DOI: https://doi.org/10.53350/pjmhs22167894

ORIGINAL ARTICLE

Comparison of Efficacy of Conventional Triple Therapy and Non Bismuth Quadruple Therapy for Helicobacter Pylori Eradication

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ABSTRACT

Objective: To compare the efficacy of conventional triple therapy and non bismuth quadruple therapy for helicobacter pylori eradication.

Setting: Gastroenterology Department, Lady Reading Hospital Peshawar.

Study Design: Randomized control trial.

Duration: 6 months 15th August, 2018 to 15th February 2019.

Materials and Methods: In this study a total of 111 patients were observed. Patients were put in two groups, group A triple Helicobacter pylori eradication therapy and group B non-bismuth quadruple Helicobacter pylori eradication therapy. Randomization of patients to either treatment group was done through lottery method. All patients were worked up with detailed history and clinical examination to look for any known allergy to drugs used in this study, to document any comorbidity and to exclude alarm features, baseline investigations including complete blood count, Random blood sugar, liver function tests and renal function tests. H pylori stool antigen was reported from Lady Reading Hospital laboratory at time of inclusion and four weeks after completion of therapy. The purpose and benefits of study was explained to patients and written consent for participation in study was obtained. Patients were asked on follow up about adherence to the treatment.

Results: In this study mean age in Group A was 44 years with SD ± 2.77. Whereas mean age in Group B was 42 years with SD ± 3.12. In Group A 55% patients were male and 45% patients were female. Where as in Group B 58% patients were male and 42% patients were female. More over Group A (triple Helicobacter pylori eradication therapy) was effective in 75% patients. Where as Group B (non-bismuth quadruple Helicobacter pylori eradication therapy) was effective in 94% patients and was not effective in 6% patients.

Conclusion: Our study concludes that non bismuth quadruple therapy is more effective than triple therapy in the treatment of Helicobacter pylori eradication.

Keywords: Conventional triple therapy, Non-bismuth quadruple therapy, Helicobacter pylori eradication

INTRODUCTION

Helicobacter pylori is a microaerophilic, spiral-shaped, gram-negative bacteria that has numerous flagella for movement [1]. More than half of the world's population has Helicobacter pylori [1], with the rate being highest in developing countries. The frequency of Helicobacter pylori infection is very high in Pakistan, where 92% of the adult population is affected [2]. Helicobacter pylori has been associated with several digestive disorders [3, 4], including peptic ulcer disease, atrophic gastritis, dyspepsia, gastric cancer, and gastric mucosa-related lymphoid tissue lymphoma. Several extraintestinal diseases, including immune thrombocytopenic purpura, refractory iron deficiency anaemia, and vitamin B12 deficiency3, have been related to H. pylori in recent years. Preventing these illnesses and the complications that can emerge from them requires early and thorough elimination of Helicobacter pylori [3].

First-line therapy for Helicobacter pylori eradication is typically the triple Helicobacter pylori eradication therapy. According to the Maastricht V criteria [4,] a reduction in effectiveness of triple therapy below 80% is unacceptable. The reason for this is the growing antibiotic resistance of Helicobacter pylori. Amoxicillin resistance sits at 23.61 percent, with clarithromycin at 27.46 percent, and metronidazole at 46.75 percent among Asians [5]. In 1998, researchers in Germany and Japan independently developed a non-sequential four-drug, non-bismuth containing quadruple regimen [6] consisting of a proton pump inhibitor (PPI), amoxicillin, clarithromycin, and mitronidazole. This action was taken to beat back opposition and boost efficiency. Significant cure rates (>90% when judged by intention-to-treat) were achieved with this approach despite the short duration of therapy (an average of 5 days) [6]. An international study found that compared to the standard triple treatment, non-bismuth quadruple therapy is significantly more effective in completely eliminating H. pylori [7]. There was a statistically significant difference (p=0.0014) between the eradication rates of H. pylori in the non-bismuth quadruple group and the usual triple group (93.3% versus 78.5%) [7].

There have been no local investigations comparing the efficacy of these two treatment regimens, despite the fact that a randomised control trial conducted globally has shown that non-bismuth quadruple therapy is preferable to triple therapy for the eradication of helicobacter pylori. In order to confidently implement a more efficient regimen, the current study aims to compare the two subsets of the local population. Patients will benefit greatly from a more efficient treatment plan, as this will not only reduce their discomfort but also reduce the risk of more serious complications like cancer and gastrointestinal bleeding.

MATERIALS AND METHODS

This randomized controlled trial was conducted at Gastroenterology Department, Lady Reading Hospital Peshawar. Duration of study was six months from 15th August, 2018 to 15th February 2019. Total 222 patients of either gender having ages 18-55 years presented with dyspepsia without alarm features and positive Helicobacter pylori stool antigen were enrolled in this study. Patients who received PPIs, H_2 receptor blockers in last 4 weeks or antibiotics in last 2 weeks, patients who had received Helicobacter pylori eradication therapy previously, and patients having contraindications to drugs used in this study.

Patients were divided into two groups, group A receiving therapy to eradicate Helicobacter pylori in three doses, and group B receiving therapy to eradicate Helicobacter pylori in four doses without bismuth. A lottery served as the means by which patients were assigned to either of the two therapy groups. All of the

patients underwent a comprehensive history and clinical examination before the start of the study. This was done to look for any known allergies to the drugs that were being used in the study, to document any comorbidities, and to rule out any alarm features. Baseline investigations included a complete blood count, random blood sugar, liver function tests, and renal function tests. A positive result for H pylori stool antigen was obtained from the laboratory at Lady Reading Hospital both at the time of inclusion and four weeks after treatment was finished. Patients were given an explanation of the objectives and benefits of the trial, and their written agreement to take part in the research was collected (annexure attached). During the follow-up, patients were questioned regarding their level of treatment adherence.

In order to minimize the impact of bias on the study's findings, we were required to rigorously adhere to the exclusion criteria.

The Statistical Package for the Social Sciences (SPSS) version 22.0 was utilized in order to do the analysis on the data. The mean and standard deviation were computed for continuous variables such as patients' ages, BMIs, and the length of time they had been experiencing symptoms. Calculations were made to determine the frequency of occurrence as well as the percentages for qualitative factors such as gender, obesity, smoking, diabetes mellitus, hypertension, and effectiveness. It was decided to use the Chi square test. We considered a value of 0.05 or less to be significant. The findings were displayed in the form of tables and graphs.

RESULTS

10 (9%) of the patients in Group A were between the ages of 18 and 25, while 42 (38%) were between the ages of 26 and 35, 37 (33%) were between the ages of 36 and 45, and 22 (20%) were between the ages of 46 and 55. The average age was 44, and the standard deviation was 2.77 years. In Group B, 11 (10%) patients were between the ages of 18 and 25, 35% were between the ages of 26 and 35, 32% were between the ages of 36 and 45, and 23% were between the ages of 46 and 55. Mean age was 42, and standard deviation was 3.12. (as shown in table no 1)

Table 1: Age Distribution (n=222)

Age	Group a	Group b
18-25 years	10(9%)	11(10%)
26-35 years	42(38%)	39(35%)
36-45 years	37(33%)	36(32%)
46-55 years	22(20%)	25(23%)
Total	111(100%)	111(100%)
Mean and SD	44 year ± 10.32	42 year ± 11.06

T Test was applied in which P value was 0.1650

Among the two groups studied, 61 (55%) were male and 50 (45%) were female in Group A while in Group B had 64 male patients (58%) and 47 female patients (42%). (as shown in table no 2)

Table 2: Gender Distribution (n=222)

Gender	Group a	Group b
Male	61(55%)	64(58%)
Female	50(45%)	47(42%)
Total	111(100%)	111(100%)

Chi Square test was applied in which P value was 0.6847

Comparison of symptom duration between the two groups revealed that 30 (27%) patients in Group A had symptoms for 6 years, while 81 (73%) patients in Group B had symptoms for 6 years. Symptoms lasted, on average, 7 years (SD = 3.21). In Group B, 78 (70%) patients experienced symptoms for longer than six years, while 33 (30%) patients had symptoms for less than six years. The average symptom duration was 7 years, with a standard deviation of 3.58 years. (as shown in table no 3)

The prevalence of obesity was compared between the two groups, with the results showing that 72 (65%) of Group A patients were obese and 39 (35%) were not obese. In Group B, 75% of patients were obese whereas 32% were not. (as shown in table no 4)

Table 3: Duration of Symptoms (n=222)

Duration	Group a	Group b
≤ 6 years	30(27%)	33(30%)
>6 years	81(73%)	78(70%)
Total	111(100%)	111(100%)
Mean and SD	7years ± 3.21	7 years ± 3.58

T Test was applied in which P value was 1.0000

Table 4: Obesity (n=222)

Obesity	Group a	Group b
Non obese (BMI ≤30 Kg/m^2)	72(65%)	75(68%)
Obese (BMI >30 Kg/m^2)	39(35%)	36(32%)
Total	111(100%)	111(100%)
Mean BMI and SD	$25Kg/m^2$ ± 3.98	$25Kg/m^2$ ± 3.71

T Test was applied in which P value was 1.0000

When comparing the two groups, the smoking status was broken down as follows: Twenty patients in Group A (18%) were smokers, while 91 patients (82%) were not smokers. Only 22 patients in Group B (which accounts for 20% of the total) smoker, the remaining 89 individuals account for 80% of the total were non-smoker. (as shown in table no 5)

Table 5: Smoking (n=222)

Smoking	Group a	Group b
Yes	20(18%)	22(20%)
No	91(82%)	89(80%)
Total	111(100%)	111(100%)

Chi square test was applied in which in which P value was 0.7318

Status of diabetes mellitus among two groups was analyzed as in Group A 26(23%) patients were diabetic and 85(77%) patients were non diabetic. Where as in Group B 28(25%) patients were diabetic and 83(75%) patients were non diabetic. (as shown in table no 6)

Table 6: Diabetes Mellitus (n=222)

Diabetes mellitus	Group a	Group b
Yes	26(23%)	28(25%)
No	85(77%)	83(75%)
Total	111(100%)	111(100%)

Chi square test was applied in which in which P value was 0.7543

Status of hypertension among two groups was analyzed as in Group A 17(15%) patients were hypertensive and 94(85%) patients were non hypertensive. Where as in Group B 20(18%) patients were hypertensive and 91(82%) patients were non hypertensive. (as shown in table no 7)

Table 7: Hypertension (n=222)

Hypertension	Group a	Group b
Yes	17(15%)	20(18%)
No	94(85%)	91(82%)
Total	111(100%)	111(100%)

Chi square test was applied in which in which P value was 0.5890

Efficacy among two groups was analyzed as Group A (triple Helicobacter pylori eradication therapy) was effective in 83(75%) patients and was not effective in 28(25%) patients. Whereas Group B (non bismuth quadruple Helicobacter pylori eradication therapy) was effective in 104(94%) patients and was not effective in 7(6%) patients. (as shown in table no 8)

Table 8: Efficacy Between Both Groups (n=222)

Efficacy	Group a	Group b
Effective	83(75%)	104(94%)
Not effective	28(25%)	7(6%)
Total	111(100%)	111(100%)

Chi Square test was applied in which P value was 0.0001

DISCUSSION

Helicobacter pylori is a spiral-shaped, gram-negative, microaerophilic bacterium that moves with the help of many flagella [1]. More than half of people around the world have Helicobacter pylori [1], with the rate being even greater in underdeveloped nations. Statistics show that 92 percent of Pakistani adults have Helicobacter pylori [2]. Several gastrointestinal disorders are linked to Helicobacter pylori, including peptic ulcer disease, atrophic gastritis, dyspepsia, gastric cancer, and gastric mucosa-associated lymphoid tissue lymphoma [3]. The possibility that H. pylori is linked to disorders beyond the gut has emerged more recently [3, 4]. These diseases include immune thrombocytopenic purpura, refractory iron deficiency anaemia, and vitamin B12 insufficiency. According to our findings, the average age of those in Group A was 44 years old, with a standard deviation of 2.77 years. Group B had a mean age of 42 years and a standard deviation of 3.12 years. The gender breakdown in Group A was 55% male and 45% female. In Group B, 58% of the patients were men and 42% were women. Group A (treatments to completely eradicate Helicobacter pylori) was successful in 75% of patients. Group B's (non-bismuth triple Helicobacter pylori eradication therapy) treatment was successful in 94% of patients and failed in 6%.

A separate study with the same number of participants, 246, was done by Georgopoulos S et al [8]. Per protocol, the cure rates were 93.3% (95% CI, 87.2% -97.1%) and 78.5% (95% CI, 70.3%-84.9%), whereas the intention-to-treat cure rate was 90.5% [95% CI, 84.1%-95%] and 73.8% (95% CI, 65.6%-80.7%). With regards to eradication rates, the concurrent group outperformed the triple therapy group in both the intention-to-treat (P=0.0006) and the per protocol (P=0.0014) populations. In both groups, adherence was excellent (96.6% and 98.5%, respectively, P=0.44), and adverse events were mainly mild to moderate in degree.

Another study by Essa AS et al [9] found similar outcomes, comparing the efficacy of concurrent (293 participants, length 3–5 days) against triple treatment (283 subjects, duration 5–10 days) in a total of 5 randomised controlled trials (RCTs) involving 576 subjects (478 subjects, duration 3 to 7 days). The pooled OR for concurrent therapy was 3.52 (95% CI: 1.95-6.38), whereas the pooled OR for triple therapy was 2.86 (95% CI: 1.73-4.73). These results are from a meta-analysis of 5 randomised controlled trials. ITT eradication rate was 89.7% (95% CI: 86.8%-92.1%) and PP was 92.9% (95% CI: 90.2%-94.8%) across all 10 treatment groups.

Patients with clarithromycin-resistant H. pylori have a better chance of eradication with sequential therapy compared to the standard triple therapy [i.e. 89% (8 of 9, 95% CI 51.0-99%) [10]. As a result, this is probably also the reason why concurrent therapy is preferable to triple therapy. Success rates of concurrent therapy in clarithromycin-resistant infections were reported by Okada et al. [11], who found that among susceptible strains, 95% (140 of 147, 96% CI: 90-98%) were cured, whereas among resistant strains, 100% (12 of 12, 95% CI: 73-100%) were cured. Additionally, 50% (2 of 4) were eradicated after 5 days of simultaneous medication [12] and 75% (3 of 4) were eradicated after 7 days of concomitant therapy [11] with primary double resistance for macrolide and imidazole. With the presence of dual resistance, sequential therapy was useless (i.e., 0% or none of the four) [10].

Due to the limited sample size, it is impossible to determine whether the observed variations are truly attributable to the usage of four versus three medications or to random chance. Considering the existence of this dual resistance, it is unlikely that either concurrent or sequential treatment would be effective [13]. In conclusion, despite the fact that many of the studies are 8-10 years old, clarithromycin resistance has been the leading cause of poor result with standard triple therapy then and now. Unfortunately, most studies, including the vast majority of recent investigations of sequential therapy, have not systematically addressed this. At the 2008 Digestive Disease Week, researchers published the results of a randomised trial comparing a 10-day sequential regimen to a 7-day concurrent one. Compliance and adverse effects were comparable between the two treatments [14], as were eradication rates (89% vs. 87% by ITT and 93% vs. 91% by PP).

CONCLUSION

Our study concludes that non bismuth quadruple therapy is more effective than triple therapy in the treatment of Helicobacter pylori eradication.

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