

H pylori

Does delayed gastric emptying shorten the *H pylori* eradication period? A double blind clinical trial

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RESULTS: Thirty patients were excluded. Per-protocol analysis showed successful eradication in 53% in group 1, 56% in group 2, 58% in group 3, 33.3% in group 4, 28% in group 5, and 53% in group 6. Eradication rate, patient compliance and satisfaction were not significantly different between the groups.

CONCLUSION: It seems that adding sugar or levodopa or both to anti *H pylori* eradication regimens may lead to shorter duration of treatment.

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Key words: *H pylori*; Gastric emptying; Glucose; Levodopa

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Abstract

AIM: To evaluate the gastric emptying inhibitory effects of sugar and levodopa on *H pylori* eradication period.

METHODS: A total of 139 consecutive patients were randomized into 6 groups. The participants with peptic ulcer disease or non-ulcer dyspepsia non-responding to other medications who were also *H pylori*-positive patients either with positive rapid urease test (RUT) or positive histology were included. All groups were pretreated with omeprazole for 2 d and then treated with quadruple therapy regimen (omeprazole, bismuth, tetracycline and metronidazole); all drugs were given twice daily. Groups 1 and 2 were treated for 3 d, groups 3, 4 and 5 for 7 d, and group 6 for 14 d. Groups 1 to 4 received sugar in the form of 10% sucrose syrup. Levodopa was prescribed for groups 1 and 3. Patients in groups 2 and 4 were given placebo for levodopa and groups 5 and 6 received placebos for both sugar and levodopa. Upper endoscopy and biopsies were carried out before treatment and two months after treatment. Eradication of *H pylori* was assessed by RUT and histology 8 wk later.

INTRODUCTION

H pylori has been implicated as a predisposing factor in gastric cancer, chronic active gastritis, duodenal ulcer, gastric ulcer and gastric lymphoma^[1]. The incidence rate of stomach cancer in Iran is high, well above the world average; it is the most common cancer in males and the third one in females^[2]. Also, the reinfection rate in our country is high enough (20%, 3 years after successful eradication)^[1] to justify wide investigations to find safe and short *Helicobacter* treatments. However, *H pylori* eradication is a multifactor problem and depends on histological findings and ulcer depth, kind of medication and duration of treatment, age, patient compliance, genetic predisposition, geographical area of living, *H pylori* resistance, non-steroid anti-inflammatory drugs (NSAIDs) exposure and finally stomach dynamicity (gastric emptying)^[3-16].

The current approach to the patient with suspected *H pylori* infection consists of an adequate indication to test for the presence of the infection, choice of an appropriate antimicrobial regimen, and education about its use and

side effects, followed by post-therapy testing to confirm cure^[17]. In order to achieve the best results from this approach, patient compliance is of outmost importance and the favored regimen should have the least side effects; otherwise, treatment failure may ensue^[3,18].

H pylori infection plays a role in gastric emptying in type 1 diabetic patients; a delay in gastric emptying is observed with the disappearance of gastritis associated with *H pylori* infection after eradication treatment in those patients^[19]. In contrary, others have shown that *H pylori* infection is not associated with delayed gastric emptying in diabetes^[20,21]. Barnett *et al*^[22] revealed that not only gastroparesis does not predispose to *H pylori* infection or chronic gastritis, but also there is a significantly lower incidence of *H pylori* in individuals with delayed gastric emptying compared to those with normal emptying (5% *vs* 31%, respectively). Moreover, there is no link between anxiety and gastric emptying in chronic duodenal ulcer whether in “fast” emptiers ($t_{1/2}$ less than 90 min) or “normal” emptiers ($t_{1/2}$ more than 90 min)^[23]. Thus, inhibition of gastric emptying by physiologic and pharmacological methods may enhance local delivery of therapeutic agents to the stomach which is a useful strategy in the treatment of *H pylori* infection^[24-27] especially given that *H pylori* is found both attached to mucous cells of the human stomach and under the mucous layer; there is no evidence that attachment of *H pylori* to eukaryotic cells increases their resistance to antibiotics compared with free-floating bacteria^[28] and that omeprazole may displace *H pylori* from the antrum to the stomach body which could interfere with colonization studies in patients receiving the drug^[17]. However, omeprazole has shown no significant effect on solid or liquid gastric emptying in duodenal ulcer^[29]. Also, various alterations of gastric emptying in duodenal ulcer have been demonstrated by different studies^[30-33].

Sugar^[34-39] and levodopa^[40] are among the safest agents that prolong gastric emptying. Glucose in the pylorus has an inhibitory effect on gastric emptying which will be even slower with progressive increases in glucose concentration^[36,37]. Dopamine receptor antagonists (metoclopramide, domperidone) also play an important role in the treatment of gastric emptying disorders^[41].

One of the problems of the currently used anti-*H pylori* drug regimens is their long period of treatment which will be accompanied by more frequent side effects and lower compliance. In this study, we aimed to evaluate the gastric emptying inhibitory effects of sugar and levodopa on *H pylori* eradication period.

MATERIALS AND METHODS

Design

This is a double blind randomized placebo-controlled mono-center trial with 6 parallel groups which was conducted at a university hospital.

Participants

Patients with peptic ulcer disease or non-ulcer dyspepsia non-responding to other medications who were also *H pylori*-positive either with positive rapid urease test (RUT)

or positive histology were included in the study. Written informed consent was obtained from all patients. Since administration of glucose in diabetic patients is not ethical and both gastroparesis and accelerated gastric emptying are seen in these patients^[20,42], those with diabetes mellitus or abnormal fasting blood sugar were not included in the study. The same was applied to those who received NSAIDs or those with other systemic diseases in which quadruple therapy was harmful, such as epilepsy. Exclusion criteria were refusal to undergo re-endoscopy, medication side effects and non-compliance.

Interventions

A total of 139 consecutive patients, who were eligible to undergo *H pylori* eradication based on endoscopic findings, were randomized into 6 groups (Table 1). The subjects' gastrointestinal signs and symptoms were recorded. They were then referred to the clinical pharmacist responsible for prescriptions and completion of the questionnaires on medication side effects and compliance. All groups were pretreated with omeprazole (20 mg bid administered at 6 AM and 6 PM) for 2 d and then, treated with quadruple therapy; i.e. omeprazole (20 mg bid administered at 6 AM and 6 PM), bismuth (240 mg bid administered at 6:35 AM and 6:35 PM), tetracycline (750 mg bid administered at 6:35 AM and 6:35 PM) and metronidazole (500 mg bid administered at 6:35 AM and 6:35 PM); groups 1 and 2 were treated for 3 d, groups 3, 4 and 5 for 7 d, and group 6 for 14 d. Groups 1 to 4 received sugar in the form of 10% sucrose syrup. Since glucose solutions empty biphasically, rapidly for the first minutes, then slowly and proportionately to glucose concentration to deliver glucose calories through the pylorus at a regulated rate (0.4 kcal/min)^[38], we administered 125 cc of solution, 5 min before taking medications (6:30 AM and 6:30 PM) and then, 375 cc with medications. For groups 1 and 3 sinemet (levodopa 125 mg plus 62.5 mg carbidopa) was administered twice daily at 6 AM and 6 PM. Patients in groups 2 and 4 were given placebo for levodopa and groups 5 and 6 received two placebos for sugar and levodopa. All patients were repositioned to prone, supine, left and right lateral decubitus positions and remained in each position for 5 min twice daily at 7 AM and 7 PM. Each of the *H pylori* eradication regimens was followed by famotidine administration for 4 wk (40 mg/d at bedtime).

Outcome measures

Upper endoscopy was carried out before treatment and two months after initiation of treatment. This was to allow for a 6-wk antibiotic-free period and also a 2-wk antisecretory-free period before re-evaluating *H pylori* positivity. Four antral (two for RUT and two for histology) and four corpus (two for RUT and two for histology) biopsy specimens were taken. Eradication of *H pylori* was considered as the main outcome measure which was assessed by RUT and histology 8 wk after initiation of intervention^[43]. Also, peptic ulcer symptoms and signs as well as endoscopic findings were recorded by gastroenterologist before, and 8 wk after initiation of treatment. Medication side effects were asked and recorded before starting and after ending

Table 1 Summary of drug regimens administered double-blindly for 6 groups

Group	Quadruple therapy	Pretreatment with omeprazole for 2 d	Sugar (10% sucrose)	Levodopa (Sinemet)	Placebo for sugar	Placebo for levodopa	Duration of treatment
1	✓	✓	✓	✓			3
2	✓	✓	✓			✓	3
3	✓	✓	✓	✓			7
4	✓	✓	✓			✓	7
5	✓	✓			✓	✓	7
6	✓	✓			✓	✓	14

Table 2 Comparison of the frequencies of peptic ulcer symptoms before and two months after initiation of intervention

	Pyrosis		Abdominal pain		Night awakening pain		Flatulence		Early hungeriness		Early satiety		Fullness		Severe weight loss	
	Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy
Group 1 (SL3)	12	0	16	0	11	0	11	4	13	1	6	1	11	2	4	0
Group 2 (SP3)	9	2	16	2	12	0	10	0	11	2	5	0	12	2	1	0
Group 3 (SL7)	11	3	16	3	15	0	10	1	12	2	7	0	15	4	5	2
Group 4 (SP7)	10	4	16	5	8	1	12	3	7	0	8	0	13	5	4	0
Group 5 (PP7)	14	2	12	2	9	0	13	2	8	1	7	0	14	3	4	0
Group 6 (PP14)	7	3	16	4	8	1	10	2	11	2	4	1	11	3	3	2

Group 1: Quadruple Therapy + Sugar (S) + Levodopa (L) for 3 d; Group 2: Quadruple Therapy + Sugar + Placebo (P) for 3 d; Group 3: Quadruple Therapy + Sugar + Levodopa for 7 d; Group 4: Quadruple Therapy + Sugar + Placebo for 7 d; Group 5: Quadruple Therapy + Placebo + Placebo for 7 d; Group 6: Quadruple Therapy + Placebo + Placebo for 14 d.

the period of each regimen by the clinical pharmacist who was also responsible for inquiring about patient compliance.

Statistical analysis

Kruskal-Wallis test was used to assess differences in eradication rates, rates of medication side effects, frequencies of symptoms and endoscopic signs, patient compliance and satisfaction rates among 6 groups. Wilcoxon test was applied to evaluate the above-mentioned factors within the groups before and after intervention. ANOVA and paired *t*-test were used to find the differences in size and number of ulcers between, and within the groups, respectively. *P* value of less than 0.05 was taken as significant.

RESULTS

Thirty patients were excluded from the study either due to refusal to undergo re-endoscopy (18 patients) or because of medication side effects (11 patients) or non-compliance (interruption of therapy, 1 patient).

The frequencies of symptoms before and after intervention were not significantly different between the groups but were all significant within the groups except for severe weight loss (Table 2). The only side effect showing

significant difference between the groups was nausea ($P < 0.05$), which was least frequent in groups 2 and 1 (56% and 59% respectively) and most frequent in group 6 (79%), 5 (73%) and 3 (70%). This comparison shows that the duration of treatment has a direct relationship with nausea. Other reported side effects included vomiting, anorexia, dry mouth, metal taste, diarrhea, tinnitus, headache, dyskinesia, vertigo, paresthesia and insomnia.

The frequencies of endoscopic results including fundal erythema and ulcer, antral erythema and ulcer, body erythema and ulcer, duodenal erythema and ulcer, ulcer hemorrhage and number and size of ulcers before and after intervention did not show any significant difference between the groups. On the other hand, treatment was significantly effective in all groups because eradication rates, ulcer numbers and ulcer sizes were significantly different within the groups. Index of successful *H. pylori* eradication was defined as negative RUT plus negative pathology report; both were evaluated 8 wk after the first day of intervention. Per-protocol analysis showed successful eradication in 10/19 (53%) patients in group 1, 10/18 (56%) in group 2, 11/19 (58%) in group 3, 6/18 (33.3%) in group 4, 5/18 (28%) in group 5, and 9/17 (53%) in group 6. Intention-to-treat analysis resulted in successful eradication in 10/20 (50%) patients in group 1, 10/20 (50%) in group 2, 11/21 (52.5%) in group 3, 6/20 (30%) in

group 4, 5/20 (25%) in group 5, and 9/20 (45%) in group 6. Eradication rate, patient compliance and satisfaction rates were not significantly different between the groups.

DISCUSSION

Multiple therapeutic regimens involving different combinations of omeprazole, lansoprazole, ranitidine, famotidine, amoxicillin, bismuth, clarithromycin, furazolidone and metronidazole have been tested during various periods of time to determine the optimal regimen(s) for *H pylori* eradication, leading to very different results depending on the geographical area.

A group of gastroenterologists at Jichi Medical School, Japan, instilled triple antibiotics (bismuth subnitrate, amoxicillin and metronidazole) plus pronase into the stomach through a nasally introduced intestinal tube. They showed that 1 to 2 h of topical therapy was a safe, effective, and well-tolerated procedure for the treatment of *H pylori* infection^[25-27]. In another study, by contrast, the 1-h topical method with the same antibiotics and pronase did show low eradication rates in patients with duodenal ulcer. In addition, the topical treatment was characterized by a high rate of side effects and poor tolerance^[44]. On the other hand, Atherton *et al*^[24] demonstrated that dosing after food profoundly prolongs gastric residence of the drug label and also improves intragastric distribution by increasing delivery to the body and fundus. Omeprazole enhanced the effect of food, but had no effect in fasted subjects. Post-prandial dosing may, therefore, be useful for improving delivery of some anti-*H pylori* agents.

Currently, successful cure of *H pylori* infection requires 2 or more antibiotics and the ideal duration of therapy is unknown, but in general, some believe that therapy for one-week or less is not as effective as therapies of longer durations^[3,17,45-51]. Meanwhile, others have shown one-week treatment or even shorter could be curative^[52-65]. Our findings revealed that both 7 d and 14 d of metronidazole-based quadruple therapy with no sugar or levodopa resulted in suboptimal (< 75%)^[66] eradication of *H pylori* infection which can be explained by the high rate of metronidazole resistance in Iran (50%-60%)^[66-68]. Clarithromycin is expensive and has low availability in Iran^[67,69] and there is a nearly 20%-25% rate of resistance to this macrolide^[68,70] despite the fact that clarithromycin has not yet been introduced to the Iranian formulary as a generic drug. Furazolidone may also interfere with levodopa^[71]. In countries with a high prevalence of metronidazole resistance, higher doses of metronidazole^[72] and increased drug concentration in situ^[73] augment the eradication rate of *H pylori*. All of these factors and the 0% dual resistance of *H pylori* to metronidazole and tetracycline^[68] led us to use metronidazole-based quadruple therapy combined with delayed gastric emptying in the current study. We found only one study in the literature using levodopa to delay gastric emptying in the presence of *H pylori* which showed pretreatment with levodopa would not modify either the sensitivity or the specificity of the urease breath test in identifying *H pylori* infection^[74].

In conclusion, shorter duration of *H pylori* eradication in groups 1, 2 and 3 (which included sugar, levodopa or

both) combined with the eradication rate seen with the 14-d regimen (with no sugar or levodopa) indicates that adding sugar or levodopa to anti-*H pylori* regimens through increasing gastric emptying time may lead to short-term treatments. Nonetheless, there were less than 30 subjects in each group which is the minimum requirement for normal distribution. Further evaluation with larger sample size is warranted.

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