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Comparative Study of the Efficacy of Different Regimens of Triple Therapy for Treatment of Egyptian Patients with Gastric and Duodenal Ulcer Due To *Helicobacter Pylori.*

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ABSTRACT

Helicobacter pylori (*H. Pylori*) is associated with over 90% duodenal ulcer, 80% gastric ulcer, mucosa-associated lymphoid tissue lymphoma and gastric adenocarcinoma So its eradication success could cure this diseases and prevent its complications.This study was performed to compare the efficacy of different regimens of triple therapy for treatment of gastric ulcer and duodenal ulcer due to HP. 100 Consecutive H. pylori-infected subjects were randomly assigned to 6 groups as follow: Group (A) included 18 patients and received omeprazole 20 mg,tinidazole 500 mg and clarithromycin 250 mg twice daily for 7 days($O_{20}T_{500}C_{250}$- 7d/n=18).Group (B) included 18 patients and received the same regimen used in group A for 14 days ($O_{20}T_{500}C_{250}$- 14d/n=18). Group (C) included 15 patients and received omeprazole 20 mg, tinidazole 500 mg and doxycycline 50 mg twice daily for 7 days($O_{20}T_{500}D_{50}$– 7d/n=15).Group (D) included 15 patients and received the same regimen used in group C for 14 days($O_{20}T_{500}D_{50}$ – 14d/n=15). Group (E) included 17 patents and received esomeprazole 20 mg, amoxycillin 1gm and clarithromycin 500 mg twice daily for 7 days($E_{20}A_{1gm}C_{500}$ - 7d/n=17).Group (F) included 15 patients and received the same regimen used in group E for 14 days($E_{20}A_{1gm}C_{500}$– 14d/n=17). *H. Pylori* eradication was confirmed by histopathological examination and biopsy urease test (CLO test) at least 8 weeks after cessation of therapy. Results: H. Pylori eradication rates were as follow Group (A) 66.66%, Group (B)72.2%, Group (C) 53.3%, Group (D) 60%, Group (E) 88.23% and Group (F)100%.Conclusion:($E_{20}A_{1gm}C_{500}$-14d) is the highest active regimen for the eradication of h. pylori.

Keywords: Helicobacter pylori, Gastric ulcer, Duodenal ulcer, CLO test, Triple therapy.

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INTRODUCTION

Peptic ulcer(PUD) is a sore in mucosal lining of the stomach (gastric ulcer) or the first part of the small intestine (duodenal ulcer) (1).It was found to be due to an imbalance between aggressive factors such as hydrochloric acid (HCL), pepsin, refluxed bile, leukotrienes (LTs), reactive oxygen species (ROS) and defensive factors, which include the function of the mucus-bicarbonate barrier, prostaglandins (PGs), mucosal blood flow, cell renewal and migration, non enzymatic and enzymatic antioxidants and some growth factors (2) which is mainly caused by *Helicobacter pylori* infection, abundant use of NSAIDs, excessive alcohol intake and stress, etc (3).

Helicobacter pylori is a slow-growing, spiral-shaped, highly motile, microaerophilic, gram-negative bacteria ,survives in the acidic environment of the gastric mucosa, causing chronic gastritis, peptic ulcers, mucosa-associated lymphoid tissue lymphoma and gastric adenocarcinoma(4).

HP infects Approximately half of the world's population in the first few years of life.Of those infected, about 10% develop peptic ulcer disease and roughly 1% develop gastric cancer(5).

The infection invariably becomes persistent due to highly specialized mechanisms that facilitates H. pylori's avoidance of initial line of host defense as well as adaptive immune mechanisms. The host response is thus unsuccessful in clearing the infection and as a result becomes established as a persistent infection promoting chronic inflammation (6).

The World Health Organization classified *H. pylori* as a group I carcinogen with an attributable risk of gastric cancer of 50%-60%. Therefore, it is recommended that all patients with peptic ulcers be tested for *H. pylori* infection. The majority of patients (up to 85%) with *H. pylori* infection do not develop any clinically significant complications(7,8).

Recent studies have identified a potential relationship between *H. pylori* infection and the pathogenesis of cardiovascular, neurological, dermatological, immunological, hematological, hepatobiliary, ophthalmological and gynecological diseases, as well as diabetes mellitus (9, 10, 11).

Therefore, the eradication of *H. pylori* might cure dyspepsia, peptic ulcer, and MALT lymphoma and may prevent the development of gastric cancer as well (12).

standard triple therapy consisting of a proton pump inhibitor (PPI), clarithromycin, and amoxycillin (or metronidazole) for 7 to 14 days is recommended as the first-line therapy of H. pylori infection in most guidelines, such as the American College of Gastroenterology, Maastricht Ⅳconsensus and the Asia-Pacific Consensus Guidelines (13, 14).Recently, the eradication rates of standard triple therapy have declined to 80% in many countries, largely owing to emerging organism resistances (15).

Several strategies, including bismuth-containing quadruple therapy and non-bismuth-containing quadruple therapy (either sequential or concomitant therapy), have therefore been proposed to increase the eradication rate (16).we conducted a randomized controlled trial to compare the efficacy of different regimens for eradicating H.Pylori in patients with gastric ulcer and duodenal ulcer.

PATIENTS AND METHODS

This was a randomized controlled clinical trial conducted on 346 egyptian patients with peptic ulcer symptoms presented to the endoscopy unit at El-agouza hospitalbetween October 2014 and August 2015. Out of the 156 patients with gastric and duodenal ulcer, only 100 patients of them (78 male and 22 females with ages ranged between 24 and 68 years) were positive for H.Pylori whom the study was carried out. Informed consent was obtained from all patients.

Exclusion criteria:

•Age<16 and >80 years

•History of taking NSAIDS, proton pump inhibitors and anti microbials within 4 weeks before endoscopy
•Pregnant or lactating women •concurrent renal or hepatic insufficiency
•malignancy •active upper G.I.T bleeding
•allergy to any medication used in the study •Unconscious patients
• Patients who did not return to follow up • Severe cardiopulmonary disease

All selected patients included in the study were subjected to the following

Full medical history

● Age, sex and special habits such as smoking.
●History of portal hypertension: haematemesis, melena etc……
●History of hepatic dysfunction as: weakness, jaundice, bleeding tendency etc…..

Complete clinical examination

Abdominal ultrasound

Upper GIT endoscopy:

Endoscopy was done under mild sedation (I.V clonazepam 5 mg),we examined the esophagus, stomach and duodenum in all patients using fibroptic endoscope after being disinfected using thestandard regimensat each endoscopic examination, biopsies Were taken preferably from the greater curvature of the middle antrum and corpus using 5 mm biopsy forceps after being disinfected thoroughly, these biopsies were examined for H.Pyloriusing Helicobacter pylori Quick Test "CLO test".

Biopsy urease test "CLO test":

biopsies were taken directly from the biopsy forceps and submersed into the gel. The presence of urease from H. pylori results in hydrolysation of natural urea to alkaline ammonia, together with a PH change and a color change. Change in the color of the gel from yellow to red indicated a positive result.

Patients who were positive for H.Pylori were randomly subdivided into six groups as follow

Group A ($O_{20}T_{500}C_{250}$- 7d/n=18)

Consisted of 18 patients, (12 males and 6 females) received one week course of triple therapy (omeprazole 20 mg, tinidazole 500 mg, clarithromycin 250 mg). The combination taken b.i.d for 7 days.

Group B ($O_{20}T_{500}C_{250}$-14d/n=18)

Consisted of 18 patients, (16 males and 2 females) received two weeks course of triple therapy (omeprazole 20 mg, tinidazole 500 mg, clarithromycin 250 mg). The combination taken b.i.d for 14 days

Group C ($O_{20}T_{500}D_{50}$ – 7d/n=15)

Consisted of 15 patients, (11 males and 4 females) received one week course of triple therapy (omeprazole 20 mg, tinidazole 500 mg, doxycycline 50 mg). The combination taken b.i.d for 7 days

Group D ($O_{20}T_{500}D_{50}$ – 14d/n=15)

Consisted of 15 patients, (12 males and 3 females) received two weeks course of triple therapy (omeprazole 20 mg, tinidazole 500 mg, doxycycline 50 mg). The combination taken b.i.d for 14 days

Group E ($E_{20}A_{1gm}C_{500}$ - 7d/n=17)

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Consisted of 17 patients, (15 males and 2 females) received one week course of triple therapy (esomeprazole 20 mg, amoxycillin 1 gm, clarithromycin 500 mg). The combination taken b.i.d for 7 days.

Group F ($E_{20}A_{1gm}C_{500}$ - 14d/n=17)

Consisted of 17 patients, (12 males and 5 females) received two weeks course of triple therapy (esomeprazole 20 mg, amoxycillin 1 gm, clarithromycin 500 mg). The combination taken b.i.d for 14 days.

Follow up

The mentioned 6 groups were followed up by biopsy urease test "CLO test" at least 8 weeks after completion of the therapy to detect eradication of H.Pylori.

We also evaluated the degree of improvement of symptoms and ulcer after therapy.

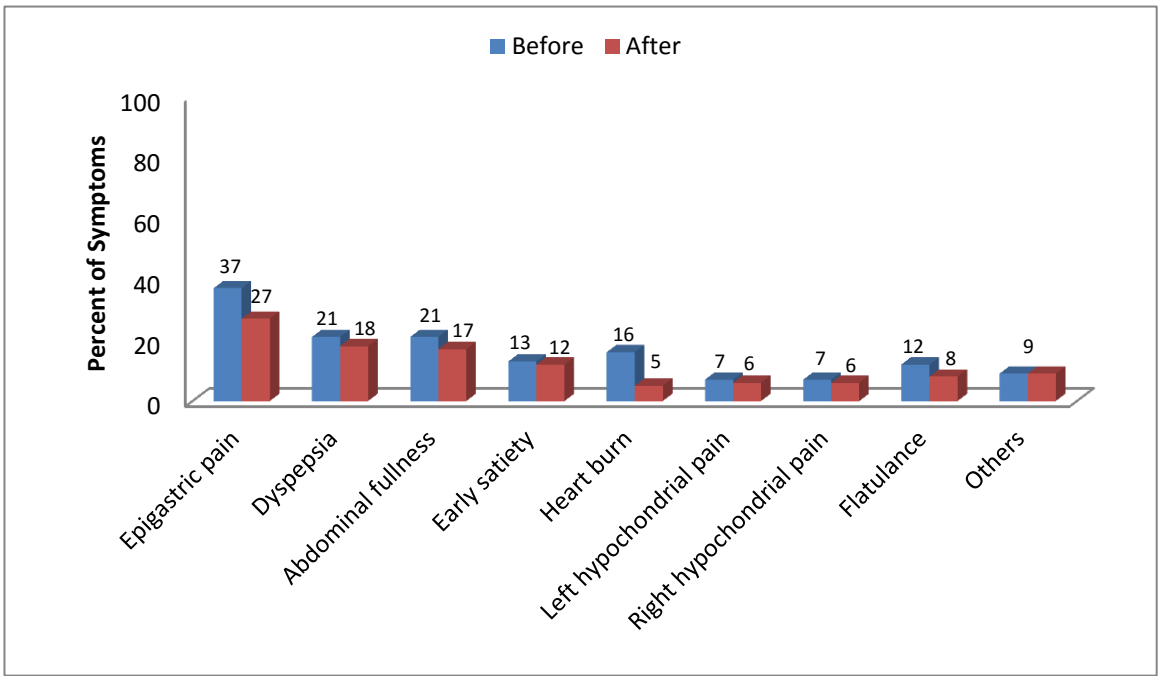
Statistical analysis

Statistical analyses were carried out using the Statistical package for Social Sciences for Windows version 22.0 (SPSS, Chicago, IL, USA). Descriptive statistics for each variable were determined. Results for continuous variables were demonstrated as data were expressed as χ^2-test and test of proportion; two-sided. *P-values* of lessthan 0.05 were considered statistically significant.

RESULTS

Table1 :Baseline characteristics of the treated population

Groups / Variables		Group A N=18	Group B N=18	Group C N=15	Group D N=15	Group E N=17	Group F N=17	P value
Sex	Males	12 (66.7%)	16 (88.9%)	11(73.3%)	12 (80%)	15(88.2%)	12(70.6%)	<0.01
	Females	6 (33.3%)	2 (11.1%)	4 (26.7%)	3 (20%)	2 (11.8%)	5 (29.4%)	
Age range(years) Mean±SD		28-65 44.7±10.1	29-59 45.2±8.2	32-58 43.3±7.6	24-64 39.9±12.1	26-68 40.9±11.2	32-56 42.8±9.02	NS
Smoking	Smokers	11(61.1%)	15(83.3%)	11(73.3%)	12(80.0%)	13(76.5%)	9(52.9%)	<0.05
	Non smokers	7(38.9%)	3(16.7%)	4(26.7%)	3(20.0%)	4(23.5%)	8(47.1%)	



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Figure(1) the degree of improvement of symptoms after treatment.

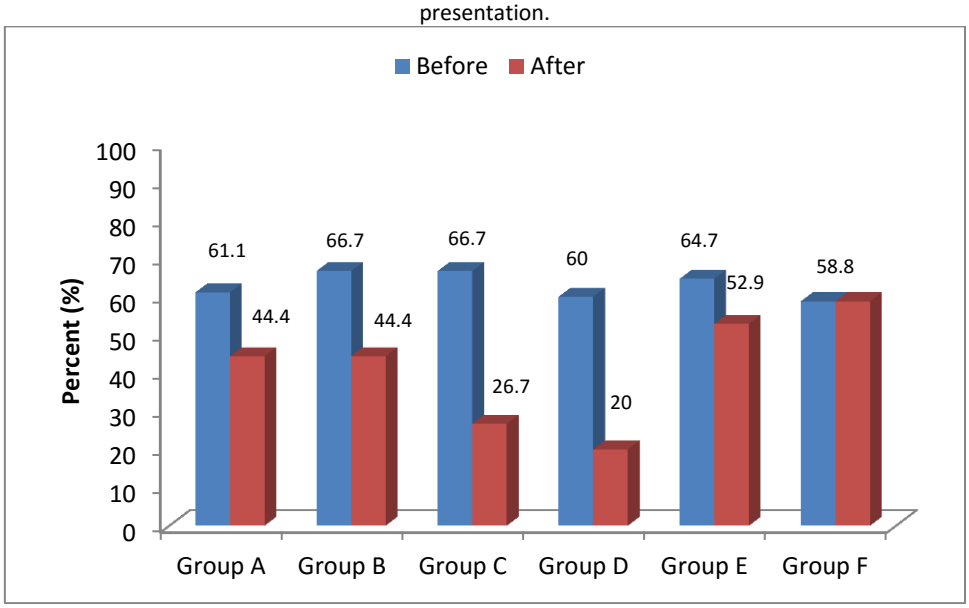
Others include nausea(5/5), constipation(2/2) and indigestion(2/2)

Table (2)Endoscopic findings before treatment for all groups

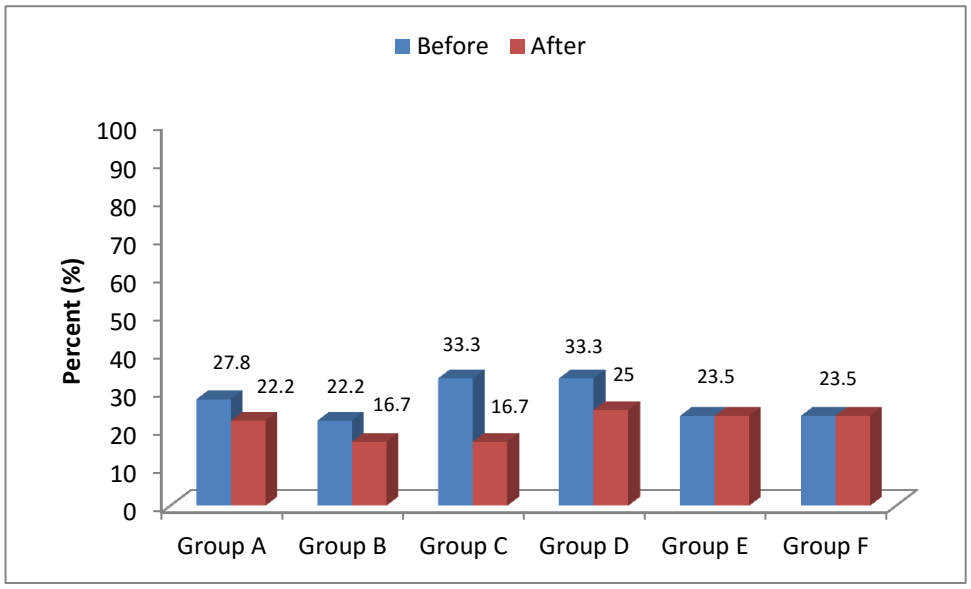
Endoscopy	Group A n=18	Group B n=18	Group C n=15	Group D n=15	Group E n=17	Group f n=17	Total n=100	P value
Gastric ulcer	11 (61.1)	12(66.7)	10(66.7)	9(60)	11(64.7)	10(58.8)	63	
Duodenal ulcer	5(27.8)	4(22.2)	5(33.3)	5(33.3)	4 (23.5)	4(23.5)	27	
Gastroduodenal ulcer	2(11.1)	2(11.1)	----	1(6.7)	2 (11.8)	3(17.6)	10	<0.01

** *p<0.01 significant increase than other groups*

This table shows that gastric ulcer was significantly different than both duodenal ulcer and gastro-duodenal ulcer at presentation.



Figure(2) the degree of improvement of gastric ulcer after treatment in the six studied groups.



Figure(3): The degree of improvement of duodenal ulcer after treatment in the six studied groups.

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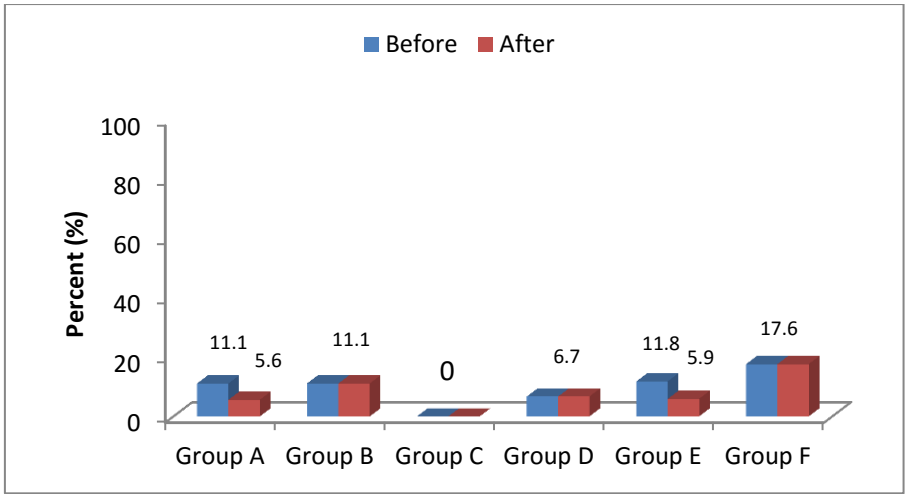

Figure(3): the degree of improvement of gastroduodenal ulcer after treatment in the six studied groups.

Table 2 :Outcome of H. pylori eradication and ulcer healing in relation totreatment groups

Biopsy urease test	H.Pylori eradication N,(%)	Ulcer healing N, (%)
Total number	73(73%)	73(73%)
Group A($O_{20}T_{500}C_{250}$- 7d/n=18)	12/18(66.7%)	13/18(72.2%)
GroupB($O_{20}T_{500}C_{250}$- 14d/n=18)	13/18(72.2%)	13/18(72.2%)
P value	<0.01	>0.05
Group C($O_{20}T_{500}D_{50}$ – 7d/n=15)	8/15(53.3%)	7/15(46.7%)
Group D($O_{20}T_{500}D_{50}$ – 14d/n=15)	9/15(60%)	9/15(60%)
P value	<0.05	<0.01
Group E($E_{20}A_{1gm}C_{500}$ - 7d/n=17)	15/17(88.2)	14/17(82.4%)
Group F($E_{20}A_{1gm}C_{500}$ - 14d/n=17)	17/17(100%)	17/17(100%)
P value	<0.01	<0.01

*P <0.05 is significant

Table 3: Univariate Analysis for Possible Confounders Influencing the Efficacy of H. pylori Eradication Therapy.

Parameter	Number of patients	Eradication rate	P value
Age, yr			
<50 years	74	56 (75.7%)	>0.05
> 50 years	26	17 (65.4%)	
Sex			
Males	78	54 (73.97%)	<0.01*
Females	22	19 (26.03%)	
Smoking			
Yes	71	47(66.2%)	0.01*
No	29	26 (89.7%)	
Site of ulcer			
Gastric	63 (63%)	43(68.3%)	
Duodenal	27 (27%)	22(81.5%)	<0.05
Gastroduodenal	10 (10%)	8 (80%)	
Duration of therapy			
One week duration	50	35 (70%)	0.05*
Two weeks duration	50	39 (78%)	

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Types of Medications			
($O_{20}T_{500}C_{250}$)	36	25 (69.4%)	
($O_{20}T_{500}D_{50}$)	30	17 (56.7%)	0.002*
($E_{20}A_{1gm}C_{500}$)	34	32 (94.1%)	

($O_{20}T_{500}C_{250}$):Omeprazole ,tinidazole, clarithromycin; ($O_{20}T_{500}D_{50}$) : Omeprazole, Tinidazole, Doxycycline; ($E_{20}A_{1gm}C_{500}$) : Esomeprazole, Amoxycillin,Clarithromycin

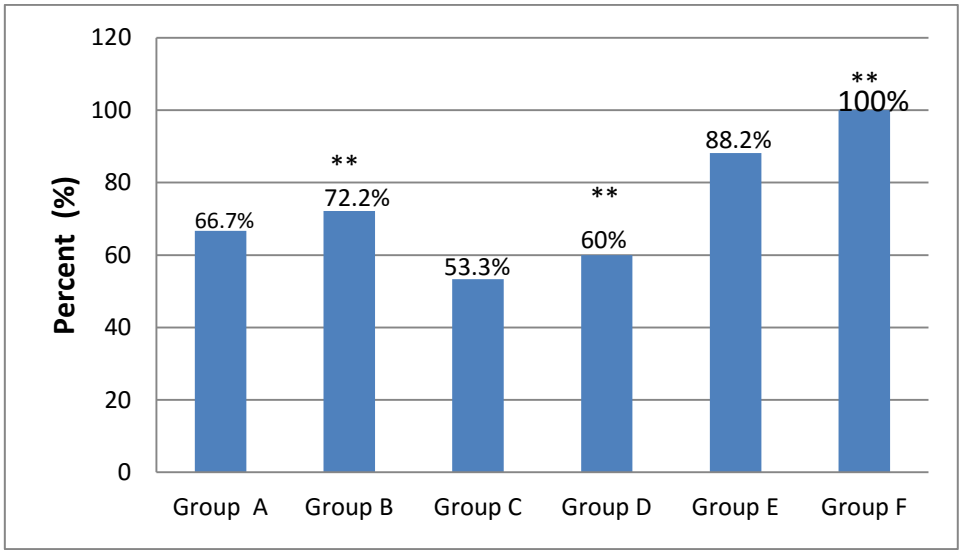

Figure (4) Comparison of biopsy urease test after treatment among 7 days and 14 days regimens in the studied groups
** *p<0.01 significant difference between 14 days and 7 days*

DISCUSSION

Peptic ulcer disease (PUD) refers to a disruption of the mucosal integrity of the stomach, duodenum, or both caused by local inflammation, which leads to a well-defined mucosal defect . Efficient treatment with medications and successful Helicobacter pylori eradication result in clinical improvement and cure as well as in long-term healing of ulcers, most ulcers develop as a result of infection with bacteria called HP(1).

The 2007 American College of Gastroenterology (ACG) guidelines recommend 10 to 14 days of a triple-drug regimen containing a (PPI), clarithromycin, and either amoxicillin or metronidazole (17). Although 10 to 14 days is recommended, the ACG also indicates that giving therapy for two weeks may be preferred (18).

Current guidelines recommend a PPI as part of any standard therapy regimen in the treatment of HP (17,18). PPIs enhance therapy by effectively increasing gastric pH, which serves to enhance the activity of the antibiotics and disrupt the acidic environment preferred by H.Pylori (19).

The antibiotics used in this study (amoxicillin, clarithromycin, tinidazole, doxycycline) were selected because of ease of dosing twice daily and supportive data indicating these agents are active against HP. (20,21,22).

According to current recommendations, which consider an effective therapeutic scheme that achieves an eradication rate of at least 80% based on an intention-to-treat analysis, or 90% based on per protocol analysis, the scheme PPI/AC is adequate as the primary option for *H. pylori* eradication(23).

Esomeprazole-based triple therapy may effectively eradicate Hp infection and promote duodenal ulcer healing with good tolerance, capable of achieving more speedy pain relief than omeprazole-based therapy(24).

Esomeprazole-based triple therapies offer comparable efficacy to omeprazole-based therapies used in previous studies. Increasing the dose of esomeprazole or prolonging the treatment does not improve the results. Therefore, if esomeprazole-based triple therapy is used in duodenal ulcer patients, a regimen with only 20 mg twice daily of esomeprazole and for only 7 days may be sufficient(25).

Meta-analysis of published works regarding the differences between the PPI in *H. pylori* treatment regimens showed eradication rates between 82% and 84% when they were combined with amoxicillin and clarithromycin(26)

The response of triple therapy for treating H. pylori infection vary around the world. The cause of this variation are not clear, but factors such as difference in drug doses and combinations, medications schedules, duration of treatment, and rates of antibiotic resistance have been studied and are known to play a role in explaining these variations (27).

Several studies and meta-analyses have shown that triple therapy works better if the PPI is dosed twice daily and when clarithromycin 500 mg rather than 250 mg, BID is used(28).

A meta-analysis suggested that extension of PPI-based triple therapy from 7 to 14 days was associated with a 5 percent increase in eradication rates (29).

Our study assessed the influence of smoking on treatment and found that smoking affect significantly the eradication rate, this finding is consistent with Cutler and Schubert(30)while in contrast with Kadayifci and Simesek; Silva et al.(31,32)

In our study, Epigastric pain and dyspepsia are the main presenting symptoms and this is in agreement with (33).

Follow up was done after 8 weeks to be enough time for ulcer improvement up on treatment.in our study patients in group F(EAC -14d/n=17) achieved 100% ulcer improvement rate and this result is in accordance with Hsu et al.who achieved the same rate using the same regimen(34).

The goal of H pylori therapy should be to cure all patients with therapies achieving at least 90%, and preferably 95% or more, cure rates. The therapy of choice should be the one that offers the highest eradication rate and thus produces the smallest proportion of patients requiring repetition of treatment (35).

In this study, regression analysis disclosed that the site of peptic ulcer,sex, smoking, duration of therapy and type of regimen was independent factors predictive of treatment outcome. The other factors such as age didnot affect the eradication efficacy.

In our study the ulcer healing rates in our study were around 72.2% in ($O_{20}T_{500}C_{250}$)therapy regimens but around 91.2% for the ($E_{20}A_{1gm}C_{500}$) therapy regimen, the group using ($O_{20}T_{500}D_{50}$)therapy had a lower H. pylori eradication rate which therefore affected the rate of ulcer healing (53.35%). This was in agreement with earlier study that duodenal ulcers healed in 86% in whom H. pylori eradication was achieved but in 52% in whom eradication failed(36).

In our study,The eradication rate of (OTC_{250}-7d B.I.D) regimen was 66.66%.our result is consistent with Choi et al; Silva et al;Moayyedi et al with eradication rates 64.8%,65%,73.4% respectively when given also for 7 days(37,32,38) while in contrast with de Silva et al;Moayyedi et al;Luman et al;Goddard et al;Bazzoli et al;Moshkowitz et al with eradication rates87.5%,88%,89.6%,95%,95% and 96% respectively(39,40,41,42,43,44).

In our study,The eradication rate of(OTC_{250}-14d B.I.D) regimen was 72.2% and this finding was in agreement with Amer et al with eradication rate 75.5%(45) while in contrast with de Silva et al.with eradication rate 90%(39).

The eradication rate of OTD for 7 days was 53.2% while for 14 days was 60%.

Borody et al. concluded that doxycycline-containing triple therapy is less effective for H. pylori eradication and offers no clinical advantage over tetracycline HCl-containing triple therapy(46).also Almeida N et al. concluded that triple therapy with a proton-pump inhibitor, amoxicillin, and doxycycline is useless in patients with multidrug-resistant *H. pylori* infection(47).

Theoretically, amoxicillin is a better choice of antibiotic than metronidazole. Our data indicate that PPI/AC therapy had a higher eradication rate than PPI/TC and PPI/TD regimen. The finding was comparable with results of a previous study, in which the substitution of amoxicillin for metronidazole in the bismuth/tetracycline/metronidazole triple therapy markedly reduced cure rate in first-line therapy(48).

the eradication rate of $E_{20}AC_{500}$ regimen for 7 days was 88.23%.this finding is consistent withAssem et al;Gisbert et al;Veldhuyzen Van Zanten et al;Sokwala et al;Hsu et al with eradication rates 81.3%,83.5%,91%,92% and 93.2% respectively(49,25,50,51,34) While in contrast with Sereni et al;Iacopini et al.with eradication rates 74.7% and 76% respectively(52,53).

The eradication rate of $E_{20}AC_{500}$ regimen for 7 days is comparable to the 84% using the same regimen obtained byWilmington (54)but for 10 days.

The 88.23% eradication rate of $E_{20}AC_{500}$ regimen for 7 days is comparable to the 89.2% and 83.6% achieved by $O_{20}A_{1gm}C_{500}$ regimen for the same duration in a study by (Multiple Center Study Group In Beijing Area, China;Kim et al respectively(55,56).

In our study , $E_{20}AC_{500}$-7d regimen obtained an eradication rate of 88.23% .this rate is comparable to the 84.8%,88.2% achieved by($E_{40}A_{1gm}C_{500}$ 7d),($E_{40}A_{1gm}C_{500}$-10d) respectively(25).also comparable to the 88.9% and 86.2% achieved by ($R_{20}A_{1gm}C_{500}$-7d) and($R_{20}A_{1gm}C_{500}$-10d) respectively (57).

In our study , $E_{20}A_{1gm}C_{500}$-14d regimen obtained an eradication rate of 100% .this rate is comparable to the 95% and 97% achieved by $E_{40}A_{1gm}C_{500}$-7d and $E_{40}A_{1gm}C_{500}$-7d respectively(58,59).

The 100% eradication rate of $E_{20}A_{1gm}C_{500}$ regimen for 14 days is consistent with (Sokwala et al (51)with eradication rate 93.6% while in contrast with Alsohaibani et alwith eradication rate 67.6%(60).

Fuccio et al. revealed that the eradication rates of standard triple therapy were higher with a 14-day regimen than with a 7-day regimen(61).

In conclusion,Esomeprazole based triple therapy with amoxicillin and clarithromycin for two weeks is the best regimen for treatment of patients with HP positive gastric and duodenal ulcer disease and ulcer healing.

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