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Favorable effects of close telephone follow-up on *Helicobacter pylori* eradication success

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Abstract

Introduction: To determine whether close follow-up by telephone calls is of benefit in *Helicobacter pylori* (HP) eradication rates.

Material and Method: This is a prospective, randomized, controlled clinical trial. Patients were randomized into two groups as patients who were followed up by telephone calls (TFG) and those who were not (NTFG; controls). Patients in the TFG group were called every 3 days for the 14 days during Hp treatment and were supported for treatment. Patients in the NTFG group were explained the treatment protocol in detail at treatment initiation and were instructed to return for a follow-up visit 4 weeks after treatment end. The latter group was not given support via telephone calls. All patients were examined by fecal HP antigen assay 4 weeks after eradication treatment.

Results: The 242 patients' age range was 19-82 and their mean age was 45.01±14.6 years. Of the patients, 52.1% (n=126) were women and 47.9% (n=116) were men. At treatment initiation and during medical examinations, 6.2% (n=15) of the patients voluntarily withdrew from the study. Treatment was discontinued in 5.8% (n=14) during the course of treatment due to side effects. Of the remaining 213 patients, 108 were randomized to the TFG group and 105 to the NTFG group. Eradication was achieved in 80% (n=84) and could not be achieved in 20% (n=21) of the patients in NTFG. Eradication was achieved in 91.6% (n=99) and could not be achieved in 8.4% (n=9) of the patients in TGF (p<0.001).

Conclusions: Supportive close telephone follow up significantly positively contributed to the Hp eradication success.

Keywords: *Helicobacter pylori*, eradication, antibiotic resistance, telephone follow up

INTRODUCTION

Helicobacter pylori's (HP) mean prevalence (carrier or asymptomatic infection) in the Northern Europe and Northern America is about 30%. The percentage is higher than 70% in low-income nations (1,2). In the past years, initial treatment for HP infection included dual antibiotic therapy with a proton-pump inhibitor. Triple eradication treatment with two antibiotics from clarithromycin, amoxicillin or metronidazole and a proton-pump inhibitor was used more commonly in the past. However, antibiotic resistant development, which reduced treatment success years during the recent years, significantly complicates the treatment (3-9). Besides, there is limited information on HP antibiotic resistance rates to guide the treatment. The selected treatment regimen should take into account local antibiotic resistance patterns (if known), previous exposure to specific antigens and allergy, cost, side effects and convenience of treatment. Lately, poor compliance seems to confound treatment in patients treated for HP eradication. Poor compliance and bacterial resistance are two important factors that lead to unacceptable HP eradication rates (≤80%) (10,11).

Given this resistance setting, patient compliance to current treatment is at least as important as resistance. The present study aims to evaluate the effect of close follow-up by telephone calls on Hp eradication rates.

MATERIALS AND METHOD

This study was approved by the Ethics Committee of Sultan Abdülhamid Han Training and Research Hospital, under

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number 1491-10-16/1539. All procedures were performed adhered to the ethical rules and the Helsinki Declaration of Principles.

Patients who presented for dyspeptic complaints to the internal disease and gastroenterology clinic of our hospital between January 2017 and December 2017 were evaluated. Patients with active malignancies, hepatitis B, C, D, E with HIV and other viral infections or autoimmune disorders were excluded from the study. Esophagogastroduodenoscopy was performed to all patients to evaluate dyspeptic symptoms where indicated. Presence of HP infection was confirmed by histopathological analysis. All biopsy samples were stained with hematoxylin and eosin. Sections with hematoxylin and eosin stains were evaluated by experienced pathologists for presence of HP using Sydney classification.

All patients included in the study were given quadruple eradication therapy consisting of tetracycline 500 mg 4x1, metronidazole 500 mg 3x1, bismuth subsalicylate 262 mg 2x2 and pantoprazole 40 mg 1x1. Each patient was described in detail the treatment protocol they will use before they were given their prescriptions. The patients were then divided into two equal groups of 121 individuals in each. The first group (TFG) was called every 3 days during the 14 days they received treatment and the patients were asked about treatment compliance difficulties and drug side effects. If the patients desired, they were given information on short- and long-term consequences of HP infection and they were encouraged to continue treatment. Approximately 4 weeks after treatment end, all patients were invited to return for a follow-up visit. Patients who did not return for the follow-up visit were called back again once a month for 2 consecutive months and were reminded to return for follow-up. The patients in the second group were explained the treatment protocol in detail at treatment initiation and were instructed to return for a follow-up visit 4 weeks after treatment end. They were not given support via telephone calls. Then the difference between eradication rates of the two groups was evaluated by fecal HP antigen test to assess the response to 14-days of treatment. Fresh feces samples in sterile containers were sent immediately to the laboratory. The test was repeated under optimal conditions for patients who provided diarrheic or inadequate sample. Analysis of fecal samples to assay HP antigen was performed using Hp Ag fecal enzyme-linked immunosorbent assay (ELISA) kits (ACON, San Diego, USA).

Statistical Analysis

Statistical Package for Social Sciences, version 15.0 (SPSS Inc., Chicago, IL, USA) was used for analysis. $p<0.05$ was considered as statistically significant. Distributions of variables were determined by visual and analytic tests as Kolmogorov-Smirnov test. Student T and Mann Whitney U tests were used for comparisons of independent continuous variables. Dependent T test and Wilcoxon test were used for comparisons of related continuous variables. Mc Nemar test were used for comparisons of related categorical variables. Categorical independent variables were analyzed using the chi-square test or Fisher's exact test.

RESULTS

The patients were divided into two groups similar in terms for demographics, comorbidities, socioeconomic and educational status, smoking, drinking and medication history. The 242 patients' age range was 19-82 and their mean age was 45.01±14.6 years. Of the group, 52.1% (n=126) were women and 47.9% (n=116) were men.

A total of 11 (4.5%) individuals, 6 from the first and 5 from the second group, did not return for the first outpatient clinic follow-up after endoscopy. Four (1.7%) individuals, two from each group, were then lost to follow-up after start of treatment. Thus, 15 (6.2%) patients discontinued, and the study was initiated with the remaining 227 patients. Fourteen (5.8%) individuals discontinued treatment due to side effects. Of the remaining 213 patients, 108 were randomized to TFG and 105 to NTFG (**Figure 1**).

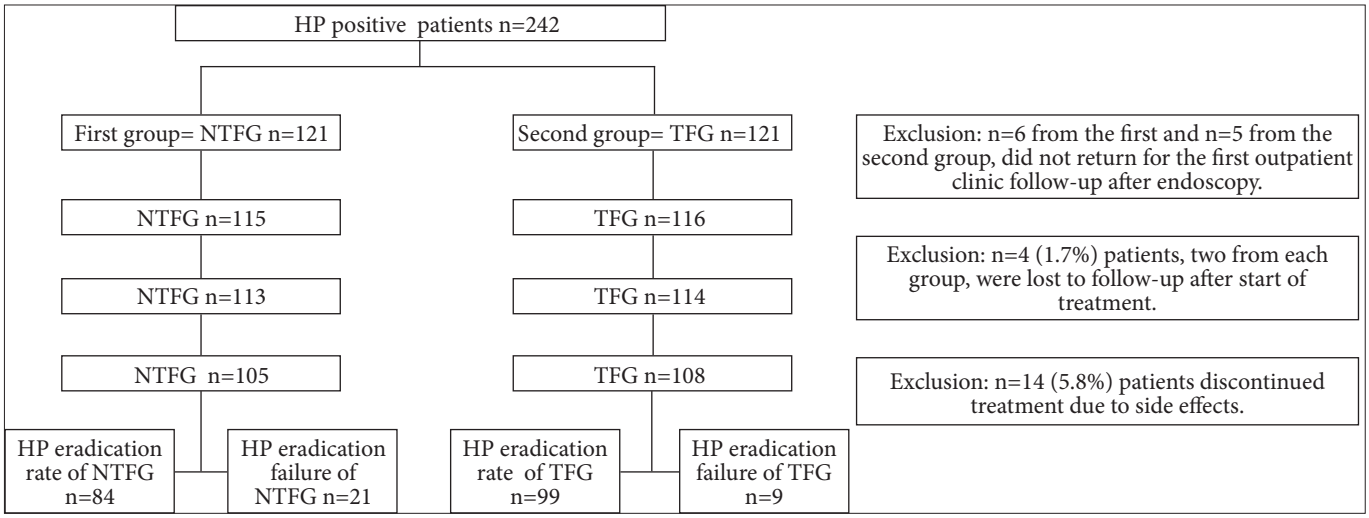

Figure 1. Study flow chart. We enrolled 242 HP positive patients to this study and randomized to two groups

In NTFG, eradication was achieved in 80% (n=84) and could not be achieved in 20% (n=21). In TGF, eradication was achieved in 91.6% (n=99) and could not be achieved in 8.4% (n=9) (p=0.014) (**Table, Figure 2**).

Table. HP eradication rates of TFG and NTFG groups

	HP eradicated (stool test negative)	HP not eradicated (stool test positive)	Total	p value
NTFG	84	21	105	0.014
TFG	99	9	108	
Total	183	30	213	

NTFG: non telephone follow-up group TFG: telephone follow up group

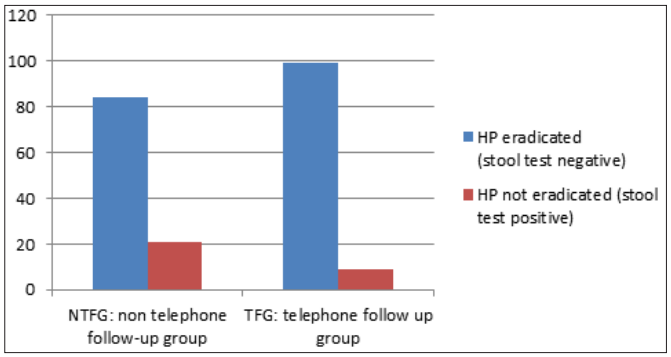

Figure 2. Graphic presentation of HP eradication rates of two study groups

DISCUSSION

To the best of our knowledge, it is the first study which investigates the effect of supportive telephone follow-up in Hp eradication success. Substantial changes have occurred in the diagnosis and treatment of many gastrointestinal diseases such as gastritis and ulcer when HP was first discovered in 1983 (12). In 1994, it was concluded that HP had a causal relationship with stomach carcinogenesis and is definitely a carcinogen for humans, following which the World Health Organization and World Health Organization International Agency for Research on Cancer (IARC/WHO) focused all their attention on this bacterium (13). The estimated risk of developing cancer with HP varies between 50 to 73% (14).

Many treatment protocols are used today for HP eradication. Success rates of up to 95% with standard triple eradication therapies were being mentioned before 2000s (12). The rates fell back to around 55% over the course of years, especially with increasing resistance to clarithromycin (15). An inclination towards quadrupled protocols containing bismuth therefore occurred. Bismuth has antibacterial (against HP) and mucosal cytoprotective effects. Bismuth-containing therapies are known to be more effective in treatment of peptic ulcer and HP infection (16).

An antibiotic treatment cannot be claimed to result in success unless it is taken for an appropriate length of time at the right dosage. Poor compliance to HP eradication regimen inversely correlated with the chance of therapeutic success. It was reported that 12% of the patients prematurely discontinued eradication therapy due to side effects of the drugs used in treatment (17) Unfortunately, approved eradication regimens require combination of 3 or 4 different drugs at multiple daily doses. Complexity of treatment regimen and common occurrence of side effects are linked with patient compliance. Therefore, persuasiveness of the physician and informing the patient of possible effects are essential for therapeutic success (18).

A study performed in 2008 in Italy compared eradication rates and side effect profiles of triple therapy with lansoprazole, amoxicillin and clarithromycin and quadruple therapy with lansoprazole, metronidazole, bismuth and tetracycline for HP eradication, and included 50 subjects in the first group and 44 in the second. Treatment-emergent side effects occurred in 90% of the patients in the first group and in 95% in the second group with 6 (13.6%) patients discontinuing treatment in the second group (19). As in this study, high side effect rates are seen with eradication therapy in many other studies as well, and hence total eradication rates are affected by the patients withdrawing from the study.

Many antibiotic combinations have been tried to increase eradication rates, reduce side effects and improve treatment comfort. A randomized controlled study evaluating two groups, 192 patients in each, treated either with metronidazole, tetracycline and omeprazole added to the new single-capsule bismuth or with omeprazole, amoxicillin and clarithromycin added to the new single-capsule bismuth for eradication and side effects found no difference regarding these variables. Adverse effects were seen in 76% and in 70% of the patients in the first and second groups, respectively (20).

Attempts are being made using a number of methods to increase eradication rates with the given treatments. In some previous studies, probiotics were added with the aim of increasing eradication rates which produced no further benefits other than reducing side effects.

Gong et al. reported lower rates of *H. pylori* eradication with triple therapy compared with probiotic-supplemented triple therapy (hazard ratio [HR] 0.58; 95% confidence interval [CI], 0.50-0.68; p<0.05). Significant reductions in side effects including nausea, vomiting flatulence, epigastric pain, diarrhea, constipation, distorted taste and rash were observed (21).

In a randomized controlled study on probiotic and side effects published in the American Journal of Gastroenterology in 2002, 85 HP-positive patients were

divided into 4 groups and started antibiotic treatment with rabeprazole 20 mg b.i.d, clarithromycin 500 mg b.i.d., and tinidazole 500 mg b.i.d. The first two groups were given different probiotic replacements, the third group was given combined prebiotic replacement and the third group was given placebo, and the groups were compared for eradication rates and side effects. Tolerability was significantly better in treated patients compared with the placebo group. No difference was observed in side effect incidence across probiotic groups and HP eradication rate was almost the same between probiotic and placebo groups (22). As seen in these studies, adding a probiotic to eradication therapy has no effect on eradication rates.

Two studies were performed in China in 2015 and 2017 which evaluated eradication rates using a telephone-based close follow-up. Both studies demonstrated that follow-up by telephone calls had no significant effect on patients' compliance, satisfaction or HP eradication but resulted in reduced undesirable effects (23,24).

Despite these similarly performed studies, we determined in our study that close follow-up by telephone calls affects eradication rates. We believe that this may be due to intercultural differences between countries and the fact that supportive information was given with each call. This demonstrated that supporting patients during treatment increases response rates to this challenging treatment although high eradication rates were seen in both groups.

Fecal antigen testing performed with a monoclonal antibody-based ELISA assay has high sensitivity and specificity but it may not always provide satisfactory results for diagnosis (25). This was the most important limitation for our study. Repeat endoscopy to evaluate eradication following treatment is not considered ethical or cost-effective. However, since eradication assessment was performed with the same method for both groups included in the study, we believe this had no impact on the study outcome.

CONCLUSION

Besides detailed informative talking about Hp treatment at the beginning, supportive treatment by telephone calls may favorably positive contributed significantly to the success of eradication.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Ethics Committee of Sultan Abdülhamid Han Training and Research Hospital, under number 1491-10-16/1539.

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.
Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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