Comparison of Ten-Day Sequential and Standard Triple Therapy for Helicobacter *pylori* Eradication

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Abstract- Helicobacter pylori (HBP) is reported as one of the main causes of peptic ulcer disease (PUD) and gastric cancer in the world. The challenge for finding an optimal treatment regimen for HBP eradication is still a matter of concern. The aim of this study was to compare the HBP eradication rate as well as side effects between two 10-days treatments of the standard triple and sequential regimen. This study was performed on patients with dyspepsia and HBP positive. Patients were categorized in two treatment groups including; standard (Omeprazole, Amoxicillin, and Clarithromycin) and sequential treatment (Omeprazole, Amoxicillin, Clarithromycin, and Metronidazole). HBP eradication rate, side effects, and treatment costs were compared between two groups. One hundred thirty-two patients (58 males, 74 females) with a mean age of 42.7±14.2-year-old were studied in two groups of Standard Treatment (n=66) and Sequential Treatment (n=66). There were not any significant differences between two groups regarding baseline features. The overall rate of HBP eradication was estimated to be 79.5%. Although, there was not any significant difference between the observed side effects, the mean cost of treatment in standard was significantly lower than that in the sequential group (*P*=0.001). It seems that there are not any clinical differences between 10-day treatment plan of the standard triple and sequential therapy in the case of HBP eradication and side effects. However, the sequential treatment might be a better option as the economic point of view.

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Introduction

Helicobacter pylori (HBP) is known as the main cause of peptic ulcer disease (PUD), atrophic gastritis, MALT (mucosa-associated lymphoid tissue) lymphoma, and gastric adenocarcinoma in the world (1,2). There is also correlation between prevalence of HP and gastric cancer. Elimination of H. pylori cures gastritis and may alter the progression to long-term complications of infectious gastritis. Antibiotic resistance and non-compliance cases are the main limitations in HBP elimination. Standard triple therapy including clarithromycin plus amoxicillin or metronidazole and a proton pump inhibitor (PPI) for at least seven days has been used for the HBP elimination (1,3-6); however, its efficacy has been shown to be decreased in some of the recent studies (1,2,7). Increasing the drugs dosage or the number of medications is believed to be the available options to improve the treatment rate (8-10). Indeed, with treatment failure, patients are required to undergo a new treatment option and additive diagnostic tests to confirm the HBP eradication, which leads to an extra cost for both patients and healthcare system. Therefore, the first-line treatment success is really important for medical practitioners. A meta-analysis including over 53,000 patients reported that the elimination rate is currently below 80% after a standard triple treatment (11), showing that the eradication is not achieved in at least 20% of the patients. Some European studies have also reported even lower rates of eradication, with a failure rates up to 35-40% (8-10,12). Therefore, there is still a controversy in optimal treatment regimen. This study was done using three antibiotics instead of two of classic therapy with shorter time of each antibiotic usage to reach a probably more eradication rate and better tolerance of patients. Aim of this study was to compare the HBP eradication and side effects between two ten-

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day's treatment plans of the standard triple and sequential therapy regiments.

Materials and Methods

Study design and participants

This double blind-randomized clinical trial study was performed on symptomatic HBP positive patients who were referred to Emam Reza Hospital (Mashhad, Iran) between 2010 to-2012. The sample size was calculated as 130 cases (65 patients per group). Adult patients with chronic dyspepsia were included in present study who were HBP positive based on upper gastric endoscopy biopsy for rapid urease test or histology. Patients who had a positive history of HBP eradication, PPI, H2 blocker or antibiotic consumption (in the last four weeks), pregnancy, renal failure, liver dysfunction, allergy, malignancy, and previous gastric surgery were excluded from current study.

Randomization and blinding

In this study, patients were randomly allocated to one of the two groups of standard or sequential treatment on a 1:1 ratio via random sampling numbers. One of the researchers who was not aware of the treatment protocols was responsible for randomizing. Patients were also unaware of the treatment drugs and protocols. The study outcomes were also recorded by a gastroenterologist who was unaware of study protocol.

Interventions

Standard treatment group received a standard triple therapy including Omeprazole (20 mg BD), Amoxicillin (1 g BD), and Clarithromycin (500 mg BD) for 10 days. Sequential treatment group received Omeprazole (20 mg BD) and Amoxicillin (1 g BD) for the first 5 days, followed by Omeprazole (20 mg BD), Clarithromycin (500 mg BD), and Metronidazole (500 mg BD) for 5 days. Some of the patients had PUD and we had to treat them at least four weeks with PPI. Because of suppressing effect of Omeprazole on HP, we continued Omeprazole (20 mg BD) consumption to have similar situation for an additional 20 days after the first period of 10-days therapy in both groups.

Outcomes and follow-up

The primary outcomes were the rate of HBP eradication. The second outcome was the incidence of side effects in both groups. In the current study, side effects were bitter taste of mouth, nausea, and vomiting. Patient cooperation and protocols cost (Iranian RLS) for HBP infection treatment were also the other important outcomes. Patients were followed-up and asked about the possible side effects three times in the 5th, 10th, and 30th day of treatment process.

HBP eradication

An upper endoscopy was done before the patient's enrolment via biopsy for rapid urease test or pathology. H. pylori status was assessed by pathological or rapid urease test. Information about base line conditions such as duodenal ulcer, erosion, gastric ulcer, and non-ulcer dyspepsia which were confirmed by endoscopy were gathered by questionnaire. HBP infection eradication was determined via urea breath test (UBT) in all patients 4-6 weeks after the end of ten-day regimes or 2-4 weeks after the end of PPI. Patients received 37 kB (1 mCi) of 14C-urea/citric acid (Helicap, Sweden) following an overnight fasting (20). Breath samples were collected by a dry-cartridge system 10 minutes later (Heliprobe BreathCard, Sweden). Patients were asked to exhale into the cartridge mouthpiece until the colour of indicator membrane was changed from orange to yellow. Afterwards, the breath card was analyzed using Geiger-Muller counter (Heliprobe analyser, Noster System AB). Results were exported both as counts per minute (CPM) and as grades (0: not infected: CPM <25; 1: equivocal: CPM 25-50; 2: infected: CPM>50). CPM lower than 25 or 0 grade were considered as HBP eradication.

Statistical methods

Chi-square test and independent-samples t-test were used for the comparison of qualitative and quantitative variables between two groups, respectively (P<0.05). SPSS (version.19) was used for data analysis.

Results

Baseline features

Patients were categorized in two groups of standard treatment (n=66) and sequential treatment (n=66). Finally, 132 patients (58 males, 74 females) with a mean age of 42.7±14.2 years old were studied. There was not any significant difference between two groups in the case of age, gender, smoking, addiction, and NSAID usage (Table 1). Two groups were statistically similar in epigastric pain, bloating, vomiting, and reflux (Table 1). Upper gastrointestinal endoscopy also revealed no significant difference between two groups in terms of ulcer location, presence of antrum nodules, and gastric erosions (Table 1). HBP eradication was achieved in 51 patients (78%) of the standard group and 58 patients

(87.8%) of the sequential treatment group (*P*=0.167). The overall rate of HBP eradication was estimated to be 79.5% (105 out of 132 patients).

Table 1. Comparison of demographic characteristics, patients' gastrointestinal symptoms and endoscopic findings in two study groups of the standard treatment and the sequential treatment

Variables, units	Sequential treatment (n = 66)	Standard treatment (n = 66)	*P*
Age, year, mean (SD)	42.2 (14.2)	43.3 (14.3)	0.559
Gender, (male/female), n	28 / 38	30 / 36	0.552
Smoking, n (%)	5 (7.6%)	3 (6.1%)	0.789
Addiction, n (%)	3 (4.6%)	2 (3.1%)	0.615
NSAID consumption, n (%)	26 (39.4%)	15 (27.7%)	0.263
Epigastric pain, n (%)	50 (75.7)	47 (71.2)	0.787
Bloating, n (%)	44 (66.7)	50 (75.7)	0.247
Vomiting, n (%)	17 (15.8)	20 (30.3)	0.572
Reflux, n (%)	55 (83.3)	54 (81.8)	0.756
Ulcer location, (gastric/duodenal) n (%)	15 (23.8)/ 51 (77.2)	24 (36.3)/ 42 (63.7)	0.199
Antrum nodule, n (%)	44 (66.7)	40 (60.6)	0.780
Gastrointestinal erosions, n (%)	50 (23.8)	41 (62.1)	0.249

Side effects and costs

Nine patients experienced bitter taste in their mouth and six patients complained about nausea and the other cases also claimed of vomiting. The overall rate of observed side effects was 16.6% (22 out of 132 patients) in which 13 patients (19.6%) of the sequential group and nine patients (13.6%) of the standard group experienced at least one of the side effects. However, there was not any significant difference between two study groups (*P*=0.675). There was not also any significant difference in cooperation of patients for completing treatment plan in two groups. According to the results, the mean cost of treatment was 208,600 Iranian Rials in the sequential group and 348,000 Iranian Rials in the standard group (*P*=0.001).

Discussion

The overall purpose of the current study was to compare the eradication rate of H. pylori in two study groups receiving different treatment regimens including; ten-day sequential and standard triple therapy. The results demonstrated that H. pylori was eradicated in the majority of research units. Although, eradication rate in the sequential group was slightly higher than the standard triple group, this difference was statistically insignificant. However, in Sanchez *et al*., study it was shown that the success rate of these two treatment regimens was not significantly different and eradication rates in sequential and standard triple therapy were 90.7% and 84.2%, respectively (13). Eradication rates in our study were lower than the mentioned study which can probably be due to geographical and antibiotic resistance differences. Moghaddaszadeh *et al*., also showed that there is not any significant difference between sequential and non-sequential treatments. However, a four-drug combination regime was used instead of a three-drug combination (14). Therefore, eradication success rate reached to 85-90%. Despite alignment with the results of Moghaddaszadeh and our study from the perspective of difference between sequential and non-sequential regimes, the success rate of HBP eradication in Moghaddaszadeh's study was about 10% higher than that in our study which might possibly be due to taking more number of antibiotics by patients. One of the factors that can increase the chances of HBP eradication and patient recovery is the number of medications in each treatment regime. On the other hand, a shorter duration and a lower number of medications in a specific treatment protocol facilitate the patients' compliance resulting in an improvement of eradication rates (15). We had two follow ups (after 5 and 15 days) to make sure the cases are using drugs in correct way and probable side effects. Lower eradication rates of HBP in the present study might be because of shorter treatment duration in comparison with base therapy (14 days). Another hypothesis in this regard is the extensive use of antibiotics in our society that may have caused bacterial drug resistance (15). In this regard, it has been reported that the previous usage of Macrolides failed as a predictive factor for HBP treatment (16). However, there have been other studies indicating low success rates for sequential and triple drug regimens (17). Therefore, it seems that regardless of drug types or drug prescription methods, we should also consider people's genetic differences, race, and geographical location to predict the response to medications. There

have been other studies that have shown a higher success rate for sequential therapy in comparison with triple therapy which is close to the results of present study (18). However, we observed better eradication rate with sequential therapy which is probably related to the usage of Ciprofloxacin. According to a lower available bacterial resistance toward Fluoroquinolones, better effects are predicted to be achieved with sequential regimens based on such compounds (2,10,13,19). Since there are differences in individual response to a same treatment regime in different geographical regions, it is recommended that further studies should be conducted in other parts of the world. On the other hand, another aim of this study was the evaluation of adverse drug effects in two study groups and also comparing them together. The overall incidence of drug side effects in our study was approximately 17%. However, there was not any statistically significant difference in the incidence of drug side effects between two study groups. Although, until now, few studies have compared the side effects of these treatment regimens together, they have demonstrated that these regimes are not significantly different in terms of drug side effects (2,10,13,19). We observed the lower cost of treatment in sequential therapy in comparison with the standard triple therapy, same HBP eradication rate of, and the same drug side effects in both regimens. This helps the physicians to choose a treatment protocol considering patient's economic situation. Another group also has demonstrated that the cost of sequential therapy regime is less than standard triple therapy (20). Not only low cost of treatments helps to improve the patients' compliance, but also it increases their tendency to continue treatment protocols and follow-up programs .

Although, HBP eradication rate of patients receiving sequential therapy regime is higher than the patients who were undergone the standard triple therapy, there is not any significant difference between these two groups. Moreover, there was not any significant difference in the incidence of drug side effects between these two groups. Therefore, regarding the lower cost of sequential therapy in comparison with standard triple therapy, physicians might consider sequential treatment regimen for the eradication of HBP. However, longer treatment duration on HBP eradication, more sample size, and higher medication dosages are recommended to be evaluated in future studies.

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