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Treatment of Helicobacter Pylori Infections using Moxifloxacin-Triple Therapy Compared to Standard Triple and Quadruple Therapies

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Abstract

Helicobacter pylori (H. Pylori) is one of the most common infectious human pathogens. *H. pylori* could induce inflammation, that causes illnesses and disorders of upper gastrointestinal which including peptic ulcer diseases, dyspepsia, gastroesophageal reflux disease and gastric mucosa-associated lymphoid tissue (MALT) lymphoma. It is important to use a better tolerated and greatly effective eradication regimen. This study aimed to evaluate the efficacy, safety, tolerability of prescribing moxifloxacin-based triple therapy compared to that of using bismuth-based quadruple therapy and clarithromycin-based triple therapy in treatment of H. Pylori infection, and the patients ABO blood group phenotypes as an interrelated disease affecter. In this study, 75 newly diagnosed adult patients with *H. pylori* infection were included and completed the study. They were allocated into three groups with three different treatment regimens for *H. pylori* eradications; Group A (25 patients) received oral standard clarithromycin-based triple therapy for 14 days. Group B (25 patients) received oral bismuth based-quadruple therapy for 10 days. Group C (25 patients) received oral moxifloxacin-based triple therapy for 14 days. The results reported in this study indicated a significant higher eradication rate of Group B and Group C (84% and 80%, respectively) of patients with *H. pylori* infections compared to that of Group A (52%). The incidence of adverse effects was appeared as 64%, 72% and 24% of patients in group A, B and C respectively. The use of moxifloxacin triple regimen for *H. pylori* eradication, present with eradication efficacy parallel to that of quadruple regimen which was significantly higher compared to that of clarithromycin triple regimen. In this study, the eradication rates of triple clarithromycin regimen, quadruple regimen and triple moxifloxacin treatment regimen were low in *H. pylori* infected patients whom carrying blood group O phenotype compared to those having other blood groups phenotype. However, no statistically significant differences were yielded in eradication rates of all treatment regimens in regards to the type of blood groups phenotype. Also, moxifloxacin triple therapy is more tolerable and does not increase the incidence of overall adverse effects compared to other regimens used in this study.

Keywords: H. pylori, Moxifloxacin, Clarithromycin, Triple therapy, Quadruple therapy.

علاج عدوى البكتريا البوابية باستخدام الموكسيفلوكساسين الثلاثي مقارنة بالعلاجات القياسية الثلاثية والرباعية

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الخلاصة

البكتريا الملوية البوابية هي واحدة من أكثر مسببات الأمراض البشرية المعدية شيوعًا. يمكن أن تسبب الملوية البوابية الالتهاب الذي يسبب أمراضًا واضطرابات في الجهاز الهضمي العلوي بما في ذلك أمراض القرحة الهضمية وعسر الهضم ومرض الاسترجاع المعدي المريئي والأنسجة اللمفاوية المرتبطة بالغشاء المخاطي المعدي (.(MALT). من المهم استخدام نظام استئصال جيد يمكن تحمله وفعال للغاية. هدفت هذه الدراسة إلى تقييم فعالية وسلامة وملائمة وصف العلاج الثلاثي المعتمد على الموكسيفلوكساسين مقارنةً باستخدام العلاج الرباعي المعتمد على البزموت والعلاج الثلاثي المعتمد على كلاريثروميسين في علاج عدوى الملوية البوابية ، وأنماط فصيلة الدم ABO للمرضى كعامل مرتبط بالمرض. في هذه الدراسة ، تم تضمين ٧٥ مريضًا بالغًا تم تشخيصهم حديثًا بعدوى الملوية البوابية واستكملوا الدراسة. تم تقسيمهم إلى ثلاث مجموعات مع ثلاثة أنظمة علاج مختلفة لاستئصال الملوية البوابية ؛ تلقت المجموعة أ (٢٥ مريضًا) علاجًا ثلاثيًا قياسيًا يعتمد على الكلاريثروميسين لمدة ١٤ يومًا. تلقت المجموعة ب (٢٥مريضًا) علاجًا رباعيًا يعتمد على البزموت الفموي لمدة ١٠ أيام. تلقت المجموعة ج (٢٥مريضًا) علاجًا ثلاثيًا يعتمد على الموكسيفلوكساسين عن طريق الفم لمدة ١٤ يومًا. أشارت النتائج المثبتة في هذه الدراسة إلى ان معدل استئصال أعلى للمجموعة ب والمجموعة ج هي)٨٤٪ و ٨٠٪ على التوالي) من المرضى المصابين بالبكتيريا الملوية البوابية مقارنةً بالمجموعة أ (52٪). ظهرت نسبة حدوث التأثيرات . الضائرة بنسبة ٦٤٪ و ٧٢٪ و ٢٤٪ من المرضى في المجموعة (أ) و (ب) و (ج) على التوالي. إن استخدام نظام موكسيفلوكساسين الثلاثي لاستئصال الملوية البوابية

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اظهر فاعلية استئصال موازية لتلك الخاصة بالنظام الرباعي الذي كان أعلى بكثير مقارنة بالنظام الثلاثي كلاريثروميسين. في هذه الدراسة ، كانت معدلات الاستئصال لنظام الكلاريثروميسين الثلاثي والنظام الرباعي ونظام العلاج الثلاثي موكسيفلوكساسين منخفضًا في المرضى .

المصابين بالبكتيريا الملويةة البوابية الذين يحملون النمط الظاهري لفصيلة الدم O مقارنة بأولئك الذين لديهم النمط الظاهري لفصيلة الدم الأخرى. ومع ذلك ، لم تسجل فروق ذات دلالة إحصائية في معدلات الاستئصال لجميع نظم العلاج فيما يتعلق بنوع النمط الظاهري لفصائل الدم. أيضًا ، يعد العلاج الثلاثي موكسيفلوكساسين أكثر قابلية للتحمل ولا يزيد من حدوث الآثار الضارة الكلية مقارنة بالأنظمة الأخرى المستخدمة في هذه الدراسة.

الكلمات المفتاحية: الملوية البوابية ، موكسيفلوكساسين ، كلاريثروميسين ، العلاج الثلاثي ، العلاج الرباعي.

Introduction

Helicobacter Pylori is one of the most common infectious human pathogens, and accounts for high risk of morbidity and suffering [(1)]. Worldwide, H. Pylori infects about fifty percent of populations and it highly associated with duodenal ulcers (DU) and benign gastric ulcers (GU) [(2)]. The incidence is more in developing countries compared with developed countries [(3)]. H. pylori infection is usually transmitted via feco-oral or oro-oral routes, in addition to gastro-gastric route [(2)]. H. pylori is one of the most important causes of upper gastrointestinal illnesses, 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)], and because the high prevalence and serious health burden of such infection, it is necessary to use a highly effective and well tolerated eradication regimens [(3)].

Different therapeutic regimens used for eradication of peptic ulcer infection includes antisecretory medications; proton pump inhibitors (PPIs), H2-receptor antagonists (H2RAs) and other medications [(6)]. Anti-infective drugs for H. pylori eradications are included in many regimens as;

1) clarithromycin-based triple drugs regimens, for 14 days. Howover, due to the high clarithromycin resistances reported in north America, its use as first-line treatment option is diclined recently [(5, 7)];

2) Anothor drug regimen is a quadruple regimen; which include 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 10–14 days.

Other drug regimens also used for treatment of H. pylori infection include hybrid regimen , and sequential regimens [(5,8,9)].

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 to the standard clarithromycin-triple therapy in either first-line or second-line therapies in the treatment of patients with H. pylori infections [(10-12)].

This study aimed to evaluate the efficacy, safety, tolerability of prescribing moxifloxacin-based triple therapy compared to that of using bismuth-based quadruple therapy and clarithromycin-based triple therapy in the treatment of H. Pylori infection, and the patients ABO blood group phenotypes as an interrelated disease affecters i.e. eradication rate of moxifloxacin-based triple therapy compared to other standard H. Pylori eradication therapies and their relations to ABO blood group phenotypes.

Patients and Methods

The current study was a prospective randomized-controlled interventional open-label clinical trial, performed in a single health center. This study was conducted on Iraqi patients, who attended the gastrointestinal endoscopy unit of AL-Zahraa Teaching Hospital/ Wassit province from October 2016 to September 2017 and screened with suspected H. pylori infection. The patients were selected by a gastroenterologist physician and assigned as having a positive endoscopic examination of H. pylori infection (with clinical indications for H. pylori treatment and presented with positive stool antigen test). However, patients with H. pylori negative test, patients who previously received eradication therapy for H. pylori infection, patients with poor compliance, patients with advanced gastric cancer or other malignancy or comorbid disease, in addition to pregnant or lactating women were excluded from the study.

Eligible patients were allocated randomly into three groups and the treatments were divided as follows: Group A (25 patients; 13 male and 12 female) received oral standard conventional triple therapy. Group B (25 patients; 11male and 14 female) received oral bismuth quadruple therapy. Group C (25 patients; 14 Male and 11 female) received oral moxifloxacin-based triple therapy. Dempgraphic data and clinical symptoms were collected through direct interview with the patient. Eligible patients were allocated randomly into three groups and the treatments were divided as follows: Group A received oral standard conventional triple therapy (esomeprazole tab. 40 mg twice daily (b.i.d), amoxicillin tab. (1000 mg b.i.d), clarithromycin tab. (500 mg b.i.d)) for fourteen days. Group B received oral bismuth quadruple therapy (esomeprazole 40 mg b.i.d, a capsule containing three agents (Pylera®); metronidazole 125mg, bismuth subcitrate potassium 140mg, and tetracycline 125mg, were taken four times daily (q.i.d)) for ten days. Group C received oral moxifloxacin-based triple therapy (moxifloxacin

tab. 400 mg once daily, amoxicillin tab. (1000 mg b.i.d.) and esomeprazole 40 mg b.i.d) for fourteen days. Six weeks after completion of treatment, clinical outcomes were evaluated by the following:

1. H. Pylori eradication was checked by using stool antigen test. Patients with negative stool antigen test were classified as H. Pylori free [13], while those who presents with positive stool antigen test were considered as H. Pylori infected. Furthermore, a clinical examination was done for each patient to assess their condition and response to therapy.

2. Adverse drug reactions associated with the three H. pylori eradication regimens.Biopsy samples: because H. pylori does not evenly distribute throughout the gastric mucosa, three to four gastric antral and two body mucosal biopsy specimens were taken from every patient in the endoscopy unit before starting the study as a gold standard diagnostic tool [14]. For all GI mucosal biopsies that were used for histopathological diagnosis, 10% buffered formalin was used as a fixative agent. Two experienced histopathologists reviewed samples and they were blinded to the endoscopic findings.

Stool sample: Stool specimens were collected from each patient before starting the study (as a diagnostic tool) and 6 weeks after the study ends (to assess the eradication regimen activity) , and the stool antigen test was performed according to the principle of H. pylori rapid antigen test [15]. The H. pylori antigen rapid test device (feces) used from Abon Biopharma, China.Blood samples: Blood samples were drawn and collected immediately after endoscopy from all patient groups. H. pylori test was performed based on the principle of H. pylori antibody rapid test device (Serum/Plasma) [16]. The Anti H. pylori IgG antibody rapid device used from Abon Biopharma, China. And Anti ABO and Anti-D monoclonal kit used from Spinreact, Spain.

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), and categorical variables (expressed as number (N) and percentage (%)) like demographic data, eradication rate, eradication rate according to ABO blood group phenotypes, and incidence of adverse effects. Demographic data (age, BMI, gender, family history and duration of symptoms) were converted to categorical data and analyze statistically by Chi square test, in addition to eradication rate and incidence of adverse effects among the three groups. Fisher's Exact test used to analyze ABO blood group phenotypes distribution, and eradication rate with their relations to ABO blood group phenotypes. *P* value less than 0.05 was considered to be statistically significant.

Results

This study was conducted on 119 Iraqi patients, who attended the gastrointestinal endoscopy unit, screened for suspected H. pylori infection, from them, 88 patients were H. pylori positive and the other 31 patients were H. pylori negative who were excluded, only 75 adult patients were with H. pylori infection whom completed the study by per protocol analysis.The results of this study presents with no significant differences among the three groups regarding to age (p value = 0.553), BMI (p value = 0.806) and gender (p value = 0.688). Moreover, blood group phenotype, A, B, AB and O represented by 24%, 30.7%, 12% and 33.3% of all patients, respectively. Regarding to each blood group phenotype, no significant differences were reported among the three groups (p value = 0.326). Finally, no significant association between family history of dyspepsia and type of treatment used in this study (p value = 0.820), as seen in Table 1.

Table 1. Demographic distribution and disease characteristics

Variables		Study Groups			*P* value
		Group A	Group B	Group C	
Age (years)	Mean±SD (Range)	38.6±11.1 (20-65)	38.9±14.4 (20-63)	36.8±9.6 (22-60)	0.553 [a]
BMI (kg/m2)	Mean±SD (Range)	25.7±3.7 (19-32)	25.5±3.6 (19-31)	26.1±4.5 (19-35)	0.806 [a]
		No (%)	No (%)	No (%)	
Gender	Male	13 (52)	11 (44)	14 (56)	0.688 [a]
	Female	12(48)	14(56)	11(44)	
ABO Blood group	A	5 (20)	5 (20)	8 (32)	0.326 [b]
	B	4 (16)	12 (48)	7 (28)	
	AB	5 (20)	2 (8)	2 (8)	
	O	11 (44)	6 (24)	8 (32)	
Family history	+ve	6 (24)	7 (28)	8 (32)	0.820 [a]
	-ve	19(76)	18(72)	17(68)	
Duration of symptoms	<1 year	13 (52)	6 (24)	13 (52)	0.069 [a]
	≥ 1 year	12 (48)	19 (76)	12 (48)	

BMI = body mass index

[a] Fisher's Exact test used for ABO blood groups to examine the degree of significance.

[b] Pearson Chi square test used for other demographic and disease characteristics to examine the degree of significance.

P >0.05 are not significantly different

The prevalence of H. pylori infection in this study that determined by stool antigen test, histology, and antibody test shows that 88 (73.95%) of enrolled patients were H. pylori positive (However, 75 patients only completed the study) while 31 (26.05%) of the patients were H. pylori negative.

Table-2 shows that the use of quadruple regimen (pylera®) eradicated 84% of patients with H. pylori infection, triple moxifloxacin regimen eradicated 80% of patients with H. pylori infection, while triple clarithromycin regimen eradicated only 52% of patients with H. pylori infection. The best eradication rate was achieved by quadruple regimen and triple moxifloxacin regimen which were significantly different to that achieved by triple clarithromycin regimen (p value = 0.023)

Table 2. Eradication rate of moxifloxacin-based triple therapy compared to other standard H. Pylori eradication therapies

Study groups	Patients number N	Eradication rate N (%)
Group A	25	13 (52)
Group B	25	21 (84)
Group C	25	20 (80)
P Value	---	0.023*

Significant difference among different groups (P<0.05). Data analyzed by Pearson Chi-square test.
Group A patients received oral standard clarithromycin-based conventional triple therapy
Group B patients received oral bismuth quadruple therapy
Group C patients received oral moxifloxacin-based triple therapy

Table-3 shows that there was no statistically significant association between type of drug regimens and blood group phenotypes of patients; p value is > 0.05 in all conditions with lower percent of eradication rate of O blood group phenotype compared to others for the three study groups.

Table 3. Eradication rate of moxifloxacin-based triple therapy compared to other standard H. Pylori eradication therapies and their relations to ABO blood group phenotypes

Blood group	A	B	AB	O	P value
Study groups	Eradication rate				
	N (%)	N (%)	N (%)	N (%)	
Group A	4 (80)	2 (50)	3 (60)	4 (36.4)	0.530
Group B	4 (80)	11 (91.7)	2 (100)	4 (66.7)	0.574
Group C	6 (75)	6 (85.7)	2 (100)	6 (75)	1.000
P value	0.939	0.253	0.482	0.411	

Data presented as N= number and (%) = percentage
The data were analyzed by Fisher's Exact test to examine the degree of significance.
P >0.05 are not significantly different

The overall adverse effects of drug regimens appeared during the treatment were documented to determine the tolerability of drug regimens. Low incidence of taste disturbance (bitter taste), diarrhea and gastric upset were observed in some patients. All adverse effects were mild to moderate and there was no sever adverse effect which necessitates cessation of the treatment. Table-4 shows that overall adverse effects appeared on 72%, 64% and 24% of patients used quadruple Pylera®, triple clarithromycin and triple moxifloxacin respectively. The incidence of adverse effects related to triple moxifloxacin used was significantly different from that achieved in quadruple Pylera® and triple clarithromycin using patients (p value = 0.001).

Table 4. The incidence of adverse effects of moxifloxacin-based triple therapy compared to other standard H. Pylori eradication therapies.

Study group	Adverse Effects		P value
	Yes	No	
	N (%)	N (%)	
Group A	16 (64)	9 (36)	0.001[(a)]
Group B	18 (72)	7 (28)	
Group C	6 (24)	19 (76)	

Data presented as N= number and (%) = percentage
The data were analyzed by chi square test to examine the degree of significance.
[(a)] (P<0.01) high significant difference.

Discussion

In the present study, the prevalence of H. pylori infections is 73.95% were H. pylori positive. Hooi et al reported the highest prevalence in Africa (79.1%), and Asia (54.7%). In contrast, H. pylori prevalence is lowest in Northern America (37.1%), while in western Asia; Iran (59.0%), Saudi Arabia (65.9%), Turkey (77.2%) [17]. Two studies conducted in Iraq showed that (78%) and (68.97%) of adults respectively were infected with H. pylori [18, 19].

The current study explored the eradication rate of first line standard clarithromycin triple-regimen was (52%) and thus the eradication failure (resistance) was (48%). The result of this study is consistent with several studies; Malfertheiner et al founded that 55% of patients were eradicated in the standard clarithromycin therapy [20] and Makhlough et al recorded eradication rate 70% achieved with clarithromycin triple therapy as a first-line regimen [21]. 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 [19,22].

Therefore, in cases where the H. pylori resistance to clarithromycin drug regimen is higher than 20%, it recommended that treatments include clarithromycin should be avoided in the eradication of H. pylori [23]. So, because of high prevalence of resistant rate of conventional clarithromycin triple regimen we must use another type of treatment in the area of high clarithromycin resistant such as bismuth based-quadruple regimen and moxifloxacin triple regimens and considered as first-line treatment [7,24].

In the present study, the eradication rate of the first line quadruple therapy using three in one capsule (Pylera)®; plus esomeprazole was (84%) found significantly higher than standard clarithromycin based triple therapy (P value <0.023), this result was in agreement with other studies; Scalese et al which has shown that 87% of patients got eradication of H. pylori after treatment with quadruple therapy by using (Pylera®) capsule given with PPI [25].

The major effect of bismuth is to add an additional 30%–40% to the success with resistant infections [26]. Although metronidazole resistance is high worldwide, but it does not interfere with the therapeutic effects of bismuth, tetracycline and metronidazole combination due to metronidazole synergism with bismuth [20, 27]. The duration of quadruple therapy (Pylera)® is prepared for a ten days duration, if extending the duration to 14 days, would not increase the therapeutic effectiveness [28]. This differs to what has been suggested for standard triple therapies with 14 days duration [29].

The eradication rate of moxifloxacin-based triple therapy in the current study, equal to (80 %). This result was in consistent with data reported that per protocol eradication rate was (84.8%) by using triple regimen consist of moxifloxacin, amoxicillin and esomeprazole [30]. Other studies showed that the moxifloxacin-based triple therapy eradication rate was found to be over (90 %) by per protocol analysis [23]. A study compared moxifloxacin based-triple regimen for 10 days, and bismuth based-quadruple regimen for 14 days resulted with eradication rates of 82.6%, and 90.5% respectively [11]. Consequently, moxifloxacin-based triple therapies could be safe and could be suggested in clinical practice and showed higher rates of eradication compared to the standard triple therapy in the treatment of H. pylori infection and well tolerated with a good compliance and few adverse effects in comparing with the standard triple therapy [12, 23, 31].

It is obvious in this study that the eradication rates of triple clarithromycin regimen, quadruple regimen and triple moxifloxacin treatment regimen were low in H. pylori infected patients whom carrying blood group O phenotype (36.4%, 66.7% and 75% respectively) compared to those having other blood groups phenotype. However, no statistically significant differences were yielded in the eradication rates of all treatment regimens in regards to the type of blood groups phenotype, as shown in Table-3.

The blood group O individuals express higher inflammatory responses to H. pylori, demonstrating significant association between positive cagA H. pylori strain and the development of peptic ulcers among patients belonging to the blood group O [32]. It was demonstrated that bacterial load in patients with positive cag A was greater than in patients with a negative cag A, both in the corpus and antrum [33]. A significant reduction in the eradication rate after H. Pylori treatment was associated with high antral density of H. pylori [34]. Moreover, blood group O phenotype possibly has higher antibiotic resistance compared with other blood groups phenotypes [35, 36] . In total, these may provide a possible explanation to the low response of blood group O patients to H. pylori treatment by standard clarithromycin triple therapy, and for both quadruple drug therapy and moxifloxacin triple therapy.

The incidence of overall adverse effects in this study showed statistically highly significant differences among the three study groups with more frequency for Group B, bismuth quadruple therapy, and most of the adverse effects were mild to moderate in suffered patients. These results come in consistent with other studies which showed that 60% and 51% of patients respectively had medication adverse effects due to the treatment with clarithromycin triple therapy [20, 37].

A study by Delchier et al reported that in patients treated for 10 days with quadruple pylera®,

67.3% of patients reported adverse events [38]. Other study done by Liou et al found the frequency of adverse events was 47% in patients treated with 14-day clarithromycin triple therapy and 67% in patients treated with 10-day bismuth quadruple therapy [39]. Quadruple regimen needs more frequent use of drugs that may affect patient's adherence and its cost-effectiveness is an important issue, so bismuth-quadruple therapy still a challenge for both the physician and the patient [40]. Finally, the reported adverse effects were mild, self-limited, and had no influence on the patient's tolerability to medications.

Conclusions

Both 14 days moxifloxacin triple regimen and ten days quadruple regimen showed higher eradication effectiveness and symptoms improvement compared with standard clarithromycin triple regimen. Moreover, moxifloxacin triple therapy is more tolerable and does not increase the incidence of overall adverse effects compared to other regimens.

Limitations

This study has few limitations, 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.

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