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Smoking and drinking habits are important predictors of *Helicobacter pylori* eradication

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ABSTRACT

Purpose: The aim of the study was to evaluate the effect of smoking and drinking habits, in separate and joint analyses, on the efficacy of *H. pylori* eradication.

Materials and methods: A total of 250 patients were recruited. They were treated with a 7-day course of omeprazole, amoxicillin, tinidazole (OAT), omeprazole amoxicillin, clarithromycin (OAC) or omeprazole, clarithromycin, tinidazole (OCT). The efficacy of *H. pylori* eradication was tested with a CLO-test and histology 4 weeks after the completion of antibacterial therapy.

Results: Drinking was found not to affect the efficacy of *H. pylori* eradication in any therapeutic group, while smoking decreased it in the OAC group (smokers 69.6%, non-smokers 94.3%, p=0.006). In the OAT treated group *H. pylori* eradication rate was lower in smokers-non-drinkers than in smokers-drinkers and non-smokers-non-drinkers (38.9% vs 83.2% and 70.0%, p=0.002 and p=0.034, respectively), while in the OAC treated group, smokers-non-drinkers had lower eradication efficacy than non-smokers-drinkers and non-smokers-non-drinkers (59.1% vs 100% and 91.3%, p=0.01 and p=0.012, respectively). In the OCT treated group, differences between subgroups were not significant.

Conclusions: Smoking and drinking habits when analyzed jointly are more useful to predict the outcome of *H. pylori* eradication than when analyzed separately.

Key words: drinking, Helicobacter pylori eradication, smoking

INTRODUCTION

Although *H. pylori* eradication therapy has made great progress in the treatment of peptic ulcer, its efficacy is still not perfect; as many as 15-20% of treated ulcer patients remain infected. One of the reasons is bacterial resistance to antibiotics, but also some host factors, including smoking and drinking habits, may be involved. Opinions regarding the role of smoking and drinking habits in *H. pylori* eradication therapy are divergent. Smoking has been shown to either decrease or have no effect [1-9]; while drinking either to decrease, increase or have no effect on eradication efficacy [2-5,10]. The discrepancy may result, at least in part, from the differences in smoking and drinking among individuals, and from the eradication regimen used [1,2,5,6,11]. Since smoking cigarettes is usually associated with alcohol consumption, i.e. those who smoke usually drink [12], the aim of the present study was to evaluate the role of smoking and drinking habits, in separate and joint analyses, on the efficacy of *H. pylori* eradication.

MATERIALS AND METHODS

Subjects

A total of 250 peptic ulcer patients (182 duodenal ulcer, 68 gastric ulcer) were recruited for the study. The recruitment was based on the following criteria: ulcer crater 0.5-1.0 cm in diameter (evaluated endoscopically), gastric *H. pylori*

infection (confirmed by serology, CLO-test, and histology), a minimum of 7 days without the use of anti-ulcer drugs (only antacids were allowed) and 30 days without antibiotics, good general health, and normal basic laboratory tests. Pregnant and lactating women, patients with complicated ulcers, with a history of alcohol abuse (drinking more than 100 g alcohol daily) and gastric surgery, with previously unsuccessful *H. pylori* eradication, as well as those whose ulcers might be caused by non-steroidal anti-inflammatory drugs were excluded from the study.

Detailed information on smoking and drinking habits were obtained from a questionnaire filled by all subjects at the beginning of the study. For the needs of this study patients were defined as smokers if they smoked 5 or more cigarettes per day and as drinkers if they consumed 25 g or more alcohol per week. Data on alcohol consumption were presented in the form of 100% alcohol. The following calculations were made: 100 ml of beer – 5 g alcohol, 100 ml of wine - 14 g alcohol, 100 ml of vodka, brandy or whisky – 40 g alcohol. Based on criteria used in the study for smokers and drinkers, the patients who changed their smoking and drinking habits within the last year were not included.

The local Ethical Committee approved the research and all subjects gave informed consent for participation in the study.

Eradication therapy

Patients were randomly selected for one of three therapeutic groups receiving a 7-day course of oral treatment with: 1/ omeprazole (Losec, AstraZeneca) 20 mg bid, amoxicillin (Ospamox, Biochemie) 1000 mg bid, and tinidazole (Tindazolum, Polpharma) 500 mg bid (OAT), 2/ omeprazole 20 mg bid, amoxicillin 1000 mg bid, clarithromycin (Klacid, Abbott) 500 mg bid (OAC), and 3/ omeprazole 20 mg bid, clarithromycin (Klacid, Abbott) 250 mg bid, tinidazole 500 mg bid (OCT). The drugs were taken 30 minutes before meals with half a glass of water. The anti-secretory treatment was stopped with the end of eradication therapy, and then only antacids were allowed as a drug on demand in the case of abdominal complaints.

Gastroscopy examination and *Helicobacter pylori* testing

Two endoscopic examinations were performed, one at the start and the other 4 weeks after completion of the eradication therapy, with gastroscope GIF V2 or Q145 (Olympus, Tokyo, Japan) by one experienced endoscopist. During endoscopy, the diameter of the ulcer crater was evaluated and gastric mucosa specimens were taken from both the prepyloric and gastric body regions. In one specimen of each series, *H. pylori* infection was determined with a rapid urease test (CLO-test) and in the remaining two specimens the histological method was used. The CLO-test was prepared at the Physiology Department of the Medical University of Białystok according to the Marshall et al. method [13]. The sensitivity and specificity of this test compared to the histologic examination was 98.1% and 90.2%, respectively. The results were considered positive if the color of the medium turned from yellow to pink [13]. The gastric mucosa specimens for histological examination were fixed in formalin and processed according to standard protocols: 2 μm paraffin wax sections were cut and then stained with hematoxylin-eosin and Giemsa to identify *H. pylori*. One experienced pathologist did the pathology analysis. Serum samples were examined for *H. pylori* IgG and IgA antibodies using enzyme-linked immunosorbent assay (*recom*Well*Helicobacter*, Microgen).

Before treatment, patients were considered infected if the findings of the three tests for *H. pylori* (serology, CLO-test, and histology) were positive. Eradication of *H. pylori* was considered successful if the findings of the two tests for *H. pylori* in the gastric biopsies performed 4 weeks after the completion of antibacterial treatment were negative.

Data analysis

All randomized patients who had taken at least one dose of study medication were included in the intention-to-treat (ITT) analysis, except those in whom a CLO-positive test was not verified by a positive histology at the baseline visit (*Fig. 1*). Patients who did not complete the study were considered as treatment failure for the purposes of the ITT analysis. The per protocol (PP) analysis excluded patients with unknown *H. pylori* status post-therapy (consent withdrawal) and those with major protocol violations (insufficient compliance, use of disallowed medication).

The results (means ± S.D.) were subjected to statistical analysis using the Mann-Whitney U-test, χ^2 test, and Fisher exact test as appropriate; significant differences were accepted at $p<0.05$.

RESULTS

A total of 237 of the 250 subjects enrolled completed the study; 78 treated with OAT, 81 with OAC and 78 with OCT regimens (characteristics of those who completed the study are given in *Tab. 1*). Of those who did not complete the study, 3 were excluded due to lack of histological evidence of *H. pylori* infection at the baseline, 2 for the improper use of drugs for *H. pylori* eradication, 3 for the use of proton pump inhibitors after the completion of eradication therapy, and 5 due to consent withdrawal (*Fig. 1*). Intention-to-treat analysis has shown that efficacy of *H. pylori* eradication was 63.5%, 77.3%, 84.0% for OAT, OAC and OCT regimens, while PP analysis 66.7%, 80.2%, and 87.4%, respectively.

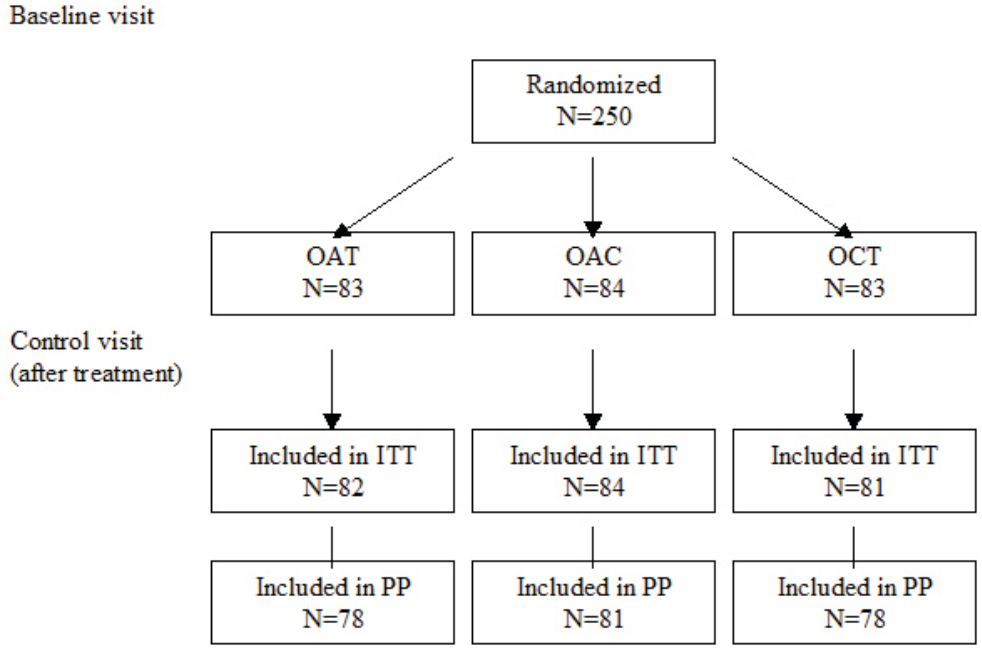
In the population that completed the study, drinking did not affect the efficacy of *H. pylori* eradication in any therapeutic group, while smoking decreased it in OAC group (smokers 69.6%, non-smokers 94.3%, p=0.006). If the subjects of the three groups were pooled, the differences in *H. pylori* eradication efficacy were significant between smokers and

Table 1. **Patients' data, including smoking and drinking habits.**

	OAT	OAC	OCT
n	78	81	78
Age (mean ± SD) (years)	52.2±14.6	47.9±13.9	50.4±15.4
Sex (M/F)	53/25	53/28	49/29
Diagnosis			
Duodenal ulcer	63	63	56
Gastric ulcer	15	18	22
Cigarette smoking			
None	36 (46.2%)	32 (39.5%)	42 (53.8%)
< 5/ day	3 (3.8%)	3 (3.7%)	3 (3.8%)
5 - 9/ day	6 (7.7%)	2 (2.5%)	3 (3.8%)
10 - 19/ day	11 (14.1%)	18 (22.2%)	16 (20.5%)
20 or more/ day	22 (28.2%)	26 (32.1%)	14 (17.9%)
Alcohol consumption			
None	34 (43.9%)	34 (42.0%)	28 (35.9%)
< 25 g/ week	14 (17.9%)	11 (13.6%)	13 (16.7%)
25 – 49 g/ week	2 (2.6%)	8 (9.9%)	10 (12.8%)
50 – 99 g/ week	12 (15.4%)	18 (22.2%)	11 (14.1%)
100 g or more/ week	16 (20.5%)	10 (12.3%)	16 (20.5%)

OAT, omeprazole, amoxicillin, and tinidazole; OAC, omeprazole, amoxicillin, and clarithromycin; OCT, omeprazole, clarithromycin, and tinidazole

Figure 1. **Study flow chart.**



non-smokers (70.2% vs 84.9%, p=0.007) and drinkers and non-drinkers (84.5% vs 72.4%, p=0.027) (*Tab. 2*).

The subjects of each therapeutic group were also analyzed after division into four subgroups: 1/ smokers-drinkers, 2/ smokers-non-drinkers, 3/ non-smokers-drinkers, and 4/ non-smokers-non-drinkers. According to this classification, the lowest *H. pylori* eradication efficacy was observed in smokers-non-drinkers; in the OAT treated group, the efficacy was lower in smokers-non-drinkers than in smokers-drinkers and non-smokers-non-drinkers (38.9% vs 83.2% and 70.0%, p=0.002 and p=0.034, respectively), while in the OAC treated group the efficacy in smokers-non-drinkers was lower than in non-smokers-drinkers and non-smokers-non-drinkers (59.1% vs 100% and 91.3%, p=0.01 and p=0.012, respectively). The

Table 2. **Efficacy of *H. pylori* eradication in peptic ulcer patients analyzed separately in relation to smoking and drinking habits.**

	Drinkers	Non – drinkers	Smokers	Non - smokers
OAT	23/30 (76.7%)	28/48 (58.3%)	24/39 (61.5%)	27/39 (69.2%)
OAC	31/36 (86.1%)	34/45 (75.6%)	32/46 (69.6%)	33/35 (94.3%)*
OCT	33/37 (89.2%)	35/41 (85.4%)	27/33 (81.8%)	41/45 (91.1%)
Total	87/103 (84.5 %)	97/134 (72.4 %)*	83/118 (70.2 %)	101/119 (84.9 %)†

OAC: *p=0.006 vs smokers
Total: *p=0.027 vs drinkers; †p=0.007 vs smokers
OAT, omeprazole, amoxicillin, and tinidazole; OAC, omeprazole, amoxicillin, and clarithromycin; OCT, omeprazole, clarithromycin, and tinidazole

Table 3. **Efficacy of *H. pylori* eradication in peptic ulcer patients analyzed jointly in relation to smoking and drinking habits.**

	Smokers Drinkers	Smokers Non - drinkers	Non - smokers Drinkers	Non - smokers Non - drinkers
OAT	18/21 (83.2%)*	7/18 (38.9%)	6/9 (66.7%)	21/30 (70.0%)†
OAC	19/24 (79.2%)	13/22 (59.1%)	12/12 (100%)*	21/23 (91.3%)†
OCT	19/22 (86.4%)	8/11 (72.8%)	14/15 (93.3%)	27/30 (90.3%)
Total	56/67 (83.6%)*	28/51 (54.9%)	32/36 (88.9%)†	69/83 (83.1%)‡

OAT: *p=0.002, †p=0.034 vs smokers-non-drinkers
OAC: *p=0.01, †p=0.012 vs smokers-non-drinkers
Total: *p=0.007, †p=0.007, ‡p=0.004 vs smokers-non-drinkers
OAT, omeprazole, amoxicillin, and tinidazole; OAC, omeprazole, amoxicillin, and clarithromycin; OCT, omeprazole, clarithromycin, and tinidazole

Table 4. **Efficacy of *H. pylori* eradication with weak and strong antibacterial regimens in relation to smoking and drinking habits.**

	Smokers Drinkers	Smokers Non - drinkers	Non - smokers Drinkers	Non - smokers Non - drinkers
OAT	18/21 (83.2%)	7/18 (38.9%)	6/9 (66.7%)	21/30 (70.0%)
OAC+OCT	38/46 (82.6%)	21/33 (63.6%)	26/27 (96.3%)*	48/53 (90.6%)†

*p=0.014; †p=0.016 vs OAT
OAT, omeprazole, amoxicillin, and tinidazole; OAC, omeprazole, amoxicillin, and clarithromycin; OCT, omeprazole, clarithromycin, and tinidazole

differences were not significant in the OCT treated group (*Tab. 3*). If the three therapeutic groups were analyzed jointly (OAT+OAC+OCT), the lowest eradication rate was found in smokers-non-drinkers and the difference was significant in relation to the other subgroups (*Tab. 3*).

Comparing the weak (OAT) and pooled strong regimens (OAC + OCT), we found out that in non-smokers-drinkers and non-smokers-non-drinkers strong regimens were more effective than the weak regimen (p=0.014 and p=0.016, respectively), while in smokers-non-drinkers the difference was not significant (p=0.089) (*Tab. 4*). In smokers-drinkers the eradication efficacy was the same in the strong and weak regimens.

DISCUSSION

H. pylori eradication efficacy depends upon a number of factors including smoking and drinking habits. The finding of the current study is that drinking and smoking habits are more useful to predict the outcome of *H. pylori* eradication when studied jointly rather than in a separate analysis.

There are a few mechanisms by which alcohol could affect *H. pylori* in the stomach. Most notable is the direct antibacterial action of alcohol [14], although its indirect effect should also be taken into account; alcohol has been reported to modify gastric emptying and acid secretion [15,16]. Literature data concerning the influence of alcohol consumption model on eradication efficacy are scarce. Our observation that alcohol consumption improves the efficacy of *H. pylori* eradication does not suggest its direct effect, since the subjects did not use alcohol during antibacterial therapy. It may indicate that alcohol has a beneficial impact on eradication therapy either before or after antibacterial treatment, though its mechanism still remains elusive.

Smoking has been identified in many studies as a factor contributing to poor eradication rates of *H. pylori* in different treatment regimens [1-5,8,9]. Many factors that might modify *H. pylori* eradication such as specific and non-specific immune response, mucosal blood flow, gastric mucus secretion, the metabolism of omeprazole in the liver, and the concentration of vitamin C in gastric juice were affected by smoking [17-20].

Formerly, using the same qualifying criteria for smokers and drinkers, we found that a 14-day course with OAT exhibited the eradication efficacy close to the level reached in the current study following the 7-day course in smokers-drinkers and smokers-non-drinkers but higher in non-smokers-drinkers and non-smokers-non-drinkers [3]. This indicates that a 14-day treatment with OAT provides an opportunity to increase eradication efficacy only in the non-smoking population. In the same study, a OAC regimen (7-day course) with a 500 mg daily dose of clarithromycin was tested, and *H. pylori* eradication was less effective compared to current results, when 1000 mg was used as a daily dose. However, this effect was observed in the subgroup of smokers-drinkers only. By comparing the results of the earlier study to the present clarithromycin study, it can be speculated that if smoking and drinking habits are taken into account, eradication efficacy might be comparable in the majority of the subjects even with a lower dose of the drug. Among the therapeutic groups, the OCT regimen appears to be the most universal, since the differences between the subgroups distinguished according to smoking and drinking habits were not significant.

In the past, the majority of studies performed separate analyses of the effect of drinking and smoking habits on *H. pylori* eradication efficacy [1,2,4-7,9,10]. When analyzed jointly, smoking and drinking habits have been shown to have higher predictive values for the outcome of eradication therapy than when analyzed separately. Based on the present data, it can be concluded that in smokers-drinkers all tested regimens (OAT, OAC, OCT) are equally effective, while in smokers-non-drinkers only the OCT regimen, and in non-smokers-drinkers and non-smokers-non-drinkers both OCT and OAC regimens could be recommended.

Some limitations of this study should be mentioned. Because of the second gastroscopy performed 4 weeks after the cessation of eradication therapy to control the ulcer healing, we did not use the urea breath test recommended for the evaluation of post-treatment *H. pylori* status but CLO-test and histology of gastric biopsies. A questionnaire completed by each participant is not an ideal source of data. In our study, we defined subjects as drinkers if they drank weekly 25 g of alcohol or more. However, we are aware that in a questionnaire, subjects sometimes deliberately decrease the amount of alcohol consumption. We defined subjects as smokers if they smoked 5 or more cigarettes per day, thus, among non-smokers were those who smoked 4 or fewer cigarettes, although their number in the whole study population was small (9 subjects). We used this qualifying criteria for smokers assuming that among those who do not smoke, some are passive smokers whose daily exposure to cigarette smoke may be equivalent to smoking 1-4 cigarettes.

Although many other factors than those currently studied affect *H. pylori* eradication from the stomach, our results indicate that acquiring information regarding the smoking and drinking habits of patients may help to establish an optimal course of eradication therapy.

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