Original Article

Zahedan Journal of Research in Medical Sciences

Journal homepage: www.zjrms.ir

Comparison of Triple Therapy plus Probiotic Yogurt vs. Standard Triple Therapy on Helicobacter Pylori Eradication

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Article information

Article history:
Received: 19 Feb 2012
Accepted: 5 May 2012
Available online: 5 Nov 2012
ZJRMS 2013; 15(4): 12-16

Keywords:
Helicobacter
Pylori
Probiotic yogurt
Triple therapy
Eradication

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Abstract

***Background*:** Treatment of *Helicobacter pylori* as a major cause of gastric diseases is of utmost concern. We aimed to assess efficacy of triple therapy (amoxicillin, clarithromycin and pantoprazole) plus probiotic yogurt (PY) on eradication of *H. pylori*.

***Materials and Methods*:** Total 102 *H. pylori* positive patients were divided to 3 groups equally and randomly. For treatment of each group amoxicillin, clarithromycin and pantoprazole were used. Group A had additional PY and Group B ordinary low fat yogurt in their regimen as well. These groups were compared regarding treatment success.

***Results*:** Total number of 88 patients finished the treatment course. The most common experienced side effects were dysgeusia in groups A and B (25.8% and 32.3%, respectively), and dysgeusia with diarrhea and abdominal pain (30.8%) in group C. Eradication rate was, respectively, 61.3%, 64.5% and 71.3% in group A, B and C of which difference was not statistically significant. However, the difference between 3 groups in regard to education level was statistically significant (p=0.005).

***Conclusion*:** PY enriched triple therapy has decreased side effects of antibiotics consumption; however, this has no impact on eradication of *H. pylori*. PY and triple therapy can be used concomitantly to increase the patient tolerance.

Introduction

Helicobacter pylori (*H. pylori*) is a very common infection worldwide which can cause variety of upper gastrointestinal (GI) disorders such as peptic ulcer disease, dyspepsia, atrophic gastritis, gastric hyperplasic polyps, gastric mucosa-associated lymphoid tissue (MALT) lymphoma and gastric carcinoma [1-3]. It is believed that about 50% of world population is contaminated with this bacterium which tends to be more in developing countries [4]. Eradication of *H. pylori* is based on regimens of triple- and quadruple therapy including proton pump inhibitor (PPI) + clarithromycin + amoxicillin/metronidazole or bismuth + PPI + tetracycline + metronidazole which are still valid and can be used as first and second lines of treatment, respectively [5]. Noticeably, however, increasing pattern of antibiotic resistance is observed within the regimens and alternative regimes have been proposed (e.g. levofloxacin/rifabutin + PPI + amoxicillin) which should be validated before their worldwide consumption [5, 6]. Apart from that, the curative impact of probiotic yogurt (PY) on acute non-inflammatory gastroenteritis, atopic eczema, post-operative pouchitis and inflammatory bowel disease has been demonstrated [7-10]. Moreover, it has been suggested that PY can increase patient compliance of *H. pylori* eradication agents through decreasing the adverse effects [11, 12].

In a recent clinical trial it concluded that addition of PY to standard triple therapy cannot change the rate of eradication but it can reducannotatitis and constipation [13].In other clinical trials the results are in controversy [14, 15]. According to anti-inflammatory effect of PY, increasing bacterial resistance to antibiotics specially clarithromycin and negative impact of drug adverse effects on patient compliance [16], for the first time we aimed to perform this study to compare the eradicative influence of triple therapy (PPI + clarithromycin + amoxicillin) in groups of patients who receive probiotic and non-probiotic yogurt.

Materials and Methods

From Feb 2009 to Sep 2010 all patients of upper GI tract complaints (age range 18-85 years) who had came/been referred to the Gastroenterology Clinic at Ali-ebn-Abi Taleb Hospital were considered for the study. According to the statistical analysis, 34 patients in each of the below mentioned group (17 females and 17 males) are needed. Therefore urea breath test (UBT) with carbon-13 (13C) for all cases suspicious for *H. pylori* infection was performed and patients with positive results, who did not match the exclusion criteria, were registered so that they would be allocated in the 3 treatment groups.

The exclusion criteria included past history of complete or incomplete *H. pylori* eradication, suspicious or proven ongoing malignancy, history of gastric surgery, pregnant or breast-feeding women, intake of antibiotics, PPIs or bismuth within past 2 months and present history of hypersensitivity reaction to penicillin or clarithromycin and other drugs.

Questionnaires were used to record demographics and medical history/exam. Result of treatment and follow-up was recorded as well. Using table of random numbers, patients were allocated equally to one of the following treatment categories: A) pantoprazole 40 mg once daily, amoxicillin 1 g twice daily, clarithromycin 500 mg twice daily and PY (1.5% fat) 150g twice daily. B) pantoprazole 40 mg once daily, amoxicillin 1 g twice daily, clarithromycin 500 mg twice daily and non-PY (1.5% fat and from the same dairy) 150g twice daily. C) pantoprazole 40 mg once daily, amoxicillin 1g twice daily and clarithromycin 500 mg twice daily. All drugs were administered orally for 7 days and patients were asked not to have dairy products in their food regimen unless as it was ordered. As the Dairy Company answered us by email they used ABY-1 (Christian Hansen, Hoersholm, Denmark) starter to ferment their PY. This starter contains *Lactobacillus acidophilus* and bifid bacterium lactic in addition to traditional yogurt bacteria.

After treatment commenced, all patients have been assessed for compliance, adverse reaction and any problem in GI tract and, in the end, follow-up UBT was performed 4 weeks after treatment ended to evaluate if the eradication strategies were successful.

Urea breath test (UBT): UBT was done while all patients had been requested not to eat or have injection four hours prior to the test. First sample was obtained before ingestion of oral radionuclide. Second sample was obtained 30 minutes after when the 13C-containing urea tablet with one glass orange juice was ingested. Isotope ratio mass spectrometry (IRMS) was used for sampling.

Patients who have not properly followed the instructions of drug and/or yogurt use due to any reason and who have not participated in UBT were all disregarded.

The SPSS-17 was used for statistical analysis. The positive or negative result of UBT was compared by ANOVA test among the 3 groups. Moreover, a comparison between each demographic character within our groups and the result of UBT was performed by t-test. The level of statistical significance and the confidence interval (CI) were established as $p<0.05$ and 95%, respectively. This cohort was approved by the Ethical Board of the Rafsanjan Medical University by the code of IRCT138904011061N9 and all patients signed the consent form of study enrollment.

Results

In total, 102 patients with proven Hpylori infection were selected for the study from which 34 individuals (17 females and 17 males) were allocated into 3 groups using table of random numbers. Three individuals in group A (1 female, 2males), 3 individuals in group B (3 females) and 8 individuals (2 females, 6 males) in group C left the study.

Mean and standard deviation (SD) of age, body mass index (BMI), delta over baseline (DOB) levels of before and after treatment (DOBB and DOBA) are summarized in table 1. Moreover, education level and job category of patients are demonstrated in figures 1 and 2, respectively. Figure 3 demonstrates adverse effects occurred within our population. Dysgeusia was the most frequent adverse effect in patients who had yogurt in their treatment. In group C, however, dysgeusia, diarrhea and abdominal pain were most noticed.

In groups A, B and C, in 19 (61.3%), 20 (64.5%) and 19 (73.1%) patients eradication regimen were successful, respectively. The achieved eradication rate was the highest in group C, however, this was not statistically significant.

Successful *Helicobacter pylori* eradication (HPE+) and unsuccessful *Helicobacter pylori* eradication (HPE−) categories were compared in regard to each of age, sex, education level, job category, BMI, DOBB, DOBA and adverse reaction parameters of which results follow (Table 2).

Group A: Between HPE+ and HPE − patients, DOBB and DOBA levels were significantly different ($p<0.001$ for both). The mean values were 14.7±8.4 and 31.7±13.1, 1.0±2.0 and 16.4±9.2 for DOBB and DOBA, respectively. No other parameter was found to be significantly different between HPE+ and HPE − patients.

Group B: as well as previous group, DOBB and DOBA levels were detected to have significant difference between HPE+ and HPE− patients ($p=0.007$and $p<0.001$, respectively). The mean values were 16.0±11.3 and 29.0±13.1, 1.5±2.9 and 10.4±6.9 in DOBB and DOBA, respectively. None of the other parameters were found to bring significant difference between HPE+ and HPE− patients.

Group C: HPE+ and HPE − subgroups were significantly different in DOBA category (means: 0.8±3.0 and 7.4 ±8.0, respectively and $p=0.005$). However, this difference was not significant in DOBB and other parameters.

In addition to the above mentioned results, analysis of variance (ANOVA) was performed between the three groups in each of HPE+ and HPE− subgroups (Table 3). As it has been shown, education level of HPE+ population ($p=0.005$) and job category of HPE− population ($p=0.020$) were significantly difference between the 3 groups.

Table 1. Mean of age, BMI and DOB in each group

Mean	Age(yr)	BMI	DOB before treatment	DOB after treatment
Group A	31.3±12.6	23.2±3.1	21.3±13.2	6.9±9.5
Group B	35.2±8.0	24.2±4.2	20.6±13.3	4.8±6.4
Group C	39.1±14.5	22.7±3.1	14.3±11.0	2.5±5.5

BMI: body mass index, DOB:Delta over baseline

Table 2. Comparison of eradication success in each group regarding age, sex, education level, job category, BMI, DOB and adverse reaction.

	HPE	Group A Mean±SD	*p*-Value	Group B Mean±SD	*p*-Value	Group C Mean±SD	*p*-Value
Age (years)	+	31.4±12.1	0.985	34.2±8.4	0.318	37.2±14.6	0.285
	−	31.3±13.9		37.2±7.3		44.2±14.3	
Sex	+	1.4±0.5	0.195	1.4±0.5	0.453	1.5±0.5	0.974
	−	1.6±0.5		1.5±0.5		1.5±0.5	
Education level	+	3.3±1	0.132	3.1±1.0	0.176	2.3±0.7	0.061
	−	2.7±0.9		2.4±1.5		1.7±0.4	
Job	+	3.3±1	0.971	4.1±1.3	0.480	3.1±1.6	0.607
	−	3.3±1.4		4.4±0.5		2.7±1.7	
BMI	+	22.9±3.1	0.599	24.7±3.8	0.399	22.1±3.1	0.117
	−	23.6±3.2		23.3±5.1		24.3±2.4	
DOB before treatment	+	14.7±8.4	<0.001	16.0±11.3	0.007	12.0±9.6	0.086
	−	31.7±13.1		29.0±13.1		20.5±13.5	
DOBafter treatment	+	1.0±2.0	<0.001	1.5±2.9	<0.001	0.8±3.0	0.005
	−	16.4±9.2		10.4±6.9		7.8±8.0	
Adverse reactions	+	1.0±1.1	0.382	1.1±1.0	0.830	1.6±1.1	0.289
	−	1.4±1.0		1.1±0.9		2.1±0.9	

HPE: helicobacter pylori eradication, BMI: body mass index, DOB: Delta over baseline

Table 3. Comparison of study groups with each other regarding age, sex, education level, job category, BMI, DOB and adverse reaction

	Group	HPE + Mean±SD	*p*-Value	HPE − Mean±SD	*p*-Value
Age(years)	A	31.4±12.1	0.328	31.3±13.9	0.092
	B	34.2±8.4		37.2±7.3	
	C	37.2±14.6		44.2±14.3	
Sex	A	1.4±0.5	0.492	1.6±0.5	0.841
	B	1.4±0.5		1.5±0.5	
	C	1.5±0.5		1.5±0.5	
Education level	A	3.3±1	0.005	2.7±0.9	0.172
	B	3.1±1.0		2.4±1.5	
	C	2.3±0.7		1.7±0.4	
Job	A	3.3±1.2	0.062	3.3±1.4	0.020
	B	4.1±1.3		4.4±0.5	
	C	3.1±1.6		2.7±1.7	
BMI	A	22.9±3.1	0.060	23.6±3.2	0.877
	B	24.7±3.8		23.3±5.1	
	C	22.1±3.1		24.3±2.4	
DOB before treatment	A	14.7±8.4	0.453	31.7±13.1	0.217
	B	16.0±11.3		29.0±13.1	
	C	12.0±9.6		20.5±13.5	
DOB after treatment	A	1.0±2.0	0.656	16.4±9.2	0.066
	B	1.5±2.9		10.4±6.9	
	C	0.8±3.0		7.8±8.0	
adverse reactions	A	1.0±1.1	0.198	1.4±1.0	0.153
	B	1.1±1.0		1.1±0.9	
	C	1.6±1.1		2.1±0.9	

HPE: helicobacter pylori eradication, BMI: body mass index, DOB: Delta over baseline

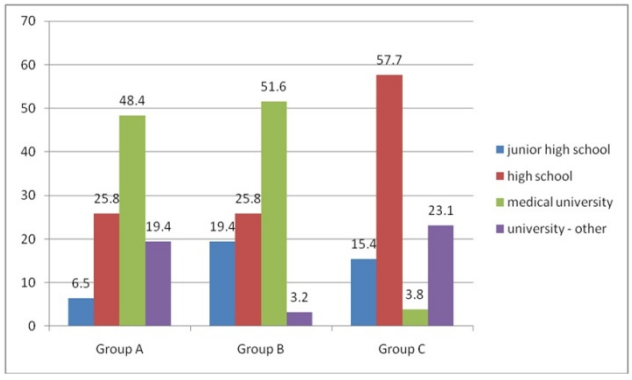

Figure 1. Frequency of each of the four education levels within our groups (%)

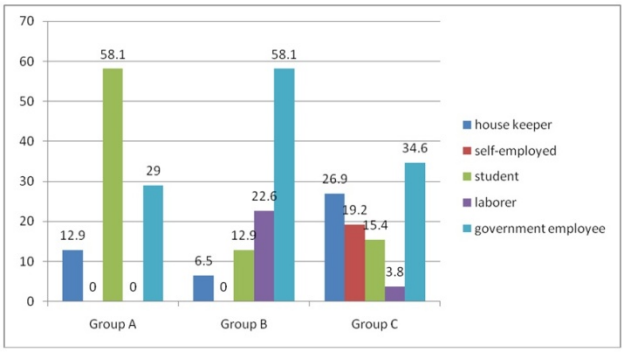

Figure 2. Frequency of job categories within our groups (%)

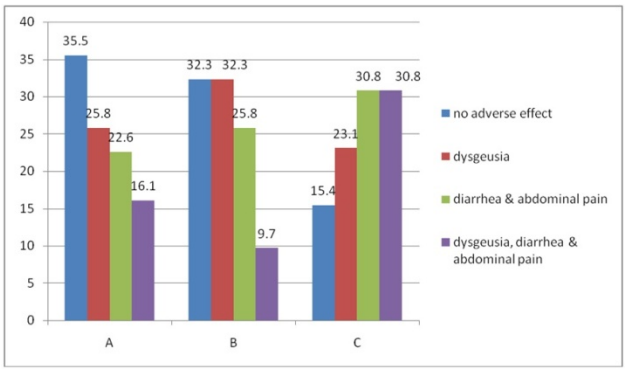

Figure 3. Frequency of adverse effects observed within our groups (%)

Hence, we have reached the fact that the mentioned difference in education level is resulted from the significant difference between groups A and C and groups B and C (p=0.006 and 0.034, respectively), however, no significant difference was found between groups A and B (p=0.761). Additionally, the achieved significant difference in jobs of HPE− patient groups is limited to the difference between groups B and C (p=0.021) only and this parameter had no significant difference between groups A and B, A and C, (p=0.102 and 0.563, respectively). Statistically significant difference between

the study groups was found regarding none of the remaining parameters.

Discussion

H. pylori infection is a highly common disorder across the globe and considering its problematic consequences, potent treatment strategy is essential. A cohort study was carried out to assess the outcome of HPE with the use of triple therapy + PY. This is performed according to the increasing number of *H. pylori* resistance cases resulted from reasons such as low compliance of patients and high cost of eradication regimens. To tackle this problem, new antibiotic combinations have been proposed which, nevertheless, have not been proven to be administrable worldwide and is more expensive than to be economically affordable by patients and insurance institutions. Besides, classic effective and inexpensive triple therapy (either of amoxicillin or metronidazole + clarithromycin + PPI) is still preferred. Furthermore, probiotics are postulated to be an effective adjuvant in reduction of undesirable effects of antibiotics being used for HPE as well as their proven anti-inflammatory effects [17-19]. Moreover, Kim et al. has shown that concomitant administration of probiotics and triple therapy can increase the eradication rate; however, they found this approach to have no effect on lowering the adverse effects [20].

According to what we has been found, in contrast and despite the detected different eradication rates between the 3 groups which represented more success by group C (success rates: A: 61.3%, B: 64.5% and C: 73.1%), none of these differences were significant and apparently triple therapy with PY is unlikely to have a significant impact on HPE than other regimens used in this study and, therefore, cannot be effectively yielded by PY-enriched regimens. Nonetheless, patients who have not received yogurt -of any type- (group C) have more adverse reaction and they suffered most from abdominal pain and dysgeusia. Although patients who had PY or non-PY in their treatment regimen experienced less adverse reactions and only dysgeusia without abdominal pain was the prominent one, this differences were not significant for both HPE+ and HPE − patients (p=0.198 and p=0.153, respectively).

This, however, is similar to the reports of other investigators who have suggested the use of probiotic bacteria to increase the compliance and intend to treat of patients [13, 19, 20]. Apart from that, the levels of DOBB and DOBA were compared between HPE+ and HPE − and we realized that HPE+ patients have significantly lower amount of DOB. Mean DOBB levels of HPE − patients in groups A, B and C were 17.0 %, 13 % and 8.5 % lower than of HPE+ patients. Similarly, mean DOBA levels of HPE− individuals were significantly lower than of HPE+ individuals for 15.4, 8.9 and 7 % in A, B and C groups, respectively. This may suggest the correlation between level of DOB and severity of *H. pylori* infection which may demand more effective treatment. Nevertheless, no study has evaluated this correlation so far.

In parallel, parameters such as age, sex, education level, job, BMI, DOBB, DOBA and presented adverse reactions were analyzed to evaluate if each of them differs among the 3 groups while HPE+ and HPE − patients are divided. We found that age, sex, BMI, DOB and adverse reactions of the treatment do not differ significantly between the 3 groups within both HPE+ and HPE − individuals. In addition, education level and job of our population were not significantly different in HPE − and HPE+, respectively.

This represents the normal distribution pattern of total population among the groups. However, HPE+ and HPE − patients were significantly different regarding education level and job, respectively. This is occurred due to the fact that our patients have not been matched unless for sex. Besides, the role of race [21] should not be neglected which can confound the results specially studies with great sample size such as national, international or referral centers' studies. The limitation of our study was the poor cooperation of patients for follow up but we tried to follow them exactly. It seems to be beneficial to evaluate the effect of other types of probiotics on Hpylori eradication and finally analyze the available data as a review article or Meta-analysis. We conclude that PY cannot affect the result of HPE however, can be used to decrease the adverse effects (e.g. abdominal pain) which can indirectly maximize the success rate of eradication.

Acknowledgements

This study is adapted from MSc thesis in the field of hematology, Mr. Ali Dehghani Fard with financial support of Medical Science faculty of Tarbiat Modares University under the code 2027399. Hereby; the cooperation of officials of Stem Cell Institute and Molecular Genetics Laboratory of Specialist Hospital of Sarem as well as Dr. Nikogoftar in Iranian Blood Transfusion Organization and Dr. Atashi in Stem Cell Technology will be highly appreciated.

Authors' Contributions

All authors had equal role in design, work, statistical analysis and manuscript writing.

Conflict of Interest

The authors declare no conflict of interest.

Funding/Support

Vice chancellor of education and research, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

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Please cite this article as: Mirzaee V, Hosseini O. Comparison of triple therapy plus probiotic yogurt vs. standard triple therapy on Helicobacter pylori eradication. Zahedan J Res Med Sci (ZJRMS) 2013; 15(4): 12-16.