Effect of Moxifloxacin-Triple Therapy Versus Clarithromycin-Triple Therapy for the Eradication of Helicobacter Pylori Infections Regarding to Age and BMI.

Ahmed Mansur Kadhim*, Mohammed Mahmood Mohammed, Hussein Muhammad Hassan Abdul-Hussein. *****

***Clinical pharmacist, Wassit health directory, Iraq**

****Department of Clinical Pharmacy/College of Pharmacy/Al-Mustansiriya University, Iraq**

*****Internal medicine specialist, AL-Zahraa Teaching Hospital/Wassit province, Iraq**

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Corresponding Author email:
pharm.drmhdclinical@uomustansiriyah.edu.iq
orcid: https://orcid.org/0000-0002-1205-4829

Abstract:

Helicobacter pylori (H. Pylori) is one of the most common infectious human pathogens, which infected more than (50%) of the populations worldwide.

H. pylori induce inflammation, which causes of upper gastrointestinal illnesses including dyspepsia, peptic ulcer diseases, gastroesophageal reflux disease and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. It is important to use a greatly effective and better tolerated eradication regimen. In this study, fifty newly diagnosed adult patients with H. pylori infection were included, they were allocated into two groups with two different treatment regimens for H. pylori eradications; Group A (25 patients) received oral conventional clarithromycin-triple therapy for 14 days. Group B (25 patients) received oral moxifloxacin triple therapy for 14 days. The results reported in this study indicated a significant higher eradication rate of triple moxifloxacin regimen (80%) of patients with H. pylori infections compared to that of triple clarithromycin regimen (52%). In the present study, using different H.pylori eradication regimens for patients with different age groups demonstrated no statistically significant differences in eradication rate achieved ($p< 0.05$). The result of this study showed that triple moxifloxacin therapy produced a significant higher eradication rate than clarithromycin triple therapy among normal weight patients with *H. pylori* infection (100% and 50% respectively (p=0.032)), while there was no significance difference among overweight and obese patients ($p< 0.05$) between the two groups. The present study concluded that the administration of moxifloxacin triple regimen for *H. pylori* eradication, demonstrated eradication effectiveness was significantly higher compared to that of clarithromycin triple regimen.

Key words: *H. pylori*, moxifloxacin, clarithromycin, triple therapy, age, BMI.

تأثيرعلاج الموكسيفلوكساسين الثلاثي مقابل علاج كلاريثروميسين الثلاثي للقضاء على عدوى الملوية البوابية بالنسبة للعمر ومؤشر كتلة الجسم

احمد منصور كاظم*، محمد محمود محمد، حسين محمد حسن***

***صيدلي سريري/ دائرة صحة واسط**

**فرع الصيدلة السريرية/كلية الصيدلة /الجامعة المستنصرية

الخلاصة:

تعتبربكتريا الملوية البوابية (H. Pylori) واحدة من مسببات الأمراض البشرية الأكثر شيوعًا ، والتي تصيب أكثر من 50٪ من سكان العالم. الملوية البوابية تحفز الالتهاب، تسبب أمراض الجهاز الهضمي العلوي، بما في ذلك عسر الهضم ، أمراض القرحة الهضمية، مرض الجزر المعدي المريئي ونوع من سرطان الغدد الليمفاوية المرتبطة بالمخاطية (MALT). من المهم استخدام نظام استئصال فعال للغاية وأفضل تحملاً. في هذه الدراسة ، تم إدراج خمسين مريض بالغ تم تشخيص إصابتهم حديثًا بعدوى البكتيريا الحلزونية ، تم تخصيصهم في مجموعتين مع نظامين مختلفين لعلاج استئصال الملوية البوابية. تلقت المجموعة (أ) (25 مريضا) علاج كلاريثروميسين الثلاثي عن طريق الفم لمدة 14 يوما. تلقت المجموعة الثانية (25 مريضاً) علاج موكسيفلوكساسين الثلاثي عن طريق الفم لمدة 14 يوماً. أشارت النتائج الواردة في هذه الدراسة إلى أن معدل قضاء الموكسيفلوكساسين (80٪) من التهاب بكتريا الملوية البوابية من المرضى المصابين أعلى بكثير مقارنة مع نظام كلاريثروميسين الثلاثي (52٪). في هذه الدراسة، عند استخدام نظم استئصال مختلفة للمرضى الذين يعانون من عدوى الملوية البوابية من مختلف الفئات العمرية أظهرت عدم وجود فروق ذات دلالة إحصائية لتحقيق معدل الاستئصال (P <0.05). أظهرت نتائج هذه الدراسة أن علاج الموكسيفلوكساسين الثلاثي أنتج معدل استئصال أعلى من علاج كلاريثروميسين الثلاثي بين مرضى الوزن الطبيعي مع عدوى الملوية البوابية (100٪ و 50٪ على التوالي (p = 0.032)) ، في حين لم يكن هناك فرق معنوي بين المرضى الذين يعانون من زيادة الوزن والبدانة (P <0.05) بين المجموعتين. من هذه الدراسة ، نستنتج إلى أن إدارة نظام الموكسيفلوكساسين الثلاثي لاستئصال بكتريا الملوية البوابية ، أثبتت فعالية القضاء كان أعلى بكثير مقارنة مع نظام كلاريثروميسين الثلاثي.

الكلمات المفتاحية: الملوية البوابية، كلاريثرومايسين، العلاج الثلاثي، العمر، مؤشر كتلة الجسم.

Introduction:

H. Pylori is one of most common infectious human pathogens, and accounts for high risk of morbidity and mortality [1]. Infecting more than 50 percent of the worldwide populations, and it associated with (90%) of Duodenal Ulcers (DU) and (70%) of benign Gastric Ulcers (GU) [2]. The overall incidence is high in developing countries compared with developed countries, and within areas of different countries [3]. Typically, transmission of H. pylori is via feco-oral or oro-oral routes and also gastro-gastric rout [2]. It is well known that H. pylori might induce inflammation, and it is one of the most important causes of upper gastrointestinal illnesses, that including dyspepsia, Peptic Ulcer Diseases (PUD), Gastroesophageal Reflux Disease (GRD) and Gastric Mucosa-associated Lymphoid Tissue (MALT) lymphoma [4]. According to The American College of Gastroenterology (ACG 2017), *H. pylori* infection testing can be done for patients with all diseases mentioned above [5].

The H. pylori infection clinical course depends on both the host susceptibility, e.g. diet, genetic predispositions, the degree of the immune response to infection and bacterial virulence factors (VF) mainly due to the release of urease enzyme[6], and because the high prevalence and serious health burden of such infection, it is necessary to use a highly effective and well tolerated eradication regimen[3].

Pharmacological treatment includes: Phytomedicines such as garlic extract, green tea, cranberry juice, [7] and curcumin [8]; Probiotics [9]; Antisecretory medications; Proton Pump Inhibitors (PPIs) are more effector in the gastric pH increment than H2-receptor antagonists (H2RAs) [10]. Anti-infective regimens for H. pylori Eradications include many drug regimens as A) Triple drugs regimens, the standard conventional therapy include proton pump inhibitors, clarithromycin, and amoxicillin, or metronidazole used instead in patients with an allergy to penicillin, for 14- days, is the most of guidelines used until recently, clarithromycin triple therapy should be avoided as first-line treatment option in regions where clarithromycin resistances is high as in many parts of North America(5, 11), B) Quadruple drug regimens; it is classified to bismuth-based quadruple drug

regimens and non-bismuth based quadruple drug regimens. The main advantage of this regimen is no clarithromycin resistance and minimal effect of metronidazole resistance which overcomes by extended duration of 10–14days [12]. Bismuth subcitrate or subsalicylate added to PPI, Tetracycline, and metronidazole for 10–14 days and can be used as first-line therapy or as salvage therapy [5]. Other drug regimens also used for treatment of *H. pylori* infection include non-bismuth based quadruple drug regimens (concomitant regimen) [13], sequential regimens [14], hybrid regimen [5]and Amoxicillin high-dose dual regimen [15].

Moxifloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin [16]. It has high efficacy in gram-negative bacteria, gram-positive bacteria, anaerobic bacteria and in atypical pathogen as Mycoplasma Species [17]. Based on available results of meta-analysis and clinical trials studies, moxifloxacin-based triple therapy is safe and effective and shows better outcome parameters compared with the standard clarithromycin-triple therapy in either first-line or second-line therapies in treatment of H. pylori infections [18-20].

Patients and Methods

The current study is a prospective randomized-controlled interventional open-label clinical trial, performed in a single health center. This study designed to include 50 Iraqi patients newly diagnosed with H. pylori infection (23 female and 27 male) with age range between 20 and 65 years, who attended the endoscopy unit of AL-Zahraa Teaching Hospital/Wassit province. Patients enrolled in the study after he/she signed a written consent, the ethical approval to conduct the research obtained and sought by the scientific committee of the hospital.

The patients selected by a senior physician and assigned as having upper gastrointestinal symptoms with H.pylori infection (with clinical indications for H.pylori treatment) and having a positive endoscopic examination of *H. pylori* infection. Before the endoscopic investigation, data was collected through direct interview with the patient. Furthermore, specific quessionniare was used to assess the intensity of clinical symptoms pre and post-treatment. The study conducted between October 2016 and September 2017. Helicobacter pylori infection defined by the following tests measured before starting the treatment: positive stool antigen test for H. pylori, positive rapid serum anti-*H.Pylori* IgG antibody tests and endoscopy; oesophagogeal-gastroduodenoscopy(OGD), with biopsy for histologic evidence of H. pylori in which gastroscopy was indicated, at least two antral mucosal biopsies and two body mucosal biopsies obtained through endoscopy[21]. According to these criteria, eligible patients allocated into two groups and the treatments were divided randomly as follows:

•Group A (25 patients; 13 Male and 12 female) received oral standard conventional triple therapy (esomeprazole tab. 40 mg twice daily (b.i.d), amoxicillin tab. (1gr b.i.d), clarithromycin tab. (500 mg b.i.d)) for fourteen days.

•Group B (25 patients; 14 Male and 11 female) received oral moxifloxacin-based triple therapy (moxifloxacin tab. 400 mg once daily, amoxicillin tab. (1gr b.i.d.), and esomeprazole (40 mg b.i.d) for fourteen days.

Biopsy Samples: Three to four gastric antral and two body mucosal biopsy specimens were taken from every patient because *H. pylori* did not evenly distribute throughout the gastric mucosa [22]. Ten percent buffered formalin was used as a fixative for all GI mucosal biopsies of histopathological diagnosis. Two experienced histopathologists reviewed sections and they were blinded to the endoscopic findings.

Stool sample: Stool specimens collected from each patient, and the stool antigen test performed according to the principle of H. pylori rapid antigen test. The test method employs specific monoclonal antibodies for *H. pylori* antigen to selectively identify *H. pylori* antigens in human fecal specimens [23].

Blood samples: Blood samples were drawn and collected immediately after endoscopy from all patient groups. Patients' serum or plasma were screened for the presence of *H. pylori* IgG antibodies, then H. pylori test performed based on the principle of H. pylori Antibody rapid test device (Serum/Plasma) [24].

Statistical Analysis: Data were analyzed by using Statistical Package for Social Sciences (SPSS) (student version 23, McGraw Hill Company 2015). Continuous variables expressed as mean ± SD, independent two samples T-test was used to find out significance of differences between means. Associations and/ or differences among categorical variables were tested by Chi-square test (fisher exact test) when needed. P value of less than 0.05 was considered statistically significant.

Results:

Demographic distribution and disease characteristics in patients with H. pylori infections:

This study showed that the mean age of two group were 38.6±11.1and 36.8±9.6 years respectively with no significant differences between them (p value = 0.542). The mean BMI of both groups were 25.7±3.7 and 26.1±4.5 with no significant differences between them (p value = 0.714). Males represented by 52% and 56% while females formed the reciprocal percentages of triple clarithromycin and triple moxifloxacin groups, respectively. However, there is no statistical significance between gender and treatment group (p value = 0.777). Positive family history of dyspepsia was given 28% of the total studied patients with no significant association between family history of dyspepsia and type of treatment given to the patients, (p value = 0.529), Table-1.

Table -1: Demographic Distribution and Disease Characteristics in Patients with *H. Pylori* Infections

Variable		Study Groups		
		Group A	**Group B**	**P value**
Age (years)	**Mean±SD (Range)**	38.6±11.1 (20-65)	36.8±9.6 (22-60)	0.542
BMI	**Mean±SD (Range)**	25.7±3.7 (19-32)	26.1±4.5 (19-35)	0.714
		No (%)	**No (%)**	
Gender	**Male**	13 (52)	14 (56)	0.777
	Female	12 (48)	11 (44)	
Family history	**+ve**	6 (24)	8 (32)	0.529
	-ve	19 (76)	17 (68)	

Data presented as Mean ± SD for BMI and age, BMI = body mass index

Data presented as n= number and (%) = percentage for other disease characteristics.

P >0.05 are not significantly different.

Eradication Effectiveness of Triple Clarithromycin and Triple Moxiflo-xacin Regimens in Patients with *H. Pylori* Infections:

The study demonstrated that the use of triple moxifloxacin regimen eradicated 80% of *H. pylori* infection, while triple clarithromycin regimen eradicated only 52% of patients with *H. pylori* infection. Significant difference between eradication rates of the two regimens was clear and drugs benefit went towards moxifloxacin triple therapy (p value = 0. 0.037), Table-2.

Table-2: Eradication Effectiveness of Triple Clarithromycin, and Triple Moxifloxacin Regimens in Patients with *H. pylori* Infections

Eradication Effectiveness			
Drug Regimen	**Yes N (%)**	**No N (%)**	**P Value**
Triple clarithromycin	13 (52%)	12 (48%)	0.037*
Triple moxifloxacin	20 (80%)	5 (20%)	

Data presented as N= number and (%) = percentage
Significant difference among different groups (P<0.05).
Data analyzed by Pearson Chi-square test

Eradication Effectiveness of Triple Clarithromycin and Triple Moxifloxacin Regimens in Patients with H. Pylori Infections Regarding to the Patient's Age and BMI:

Regarding to age, the study showed that the effectiveness of triple clarithromycin regimen in the patients of less than thirty years old was (60%), 30-39 years old (50%), 40-49 years old (37.5%), and ≥ 50 (75%). There were no significant differences between eradication rate of triple clarithromycin among different age category (p value = 0.645). While the effectiveness of triple moxifloxacin regimen in the patients of less than thirty years old was (100%), 30-39 years old (80%), 40-49 years old (66.7%), and ≥ 50 years old (66.7%). There were no significant differences between eradication rate of triple moxifloxacin according to age category (p value = 0.475). Moreover, there is no significant differences between eradication rate of triple clarithromycin and triple moxifloxacin drug regimens on patients' age groups (p value = 0.181), (0.321), (0.280) and (1) respectively, Table-3.

Table-3: Eradication Effectiveness of Triple Clarithromycin and Triple Moxifloxacin Regimens in Patients with *H. Pylori* Infections Regarding to the Patient's Age

Age Groups / Drug Regimen	**< 30 Year**	**30-39Year**	**40-49 Year**	**≥ 50 Year**	**P Value**
	N (%)	**N (%)**	**N (%)**	**N (%)**	
Triple clarithromycin	3 (60)	4 (50)	3 (37.5)	3 (75)	0.645
Triple moxifloxacin	6 (100)	8 (80)	4 (66.7)	2 (66.7)	0.475
P value	0.181	0.321	0.280	1	

Data presented as N= number and (%) = percentage
P >0.05 are not significantly different.

Regarding to BMI, the study showed that the effectiveness of triple clarithromycin regimen among normal, overweight, and obese patients were 50%, 54.5% and 50% respectively with no significant differences, (p value = 0.975). However, eradication rate of triple moxifloxacin regimen among normal, overweight, and obese patients were 100%, 88.9%, and 33.3%, respectively with statistically significant differences of eradication for the benefit of normal weight (p value = 0.004). Triple moxifloxacin and triple clarithromycin regimens eradicate 100% and 50% of H. pylori infection among normal weight patients, respectively, with significant statistical differences (p value = 0.032). While there was no significance difference among overweight and obese patients in both groups (p value = 0.157) and (1.0) respectively, Table-4.

Table-4: Eradication Effectiveness of Triple Clarithromycin and Triple Moxifloxacin Regimens in Patients with *H. Pylori* Infections Regarding to the BMI

BMI / Drug	Normal		Overweight		Obese		P value
	Total	N (%)	Total	N (%)	Total	N (%)	
Triple clarithromycin	10	5 (50)	11	6 (54.5)	4	2 (50)	0.975
Triple moxifloxacin	10	10 (100)	9	8 (88.9)	6	2(33.3)	0.004**
p. value	0.032*		0.157		1		

Data presented as N= number and (%) = percentage
(P <0.01) significant difference
(P <0.001) high significant difference.

Discussion

Eradication of *H. pylori* remain a challenge for physicians, no current therapy regimens exist are able to cure the infection in all treated patients [25]. Based on the decreased success rate of standard clarithromycin triple therapies [26, 27], new therapy regimens have been introduced. Several studies was conducted to evaluate the most effective therapeutic regimens for improving the eradication rate of *H.pylori* infection [28-31]. This study is another attempt in this respect, considering Iraqi patients, but at a smaller scale.

In the present study, there is no significant difference between all age categories of the two groups. The mean of age in all patients is 37.7 (20-65 years), this finding is similar to that reported by other studies by Sanchez Ceballos et al (2016) and Masjedizadeh et al (2012) in which the mean of age where 37.5 and 36.26 years respectively with no significant differences [32, 33]. The incidence of getting H. pylori infection in the middle age patients (30-50 years) is greater compared to those with other ages. However, this result is consistent with other studies which reported that the middle age group tends to have more social activities, and thus have higher opportunity to be exposed to the H. pylori infection [8, 34].

Regarding to BMI, there was low prevalence of obesity observed initially among *H. pylori* infected patients (mean 25.9), and no statistical differences found between groups. Several studies reported that data on H. pylori infection and obesity are still controversial [35, 36].

Percentage of male and female in H. pylori positive patients was approximately matched for the both study groups (27 male (54%) and 23 females (46%)), which coincided with most studies that reported there is no significant difference in

incidence of *H. pylori* infection between women and men in adults [37-39].

This study demonstrated that 28% of patients had *H. pylori* positive family history with peptic ulcer disease or functional dyspepsia, no statistical differences founded regarding to incidence of *H. Pylori* infection between positive and negative family history groups, as shown in table-1. This finding was close to that of Shokrzadeh et al (2012) in which there was no difference in incidence of infection with H. pylori among the patients with or without family history of gastro duodenal diseases (40). Other studies showed that, in all selected families, there was an intra-familial transmission and the majority of infections occur within families, between individuals living in the same house and in close relatives [41, 42].

The current study explored the first line conventional clarithromycin triple regimen eradication rate was (52%) and thus the eradication failure (resistance) was (48%). This result is consistent with several studies; Malfertheineret al (2011) founded that 55% of patients were eradicated in the standard clarithromycin therapy [43]. Nishizawa *et. al* (2015) and Makhlough et. al (2016) recorded eradication rate 77.2% and 70% respectively achieved with clarithromycin triple therapy as a first-line regimen [44, 45]. In Iraq, studies by Abbas et.al and Ali et.al recorded that per protocol eradication rate 57.89% and 57.8% respectively, achieved with a first-line therapy of clarithromycin based-triple regimen [8, 30].

The effectiveness of standard clarithromycin-triple therapies has substantially declined and the *H. pylori* resistance rates to clarithromycin have been increased over the last 20 years in some Middle-East countries including Saudi Arabia, Iran, and Turkey [46-48], and in Western Europe [49].Therefore, in cases where clarithromycin resistance is higher than 20%, it recommended that treatment with clarithromycin should be avoided in the eradication regimen of H. pylori [50]. However, because of high prevalence of resistant rate of conventional clarithro-mycin triple regimen must use another type of treatment in area of high clarithromycin resistant such as bismuth based-quadruple regimen and moxifloxacin triple regimens and considered as first-line treatment [11, 51].

The eradication rate of moxifloxacin-based triple therapy in the current study, equal to (80%), found significantly higher than standard clarithromycin based triple therapy (P value=0.037), as shown in table-2. This result come in agreement with data reported that per protocol eradication rate was (84.8%) by using triple regimen consist of moxifloxacin, amoxicillin and esomeprazole [52]. Other studies showed that the moxifloxacin-based triple therapy eradication rate was found to be over (90%) by per protocol analysis and could be safe and well tolerated with a good compliance and few adverse effects in comparing with the standard triple therapy could be suggested in clinical practice [50].

In the present study, and in many others, using different eradication regimens for H. pylori infection for patients with different age groups demonstrated no statistically significant differences in eradication rate achieved. Lee et al (2014) reported no significant differences among age groups and eradication effectiveness with using clarithromycin triple therapy [53]. Kim et al (2013) also showed no significant differences among age groups for both moxifloxacin triple therapy and bismuth quadruple therapy regarding to eradication rate [54]. These findings are consistent with the results of the current study. Patients with age ≥50 years may have capability for easier *H. pylori* eradication after first line eradication therapy. This is in fact due to the elderly patients may exhibit gastric acid hypo-secretion, and this could compromise their ability to inactivate the amoxicillin and clarithromycin [55]. Quinolone resistance increases with repeated of use and with aging, Rakicy et.

al (2014) study, showed quinolone resistance was found as 19.1% in patients older than 45 years of age and 2.6% in patients younger than (45) years of age (50). This can explain our results as high eradication rate in elderly patients for triple clarithromycin drug regimen were present. In contrast, (100 %) eradication rate in younger patients with age <30 years yielded after using triple moxifloxacin regimen, as shown in table-3.

The result of this study revealed that triple moxifloxacin therapy produced a significant higher eradication rate than clarithromycin triple therapy among normal weight patients with *H. pylori* infection. While there were no significant differences regarding to overweight and obese patients between the two groups, as shown in table-4. Furthermore, triple moxifloxacin therapy demonstrated a highly significant eradication rate in normal weight patients in regard to that in overweight and obese patients. These results come in agreement with study done by Abdullahi et. al (2008) using a triple therapy showed that the lower successfull eradication rate observed in (55%) of the obese and overweight group compared with (85.4%) in normal weight [56]. The drugs tissue distribution are effected by many factors including the affinity of the drug to plasma proteins and/or tissue components, regional blood flow, and body composition that may influence drug pharmacokinetics in obese patients who have larger fat masses and absolute lean body masses as well, which markedly increased in obese more than non-obese individuals of the same gender, height and age [57]. A study done by Longo et al (2013) showed that obesity is also an important risk factor for infections, in this study the disposition of antibiotics may affected by excess weight leading to sub-therapeutic drug concentrations and antibiotic treatment failure that may increase treatment resistance and has serious adverse health outcomes. Also given that obese patients often have other health problems [58].

In addition, high BMI in overweight and obese individual frequently causes delayed gastric and oesophageal emptying that may result in a decreasing the proportion of drug absorption, irrespective to the characteristics of the drug [59].

Conclusions:

From the present study, the reported results indicated that fourteen days moxifloxacin triple regimen showed higher eradication effectiveness and symptoms improvement compared with eradication therapy for H. pylori infections by standard clarithro-mycin triple regimen when used as a first line eradication therapy. No effect of patient's age on the eradication effectiveness in both regimens used. However, eradication effectiveness of moxifloxacin triple therapy significantly correlated with BMI of patients with normal weight and overweight, respectively.

Limitations:

This study has few limitations. First, it was a single-center study including small scale sample size, and difficulty to re-endoscope the patients to confirm the eradication by histopathology post-treatment due to poor patient compliance, despite a symptomatic relief confirmed in most patients. Second, the drug susceptibility test of H. pylori by using polymerase chain reaction (PCR) or culture is costly, so pre-treatment susceptibility testing was not performed.

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