91.8%) 85% to 96.2% 101 (94.4%) 88.2% to 97.9%	 91 (82.7%) 74.3% to 89.3% 91 (84.3%) 76% to 90.6%	 6.662 8.118	 0.036* 0.017*
The severity of adverse events: n (%) -None -Mild -Moderate -Severe	 61(55. 5) 33 (30) 16 (14.5) 0 (0)	 52(47.3) 28 (25.5 28 (25.5) 2 (1.8)	 65(59.1) 35 (31.8) 9 (8.2) 1 (0.9)	7.055	0.029

(ITT): Intention-to-treat, (PP): Per protocol, (CI): Confidence interval.

the Mann-Whitney test was done. Continuous data were inspected by one-way analysis of variance (ANOVA). A two-sided ($\alpha = 2$) p value of less than 0.05 was considered significant.

RESULTS

Our subjects were 160 men and 170 women with ages ranging from 18 to 56 years. All demographic and clinical data presented in table 1 showed non-significant differences between the three groups.

Group 3 had a significantly lower eradication rate of 82.7% (91 of 110) versus 92.7% (102 of 110), and 91.8% (101 of 110) in groups 1 and 2, respectively ($p = 0.036$). The post hoc analysis revealed that the main difference was found between groups 1 and group 3 ($p = 0.025$), in addition to group 2 and group 3 ($p = 0.049$). The severity of adverse reactions was significantly different between the three groups ($p = 0.023$), and the post hoc analysis clarified that this difference was between group 2 and group 3 ($p = 0.008$, table 2).

The incidence rates of adverse events in the three groups are demonstrated in table 3, with a non-significant difference among the three groups.

Table 3: Comparison of the three groups regarding adverse events of treatment.

Adverse events	Group 1	Group 2	Group 3	Test	*p* value
Non: no (%)	61 (55.5)	52 (47.3)	66 (60)	3.676	0.159
Bitter taste: no (%)	13 (11.8)	11 (10)	6 (5.5)	2.851	0.240
Nausea: no (%)	7 (6.4)	10 (9.1)	8 (7.3)	0.604	0.739
Epigastric pain: no (%)	9 (8.2)	10 (9.1)	10 (9.1)	0.075	0.963
Vomiting: no (%)	2 (1.8)	4 (3.6)	1 (0.9)	2.037	0.361
Bloating: no (%)	2 (1.8)	4 (3.6)	5 (4.5)	1.313	0.519
Diarrhea: no (%)	8 (7.3)	11 (10)	7 (6.4)	1.082	0.582
Dizziness: no (%)	2 (1.8)	2 (1.8)	2 (1.8)	0.000	1.000
Fatigue: no (%)	6 (5.5)	6 (5.5)	5 (4.5)	0.124	0.940

DISCUSSION

Cure of *H. pylori* infection principally relies on the adherence of the patient to the treatment, the duration of the antimicrobial therapy, and the occurrence of *H. pylori* resistant strains to antibiotics.[15] As *H. pylori* infection is an infective illness, the optimal plan is to cure *H. pylori* infection at a rate higher than 95%. The effectiveness of *H. pylori* therapy was categorized by Graham as F or unacceptable (80% cure rate), D or poor (81-84%), C or fair (85-89%), B or good (90-95%), and A or excellent (95-100%).[16]

As stated by the American College of Gastroenterology Clinical Guidelines, bismuth quadruple therapy is approved as the first-line therapy for *H. pylori* infection in the United States, and hybrid therapy is a second option.[17]

In the Egyptian population, different lines of treatment for *H. pylori* need to be evaluated. Our study is the first head-to-head, randomized trial to compare RHT, HT, and LOND in the Egyptian population.

The net results in the current study revealed significantly superior eradication rates in both HT and RHT (91.8% and 92.7%, respectively) versus LOND therapy (82.7%) (p = 0.036). On the contrary, LOND therapy showed significantly lower adverse events (p = 0.023).

Regarding age and sex distribution in our study, there were no significant differences between the three groups. In addition, there were no significant differences between the three groups regarding the history of smoking, caffeine consumption, previous non-steroidal anti-inflammatory drug intake, comorbid conditions, history of melena, and BMI.

In our study, group 3 had a significantly lower eradication rate (82.7%). The significantly lower eradication rate in group 3 is in agreement with Branquinho and colleagues,[18] and Sarkeshikian and co-workers,[19] who reported an eradication rate of 79% and 78.18%, respectively. On the other hand, Basu and others 13 reported an eradication rate of 88.9%, and Kale-Pradhan and colleagues [20] reported an eradication rate of 87.8%. A probable explanation for the lower rate of *H. pylori* eradication with LOND therapy in our study is the frequent use of levofloxacin and doxycycline in Egypt for urinary tract infections, chest infections, and skin infections, which increase the risk of drug resistance.

In addition, eradication rates were significantly higher in group 1 (92.7%) and group 2 (91.8%). These results are in agreement with Lin and colleagues [21] and Molina-Infante and others.[22] Perhaps this may be caused by the synergy between amoxicillin and clarithromycin, as amoxicillin inhibits bacterial cell wall synthesis that knocks down the transmembrane efflux system. Therefore, clarithromycin accumulates inside bacteria and overwhelms the bacterial resistance mechanism. [23]

In our study, the severity of adverse events in group 2 was the most severe (p = 0.023), with three patients who could not continue treatment because of marked dizziness and repeated vomiting. The adverse events with HT are like those obtained by Sardarian and colleagues [24] and Metanat and co-workers.[25] However, Kefeli and colleagues [26] and Wang and others [27] reported fewer adverse events with HT and recommended it as first-line therapy. The high incidence of adverse events in this group may be due to the prolonged course of amoxicillin treatment and the addition of multiple antibiotics in the second week of

treatment, though it cannot quite explain the difference between RHT and HT groups.

The most frequent adverse events in groups 1 and 2 were metallic taste (11.8% and 10%, respectively). While in group 3, 9.1% of the patients experienced epigastric pain. Sardarian and colleagues [24] and Chen and co-workers [28] also reported metallic taste as a major side effect in patients receiving HT. On the other hand, De Francesco and others [23] found diarrhea as the most common adverse event in the HT group.

In conclusion, we found that both RHT and HT groups had good eradication rates, but LOND therapy did not obtain enough eradication rates in the Egyptian population. However, LOND therapy had the least overall adverse reaction.

The limitations of our study were the lack of urea breath test (which is more specific than fecal antigen test) and cultures (which could give us the pattern of antibiotic resistance), due to non-availability in our locations. In addition, the lack of cost-effectiveness analysis, which is an important issue in low-income countries, can be another limitation.

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ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

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

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