Effectiveness of Triple Therapy Regimens in the Eradication of *Helicobacter pylori* in Patients with Uninvestigated Dyspepsia in Ekiti State, Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Authors OAS and AOA designed the study, wrote the protocol, collected and analyzed data and wrote the first draft of the manuscript. Author PTA collected data and managed the literature searches. Authors OEG, OA and OOS collected data. All authors read and approved the final manuscript.

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ABSTRACT

Aim and Objective: The term dyspepsia has been used inconsistently by healthcare professionals to describe different patterns of upper gastrointestinal symptoms. It denotes a symptom and does

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not itself represent a disease. In this study, we seek to determine the effectiveness of common triple therapy regimens in use in the eradication of *H. pylori* in this environment and to compare it what is obtained worldwide.

Materials and Methods: One hundred and four Consecutive adult patients, aged 18 to 50 years presenting newly with uninvestigated dyspepsia and without alarm symptoms at General Outpatient Clinics of the Ekiti State University Teaching Hospital, Ado-Ekiti and the Federal Medical Centre, Ido-Ekiti, Nigeria were randomized into five treatment groups in the study. Approval was obtained from Ethical Committees of the two study centres. Treatment outcome was computed using frequency table.

Results: The mean age of the studied population was 37.8±12.98 years. 32.7% were males while 67.3% were females. Most prevalent symptom for uninvestigated dyspepsia was abdominal discomfort 100 (96.2%), this was followed by early satiety, abdominal fullness and vomiting with 32 (30.8%), 26 (25%) and 13 (12.5%) of the participants respectively. 76.0% were positive for *H. pylori* infection by Urea Breath Test Heliprobe® System with highest prevalence of *H. Pylori* infection within age group 31-45 years (36.7%).

Rabeprazole-Clarithromycin-Metronidazole group (RCM) had the highest eradication rate per protocol [77.8%], followed in descending order by Rabeprazole-Amoxil- Levofloxacin group (RAL) [53.3%], Omeprazole-Tinidazole-Clarithromycin "ulcer kit" (OTC) [44.4%], Rabeprazole-Amoxil-Metronidazole group (RAM) [44.4%] and Rabeprazole-Amoxil-Clarithromycin (RAC) [30.0%].

Conclusion: This study showed there is difference in eradication rates of popularly known triple therapy regimens. This may be due to geographical differences in antibiotics resistant pattern to H. pylori. Further study is suggested to find out the national sensitivity pattern to the commonly used triple therapy regimens in Nigeria.

1. INTRODUCTION

Dyspepsia is an important, common and demanding clinical problem [1,2]. It denotes a symptom and does not itself represent a disease [3,4]. According to the ROME II definition, dyspepsia refers to pain or discomfort centred in the upper abdomen, that is, in or around the midline. Pain in the right or left hypochondria is not considered dyspepsia [5]. Uninvestigated dyspepsia is that in which patients with new or recurrent dyspepsia have had no investigation undertaken as to the cause of their dyspepsia. These patients are more likely to present in primary than in secondary care [6,7].

Helicobacter pylori (*H. pylori*) infection occurs worldwide with prevalence varying greatly among countries and among population groups within same country [8]. The prevalence among middle-aged adults is over 80% in many developing countries, as compared with 20 to 50 percent in industrialized world [9]. The infection is acquired by oral ingestion of the bacterium and is usually transmitted within the families in early childhood [8,10].

The clinical course of *H. pylori* infection is highly variable and is influenced by both microbial and host factors. The pattern and distribution of gastritis correlate strongly with the risk of clinical sequelae, namely duodenal or gastric ulcers, mucosal atrophy, gastric carcinoma, or gastric lymphoma [11-14].

Conventional (1st generation) Urea breath test (UBT) relies on abundant of *H. pylori* derived urease activity in the stomach. It qualitatively detects active infection with sensitivity of more than 90%. [9] The Heliprobe urea breath test (UBT) recently introduced is a non-invasive, simple, and cheap low-dose ^{14}C UBT system. UBT is less expensive and simpler than endoscopy and is useful for follow-up after treatment to confirm successful eradication [15].

Because of the reduced risk for false positive and negative results, and subsequent reduction in endoscopy requests, this may be a better option for physicians in resource limited setting.

Resistance to antibiotics is the single most important factor for declining *H. pylori* eradication rates [16]. The antibiotics used for the treatment of *H. pylori* include clarithromycin, amoxicillin, metronidazole, tetracycline, tinidazole, rifabutin and fluoroquinolones (i.e. levofloxacin and moxifloxacin). Resistance rates vary remarkably

in different geographic areas and therefore the selection of therapeutic regimes needs adjustments according to local resistance pattern. The prevalence of antibiotic resistance in various regions is correlated with the general use of antibiotics in the region [17,18].

In this study, we seek to determine the effectiveness of common triple therapy regimens in use in the eradication of *H. pylori* in this environment.

2. PATIENTS AND METHODS

The study was a randomized controlled trial of commonly used triple therapy regimens for dyspeptic patients who have positive *H. pylori* infection diagnosed by Heliprobe[R] System (UBT). It was carried out over a period of 9 months, between November 2011 and July 2012.

One hundred and four Consecutive adult patients, aged 18 to 50 years presenting newly with uninvestigated dyspepsia and without alarm symptoms at General Outpatient Clinics of the Ekiti State University Teaching Hospital, Ado-Ekiti and the Federal Medical Centre, Ido-Ekiti, Nigeria were randomized into five treatment groups in the study. Approval was obtained from Ethical Committees of the two study centres.

Participation was voluntary and from each participant a written informed consent was obtained before enrolment in the study.

Interviewer administered questionnaire which included patient's bio-data, participant residence whether rural or urban, history of dyspepsia and associated symptoms, previous history of treatment for dyspepsia, was administered to the participants.

Each subject swallowed HeliCap[TM] on empty stomach with a glass of water. The HeliCap which contained ^{14}C labelled urea rapidly disintegrates in the stomach and ^{14}C urea released. In the presence of *H. pylori* the ^{14}C urea is metabolized to carbon dioxide and ammonia by the enzyme urease produced by the bacteria. The available ^{14}C isotopes diffuse into the blood in form of [14]CO_2 and then transported into the lungs from where it is exhaled in the breath. The [14]CO_2 is captured using a BreathCard[TM] and the result analysed with Heliprobe[R] analyser.

Helicobacter pylori positive dyspeptic patients were assigned randomly using coloured beads

into different *H. pylori* eradication groups as shown below:

Rabeprazole (20 mg b.d) + Clarithromycin (500 mg b.d) + Metronidazole (400 mg b.d) (RCM)
Rabeprazole (20 mg b.d) + Amoxycillin (1 gm b.d) + Clarithromycin (500 mg b.d) (RAC)
Rabeprazole (20 mg b.d) + Amoxycillin (1 gm b.d) + Metronidazole (400 mg b.d) (RAM)
Rabeprazole (20 mg b.d) + Amoxycillin (1 gm b.d) + Levofloxacin (500 mg b.d) (RAL)
Omeprazole (20 mg b.d) + Tinidazole (500mg bd) + Clarithromycin (250 mg b.d) (OTC)

for duration of seven days. All these groups were then continued with the PPI in the groups for five weeks [14].

Subject were followed up, two days after commencement of treatment to determine if there were adverse effects from dispensed drugs that might necessitate dropping from the study and then 12 weeks after completion of treatment. Eradication of *H. pylori* was confirmed using Heliprobe[R] System (UBT) [6].

Treatment outcome was computed using frequency and Chi Square used as the test of significance

3. RESULTS

One hundred and four participants with uninvestigated dyspepsia and mean age of 37.8±12.98 years were enrolled for the study, 32.7% of which were males while 67.3% were females. Most prevalent symptom for uninvestigated dyspepsia was abdominal discomfort 100 (96.2%) of the participants, this was followed by early satiety, abdominal fullness and vomiting with 32 (30.8%), 26 (25%) and 13 (12.5%) of the participants respectively.

Overall, 76.0% (79/104) of the patients were positive for *H. pylori* infection by Urea Breath Test Heliprobe® System and were randomized into the various treatment groups (Table 1). The highest prevalence of *H. pylori* infection was found within the subjects aged 31-45 years 29 (36.7%) while the lowest (2.5%) was found within the subjects aged 61-75 years (Table 1). Treatments were assigned to participants with *H. pylori* positivity as follow; 13 (16.5%) in RAC, 12 (15.2%) in RAM, 17 (21.5%) in RCM, 20 (25.3%) in RAL and 17 (21.5%) in OTC (Table 2). RCM had the highest eradication rate per protocol, 77.8% followed in descending order by

RAL (53.3%), OTC (44.4%), RAM (44.4%) and RAC (30.0%) (Fig. 1). Similarly RCM has the highest intention to treat populations 41.2%, followed in descending order by RAL (35.0%), RAM (33.3%), OTC (23.5%) and RAC (23.1%) (Fig. 2). This association was observed not to be significant, x^2 = 4.76, p = 0.313. 30 of the 79 patients assigned to the different treatment groups were lost to follow up, giving the attrition rate of 38% (Table 2).

Table 1. Eradication rate by age group

Age group	Total positive (%)	Total positive followed up	Eradicated (%)	No eradication (%)
12 -18 years	4 (5.1%)	2	2(100%)	0 (.0%)
19 -30 years	20 (25.3%)	13	8(61.5%)	5(38.5%)
31-45 years	29 (36.7%)	18	10 (55.6%)	8 (44.4%)
45 - 60 years	24 (30.4%)	15	5 (33.3%)	10 (66.7%)
61 – 75 years	2 (2.5%)	1	0 (.0%)	1 (100%)

Table 2. Showing the various treatment groups and eradication versus none eradication

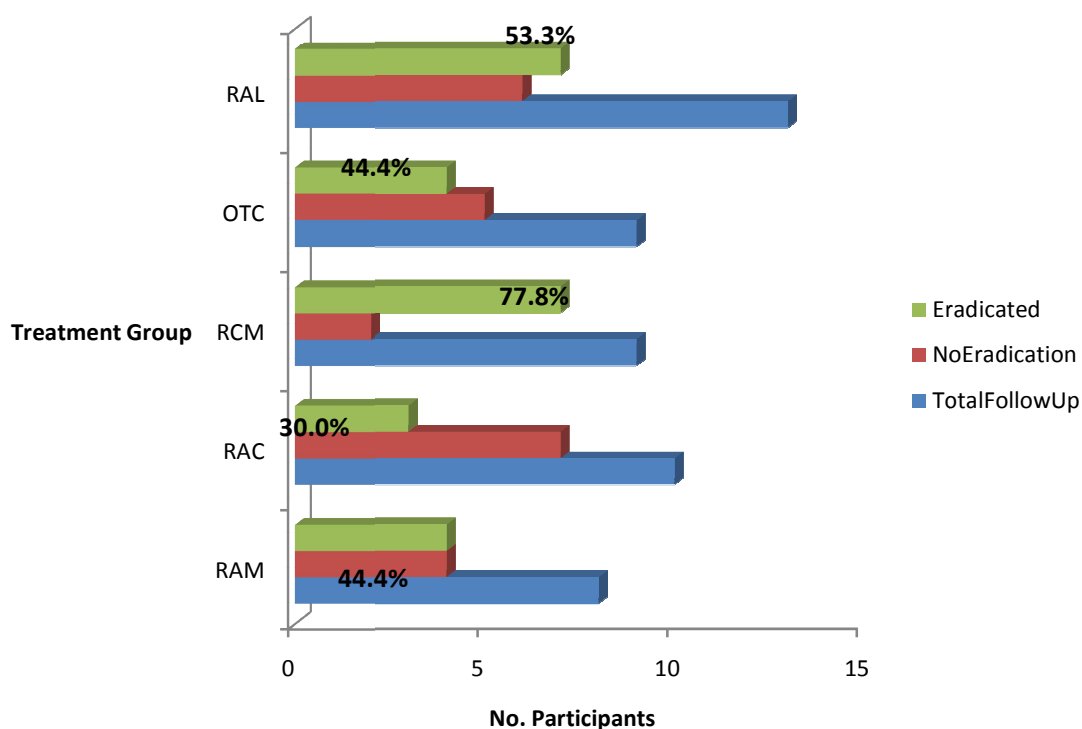| Treatment group	No assigned (%)	No. followed up (%) of those assigned	No. eradicated (%) per protocol	No. eradicated (%) per intention to treat
RAC	13 (16.5%)	10 (76.9%)	3 (30.0%)	3 (23.1%)
RAM	12 (15.2%)	8 (66.7%)	4 (50.0%)	4 (33.3%)
RCM	17 (21.5)	9 (52.9%)	7 (77.8%)	7 (41.2%)
RAL	20 (25.3%)	13 (65.0%)	7 (53.8)	7 (35.0%)
OTC	17 (21.5%)	9 (52.9%)	4 (44.4%)	4 (23.5%)
TOTAL	79 (100%)	49	25	25

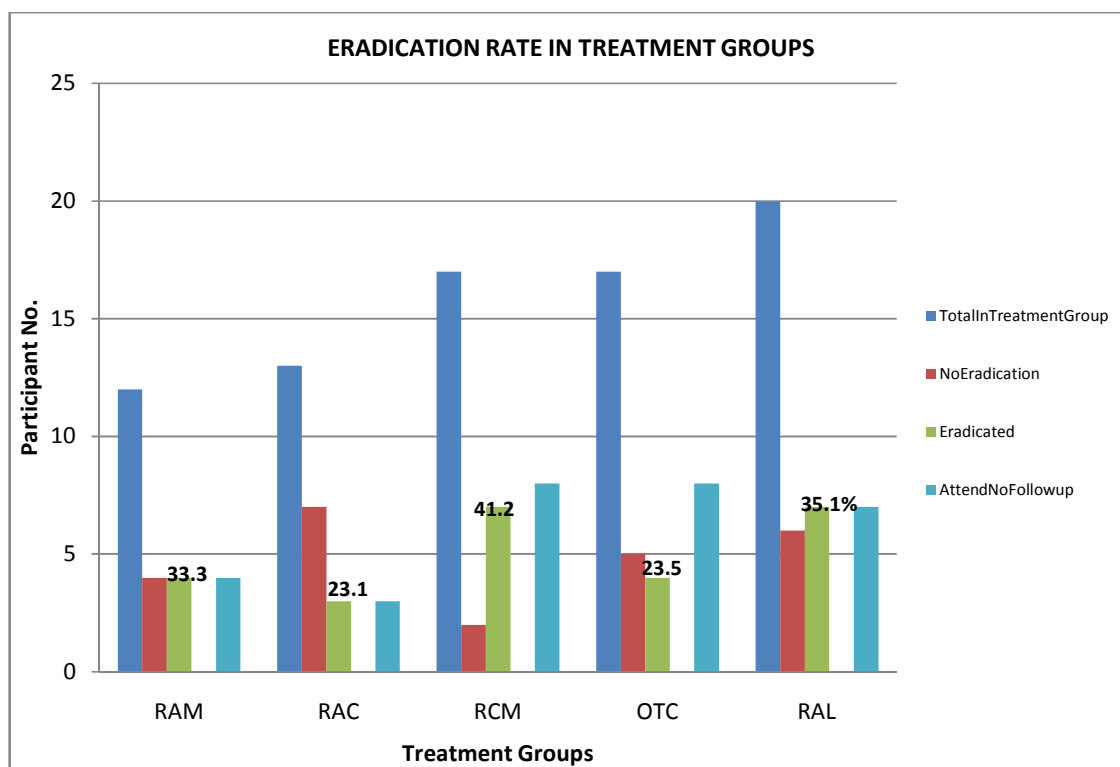**Fig. 1. Eradication rate among follow up group**

Fig. 2. Eradication rate in the treatment groups

4. DISCUSSION

Infection with *H. pylori* continues to be a cause for concern, and the search for an optimal therapy continues due to the changing antibiotic sensitivity patterns. Antibiotic resistance is a major cause of treatment failure [19]. The prevalence of antimicrobial resistance in *H. pylori* shows geographical and regional variations both within and between countries. Alternative antibiotics based on local resistance rates may accelerate eradication rates. Triple therapy with an antisecretory drug and two antibiotics (amoxicillin, metronidazole or clarithromycin) has often been advocated as the first-line therapy but the choice of the antibiotics varies, depending on local sensitivity patterns [20-22].

In our study, RCM has the highest eradication rate per protocol and Intention to treat (ITT) of 77.8% and 41.2% which is lower than the WGO recommended rate of 90%, but in keeping with recommendation made by similar organization of eradication rate of between 70-85% for developing countries [23] this is similar to the finding by Bochenek et al. [24] in a study conducted in Alaska and Hawaii, where

Clarithromycin and Metronidazole triple based regimen was found to have better eradication rate compared with amoxicillin and clarithromycin based therapy and this when compared with a study by Harris et al with Lansoprazole as PPI, eradication per protocol and ITT was 86% and 81% respectively [25]. In our study the eradication rate by RAC regimen per protocol and ITT is 30.0% and 21.3% respectively, this showed a significant reduction when compared with the eradication rate in studies by Calvet X et.al in Spain and Onyekwere et al. [22] in Lagos, where ITT was 73.8% [26] and average eradication rate of 87.2% was observed when RAC was administered for either 7 or 10 days respectively. The significant difference in eradication rates of combination that has metronidazole and clarithromycin compared to other regimens where either metronidazole (RAM per protocol - 44.4%, ITT - 33.3%) or clarithromycin (RAC per protocol - 30.0%, ITT - 23.1%) alone is present could be due to presence of resistant strains of *H. pylori* to amoxicillin which was the substitute to either of metronidazole and clarithromycin and possibly could result from the shift in the use metronidazole, which used to be one of the common over the counter antibiotics for

gastrointestinal and parasitic infections [27,28] to other antibiotics like penicillins of which amoxicillin is one and quinolones (ciprofloxacin) and hence will be desirable to have resistant pattern for *H. pylori* to common antibiotics in our environment studied. The success eradication rate seen in this study with the RCM group compared to the study of Oyedeji et al. [29] and Adeniyi et al. [30] might be due to the afore-mentioned reason.

When the eradication with RAC studied by Onyekwere et al. [22] is compared with that of our study in the same region of Nigeria; geographical differences in antibiotics resistant pattern may be responsible for wide difference and hence giving credence to the need to consider obtaining data on the antibiotic resistance patterns for *H. pylori* within a country, and potentially within regions of a country, as critical for selecting an appropriate treatment regimen [28].

In the bid to compensate for the perceived *H. pylori* resistance to metronidazole, combination containing PPI, Tinidazole and Clarithromycin had been formulated, in this study, eradication rates by OTC per protocol and intention to treat were 44.4% and 23.5% respectively. This is comparable with eradication rate of 61% in intention-to-treat analysis by Moayyedi in New Zealand showed [31] that OTC is less successful in treating *H. pylori* in dyspeptic patients in a primary care based study.

The eradication rate and ITT by RAL regimen was observed to be 53.3% and 35.0% respectively, this when compared with 92% eradication rate in a study by Cammarota G et al. [32], in Italy may be due to over the counter access to quinolones like Ciprofloxacin and Levofloxacin in our environment.

5. CONCLUSION

This study showed there are differences in eradication rates of popularly known triple therapy regimens. This may be due to geographical differences in antibiotics resistant pattern to *H. pylori*. Further study is suggested to find out the national sensitivity pattern to the commonly used triple therapy regimens in Nigeria.

CONSENT

All patients gave written informed consents.

ETHICAL APPROVAL

Approval for this study was obtained from the Ethical Committees of both the Ekiti State University Teaching Hospital, Ado –Ekiti and the Federal Medical Centre, Ido-Ekiti, Nigeria.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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