ORIGINAL ARTICLE

Efficacy of triple regimen therapy for H. pylori eradication with and without azithromycin

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Abstract

Objective: To compare the efficacy of triple therapies for H. pylori eradication with versus without azithromycin in patients with active duodenal ulcer.

Material and Methods: This clinical trial was conducted at Medical ICU of Jinnah Postgraduate Medical Centre (JPMC), Karachi, Pakistan from December 2013 to June 2014. A total of 60-patients of either gender with age ≥18 years presenting with active duodenal ulcer and confirmed H. Pylori infection with >3 months symptom duration were included. 30-patients were assigned to each of the two groups through opaque envelope randomization method. Group-A was prescribed azithromycin, 1g OD, for first 3 days (total dose 3 g), amoxicillin, 1g bid and omeprazole, 20 mg, bid (OAA regimen). Group-B received metronidazole, 500 mg bid, amoxicillin, 1g bid and omeprazole, 20 mg bid (OAM regimen). Both above regimens were 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 were repeated to confirm H. pylori eradication.

Results: Both groups were comparable regarding basic demographic characteristics. Mean age of patients in group-A and group-B was 44.06±8.70 and 43.65±8.55 years, respectively. Mean duration of symptoms of patients was 5.91±1.36 months in group-A and 5.72±1.52 months in group-B. It was found that efficacy of OAA triple therapy in H. pylori eradication was 63.3% compared to that of OAM, which was 26.7%. The difference was statistically significant (p-value= 0.004). Age, gender and duration of symptoms were significant effect modifiers.

Conclusion: The efficacy of triple therapy containing azithromycin in H. pylori eradication was significantly higher compared to traditional triple therapy in patients with active duodenal ulcer in our setting.

Keywords: Triple regimen, H. pylori eradication, azithromycin, active duodenal ulcer.

Received
Date: 5th May, 2019
Accepted
Date: 10th January, 2020

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Introduction:

Helicobacter pylori (H pylori) is one of the most common infectious diseases afflicting humankind throughout the world.[1] It causes chronic gastritis, which if persistent for long period, may lead to peptic ulcer disease and gastric cancer.[2-4] Although, it may be asymptomatic, H. pylori infection leads to dyspepsia in most of the affected individuals with varying degrees of severity.

The prevalence of H pylori is high throughout the world. In developed societies, the prevalence is about 20%-50% while in developing countries about 80% of adults are infected. To some extent, its prevalence has a direct relationship with low socioeconomic condition. The strong association between H. pylori infection and peptic ulcer disease is unarguable. Meta-analysis studies have shown superior ulcer remission rates for both gastric and duodenal ulcers in patients successfully eradicated of H. pylori infection. H. pylori eradication therapies are also more superior and cost-effective than maintenance acid suppressive therapy in preventing duodenal ul-

cer.[5-9]

The Maastricht III Consensus report has recommended a 7-day triple therapy including clarithromycin, amoxicillin and a proton-pump inhibitor (PPI) as the first-line treatment for H pylori.[10-13] With this first-line therapy, the eradication rates range from 75% to 98%, with most being near 80%.[10-13] Although effective, yet a reasonable number of patients, i.e., around 20% experience undesirable side effects or recurrence of symptoms. A higher proportion of such treatment failures can be found in areas with a high prevalence of resistant H. pylori strains. On the other hand, a quadruple regimen composed of tetracycline, metronidazole, bismuth salts and a PPI has been tested as the second-line therapy but the efficacy results are not very promising.[14,15] The low efficacy may be due to bacterial antibiotic resistance while longer duration of this regimen leads to poor compliance.[16-18]

This situation demands exploring new options against H. pylori. Azithromycin is a relatively new and most effective macrolide. It has attracted much interest of physicians as this reaches high concentrations in gastric tissue after oral administration and the levels are sustained for several days. Thus, azithromycin seems to be a potentially very useful additive for the eradication of H. pylori. Clinical trials with triple therapy regimens containing azithromycin, i.e., OAA have reported eradication rates of approximately 75% depending on the regimen and azithromycin dose, whereas the regimen without azithromycin, i.e., OAM showed eradication rates of 30.6%.[13] Another study comparing efficacy and safety of azithromycin, ofloxacin, bismuth, and omeprazole with amoxicillin, clarithromycin, bismuth, and omeprazole as second-line therapy in patients with H. pylori infection, found that the rate of H. pylori eradication in group-A (azithromycin) and B was 77.3% (85⁄110) and 64.5% (71⁄110), respectively ($p = 0.027$).[14]

Although there are a number of studies on the efficacy of azithromycin-containing regimens compared with standard triple therapy, the results are varying and sometimes conflicting; and there is a relative dearth of evidence of azithromycin efficacy in our population. The present study was aimed to assess the superiority of azithromycin-containing regimens over standard triple-drug regimens in the local population.

Materrial and Methods:

This clinical trial was conducted at Medical ICU, Unit-4 of Jinnah Postgraduate Medical Centre (JPMC), Karachi, Pakistan from December 2013 to June 2014 with the hypothesis that efficacy of triple therapy containing azithromycin for H. pylori eradication is more compared to standard triple therapy in patients with active duodenal ulcer. Active duodenal ulcer was evaluated on the endoscopy and labelled as positive in the presence of any one or more of the following: spurting artery, actively oozing blood, adherent clot and flat pigmented spots on ulcer. H. pylori was first tested by a rapid urea test (RUT) and confirmed on histology. The sample size calculated was 60. It was divided into two groups of 30 each.

Inclusion criteria were age ≥18 years, either gender, active duodenal ulcer with H. Pylori infection and duration of symptoms > 3 months. Exclusion criteria were intake of PPI, antibiotic or bismuth salts within 4-weeks prior to the study, concomitant gastric ulcer or reflux esophagitis of grade-II or more, stomach surgery, known hypersensitivity to one of the study medications and pregnancy, post-menopausal status or use of contraceptive.

Written informed consent was taken from patients for inclusion in the study. The study protocol followed the tenets of declaration of Helsinki. Randomization was performed by using opaque envelope containing group-A or B denomination picked up by the patient randomly. Group-A were prescribed azithromycin, 1g, OD for the first 3-days (total dose 3g), amoxicillin, 1g, bid and omeprazole, 20mg, bid (OAA). Group-B were given metronidazole, 500mg, bid, amoxicillin, 1g, bid and omeprazole, 20 mg, bid (OAM). Both regimens were given for 1-week, followed by monotherapy of omeprazole 20mg,

Table 1: *Basic demographic and clinical characteristics of all patients in both groups*

Variables	Group-A n=30	Group-B n=30
Age (yrs) (Mean±SD)	44.06±8.7	43.65±8.55
Weight (kg) (Mean±SD)	71.24±7.13	72.83±7.18
Height (m2) (Mean±SD)	5.12±0.61	5.22±0.55
BMI (Mean±SD)	25.95±4.32	24.51±4.71
Duration of symptoms (months) (Mean±SD)	5.91±1.36	5.72±1.52

BMI: Body Mass Index

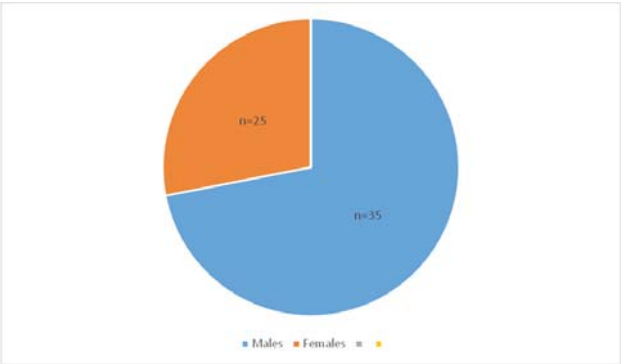

Figure 1: *Overall gender distribution of all patients (n=60)*

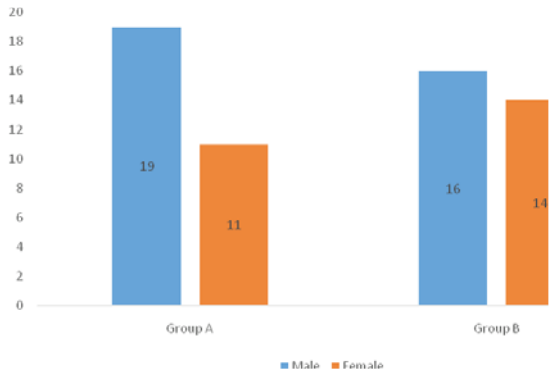

Figure 2: Gender distribution in the two groups. The figures represent absolute values

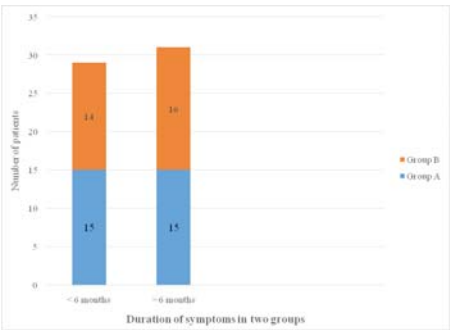

Figure 3: *Duration of symptoms in months in two groups*

OD in both groups for 3-weeks. At the end of 8th week, endoscopy and RUT were performed by gastroenterologist having more than 5-years of experience for confirming eradication of H. Pylori. This information as well as demographic data like patients' age, sex, and duration of symptoms was documented.

SPSS® version 20 was used for data entry and analysis. Mean±standard deviation (SD) was calculated for age and duration of symptoms. Frequency and percentages were calculated for gender and H. Pylori eradication rates. Chi square test was applied to determine the statistical significance. Effect modifiers were controlled through stratification of age, gender, and duration of symptoms to determine the effect of these on outcome. P value ≤0.05 was considered as significant.

Results:

Both groups were comparable regarding basic demographic characteristics. Mean age of patients in group-A and B was 44.06±8.70 and 43.65±8.55 years, respectively (table 1). There were 14 (46.67%) young adults (≤45 years) and 16 (53.33%) older adults (>45 years) in group-A while in the group-B, 18 (60%) were ≤45 years and 12 (40%) were of >45 years of age.

Figure 1 shows the gender distribution of all patients, while Figure 2 shows gender distribution in the two groups, which is almost similar. Mean duration of symptoms in patients was 5.91±1.36 months in group-A, while it was 5.72±1.52 months in group-B with no statistically significant difference between the two groups (table 1). The number of patients in both groups with duration of symptoms less than 6 months and more than 6-months was almost similar, as shown in Figure 3.

It was found that the efficacy of OAA triple therapy in H. pylori eradication (63.3%) was significantly higher than that of OAM triple therapy, which was 26.7% (p-value= 0.004). Post-stratification analysis also revealed that OAA therapy was thrice more efficacious than the OAM in older adults (> 45 years) and this was statisti-

cally significant (p-value=0.018). Another very unusual and statistically significant finding was that OAA therapy had no efficacy in ulcer of > 6 months duration while OAM therapy failed in ulcer of < 6 months duration. OAA therapy showed better results in males than in females in comparison to the OAM therapy (p values= 0.004 and 0.558, respectively).

Discussion:

Among the new generation of macrolide antibiotics, azithromycin is well known besides clarithromycin, being very effective against both gram positive and gram negative bacteria. It achieves and sustains higher gastric tissue concentrations for a longer period after reaching a peak level with oral administration. Because of this capability, azithromycin is a potentially powerful therapy for eradication of H. pylori.[3,7,8,11,14]

Evidence from western countries have found conflicting results with the azithromycin.[14,15] The current study was conducted to investigate the azithromycin efficacy when used as a part of triple therapy regimen in local context. The results show that in patients treated by OAA triple therapy, H. pylori eradication was achieved in 19 (63.3%) patients, whereas, in patients treated by OAM triple therapy, the same was achieved in 8 (26.7%) patients (p-value= 0.004). A study by Ivashkin et al., found that H. pylori was eradicated in 75% patients (95% CI: 63-87%) treated with triple therapy containing azithromycin while only less than one third patients, i.e., 30.6% (95% CI: 17.6 %- 43.6%) treated with OAM got relief from H. pylori.[22]

In another study, Khoshnood et al., in a randomized clinical trial comparing replacement of clarithromycin with azithromycin in triple therapy regimens for the eradication of H. pylori have documented that eradication rate with azithromycin was 82.9%, while for clarithromycin group, it was 77.1% (P value = 0.55).23 These findings reiterate the conclusion of the previous studies that azithromycin is superior to conventional triple regimen with a very significant difference.

Many studies have been conducted during the past 2-3 decades documenting varying results of triple therapy on H. pylori eradication. Most of these studies have shown consistent success using triple-therapy regimens with durations shorter than 14 days (some ≤ 10 days).[24, 25] However; due to chronicity and recurrence of H. pylori infection in our population, we treated our patients with prolonged courses and followed the patients till 8-weeks in the current study.

The current study noted that age, gender and duration of ulcer symptoms were associated with variation in the efficacy of azithromycin-containing triple therapy. Older adult patients had shown significantly higher efficacy than younger adults (p-value = 0.018) with OAA regimen. Males responded significantly more to azithromycin-containing regimen compared to females (p-value = 0.004). Similarly, patients with shorter duration of illness showed much higher and statistically significant (p-value < 0.001) efficacy in eradication of H. pylori and healing of duodenal ulcer.

Previous studies have noted that there was more response to azithromycin in younger age patients (< 30 years); however, other studies have found higher efficacy of this regimen in older adults. Still other studies have found no significant difference based on age of the patients.[14,15,25] Efficacy of Azithromycin in male gender was reported to be slightly more in some studies,[9,12,14] while in other studies no difference was found with respect to gender.[7,11,24,25] Irrespective of duration of illness, the response to azithromycin-containing triple therapy was much higher than other regimens as documented by most of previous studies.[9-12,14,25] The above differences in efficacy results may be due to differences of population characteristics, diet/ food patterns, eating habits and the meal timings in different regions.

The current study had certain limitations. Firstly, the sample size was relatively small, the study was conducted at only one center, no long-term follow-up was done and no placebo group was included. Despite of the above limitations, with the strength of being an experimental study, it

has yielded a strong piece of evidence that the efficacy of triple therapies containing azithromycin for H. pylori eradication is much higher compared to therapies without azithromycin in patients with active duodenal ulcer.

Conclusion:
The efficacy of triple therapy containing azithromycin for H. pylori eradication is more compared to therapies without azithromycin in patients with active duodenal ulcer.

Conflict of interest: None

Funding source: None

Role and contribution of authors:
Dr. Muhammad Tauqeer, conception and designing, collection and analysis of data, primary drafting of the paper.

Dr. Mir Tahir Hussain Talpur, conception and designing, collection and analysis of data, primary drafting of the paper, critical review and final approval of the manuscript.

Dr. Toufique Ahmed, conception and designing, collection and analysis of data, primary drafting of the paper, critical review and final approval of the manuscript.

Dr. Nasrullah Aamer, conception and designing, collection and analysis of data, primary drafting of the paper.

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