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A randomized, double-blind, placebo-controlled trial to assess the essentiality of acid inhibitors for abdominal pain after gastroscopic mucosal biopsy

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Background/aims: *Gastroscopy and gastroscopic mucosal biopsy techniques have become increasingly used as of late for evaluating symptoms presumed to be originated in the upper gastrointestinal tract. Patients often complain however of abdominal pain post-gastroscopic mucosal biopsy, and this study aimed to explore the necessity of acid inhibitors when abdominal pain worsened.* ***Materials and Methods:*** *In this randomized, double-blinded, placebo-controlled study, we screened 272 participants, and ultimately enrolled 200 into the study. These 200 participants were randomly assigned in a 1:1 ratio to receive acid inhibitors (esomeprazole, treatment group, n=100; dose,20 mg/d) or matched placebo (control group, n=100) for 3 days post-gastroscopic mucosal biopsy. The presence of abdominal pain was observed pre-and post-gastroscopy, and the therapeutic effect of esomeprazole was assessed. This study was registered at the Chinese clinical trial registry as ChiCTR-TRC-00000500.* ***Results:*** *Ten subjects were lost to follow-up (4 in treatment group; 6 in the control group). There was no significant difference in the number of subjects with aggravating abdominal pain (treatment 29.2% vs. control 22.3%; p>0.05) between the two groups. Esomeprazole did not significantly (p>0.05) affect the rate of abdominal pain within 24 h (treatment 27.1% vs. control 19.1%), 48 h (treatment 40.6% vs. control 27.7%), and 96 h (treatment 43.8% vs. control 34.0%) on abdominal pain in all in the evaluated subjects. Between the two groups however, a statistically significant difference (p<0.05) was found on overall effective treatment rates at 48 h (treatment 92.9% vs. control 66.7%) and at 96 h (treatment 100% vs. control 81%) in the subjects with worsened abdominal pain.* ***Conclusions:*** *The study suggests that routine prophylaxis with acid inhibitors is not recommended for all patients post-gastroscopic mucosal biopsy, however acid inhibitors should be administered for patients with aggravating abdominal pain.*

Key words: Randomized controlled trial, placebo, gastroscopy, mucosal biopsy, abdominal pain, treatment

Gastroskopik mukozal biyopsi ertesinde, karın ağrısı için asit inhibitörlerinin kullanımının gerekliliğinin araştırıldığı randomize, çift kör plasebo kontrollü çalışma

Giriş ve Amaç: *Gastroskopi ve gastroskopik mukozal biyopsi, üst gastrointestinal sistem kaynaklı semptomların araştırılmasında sıklıkla kullanılmaya başlanmıştır. Ancak hastalar gastroskopik mukozal biyopsiden sonra sıklıkla ağrı duymaktadırlar ve bu çalışma asit inhibitörlerinin bu hastalarda artan karın ağrısını bastırmaktaki rolünü incelemektedir.* ***Gereç ve Yöntem:*** *Bu randomize, çift-kör, plasebo kontrollü çalışmada, 272 hasta tarandı ve 200'ü çalışmaya dahil edildi. Rastgele olarak 1:1 oranında; 3 günlük asit inhibitörü (esomeprazole 20 mg/gün, tedavi grubu, n=100) ve plasebo olmak üzere iki gruba ayrıldılar. Karın ağrısı gastroskopi öncesinde ve ertesinde gözlendi ve esomeprazolun tedavi etkinliği "intention to treat" analizi ile incelendi. Çalışma, Çin Klinik Araştıma Sicilinde ChiCTR-TRC-00000500 olarak kaydedildi.* ***Sonuçlar:*** *Toplam 10 (4 tedavi ve 6 kontrol) hasta izlemde kaybedildi. Karın ağrısında artış olan hasta sayısında gruplar arası anlamlı farklılık tespit edilmedi (tedavi: %29,2 - kontrol %22,3; p>0,05). Esomeprazole ilk 24 saatteki (tedavi: %27,1 - kontrol %19,1), 48 saatteki (tedavi %40,6 - kontrol %27,7) ve 96 saatteki (tedavi %43,8 - kontrol %34) karın ağrısı sıklığında etkili bulunmadı. Buna karşılık, karın ağrısında artış olan hastalarda tedavinin 48. saatinde ve (%92,9 - %66,7) 96. saatinde (%100 - %81) karın ağrısı sıklığında anlamlı azalmaya neden olduğu tespit edildi (p<0.05).* ***Sonuç:*** *Bu çalışmanın sonuçlarına göre rutin asit inhibitörü tedavisi gastroskopik mukozal biyopsi yapılan hastalara rutin olarak önerilmemelidir ancak karın ağrısında artış olan hastalara önerilebilir.*

Anahtar kelimeler: Randomize kontrollü çalışma, plasebo, gastroskopi, mukozal biyopsi, abdominal ağrı, tedavi

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INTRODUCTION

With the continued development of new diagnostic technologies for gastrointestinal endoscopy, electronic gastroscopy techniques are increasingly being utilized. Such techniques can be used for the detection of mucosal lesions of the esophagus, stomach, and duodenum, while concurrent mucosal biopsies can be performed to achieve a histological diagnosis. It has been determined from previous clinical studies that diagnostic gastroscopy is a relatively safe procedure (1). Wolfsen et al. reported that complications after diagnostic gastroscopy were related to anesthesia in 2 of the 11.114 patients with or without biopsy, no perforations, no hematemesis, and no deaths were reported. However, patients often complain of abdominal pain, distention, and discomfort after gastroscopy with mucosal biopsy. No reports have been published in regards to the incidence of abdominal pain, distention, and discomfort after gastroscopy with mucosal biopsy. There also have been no studies concerning intervention with medication of acid inhibitors.

Proton pump inhibitors (PPI) reduce gastric acid secretion through inhibition of the H^+/K^{+-}ATPase in the gastric parietal cells (2-6), and PPI's are widely used in clinical practice to treat acid-related diseases (7). It has been reported that PPI can also protect the gastric mucosa (8-9).

This study aimed to explore the incidence of abdominal pain, and investigate the need of acid inhibitors after gastroscopic mucosal biopsy. We chose to use esomeprazole, a routinely utilized PPI, for the intervention in this study.

MATERIALS and METHODS

Subjects

Between May and June of 2010, we conducted a randomized, double-blinded, placebo-controlled exploratory study. We included subjects who required gastroscopy aged between twenty and fifty years of age who were based in a military unit health examination facility. Subjects were eligible for enrollment into the study if there was an indication for gastroscopy which included chronic gastritis (10) without peptic ulcer, reflux esophagitis, upper intestinal carcinoma, upper intestinal bleeding, pyloric obstruction, and esophagogastric varices. The exclusion criteria to this study were as follows: severe cardiac, pulmonary or hepatic dysfunction; pregnant or lactating women; patients who had taken a proton pump inhibitor, H_2 receptor antagonist or mucosal protective agent within the previous 2 weeks; any history of esophageal or intestinal surgery; and any known allergic reaction to PPI. Subjects were also excluded from the study if they failed to complete treatment over the study period, their participation in the study constituted a significant risk to their health, or if they failed to complete scheduled follow-up.

Written informed consent was obtained from all subjects. The trial was granted approval by the Ethics Committee of the People's Liberation Army (PLA) General Hospital. Researchers abided by the Declaration of Helsinki and Chinese regulations on clinical trials.

Randomization

Randomization into the treatment or control groups was performed automatically by a computer. Groups were created in a 1:1 ratio, and subject randomization was recorded within sealed opaque envelopes by assistants who were not involved with the study. Clinical investigators and subjects were blinded with regards to the grouping, and the esomeprazole and placebo tablets had the same appearance.

Gastroscopy

Gastroscopies were performed with a GIF-Q240 electronic gastroscope (Olympus, Japan) used by the same endoscopist with a 15 yr clinical experience. Subjects fasted prior to the procedure for six to eight hours, and were given 5 ml of 5% lidocaine (Shandong Hualu Pharmaceutical Co.) orally for pharyngeal anesthesia. Patients also received 5 ml simethicone emulsion (Berlin-Chemie AG) 10 minutes prior to the gastroscopy as an anti-bloating solution (11).

All subjects were positioned onto their left side, and the operator inserted the endoscope under direct vision. Two biopsies were taken two centimeters from the pyloric antrum; one was taken from the greater curvature, and the other biopsy was taken from the lesser curvature in every subject diagnosed with chronic gastritis.

Post- gastroscopy care and interventions

Esomeprazole was given as a single 20 mg tablet (AstraZeneca Pharmaceuticals LP), and the placebo tablets were made by the Department of Pharmacy of the PLA General Hospital. Both esomeprazole and the placebo were orally administered daily at 2 hours, 24 hours, and 48 hours post-gas-

troscopy. No other medications were taken during this time by any of the participants. Medications were discontinued if severe adverse events occurred.

Investigators recorded the severity scores of abdominal pain that were reported by subjects pre-gastroscopy and daily at 18:00 on the day of gastroscopy, 24 hours, 48 hours, and 96 hours post-gastroscopy, and then calculated the number of subjects who developed worsening or improving abdominal pain. The scoring system was as follows: 0: no pain; 1: slight pain that only recognized when directly asked; 2: mild pain that did not affect activities of daily living; 3: severe pain that affected normal life (12).

The absence or presence of abdominal distention and discomfort reported by the subjects was recorded pre-gastroscopy and at 18:00 on the day of the gastroscopy.

A measurement of the degree of therapeutic effect of the medical intervention was recorded as follows: significant effect: pain score decreased by 2; effective: pain score decreased by 1; non-effective: pain score remained unchanged; aggravating: pain score increased. The overall efficacy rate was therefore calculated with the following equation: (significant effect + effective cases) divided by total cases.

Our predefined primary endpoints were changes of abdominal pain severity score at 24 hours, 48 hours, and 96 hours post-gastroscopy. Secondary endpoints were changes from baseline in abdominal distention and discomfort at 18:00 in the day of the gastroscopy, and after the procedure.

Statistical analysis

Pre-specified sample-size calculations, based on the efficacy rate of esomeprazole on abdominal pain due to a peptic ulcer showed an efficacy of 90% (12), compared with a 50% response to the placebo (13,14). Assuming that α is 0.05 and B is 0.20, and the power of the test is 80%, at least twenty-two samples were needed from each of the groups. During our pre-test calculations, the rate of worsening abdominal pain was 29%, and thus seventy-three subjects were required. We decided to enroll 100 in each group to minimize the effect of data loss.

Data was analyzed using SPSS 17.0 software, and the significance of any differences in categorical data was determined using the Student's t-test, the chi-square test (Fisher's exact test) and the Wilcoxon test. Results were reported as means with standard deviations. The null hypothesis was rejected if p-values were ≤0.05, or with a=0.05 in the two-sided test.

Based on intention-to-treat (ITT) and per protocol population set (PPS) analysis, subjects in this trial were analyzed in the groups to which they were randomized, regardless of whether they received or adhered to the allocated intervention. This study was registered at the Chinese Clinical Trial Registry, with an identifying number of ChiCTR-TRC-00000500.

Role of the funding source

This randomized control trial was an academia-initiated exploratory study. No external sponsor was involved in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors take full responsibility for the contents of the article.

RESULTS

Figure 1 shows the demographic profile of the trial participants, and these demographics were comparable between the two groups. Among the 272 participants initially screened, 200 subjects were enrolled into the randomization process. Overall, 190 patients entered the evaluation. Ten subjects were lost to follow-up, including four patients in the esomeprazole group, and six patients in the placebo group. Figure 1 is a flow chart of participants through the study protocol (Figure 1). Baseline data between the two groups were comparable (Table 1).

No statistically significant difference in the levels of abdominal discomfort or distension was found between the pre- and post-gastroscopy inter-group, and between the two groups after gastroscopy (p>0.05; Table 2).

No significant difference was found in regards to the severity of abdominal pain between the two groups after gastroscopy (p>0.05; Table 3). Severity of abdominal pain was significantly different between the pre- and post-gastroscopy inter-group (p<0.05; Table 3).

An analysis of the therapeutic effect on esomeprazole on abdominal pain found no statistically significant difference (p>0.05) between the two groups at 24 hours, 48 hours, and 96 hours after gastroscopy in all of the evaluable subjects (Table 4).

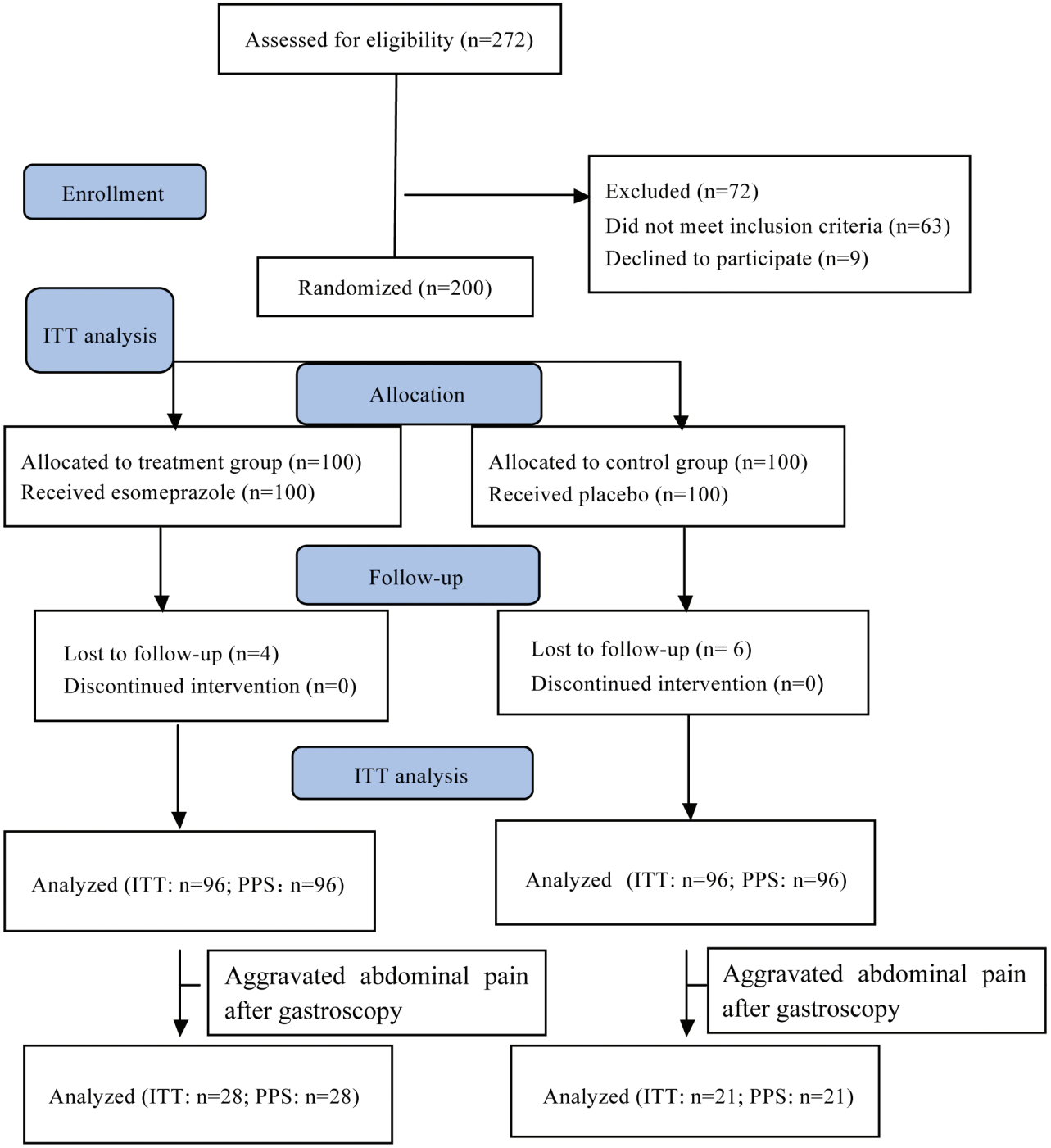

Figure 1. Flow diagram of the randomized-controlled trial.

Table 5 depicts the therapeutic effect of subjects with worsening abdominal pain after gastroscopy. No statistically significant difference ($p>0.05$) was found in the effect of abdominal pain between the treatment and control groups at 24 hours after gastroscopy, however statistically significant differences ($p<0.05$) were found at 48 hours and at 96 hours post-gastroscopy. There were no noted side effects of the medication observed in this trial.

DISCUSSION

Gastroscopy is not solely used to observe morphological changes of mucosa in the esophagus, stomach, or the duodenum. It may also be used to ob-

Table 1. Baseline demographic data of the two groups.

Parameter	Esomeprazole	Placebo	Statistical Value	p
Case	96	94		
Sex (M/F)	96/0	94/0	1,03	0,50
Mean age (x±s, yr)	29,03±5,583	28,73±5,495	0,37	0,71
Abdominal pain score (0/1/2/3)	70/22/4/0	63/29/2/0	0,76	0,48
Distension (absent/present)	76/20	64/30	3,01	0,08
Discomfort (absent/present)	73/23	65/29	1,14	0,29

Table 2. A comparison of the rates of abdominal discomfort (disc) and distension (dist) between the two groups in this study before and after gastroscopy.

		Pre- gastroscopy (absent/present)		Post- gastroscopy (absent/present)		Inter-group comparison				Aggravating rate		Among group			
						Disc		Dist		Disc	Dist	Disc		Dist	
Group	Cases (n)	Disc	Dist	Disc	Dist	X^2	*p*	X^2	*p*			X^2	*p*	X^2	*p*
Eso	96	73/23	76/20	65/31	69/27	1,65	0,2	1,38	0,24	22/96	11/96				
Placebo	94	65/29	64/30	60/34	57/37	0,27	0,6	1,14	0,29	20/94	16/94	0,07	0,79	1,27	0,27
Total	190	138/52	140/50	125/65	126/64					42/190	27/190				

Eso: Esomeprazole.

Table 3. A comparison of abdominal pain between both groups in this study before and the day after gastroscopy (data shown in terms of none/ slight/ mild/ severe).

Group	Case (n)	Pre-gastroscopy	Day 1 post-gastroscopy	Inter-group comparison		Rate of worsening pain	Among group comparison	
				Z	*p*		Z	*p*
Eso	96	70/22/4/0	49/43/4/0	3,55	0,00	28/96		
Placebo	94	63/29/2/0	51/40/3/0	2,14	0,016	21/94	1,03	0,303
Total	190					49/190		

Eso: Esomeprazole.

Table 4. A comparison of the therapeutic effects of esomeprazole between the two groups among all patients (data shown in terms of significant/ effective/ non-effective/ aggravating effects of treatment).

Group	Cases (n)	24 h post-gastroscopy	Among-group comparison		48 h post-gastroscopy	Among-group comparison		96 h post-gastroscopy	Among-group comparison	
			Z	*p*		Z	*p*		Z	*p*
Esomeprazole	96	1/25/70/0			1/38/57/0			2/40/54/0		
			1,44	0,15		1,92	0,055		1,464	0,143
Placebo	94	0/18/75/1			0/26/68/0			0/32/62/0		

Table 5. A comparison of the effects between the two groups among patients with severe abdominal pain after gastroscopy (data presented in terms of numbers of patients with significant/ effective/ non-effective/ aggravating effects).

Group	Cases (n)	24 h post-gastroscopy	Among-group comparison		48 h post-gastroscopy	Among-group comparison		96h post-gastroscopy	Among-group comparison	
			Z	*p*		Z	*p*		Z	*p*
Esomeprazole	28	0/19/9/0			0/26/2/0			1/27/0/0		
			1,51	0,131		2,32	0,02		2,48	0,01
Placebo	21	0/10/10/1			0/14/7/0			0/17/4/0		

tain histological evaluations utilizing mucosal biopsies. Gastroscopy has been shown to be the best examination for the diagnosis of lesions of the upper digestive tract, and complications are minimized if strict indications and procedures are adhered to.

It is evident from previous clinical studies that diagnostic gastroscopy is a relatively safe procedure

(1). Wolfsen et al. reported that complications after diagnostic gastroscopy were related to anesthesia in only 2 of the 11.114 patients with or without biopsy. There have been reports concerning rare or severe complications, such as bleeding, perforation, aspiration pneumonia, and Mallory-Weiss syndrome (15-18). Many minor adverse post-gastroscopy reactions which had no life-threatening consequences, but however brought down the quality of life were disregarded. In part due to the mucosal damage and erosions caused by the acquisition of biopsies as well as minor traumas including mechanical abrasions to the gastric mucosal barrier, excessive inflation, and inadequate deflation after gastroscopy with gastroscopic mucosal biopsies, often times patients complain of abdominal pain, distension and discomfort post gastroscopy.

It has been generally accepted that gastric acid and pepsin can cause erosions in the mucosa of the stomach and duodenum, and inhibition of gastric acid secretion contributes to healing of damaged mucosa. Proton pump inhibitors (PPI), which reduce gastric acid secretion through inhibition of the H^+/K^{+-}ATPase in gastric parietal cells (2-6) has been adopted by many clinicians in clinical practice to treat acid-related diseases (7). This is due in part because PPI therapy is considered to be practical, safe, and cost-effective (19-20). One report has identified that PPI protects the gastric mucosa (8) as well as decreases damage to the mucosa by non-steroidal anti-inflammatories (NSAIDs) (9, 21-24). In this study esomeprazole of the PPI family was chosen for our treatment group.

In order to retain homogeneity, we included male subjects between the ages of twenty and fifty who required gastroscopy, who were in a military unit, and who had a similar living environment. As observed in the study, the rate of worsened abdominal pain after gastroscopy with mucosal biopsy was noted to be 25.8% (49/190; treatment 28/96 vs. control 21/94; Table 3), distension 14.2% (27/190; treatment 11/96vs. control 16/94; Table 2) and discomfort 22% (42/190; treatment 22/96 *vs.* control 20/94; Table 2), but no statistically significant difference existed between the two groups ($p>0.05$). When we compared these rates to the pre-gastroscopy and post-gastroscopy inter-group, no statistically significant difference was noted for abdominal distension, nor discomfort ($p>0.05$), however a significant difference was found in the degree of abdominal pain ($p<0.05$). These findings suggest that routine gastroscopy with mucosal biopsy do not have an obvious effect on abdominal distention and discomfort, but can lead to or potentially aggravate abdominal pain, with an incidence of 25.8%. Therefore, we believe that an intervention medication is not needed for patients who feel abdominal distention and discomfort after routine gastroscopy with mucosal biopsy.

When the therapeutic effect of esomeprazole on abdominal pain of all the evaluable subjects was assessed, the rate of overall efficacy in the esomeprazole group was 27.1% (26/96), 40.6% (39/96), 43.8% (42/96) at 24 hours, 48 hours, and 96 hours after gastroscopy with mucosal biopsy, respectively, while rates in the placebo group were respectively 19.1% (18/94), 27.7% (26/94), and 34.0% (32/94) at these same time points, respectively. There was no statistically significant difference between the two groups ($p>0.05$). These results indicate that both esomeprazole and placebo have the same effect on abdominal pain after gastroscopy with mucosal biopsy (Table 4).

The rates of overall efficacy of worsening abdominal pain subjects at 24 hours after gastroscopy were not found to be different between the treatment (19/28) and control groups (10/21; $p>0.05$); statistically significant differences were found at 48 hours (treatment 26/28 vs. control 14/21%) and 96 hours (treatment 28/28 vs. control 17/21) after gastroscopy (Table 5). These results indicate that esomeprazole, which is able to reduce gastric acid (2-6) and protect gastric mucosa (8) was more efficacious in the treatment group of worsening abdominal pain after gastroscopy with mucosal biopsy.

In conclusion, routine prophylactic acid inhibitors should not be recommended for all patients after gastroscopy with mucosal biopsy, however acid inhibitors should be administered for those with obvious or severe abdominal pain. In conclusion, the results of this study indicate that oral esomeprazole at a dose of 20 mg/d for a short period can alleviate abdominal pain post-gastroscopy.

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REFERENCES

1. Wolfsen HC, Hemminger LL, Achem SR, et al. Complications of endoscopy of the upper gastrointestinal tract: a single-center experience. Mayo Clin Proc 2004;79:1264-7.
2. Shah SA, Sander S, Coleman CI, et al. Delivery of esomeprazole magnesium through nasogastric and gastrostomy tubes using an oral liquid vehicle as a suspending agent in vitro. Am J Health Syst Pharm 2006;63:1882-7.
3. Wilder-Smith CH, Röhss K, Nilsson-Pieschl C, et al. Esomeprazole 40 mg provides improved intragastric acid control as compared with lansoprazole 30 mg and rabeprazole 20 mg in healthy volunteers. Digestion 2003;68:184-8.
4. Miner P Jr, Katz PO, Chen Y, et al. Gastric acid control with esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole: a five-way crossover study. Am J Gastroenterol 2003;98:2616-20.
5. Röhss K, Wilder-Smith C, Nauclér E, et al. Esomeprazole 20 mg provides more effective intragastric acid control than maintenance-dose rabeprazole, lansoprazole or pantoprazole in healthy volunteers. Clin Drug Investig 2004;24:1-7.
6. Klotz U. Proton pump inhibitors--their pharmacological impact on the clinical management of acid-related disorders. Arzneimittelforschung 2009;59:271-82.
7. Saccar CL. The pharmacology of esomeprazole and its role in gastric acid related diseases. Expert Opin Drug Metab Toxicol 2009;5:1113-24.
8. Genta RM, Rindi G, Fiocca R, et al. Effects of 6-12 months of esomeprazole treatment on the gastric mucosa. Am J Gastroenterol 2003; 98:1257-65.
9. Koch TR, Petro A, Darrabie M, et al. Effects of esomeprazole magnesium on nonsteroidal anti-inflammatory drug-gastropathy. Dig Dis Sci 2005;50:86-93.
10. Zhang WD, Chen ZS, Wei BH. Schedule for diagnosis and treatment of chronic gastritis with integrative Chinese and Western medicine (draft). Zhongguo Zhong Xi Yi Jie He Za Zhi 2005;25:172-5.
11. Keeratichananont S, Sobhonslidsuk A, Kitiyakara T, et al. The role of liquid simethicone in enhancing endoscopic visibility prior to esophagogastroduodenoscopy (EGD): A prospective, randomized, double-blinded, placebo-controlled trial. J Med Assoc Thai 2010;93:892-7.
12. Liang XY, Gao Q, Gong NP, et al. Comparison of esomeprazole enteric-coated capsules vs esomeprazole magnesium in the treatment of active duodenal ulcer: a randomized, double-blind, controlled study. World J Gastroenterol 2008; 14:1941-5.
13. Beecher HK. The powerful placebo. AM Med Assoc 1995;159:1602-6.
14. Wlach H, sadaghiani C, Dehm C, et a1. The therapeutic effect of clinical trials: understanding placebo response rates inclinical trials-a secondary analysis. BMC Med Res methodol 2005;5:26.
15. Zubarik R, Eisen G, Mastropietro C, et al. Prospective analysis of complications thirty days after outpatient upper endoscopy. Am J Gastroentero 1999;94:1539-45.
16. Macmillan R, Hocutt JE, Coleman WH. EGD by family physicians: a national multisite study of 717 procedures. J Am Board Fam Prac 1990;3:73-9.
17. Lipper B, Simon D, Cerrone F. Pulmonary aspiration during emergency endoscopy in patients with upper gastrointestinal hemorrhage. Crit Care Med 1991;19:330-3.
18. Penston JG, Boyd EJS, Wormsley KG. Mallory-Weiss tears occurring during endoscopy: a report of seven cases. Endoscopy 1992;24:262-5.
19. Davies M, Wilton LV, Shakir SA. Safety profile of esomeprazole: results of a prescription-event monitoring study of 11595 patients in England. Drug Saf 2008;31:313-23.
20. Kale-Pradhan PB, Landry HK, Sypula WT. Esomeprazole for acid peptic disorders. Ann Pharmacother 2002;36:655-63.
21. Morgner A, Miehlke S, Labenz J. Esomeprazole: prevention and treatment of NSAID-induced symptoms and ulcers. Expert Opin Pharmacother 2007;8:975-88.
22. Colucci R, Fornai M, Antonioli L, et al. Characterization of mechanisms underlying the effects of esomeprazole on the impairment of gastric ulcer healing with addition of NSAID treatment. Dig Liver Dis 2009;41:395-405.
23. Hawkey C, Talley NJ, Yeomans ND, et al. Improvements with esomeprazole in patients with upper gastrointestinal symptoms taking non-steroidal antiin flammatory drugs, including selective COX-2 inhibitors. Am Gastroenterol 2005;100:1028-36.
24. Yeomans N, Lanas A, Labenz J, et al. Efficacy of esomeprazole (20 mg once daily) for reducing the risk of gastroduodenal ulcers associated with continuous use of low-dose aspirin. Am J Gastroenterol 2008;103:2465-73.