THE EVALUATION OF TRIPLE, QUADRUPLE, AND LEVOFLOXACIN-BASED THERAPY IN THE MANAGEMENT OF HELICOBACTER PYLORI INFECTION AMONG DYSPEPTIC PATIENTS

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ABSTRACT

Background

The eradication rate for the first line therapy in *H. pylori* infection declined worldwide as a result of resistance development; however other therapies as quadruple and levofloxacin-based therapy are also used and have different eradication rate.

Objectives

To assess the response rate of *H. pylori* infection for different drug's regimens (triple, quadruple, and levobased), and evaluate the effect of age, gender, body mass index and compliance of the patients on the regimens response rate.

Methods

A cross- sectional study, conducted in Kurdistan Center for Gastroenterology and Hepatology (KCGH) in Sulaimani, from April 2018 –November 2018. The study Included 753 dyspeptic patients, *H. pylori* were positive in 430 (57.1%) patients. Demographic data, anthropometric measures, and clinical presentations were recorded for the participants. The participants were randomly treated with one of the standard *H. pylori* eradication regimens (triple, quadruple or levobased), they have been followed up for 45 days and rechecked for *H. pylori*.

Results

The mean age of the patients was 39.8± 15.6 years, and the mean Body Mass Index was 25.7± 6.1kg/m2, 182(42.3%) were male and 248 (57.7%) were female. The rates of responses were (84.4%, 89.4%, and 97.4%) for the triple, quadruple and levobased regimens respectively. The most adverse effects were dizziness and metallic taste recorded in 30.3% in the quadruple group. Statistically, a significant difference was found between the response rate of the triple compared to levobased regimens (p= 0.033). There were no significant differences in the response rate among the three regimens group regarding age, gender, and body mass index. More than 95% in those who completed follow up were adherent to their regimens.

Conclusion

Triple and quadruple regimens are still effective for *H. pylori* eradication, but have more adverse effects than levobased regimens. Levobased regimen has highest eradication rate for *H. pylori*, better compliance, and least adverse effects.

Keywords: *H. pylori, Triple therapy, Quadruple therapy, Levofloxacin based therapy.*

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INTRODUCTION

Helicobacter pylori are gram-negative spiral- shaped bacteria; it's the main cause of peptic ulcer. Dyspeptic patient can have ulcer- like symptoms with pain and vomiting or heartburn, regurgitation, early satiety and nausea [1]. About 80% of populations in the developing countries are *H.pylori* positive compared to 40% in the industrialized countries [2, 3]. The prevalence of *H.pylori* infection increase in childhood, crowded in the family, and outside the family [4].Transmission occurs by oral-oral or fecal-oral [4- 6]. *H.pylori* can be diagnosed by urea breath test, that has 97% sensitivity [7], or monoclonal stool antigen [8, 9], in addition to endoscopy with biopsy [7, 10]. Triple therapy is the first line therapy for *H. pylori* eradication, it consists of (amoxicillin 1g, clarithromycin 500mg, and PPI) [8], the other is bismuth–based quadruple therapy (bismuth salt, metronidazole, tetracycline and PPI) [10], when these two regimens failed levofloxacin-based therapy (PPI, amoxicillin, levofloxacin) is used [7]. The study aimed to identify response rate of *H.pylori* infection to the three regimens and to assess the effects of age, gender, BMI on the response rate, and to compare drug's regimens in their adverse effects.

PATIENTS AND METHODS

This study was approved by the Ethical Committee of Faculty of Medical Science and the Scientific Committee of the college of medicine –University of Sulaimani. Across-sectional study conducted at (KCGH) in the dyspeptic patients who were *H.pylori* positive, from April 2018 –November 2018. A total of 753 patients with dyspepsia (322 male, 431 female), were investigated for *H.pylori* infection, 430 were positive, either by UBT, stool monoclonal antigen or endoscopy, depending on the American College of Gastroenterology Clinical Guideline: Treatment of *Helicobacter pylori* Infection 2017 [11].

Urea breath test was done by (Heliprobe® system, manufacture: Kibion AB, Sweden) C^{14} [12], the stool antigen test was done by *H. pylori* antigen rapid test cassette (Biozek) [13, 14], and upper GI endoscopy was performed with Exera III Olympus. The inclusion criteria was adults of both genders, positive *H.pylori* patients, the exclusion criteria were patients still on PPI or bismuth preparation in the last 2 weeks, or on antibiotics for the last month, lactating woman (for UBT) and pregnant woman. The participants randomly and taken into consideration history of drug's allergy, previous use of certain antibiotic, and clinical manifestation, were treated with one of the standard *H. pylori* eradication regimens (triple, quadruple or levobased), they have been followed up for 45 days and rechecked for *H. pylori*. The triple regimens consists of (amoxicillin 1g, clarithromycin 500mg) twice daily for two weeks and esomeprazole 40mg twice daily for 4 weeks, the other regimen was bismuth–based quadruple therapy (bismuth subcitrate 120mg, tetracycline 500 mg) 4 times daily for two weeks, tinidazole 500mg two times daily for two weeks, and esomeprazole 40mg two times daily for 4 weeks, and levofloxacin-based therapy amoxicillin 1gm two times daily for 2 weeks, levofloxacin 500mg once daily for 2 weeks, and esomeprazole 40mg two times daily for 4weeks. Patients diagnosed by endoscopy and were *H.pylori* positive were treated with one of the eradication regimens, and if they were *H.pylori* negative and had gastric ulcer they received PPI for at least 8 weeks.

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RESULTS

The general characteristics of the participants are demonstrated in Table 1.

Epigastric pain was the most common clinical presentation 65.3%, Table 2.

The main endoscopic finding was gastritis 30.2%, Table 3.

A significant difference was found between the response rate of the triple and levobased regimens (p= 0.033), Table 4.

The difference in the response rate was non-significant regarding gender in the three regimens, Table. 5.

Dizziness and metallic taste were the most common adverse effect 30.3%, both were reported in the quadruple group, Table 6.

There was no significant difference in the response rate among the three regimens group regarding age, gender, and body mass index as shown in the Tables 7.

Adherence rate in the three groups for patients who completed the follow up was 95%.

Table. 1 General characteristic of the participants.

	Variable	No.	%
Gender	Male	182	42.3
	Female	248	57.7
	Total	**430**	**100.0**
Age Group (year)	18 – 35	196	45.6
	36 – 50	131	30.5
	More than 50	103	24.0
	Total	**430**	**100.0**
Smoker	None	320	74.4
	Current - Smoker	68	15.8
	Ex-Smoker	42	9.8
	Total	**430**	**100.0**
Alcohol	No	409	95.1
	Yes	21	4.9
	Total	**430**	**100.0**
Chronic Disease	Hypertension	56	44.8
	Diabetic	28	22.4
	Hyperlipidemia	26	20.8
	Hypothyroid	8	6.4
	Hyperthyroid	7	5.6
	Total	**125**	**100.0**
Blood group	O	103	45.0
	A	54	23.6
	B	51	22.3
	AB	21	9.2
Total		**229**	**100.0**

Table 2. Clinical presentations of the participants.

	Variable	No.	%
Nausea		241	56.05
Heartburn		230	53.5
Burping		154	35.81
Regurgitation		108	25.11
Vomiting		91	21.16
Pain	Epigastric	281	65.3
	No	132	30.7
	Right hypochondria	12	2.8
	Left hypochondria	5	1.2
GI. bleeding	No	337	78.4
	Hematemesis	52	12.1
	Melena	34	7.9
	Hematemesis & Melena	7	1.6

Table 3. Endoscopic findings of the study patients.

Endoscopic findings	No.	%
Gastritis	19	30.2
Duodenal ulcer	12	19.0
Gastric Erosion	11	17.5
Esophagitis	7	11.1
Gastric ulcer	7	11.1
Normal	7	11.1

Table 4. Comparison of the response rate between different drug's regimens.

	Second Visit				Total	Chi-Square	p-value
	Positive %		Negative %				
Triple	14	21.9	50	78.1	64		
Quadruple	8	12.5	56	87.5	64	7.56	0.023
Levofloxacin	1	2.6	37	97.4	38		

Table 5. Response rate among the participants according to gender.

Groups		Positive		Negative		Total		Chi-Square	p-value
		No.	%	No.	%	No.	%		
Triple	Male	1	5.3	18	94.7	19	100	2.2	0.132
	Female	9	20	36	80	45	100		
Quadruple	Male	4	14.8	23	85.2	27	100	0.854	0.299
	Female	3	7.7	36	92.3	39	100		
Levobased	Male	0	0	15	100	15	100	0.641	0.615
	Female	1	4.2	23	95.8	24	100		

Table 6. Adverse effects of the three regimens groups.

		Triple		Quadruple		Levofloxacin	
		No.	**%**	**No.**	**%**	**No.**	**%**
The common adverse effects	**Dizziness**	12	18.75	20	30.3	3	7.7
	Nausea	3	4.69	18	27.27	2	5.13
	Constipation	1	1.56	17	25.76	2	5.13
	Headache	7	10.94	14	21.21		
	Diarrhea	6	9.37	10	15.15	2	5.13
	Vomiting	3	4.69	6	9.09		
The particular adverse effect	**Allergic**	1	1.56	-	-	-	
	Metallic taste			20	30.3		
	Stool color change			13	19.7		
	Vaginal Itching			11	16.67		
	White sores (mouth)			8	12.12		
	Insomnia	-	-	-	-	2	5.13

Table 7. Gender, age, BMI distributions of the responders in the three groups.

Variable		Groups			Total	p-value
		Triple	**Quadruple**	**Levofloxacin**		
Gender	**Male**	19	27	15	61	0.387
	Female	45	39	24	108	
Age	**18 - 35**	42	33	22	97	
	36 - 50	15	26	13	54	0.403
	More than 50	7	7	4	18	
BMI	**Under Weight**	6	3	4	13	
	Normal Weight	24	28	17	69	0.713
	Over Weight	20	25	10	55	
	Obese	14	10	8	32	

DISCUSSION

This study was done because up to authors knowledge no enough data and previous publication available regarding quadruple and levofloxacin therapy in the management of *H.pylori* infection in our region.

In our study, the response rate of the triple therapy was 84.4%, this result is higher than Abu hammour *et al.* [15] and Sheikhani *et al* [16] study, this can be attributed to the difference dose and duration of the treatment, and the uses of first-line PPI. The most adverse effects recorded was dizziness 18.75%, this was in contrast to Makhlough A. *et al*[17].

In this study, there was no significant difference in the response rate in the 3 groups regarding Gender, Age and BMI which is similar to Saracino *et al* [18], Zahraa *et al* [19] and Miftahussrur *et al* [20] who found no significant difference in the response rate regarding gender in the quadruple regimens.

Like the current study, the rate of response to triple therapy was higher in the obese group in Zahraa *et al* [19] study , unlike Abdullahi M *et al.*[21].

In the recent study, 45% of the patients belonged to blood group O, this was comparable to Mohammed *et al*. study [22] .

In our study, the rate of response to quadruple therapy was 89.4%, this is close to Lu H *et al.*[23], Zahraa *et al*[19], the higher response rate of quadruple therapy can be referred to decreased use of tetracycline and to bismuth

as an anti *H.pylori* agent . The most adverse effect in the quadruple regimen was dizziness and metallic taste, while Zahraa *et al*.[19]found change of the stool color as the most common adverse effects due to higher dose of bismuth. The response rate to quadruple therapy was non-significant in relation to gender, this was similar to Zullo A. *et al*.[24], and Kim SE. *et al*. study [25] .

In the current study, younger age patients recorded higher response rate (but not statistically significant) to the quadruple therapy, this was similar to Kim SE. *et al*. study [25].

The normal weight patients recorded higher response rate than obese patients in the quadruple therapy; this was compatible with Pan KF. *et a*l.[26], Istvan G *et al* [27] this attributed to that in the obese, the induction of cytochrome enzyme lead to increase drug metabolism, and decrease their concentration.

In the current study, the rate of response to levofloxacin was 97.4%, this was higher than Cheha *et al* (29.7%).[28], Hsu PI. *et al*[29] (69.2%), this might be contributed to the small sample size, drugs miss use , bacterial resistance and ineffective generic products. Dizziness was the most adverse effects in the levobased regimens, this was compatible with Peedikayil MC *et al*.[30].

We found that the response rate in the levobased regimens was higher in the normal weight patients 100%, this was compatible with Ahn H. *et al* [31].

The high adherence rate of the participants (95.9%) in this study can be attributed to the details explanation of the therapy, doses and duration by the researchers, this is compatible to findings by John P. *et al*. [32] who conclude that compliance with therapy is the essential factor in *H.pylori* eradication, furthermore compliance has important effect on treatment failures and developing antibiotic resistance, improving compliance and follow up by the physician lead to increase level of adherence .

In conclusions, triple therapy and quadruple regimens are still effective for *H.pylori* eradication, but quadruple therapy has more adverse effects than triple therapy. Levobased therapy has the highest eradication rate, more adherences, marked clinical improvement, and less adverse effects among the three regimens. A clinical pharmacist has a paramount role in the improvement of the patient's compliance and their outcomes.

Conflict of interes

None.

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