A New Sequential Regimen for Treatment of *H. Pylori* in Naïve and Previously Treated Patients with Traditional Triple Therapy

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Background and study aim: Helicobacter pylori bacterium is considered one of the most common pathogens that, grows in the digestive tract and has a tendency to attack the stomach lining. It has been estimated that, H. pylori infection occurs in about 50% of the world's adult population. The present consensus is that, all H. pylori infected persons should be cured unless, there are compelling reasons. This study was designed to compare the efficacy of a new sequential regimen with traditional triple and LOAD therapy for eradication of H pylori in naïve patients and patients with previously failed eradication.

Patients and Methods: A prospective cohort study was carried out on 240 Helicobacter pylori infected patients who were enrolled from outpatient clinic during the period from September 2017 to December 2020. Selected patients were classified into 4 equal groups [GI=60 naïve patients received traditional triple therapy, GII= 60 naïve patients received a new sequential therapy (14 days moxifloxacin, nitazoxanide and esmoprazole, followed by 14 days dexalanzoprazole, levofloxacin and metronidazole), GIII= 60 retreated patients with LOAD therapy after failed traditional triple therapy and GIV= 60 s retreated patients with a new sequential therapy after failed traditional triple therapy]. All participants were subjected to medical history, general and abdominal examination, laboratory investigations, abdomino-pelvic ultrasonography. All participants were evaluated by H pylori antigen test in stool at time of diagnosis and after 4- 6 weeks of full course regimens.

Results: Eradication rates were significantly higher in GII, GIII and GIV (95.0%, 96.7% and 88.3%) respectively, in comparison to GI naïve patients (66.7%) who showed the lowest cure rate while, the highest cure rate was in GIII.

Conclusion: A new quinolones based sequential therapy showed more efficacy and less resistance in eradication of H pylori in naïve patients and patients with previously failed eradication by traditional triple therapy.

INTRODUCTION

Helicobacter pylori (H. pylori) infection occurs when H. pylori bacteria infect the stomach, this usually occurs during childhood. H. pylori is considered a common cause of peptic ulcers, H. pylori infection may be present in more than half the people in the world. If symptoms and signs of a peptic ulcer are developed most probably by H. pylori infection **[1]**.

Most people with H. pylori are asymptomatic but, the microorganism colonization is strongly associated with serious diseases of the upper gastrointestinal tract. It's not clear why this is, but some people may be born with more resistance to the harmful effects of H. pylori. When signs or symptoms with H. pylori infection occur, they may include an ache or burning pain in abdomen, abdominal pain worse usually when the stomach is empty, nausea, loss of

appetite, frequent burping, bloating and unintentional weight loss **[2]**.

Complications associated with H. pylori infection include, peptic ulcers as H. pylori can damage the protective lining of the stomach and small intestine, which allow stomach acid to create an open sore (ulcer). About 10% of people with H. pylori will develop an ulcer. Also, gastritis is a common complication. H. pylori infection is a strong risk factor for gastric adenocarcinoma and MALT lymphoma **[3]**.

H. pylori infection can be diagnosed by, non-invasive techniques, such as serology, the urea breath test and H. pylori antigen in stool. Non-invasive tests are widely recommended in the primary care setting. Invasive techniques using upper gastrointestinal endoscopy and biopsy for (histopathology examination, culture and rapid urease test) also used for diagnosis especially for detection of H. pylori ulcers or to rule out other digestive conditions **[4]**.

H. pylori infections are usually treated with at least two different antibiotics at once, to help in prevention of the bacteria from developing a resistance to one particular antibiotic. Acid-suppressing drugs help in healing of the stomach lining. Drugs that can suppress acid include: Proton pump inhibitors (PPIs) which, stop acid production in the stomach like omeprazole, esomeprazole, lansoprazole and pantoprazole. Bismuth subsalicylate which, works by coating the ulcer and protecting it from acid. If the tests show the treatment was unsuccessful, another round of treatment with a different combination of antibiotic medications should be used **[3]**.

American college of Gastroenterology recommended regimens as a standard of care for eradication of confirmed H. pylori infection either; Clarithromycin based triple therapy or bismuth quadriple therapy **[3]**. However, Rokkas et al study which based on Maastricht III guidelines reported that, clarithromycin regimen failed as first line therapy to eradicate H. pylori in 30% of studied patients and bismuth based therapy failed as second line therapy in another 30% in need for an alternative eradication regimen **[3]**.

Moxifloxacin a fluroqunolone antimicrobial agent has an approved activity against H. pylori DNA gyrase enzyme and is considered as concentration dependant as higher doses are found to be correlated with increased eradication rates. An increased dosage of moxifloxacin may be warranted **[4]**. Although moxifloxacin optimal dose not determined yet, this study showed an efficacy by using a lower dose of 400 mg once daily.

Nitazoxanide a thiazolide anti parasitic agent that, posseses activity against vacuolating toxin and was found to be non-mutagenic for H. pylori, especially for metronidazole resistant strains and was unlikely to be affected by antibiotic resistant strains in patients with previously failed eradication. Using nitazoxnide in a drug regimen with a PPI and amoxicillin has shown a clinical success. Chey et al also reported that: Levofloxacin, doxycycline, PPI and nitazoxanide (LOND) regimen had a 90% cure rate **[5]**.

So, this study aimed to compare the efficacy of a new sequential regimen with traditional triple and LOAD therapy for eradication of H pylori in naïve patients and patients with previously failed eradication.

PATIENTS AND METHODS

Study design and selection of the patients:

This was a multicenter prospective cohort study on 240 patients aged 18-63 years old were selected from outpatient clinics of Menoufia University Hospitals and National Liver Institute hospital, Menoufia, Egypt. The study time was from September 2017 to December 2020. All patients were Egyptians and they came from rural areas.

Sample size estimation:

Based on published previous research studies and at power 80% and 95% sample size was calculated and found to be 60 patients in each group (total 240 patients)

Inclusion criteria:

- Naïve patients presented with dyspeptic symptoms and diagnosed as H. pylori infection by positive Ag stool test.
- Patients previously received traditional triple therapy with failed eradication of H. pylori proved by repeated stool Ag test positive.

Exclusion criteria:

- Non-compliant patients
- Age <18 years old.
- Recent antibiotic use within 4-6 weaks.

- Pregnant or lactating female.
- Patients with history of allergy to any included drug in the study.

For all patients: Complete history taking with focusing on dyspeptic symptoms e.g. epigastric pain, nausea, vomiting, hurt burn, regurgitation, fullness, hematemesis or melena and clinical examination (General and abdominal) were done.

Laboratory investigations included (complete blood count, random blood sugar, liver function tests (ALT and AST), serum creatinine level and H. pylori antigen detection in a clean collected stool samples was done at time of diagnosis and 4-6 weeks after completing the full course eradication regimen by enzyme-linked immunosorbent assay (ELISA) according to manufacturer protocol (Epitope diagnostics, USA).

Upper GI endoscopy (UGE) was done mainly in the cases presented with alarm symptoms (anorexia, weight loss or anemia) for exclusion of malignancy. UGE also had done to cases with persistant symptoms despite post eradication –ve H pylori stool Ag test.

Patients were classified into equal four groups as following:

GI: Included 60 naïve patients (not previously received any specific eradication regimen for H. pylori) with positive H. Pylori stool Ag, received traditional triple therapy (PPI 40 mg once daily, clarithromycin 500mg twice daily and metronidazole 500mg twice daily) for 14 days.

GII: Included 60 naïve patients received a new sequential therapy (14 days moxifloxacin 400 mg once daily, nitazoxanide 500 mg twice daily, esmoprazole 40mg twice daily, followed by 14 days dexalanzoprazole 60mg once daily, levofloxacin 500mg once daily and metronidazole 500mg twice daily).

GIII: Included 60 retreated patients with LOAD therapy after failed traditional triple eradication regimen (levofloxacin 250 mg once daily, omeprazole 40 mg once daily, doxycycline 100mg once daily and nitazoxanide 500mg twice daily) for 14 days.

GIV: Included 60 retreated patients with a new sequential therapy after failed traditional triple eradication regimen (14 days moxifloxacin 400 mg once daily, nitazoxanide 500 mg twice daily, esmoprazole 40mg twice daily, followed by 14 days dexalanzoprazole 60mg once daily, levofloxacin 500mg once daily and metronidazole 500mg twice daily).

Statistical Analysis:

Analyses were conducted using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). Patients' demographic data were expressed as mean ± SD or number and %. The significance of the association between the two groups for qualitative variables was tested using Pearson's chi-square ($\chi 2$) test. Kruskal-Wallis test was used to compare between more than 2 groups for non-parametric variables. A p-value was considered significant if <0.05.

RESULTS:

In This study assessed 240 patients with H. pylori infection. The mean age of studied patients was 30.39 ± 9.98 and ranged from 18.0 – 63.0 years old. Most of the patients were females (55.4%). The laboratory investigations were within normal for all patients (Table 1).

The total studied patients were distributed in equal number over groups where there was no significant difference among them regarding their age and sex (p=0.325 and 0.674 respectively) (Table 2).

Cure rate was significantly higher in GII (95.0%), III (96.7%) and IV (88.3%) in comparison to GI (66.7%) with the highest cure rate being reported in GIII followed by GII then GIV.

Different drugs side effects (bitter taste, gastric upset, nausea and fatigue) were significantly reported in GI (15%) to drop to 6.7% in GII and 8.3% in GIII & GIV. Galactorrhea was the most reported as it represented 6.7% of GI patients, 1.7% of GII patients, 3.3% of GIII and 5% of GIV patients (Table 3)

Distribution of the studied groups regarding the endoscopic finding after treatment, diffuse gastritis in G III patients (1.6%), high grade adenocarcinoma in all groups (3.3%, 5%, 1.6%, and 1.6%) respectively, GERD in GI, II and III (1.6%, 5%, 3.3%) respectively, hiatus hernia in GI, II and III (1.6%, 3.3% and 6.7%) respectively and gastrodudenitis with or without duodenal ulcer in GIV (1.6%) (Table 4).

Clinical presentations of the studied groups, epigastric pain was the most common complaint in GI (26.7%) and epigastric pain was (13.3%)

among GII. The majority of GII, GIII and GIV were asymptomatic and were H. pylori positive in routine checkup (61.7%, 68,3% and 58.3%) respectively.. The most common complaint in GIII was vomiting (10%) and the most common complaint in GIV was anorexia (11.6%). (Table 5).

Table (1): Base line demographic and laboratory characteristics of studied patients.

	N= 240
Age (years) Mean ±SD Range	 30.39 ± 9.98 17.0– 63.0
Sex: No (%) Male Female	 107 (44.6) 133 (55.4)
AST (U/L) Mean ±SD Range	 28.57 ±5.83 16.0 -41.0
ALT(U/L) Mean ±SD Range	 28.23 ± 6.37 16.0 - 49.0
RBS (mg/dl) Mean ±SD Range	 132.0 ± 35.3 86-360
Serum creatinine (mg/dL) Mean ±SD Range	 0.97 ± 0.40 0.40 - 6.0

SD (Standard Deviation) AST (Aspartate Transaminase)
ALT(Alanine Transaminase) RBS(Random Blood Sugar)

Table (2): Distribution of the studied groups regarding age and sex.

	Groups								**p value**
	GI n=60		**GII** n=60		**GIII** n=60		**GIV** n=60		
Age Mean ±SD	26.58±10.54		28.98±8.53		27.70±10.44		29.30±8.47		0.325
Sex: No (%) Male Female	25 35	41.7 58.3	24 36	40.0 60.0	28 32	46.7 53.3	30 30	50.0 50.0	0.674

***** Significant SD (Standard Deviation)

Table (3): Distribution of the cure rate and side effects among the studied groups.

	Groups								p value
	GI n=60		GII n=60		GIII n=60		GIV n=60		
Cure rate: No (%)									$P_{1,2}$ <0.001*
Yes	40	66.7	57	95.0	58	96.7	53	88.3	P_3 =0.004*
No	20	33.3	3	5.0	2	3.3	7	11.7	P_4 =0.644
									P_5 =0.186
									P_6 =0.083
Side effects: No (%)									P_1=0.141
Present	9	15.0	4	6.7	5	8.3	5	8.3	P_2=0.255
Absent	51	85.0	56	93.3	55	91.7	55	91.7	P_3=0.255
									P_4=0.728
									P_5=0.728
									P_6=1.000
Type of side effects: No (%)									
Galactorrhea	4	6.7	1	1.7	2	3.3	3	5.0	
Bitter taste	2	3.3	0	0.0	0	0.0	0	0.0	
Gastric upset	2	3.3	0	0.0	0	0.0	0	0.0	
Nausea	1	1.7	2	3.3	2	3.3	0	0.0	
Fatigue	0	0.0	2	1.7	1	1.7	2	3.3	

***: Significant**

P1: compare between group I&II, p2: compare between group I&III, p3: compare between group I&IV, p4: between group II&III, p5: between group II&IV, p6: between group III&IV.

Table (4): Number and percent distribution of the studied groups regarding endoscopic finding after treatment.

	Groups							
	GI n=60		GII n=60		GIII n=60		GIV n=60	
Diffuse gastritis	0	0.0	0	0.0	1	1.6	0	0.0
High grade adenocarcinoma	2	3.3	3	5.0	1	1.6	1	1.6
GERD	1	1.6	3	5.0	2	3.3	0	0.0
Hiatus hernia	1	1.6	0	0.0	2	3.3	4	6.7
Gastrodudenitis with or without duodenal ulcer	0	0.0	0	0.0	0	0.0	1	1.6
Total	4	6.7	6	10.0	6	10.0	6	10.0

GERD (Gastroesophageal Reflux Disease)

Table (5): Clinical presentations of the studied patients.

	Groups							
	GI		GII		GIII		GIV	
	NO	%	NO	%	NO	%	NO	%
Abdominal pain	9	15.0	0	0.0	3	5	4	6.6
Epigastric pain	16	26.7	8	13.3	2	3.3	6	10
Dyspepsia	7	11.7	3	5.0	3	5	2	3.3
Urticaria	4	6.7	6	10.0	0	0.0	0	0.0
Asymptomatic- H pylori positive in routine check up	12	20.0	37	61.7	41	68.3	35	58.3
Vomiting	1	1.7	3	5.0	6	10	0	0.0
Headache	2	3.3	2	3.3	1	1.6	4	6.6
Itching	1	1.7	1	1.7	0	0.0	2	3.3
Anorexia	7	11.7	0	0.0	4	6.6	7	11.6
Weight loss	1	1.7	0	0.0	0	0.0	0	0.0

DISCUSSION

H. pylori pathogen is a Gram-negative spiral-shaped micro-aerophilic organism which colonizes gastric mucosa, causes gastric inflammation. H. pylori infections are strongly associated with serious upper gastrointestinal tract diseases like, peptic ulcers, gastric cancer, mucosa-associated lymphoid tissue (MALT) lymphoma as it is classified as a group I carcinogen. Also, it is associated with other conditions like, vitamin B12 deficiency, iron deficiency and idiopathic thrombocytopenia **[6].**

H. pylori resistance to antibiotics has reached alarming levels worldwide, which provoked an urgent search for more efficient treatments. Despite recent introduction of new therapeutic regimens to combat Helicobacter pylori infection, the treatment still fails in more than 20% of patients, due to the increased emergence of antibiotic resistant strains so, a rational antimicrobial therapy is recommended to be susceptibility-based and regulatory to control this resistance **[7].**

Savoldi et al. stated that, since the year 2000, the H. pylori eradication rates have been decreasing because of increasing resistance to one or more of the antibiotics **[8].** Resistance has reached alarming levels worldwide, which has a major effect on treatment efficacy so, a local surveillance networks are needed for selection of appropriate regimens for eradication in each region.

In this study we focused on comparing the new sequential regimen efficacy with traditional triple and LOAD therapy for eradication of H pylori in naïve patients and patients with failed traditional triple therapy aiming to overcome this resistance. The used new sequential regimen showing interesting eradication results without the current resistance problem of metronidazole or clarythromycin with a close cost.

This study revealed that, the mean age of studied patients was (30.39 ± 9.98) and ranged from (18.0 – 63.0) years old. These results agreed with those obtained by Sitas et al. who reported that, the overall prevalence of H pylori infection was 56.9%, increasing sharply in middle age (30-34) years **[9].** Also, ***Khan et al.*** reported in a study done to determine H. pylori infection incidence in different age and sex groups that, H. pylori infection ranged from (16 to 67) years with no significant rise in the infection rate from childhood to advanced age . These data support that, H. pylori infection is often acquired early in life **[10].**

In this study, most of the patients were females (55.4%). These results disagree with that of ***Khan et al.*** who reported that, (69%) of the studied males werepositive for H. pylori and this difference could be attributed to the difference in the population sample and methods of detection H. pylori infection **[10].**

The studied patients were distributed in equal number over the 4 groups and there was no significant difference among them as regarding their age or sex (p=0.325 and 0.674 respectively)

In this study, the clinical presentations of the studied groups showed that, the most common complaint in GI was epigastric pain 26.7%, 13.3% among GII, 3.3% GIII and10% GIV. Most of GII, GIII and GIV were asymptomatic and discovered by routine checkup by stool Ag test to be H. pylori positive. Vomiting was the most common complaint in GIII (10%) but, anorexia was the most common complaint in GIV (11.6%). GII and GIV, were coming for the failed treatment with less clinical symptoms.

Laboratory investigations (ALT, AST, RBS and S. creatinine) in the studied patients, were within normal range. However, ***Salehi et al.*** concluded that, H. pylori infection can affect organs functions according to some evidences and could be a risk factor for chronic liver and kidneys diseases however, the exact effects of the infection and the underlying mechanisms mostly unclear **[11].**

The cure rates in this study were significantly higher in GII, GIII and GIV (95.0%, 96.7% and 88.3%) respectively, in comparison to GI (66.7%) who showed the lowest cure rate. This result was agreed with a meta-analysis study of ***Murata et al.*** who found that, the overall eradication rates of traditional triple therapy were ranged between (64.8% and 72.5%)**[12].** Also, ***Ruiter et al.*** reported increasing resistance rates to clarithromycin (9.8% to 18.1%), metronidazole (20.7–23.2%), and amoxicillin (6.3–10%) over the last 10 years **[13].**

Moreover, ***Hwang et al.*** concluded that, 14 days moxifloxacin-based sequential therapy was effective and showed excellent compliance and safety compared to the 14 days clarithromycin-

based sequential therapy **[14]. *Watson et al.*** found that, LOAD regimen eradication rate was around a 90% compared to 73% of the standard "triple therapy" with 17% absolute LOAD regimen eradication rate **[15].**

Different drug side effects were reported by the studied patients (bitter taste, gastric upset, galactorrhea, nausea and fatigue with percentage (15% in GI, 6.7% in GII and 8.3% in GIII and GIV). ***Saleem et al.*** stated that, side effects that occured with different H. pylori regimens are common, most often concerning the digestive tract functions as diarrhea that commonly induced by amoxicillin, nausea, vomiting, abdominal cramping, headache and clarithromycin induced allergic rash **[16].**

Galactorrhea was the most reported side effect in this study (6.7% in G I, 1.7% in G II, 3.3% in G III and 5% in GIV). ***Jabbar et al***. reported that, an important adverse effect is a rise in serum prolactin level induced by PPI although, PPI were generally well tolerated, and this rise not managed with dopamine agonists as in pathologically induced hyperprolactinemia **[17]**.

Study limitations:

- Sample size in the current study is relatively small; performing a larger sample size could have generated more accurate results.
- Long term follow up of the studied cured patients to detect early recurrence was difficult in the current study.
- We insisted on adherence to the used new sequential regimen to achieve full compliance in the studied patients as this regimen was administrated for longer duration than other ordinary regimens; however non-compliant patients was excluded and replaced by another case.

CONCLUSIONS:

The present study could state that, the new sequential regimen eradication rate was high in naïve patients and can overcome traditional triple therapy resistance with more efficacy and less resistance.

Recommendations:

- Multicentre large scale studies on this new sequential regimen are needed but with shorter duration than the current study for achieving a better compliance.
- Early diagnosis and treatment of H. pylori infection in order to decrease possible complications.
- Randomized-controlled trials are required to clarify resistance to the current available H. pylori antimicrobial regimens.

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Conflict of Interest: No COI.

Ethical considerations: The study was conducted in accordance with Good Clinical Practice guidelines and declaration of Helsinki after local ethical committee approval of Menoufia University (IRB number 2/2021TROP3). We obtained an informed, written consents from all patients prior to enrolment after thorough explanation of the study objectives.

Highlights

1-*H pylori* infection is associated with many serious complication as gastric adenocarcinoma and MALT lymphoma so early diagnosis and treatment is recommended to avoid these complications.

2- Quinolones based sequential therapy was highly effective in treating naïve and previously treated *H. pylori* infected patients.

3- Early management of *H. pylori* infection with this new sequential therapy is recommended.

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