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EFFICACY OF TRIPLE REGIMEN THERAPY FOR H. PYLORI ERADICATION WITH AND WITHOUT AZITHROMYCIN

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Abstract:
Introduction: *Among the new options against H pylori brought to light recently, azithromycin has attracted substantial interest. Clinical trials with triple therapy regimens that contain azithromycin have reported eradication rates of approximately 60%-80%, depending on the regimen and azithromycin dose used.*
Objective: *To compare the efficacy of triple therapies for H. pylori eradication with verses without Azithromycin in patients with active duodenal ulcer*
Setting: *Department of Medicine, Jinnah Post Graduate and Medical Centre, Karachi.*
Study Design: *Randomized controlled Trial*
Duration of Study: *Six months started on December 14, 2013 to June 13, 2014*
Subjects and Methods: *All patients of either gender with age 30-60 years presented with active duodenal ulcer with H Pylori and duration of symptoms more than 3 months were enrolled. Group A was prescribed Azithromycin 1 g OD for the first 3 days (total dose 3 g), amoxicillin 1 g bid and omeprazole 20 mg bid (OAA). Group B metronidazole 500 mg bid, amoxicillin 1 g bid and omeprazole 20 mg bid (OAM). Both the therapy was given for 1 week, followed by monotherapy of Omeprazole 20 mg OD in both groups for 3 weeks. At the end of the 8th week endoscopy and urea breath test was performed.**Results:** Mean age of the patients was 44.06 ±8.70 years. Mean duration of symptoms of the patients was 5.91 ±1.36 months. Male preponderance was found to be higher 35 (58.30%) as compared to female 24 (40%). In patients presented in OAA triple therapy group, efficacy was found in 19 (63.3%) patients whereas, in patients presented in OAM triple therapy group, efficacy was found in 8 (26.7%) patients (p-value 0.004).*
Conclusion: *The efficacy of triple therapies for H. pylori eradication with Azithromycin is more versus without Azithromycin in patients with active duodenal ulcer*
Key Words: *Efficacy of Triple Therapies, H. Pylori Eradication, Azithromycin, Active Duodenal Ulcer*

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INTRODUCTION:

Infection caused by *Helicobacter pylori* (*H pylori*), one of the most common pathogens worldwide, causes chronic gastritis and increases the risk of peptic ulcer and gastric cancer. Although some *H pylori*-positive individuals are asymptomatic, many experience symptoms such as dyspepsia. It is increasingly common to screen patients, even those with mild symptoms, for *H pylori* infection, and to treat them actively. The first-line treatment for *H pylori* infection, as recommended by the Maastricht III Consensus Report, is 7-d triple therapy that includes clarithromycin, amoxicillin and a proton-pump inhibitor (PPI). Even though this triple therapy is effective and its short duration helps maintain patient compliance, a considerable number of patients experience undesirable side effects.

In first-line therapy, eradication rates using combinations of PPI-based triple therapies range from 75% to 98%, with most of them near 80%.[2] This signifies that up to 20% of patients are expected to be treatment failures, a value which could be even higher in areas with a high prevalence of resistant *H pylori* strains. The recommended second-line therapy is a quadruple regimen composed of tetracycline, metronidazole, bismuth salts and a PPI; however, the efficacy of this regimen is limited by poor compliance, treatment duration, number and dose of the prescribed drugs, and bacterial antibiotic resistance.

Among the new options against *H pylori* brought to light recently, azithromycin has attracted substantial interest. Azithromycin is a macrolide antibiotic that has been shown to reach high concentrations in gastric tissue after oral administration; furthermore, these high concentrations are maintained for several days, which make it potentially useful in the eradication of *H pylori*. Clinical trials with triple therapy regimens that contain azithromycin have reported eradication rates of approximately 60%-80%, depending on the regimen and azithromycin dose used.

H. pylori infection was eradicated in 15 out of 50 patients with OAM: eradication rate was 30.6 % (95 % CI: 17.6 %- 43.6 %) Per Protocols and 30 % (95% CI: 17-43 %) Intension to treat analysis. H. pylori infection was eradicated in 36 out of 50 patients treated with OAA: eradication rate was 75% (95 % CI: 63-87 %) Per Protocols and 72 % (95 % CI: 59-85 %) - Intension to treat analysis. H. pylori status was assessed by rapid urease test and histology. The strong association between H. pylori infection and peptic ulcer disease is unarguable. Meta-analysis studies have showed superior ulcer remission rate for both gastric and duodenal ulcers in patients successfully eradicated of H. pylori infection.

H. pylori eradication therapy was also more superior and cost-effective than maintenance acid suppressive therapy in preventing duodenal ulcer. Azithromycin has been used in various combinations and studies shows no difference in different combinations as the p value found to be more than the significance level. In a Randomized Controlled Trial: Efficacy and Safety of Azithromycin, Ofloxacin, Bismuth, and Omeprazole Compared with Amoxicillin, Clarithromycin, Bismuth, and Omeprazole as Second-Line Therapy in Patients with Helicobacter pylori Infection in intention-to-treat analysis, the rate of H. pylori eradication in groups A (Azithromycin) and B was 77.3% (85 ⁄ 110) and 64.5% (71 ⁄ 110) respectively (p = 0.027). H. pylori was eradicated in 86% of patients in the early group (intention-to-treat 86%) and in 88% of patients in the late group (intention-to-treat 88%). There is variation in the outcome of azithromycin in the treatment of H Pylori infection, therefore the present study is designed to resolve the issue. In the event of higher efficacy in the either triple regime the same was used in such cases in future.

MATERIAL AND METHODS:

The design of the study is randomized controlled trial study conducted in the Department of Medicine, Jinnah Post Graduate and Medical Centre, Karachi. And the duration of this study was Six months started on December 14, 2013 to June 13, 2014. Considering the cost and easy availability of triple regimen combination of OAA and OAM, the sample size calculated on WHO calculator using the reference no. 6, which is relevant to our hypothesis on the basis of following prerequisites:

Efficacy of OAA triple therapy[6]=75%
Efficacy of OAM triple therapy[6]=30.6%%
Power of the test=80%
Significance level=5%
Total sample size=30 patients but we will take 60 patients (30 in each group) to have more valid results.

Patients meeting the inclusion criteria attending the outpatient Department of JPMC Karachi, was enrolled in the study. Informed consent was taken from the patients for inclusion in the study and for procedure after explaining the pros and cons, purpose and procedure of the study. Randomization was performed by making equal draws and draw was picked up by third person not related to this study

into two groups A and B. Group A were prescribed Azithromycin 1 g OD for the first 3 days (total dose 3 g), amoxicillin 1 g bid and omeprazole 20 mg bid (OAA). Group B metronidazole 500 mg bid, amoxicillin 1 g bid and omeprazole 20mg bid (OAM). Both the therapy was given for 1 week, followed by monotherapy of Omeprazole 20 mg OD in both groups for 3 weeks. At the end of the 8th week endoscopy and urea breath test was performed by gastroenterologist having more than 5 years of experience for eradication of H Pylori. This information as well as demographic data like patients age, sex, duration of symptoms was documented on structured Performa. SPSS version 20 was used for data entry and analysis. Mean±SD was calculated for age of the patients, duration of symptoms. Frequency and percentages was calculated for gender and efficacy. Chi square test was applied to test the hypothesis. Effect modifiers were controlled through stratification of age, gender, and duration of symptoms to determine the effect of these on outcome. Chi square test was applied and p value ≤0.05 was taken as significant.

RESULTS:

Mean age of the patients was 44.06 ±8.70 years. The minimum age of the patients was 30 years and maximum age of the patients was 60 years. (Table 1). There were 34 (56.70%) patients with age ≤45 years and 26 (43.30%) patients with age >45 years. (Figure 1). Mean duration of symptoms of the patients was 5.91 ±1.36 months. The minimum duration of symptoms was 4 and maximum duration of symptoms was 8 months. (Table 2). There were 32 (53.30%) patients with duration of symptoms ≤6 months and 28 (46.70%) patients with duration of symptoms >6 months. (Figure 2). Male preponderance was found to be higher 35 (58.30%) as compared to female 24 (40%). (Figure 3). Overall efficacy was found in 27 (45%) patients. (Figure 4).

In patients presented in OAA triple therapy group, efficacy was found in 19 (63.3%) patients whereas, in patients presented in OAM triple therapy group, efficacy was found in 8 (26.7%) patients. Chi-square test was applied and statistically sufficient evidence of significant relationship was observed as p-value found to be less than level of significance (p-value 0.004). (Table 3). Stratification was done to see the effect of age, duration of disease and gender. Chi-square test was applied. Results are shown in table 3-9.

Table 1: Age of the Patients (n=60)

Mean ±SD	Minimum	Maximum
44.06 ±8.70	30	60

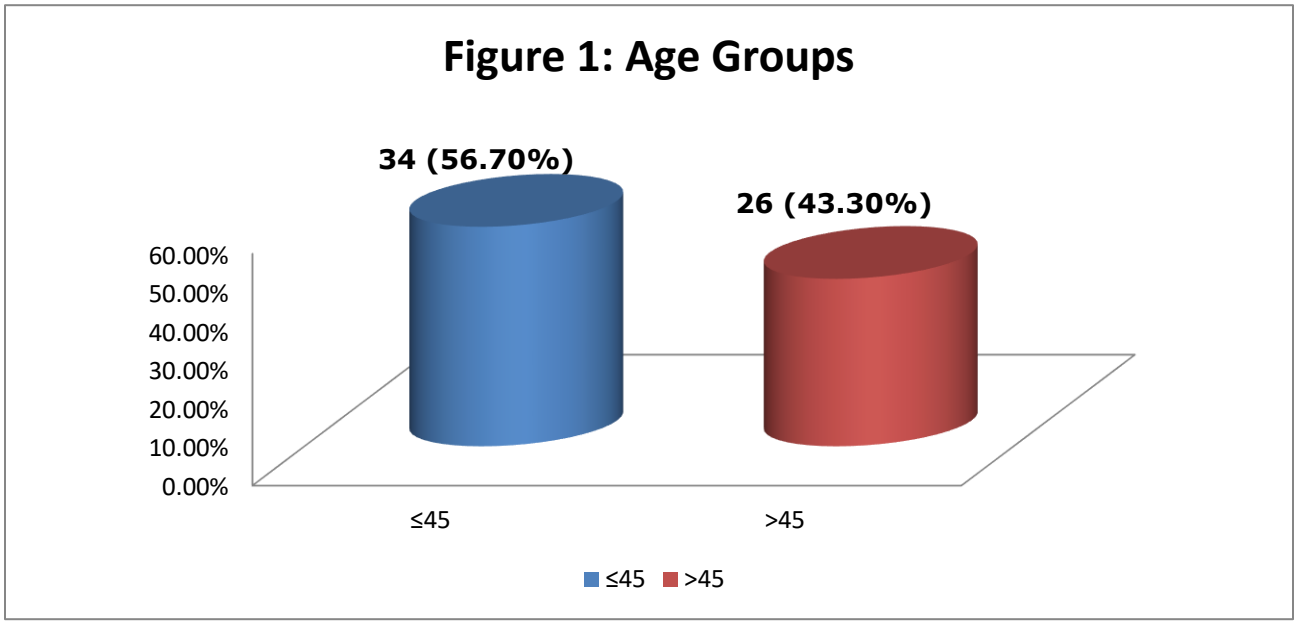

Table 2: Duration of Symptoms (n=60)

Mean ±SD	Minimum	Maximum
5.91 ±1.36	4	8

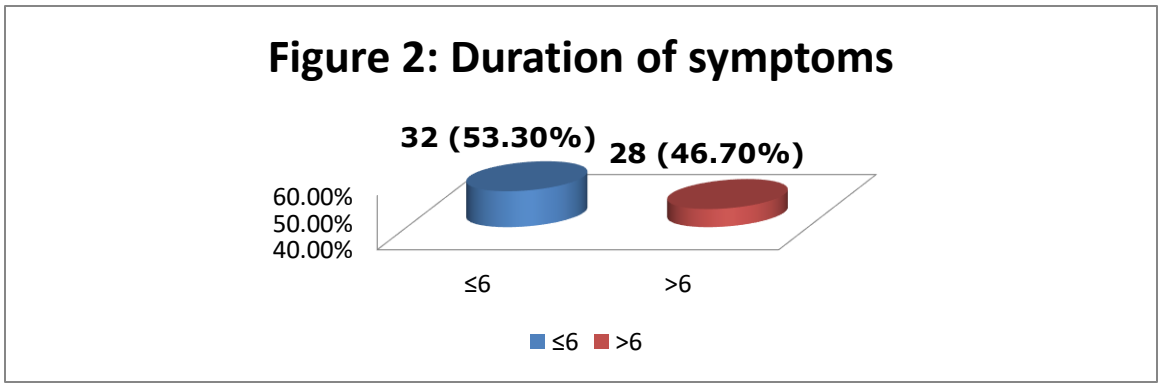

Table 3: Efficacy with Respect to Group (n=60)

Group	Efficacy		Total	p-value
	Yes	No		
OAA triple therapy	19 (63.3)	11 (36.7)	30 (100)	0.004
OAM triple therapy	8 (26.7)	22 (73.3)	30 (100)	
Total	27 (45%)	33 (55%)	60 (100)	

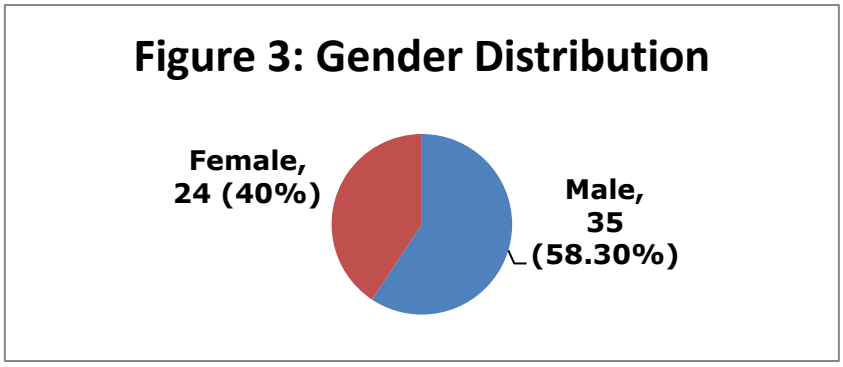

Table 4: Age ≤45 Years & Efficacy with Respect to Group (n=34)

Group	Efficacy		Total	p-value
	Yes	No		
OAA triple therapy	9 (56.3)	7 (43.8)	16 (100)	0.092
OAM triple therapy	5 (27.8)	13 (72.2)	18 (100)	
Total	14 (41.2)	20 (58.8)	34 (100)	

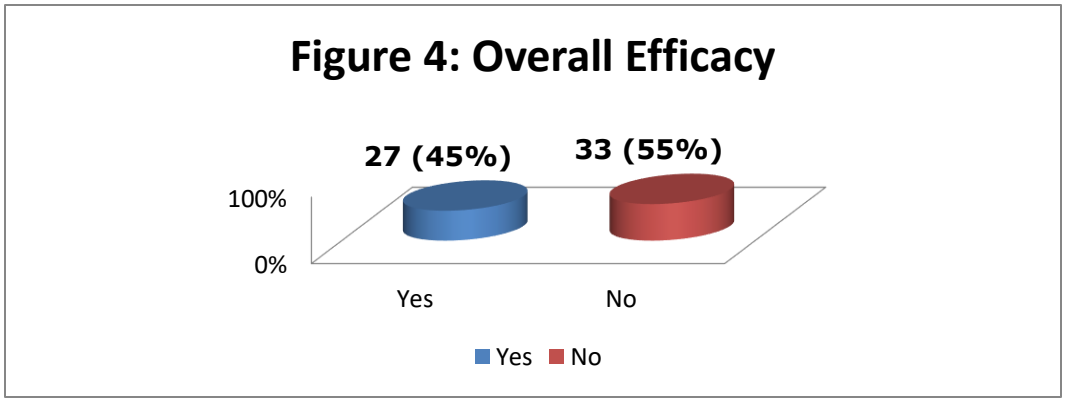

Table 5: Age >45 Years & Efficacy with Respect to Group (n=26)

Group	Efficacy		Total	p-value
	Yes	No		
OAA triple therapy	10 (71.4)	4 (28.6)	14 (100)	0.018
OAM triple therapy	3 (25)	9 (75)	12 (100)	
Total	13 (50%)	13 (50%)	26 (100)	

Table 6: Duration of Diseases ≤6 Months & Efficacy with Respect to Group (n=32)

Group	Efficacy		Total	p-value
	Yes	No		
OAA triple therapy	19 (79.2)	5 (20.8)	24 (100)	0.001
OAM triple therapy	0 (0)	8 (100)	8 (100)	
Total	19 (59.4)	13 (40.6%)	32 (100)	

Table 7: Duration of Diseases >6 Months & Efficacy with Respect to Group (n=28)

Group	Efficacy		Total	p-value
	Yes	No		
OAA triple therapy	0 (0)	6 (100)	6 (100)	0.081
OAM triple therapy	8 (36.4)	14 (63.6)	22 (100)	
Total	8 (28.6)	20 (71.4)	28 (100)	

Table 8: Male Gender & Efficacy with Respect to Group (n=35)

Group	Efficacy		Total	p-value
	Yes	No		
OAA triple therapy	14 (73.7)	5 (26.3)	19 (100)	0.004
OAM triple therapy	4 (25)	12 (75)	16 (100)	
Total	18 (51.4)	17 (48.6)	35 (100)	

Table 9: Female Gender & Efficacy with Respect to Group (n=25)

Group	Efficacy		Total	p-value
	Yes	No		
OAA triple therapy	5 (45.5)	6 (54.5)	11 (100)	0.558
OAM triple therapy	4 (28.6)	10 (71.4)	14 (100)	
Total	9 (36)	16 (64)	25 (100)	

DISCUSSION:

Azithromycin is a macrolide antibiotic that has been shown to reach high concentrations in gastric tissue after oral administration; furthermore, these high concentrations are maintained for several days, which make it potentially useful in the eradication of *H pylori*. Clinical trials with triple therapy regimens that contain azithromycin have reported eradication rates of approximately 60%-80%, depending on the regimen and azithromycin dose used. Results of present study shows that, in patients presented in OAA triple therapy group, efficacy was found in 19 (63.3%) patients whereas, in patients presented in OAM triple therapy group, efficacy was found in 8 (26.7%) patients (p-value 0.004). H. pylori infection was eradicated in 15 out of 50 patients with OAM: eradication rate was 30.6 % (95 % CI: 17.6 %- 43.6 %) Per Protocols and 30 % (95% CI: 17-43 %) Intension to treat analysis. H. pylori infection was eradicated in 36 out of 50 patients treated with OAA: eradication rate was 75% (95 % CI: 63-87 %) Per Protocols and 72 % (95 % CI: 59-85 %)- Intension to treat analysis. H. pylori status was assessed by rapid urease test and histology.

The strong association between H. pylori infection and peptic ulcer disease is unarguable. Meta-analysis studies have showed superior ulcer remission rate for both gastric and duodenal ulcers in patients successfully eradicated of H. pylori infection. H. pylori eradication therapy was also more superior and cost-effective than maintenance acid suppressive therapy in preventing duodenal ulcer. Azithromycin has been used in various combinations and studies shows no difference in different combinations as the p value found to be more than the significance level. In a Randomized Controlled Trial: Efficacy and Safety of Azithromycin, Ofloxacin, Bismuth, and Omeprazole Compared with Amoxicillin, Clarithromycin, Bismuth, and Omeprazole as Second-Line Therapy in Patients with Helicobacter pylori Infection. In intention-to-treat

analysis, the rate of H. pylori eradication in groups A (Azithromycin) and B was 77.3% (85 / 110) and 64.5% (71 / 110) respectively (p = 0.027). H. pylori was eradicated in 86% of patients in the early group (intention-to-treat 86%) and in 88% of patients in the late group (intention-to-treat 88%). Infection caused by *Helicobacter pylori* (*H pylori*), one of the most common pathogens worldwide, causes chronic gastritis and increases the risk of peptic ulcer and gastric cancer. Although some *H pylori*-positive individuals are asymptomatic, many experience symptoms such as dyspepsia. It is increasingly common to screen patients, even those with mild symptoms, for *H pylori* infection, and to treat them actively. The first-line treatment for *H pylori* infection, as recommended by the Maastricht III Consensus Report, is 7-d triple therapy that includes clarithromycin, amoxicillin and a proton-pump inhibitor (PPI). Even though this triple therapy is effective and its short duration helps maintain patient compliance, a considerable number of patients experience undesirable side effects.

In first-line therapy, eradication rates using combinations of PPI-based triple therapies range from 75% to 98%, with most of them near 80%. This signifies that up to 20% of patients are expected to be treatment failures, a value which could be even higher in areas with a high prevalence of resistant *H pylori* strains. The recommended second-line therapy is a quadruple regimen composed of tetracycline, metronidazole, bismuth salts and a PPI; however, the efficacy of this regimen is limited by poor compliance, treatment duration, number and dose of the prescribed drugs, and bacterial antibiotic resistance. From 1995 to the present, numerous clinical study results specific to *H. pylori* eradication triple therapy with pantoprazole have been published.

Most of these studies have shown consistent success using triple-therapy regimens with durations shorter than 14 days (some ≤ 10 days). Many of these studies were conducted outside the United States, where resistance patterns may be different. Pilotto et al. recently reported an *H. Pylori* eradication rate of 94% with a triple therapy consisting of 40 mg pantoprazole, 1000 mg amoxicillin, and 250 mg clarithromycin daily for 7 days among elderly patients with peptic ulcer disease in Vicenza, Italy. Other analyses have compared pantoprazole-based combination peptic ulcer disease therapies with others using omeprazole, lansoprazole or *Multidrug Regimens and Recommendations* The addition of a proton pump inhibitor (PPI) to antibiotic-containing regimens has generally been demonstrated to boost *H. pylori* eradication rates.

CONCLUSION:

The efficacy of triple therapies for H. pylori eradication with Azithromycin is more versus without Azithromycin in patients with active duodenal ulcer.

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