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Faculty of Medicine.

Internal Medicine Department.

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

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لجنة مراجعة اخلاقيات البحث العلمى
IRB

جامعة الزقازيق
كلية الطب البشرى

نموذج ٨
ZU-IRB #5089/9-1-2019

NOTICE OF APPROVAL

IRB#:5089-9-1-2019
Approval DATE: 9-1-2019
Expiration DATE: 9 -1-2020
Principal Investigator (PI): Ayman Fathy El Sayed
Title of Protocol:

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

Dear Dr: Ayman Fathy El Sayed

The IRB has reviewed and assessed the above named study regarding the potential risks and benefits based on the Declaration of Helsinki. The "ratio" of risk to benefit is reasonable, given the goals of the study. The variables assessed, including the proposed subject populations, proposed procedures and scientific background are supporting the study. The IRB approved that it is within the ethical guidelines as outlined in the Declaration of Helsinki.

Having met the requirements set forth by the Institutional Review Board by an expedited review process

your research project is now approved, effective Jan 9, 2019. This project will require annual review and will expire on' Jan 9, 2020 Research that has not received approval for continuation by this date may not continue past midnight of the expiration date.

If, during the course of the research, there are any serious adverse events, ,confidentiality concerns, these should be brought to the immediate attention of the IRB.

You should not initiate changes in the approved research protocol without IRB review and approval "except if found necessary to eliminate immediate hazards to the human subjects".

IRB APPROVED

Sincerely
CHair IRB

e-mail : IRB_123@medicine.zu.edu.eg
وحدة المراجعه المؤسسيه للبحث العلمى (IRB)

Introduction

Although the decreasing prevalence of Helicobacter Pylori (H. Pylori) worldwide, it remains high in the developing countries **[1]**. According to the most recent studies, the overall prevalence of H. Pylori in the developing countries is 50.8%, with the highest one presented in Africa (79.1%) **[2, 3]**.

Unfortunately, the data on the prevalence of H. Pylori, are not available from all the countries of Africa. There is a paucity of information about the magnitude of the problem in Egypt, according to the few available studies, the prevalence is ranging from 71.7-91.7% **[4, 5]**.

The importance of H. Pylori infection lies in the major role in chronic gastritis, gastric ulcer, and duodenal ulcer, up to gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma **[6]**.

Diagnosis of H. Pylori can be through invasive tests, which are cumbersome and expensive despite their high sensitivity and specificity. On the contrary, there are more easily and cheaper non-invasive tests, especially H. Pylori stool antigen and urea breath test have a higher sensitivity than serology **[7]**.

The decreasing eradication rate of the standard triple therapy (STT) below 80% due to the emergence of resistant strains to Clarithromycin, raise the need for newer therapies that provide higher efficacy, and in the same time, better safety and compliance **[8]**.

Bismuth-containing quadruple therapy came as the treatment of choice that avoids Clarithromycin use **[9]**, but it was a non-reasonable option for the countries that are lacking in bismuth salts and/or tetracycline **[10]**, beside of the

complex administration and low safety **[11]**. It raises the era of the competing sequential and concomitant non-bismuth (clarithromycin containing) quadruple treatments **[12]**.

A novel two-step (dual-quadruple) treatment called the hybrid therapy (HT), which is actually a combined sequential and concomitant therapy, with a lower cost and better efficacy **[13]**.

However, the adding of two drugs in the last seven days of the therapy may confuse the patient, making him less willing to complete the treatment that promote the idea of reversing the sequence (quadruple-dual) in what is called the reverse hybrid therapy (RHT), to simplify the treatment in one-step two-phase treatment **[14]**.

Another non-Clarithromycin non-Bismuth quadruple therapy that is less complex and safer than bismuth quadruple therapy, which is called Levofloxacin quadruple therapy that contains levofloxacin, omeprazole, nitazoxanide, and doxycycline (LOND), showed promising results on the level of the cure rate and low drug resistance profile **[15, 16]**.

Rational

As Helicobacter pylori is a common infection and a leading cause of gastric and duodenal ulcers with an increased incidence of gastric cancer, so we need an effective regimen as a first line in treatment of Helicobacter pylori.

Research questions

Which of the Hybrid, Reverse hybrid, and Levofloxacin quadruple therapies are more effective as a first-line eradication regimen for Helicobacter pylori in Egypt?

Hypothesis

The expected result of this study that Hybrid therapy is more effective than Reverse Hybrid and Levofloxacin quadruple therapies as a first-line eradication regimen for Helicobacter pylori infection in Egypt.

Aim of Work

We are aiming here to compare the Hybrid, Reverse hybrid, and Levofloxacin quadruple therapies as first-line therapy, trying to reach the safest, cost-effective, and compliance-inducing regimen in Egypt.

Objectives

- To assess the efficacy of Hybrid, reverse hybrid, and Levofloxacin quadruple therapies as a first line eradication regimen for Helicobacter pylori infection in Egypt.
- To evaluate the safety of each regimen.
- To determine which regimen has the best patient's compliance.

Subjects and Methods

Technical Design

A) The site of study:

The study will be conducted in Internal medicine department in Zagazig University Hospitals.

B) Sample size:

Assuming that the eradication rate in patients receiving Hybrid therapy is 91% versus 78.3% in Reverse Hybrid therapy. So, the sample size is 309 (103 in each group), using OPEN EPI at power 80% and C.I 95%.

C) Inclusion criteria:

1- Age more than 18 years.

2- Both gender.

3- Patient's approval to participate in the study.

4- Patients with positive Helicobacter pylori antigen in the stool with no previous treatment for Helicobacter pylori.

D) Exclusion criteria

1- Age < 18 years.

2- Patients who refuse to participate in the study.

3- Patients with previous treatment for Helicobacter pylori.

4- Patients with known hypersensitivity to drugs used in regimens.

Tools of data collection

The following procedures were done to all enrollees:

1- Medical history to all patients.

2- Complete clinical examination.

3- The fecal antigen test (FAT) which identifies H. pylori antigen in the stool by enzyme immunoassay was positive in all participants.

Operational design

- This is a randomized controlled (interventional) study conducted at Zagazig University Hospital, internal medicine department clinic after informed consent. All the patients are positive for H. pylori fecal antigen test.
- Steps of performance: (309) patients will be chosen from the Internal Medicine Department clinic, grouped into 3 groups:
    - Group 1: (103) patients will receive reverse hybrid regimen in the form of clarithromycin 500mg bid, omeprazole 20 mg bid, amoxicillin 1gm bid, and metronidazole 500 mg tid for 1 week, followed by omeprazole 20 mg bid, and amoxicillin 1gm bid in the 2nd week.
    - Group2: (103) patients will receive hybrid regimen in the form of omeprazole 20 mg bid, and amoxicillin 1gm bid in the 1st week, then clarithromycin 500mg bid, omeprazole 20 mg bid, amoxicillin 1gm bid, and metronidazole 500 mg tid in the 2nd week.
    - Group3: (103) patients will receive Levofloxacin quadruple regimen (LOAD) in the form of nitazoxanide 500 mg bid, levofloxacin 250 mg QD, omeprazole 40 mg QD, and doxycycline 100 mg QD for 10 days

- Retesting by the fecal antigen test (FAT) after stopping the regimen by at least one month and withholding proton pump inhibitors for 2 weeks.

Administrative design

- Approval of medical department.
- Approval of the ethical committee in the faculty of medicine.
- Institutional Review Board (IRB) approval.
- Consent from the patient sheet.

Statistical analysis plan

The software SPSS (SPSS Inc., Chicago, Illinois, USA) version 19 for Windows will be used. Quantitative variables will be described using their means and standard deviations (Mean ± SD). Categorical variables will be described using their absolute frequencies.

Comparison of categorical data will be performed using the Chi-square test and Fisher exact test when appropriate. Kolmogorov-Smirnov's (distribution-type) and Levene's (homogeneity of variances) tests will be used to verify assumptions for use in parametric tests. All normally distributed data will be interpreted using One-Way ANOVA F test. A nonparametric test (Kruskal-Wallis H Test) will be used to compare means when data is not normally distributed. A two-sided ($\alpha=2$) $p<0.05$ will be considered significant. Additional tests according to the results will be used when appropriate.

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