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Hypersenstivity to Acid in Ulcer-like Functional Dyspepsia

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Objectives : *The mechanism of pain sensation in patients with ulcer-like functional dyspepsia is unclear and there are no guidelines for its treatment. Whilst much research and many pharmacological treatments have provided symptomatic relief of ulcer-like functional dyspepsia through control of acid secretion, the role of acid in ulcer-like functional dyspepsia is unknown. We carried out this study to investigate the role of hypersensitivity to acid in the sensation of pain in ulcer-like functional dyspepsia by direct administration of acid into stomach.*

Methods : *Twelve patients with ulcer-like functional dyspepsia(5 male, 7 female, mean age 41.0 years old, 7 with mild chronic superficial gastritis, 2 with metaplastic gastritis and 3 with normal endoscopic findings) and seven healthy control subjects(3 male, 4 female, mean age 36.0 years old, 7 with normal endoscopic findings) participated in the study. After overnight fasting, a nasogastric sump tube was inserted and its tip was positioned in the antrum under fluoroscopic guidance. Normal saline or 0.1N hydrochloric acid was administrated in random and single blind cross over fashion. The test was considered positive only if similar pain developed-similar to that experienced by the patient under nonstudy condition- during the administration.*

Results : *Five patients(41.7%) developed pain with 0.1N hydrochloric acid administration, but none with normal saline($p<0.05$). None of the healthy controls developed pain upon administration of 0.1N hydrochloric acid or normal saline.*

Conclusion : *We suggest that acid hypersensitivity plays a role in the sensation of pain in ulcer-like functional dyspepsia.*

Key Words : *Acid hypersensitivity, Ulcer-like functional dyspepsia*

INTRODUCTION

Ulcer-like functional dyspepsia is a symptom complex characterized by epigastric discomfort, burning and/or abdominal pain at times associated with eating and often accompanied by belching, nausea and/or vomiting[1]. The origin of gastric pain has puzzled researchers and clinicians for over 60 years. The pathogenesis of functional dyspepsia is poorly understood and there are no clear guidelines for its treatment. Drugs that decrease gastric acidity have been used commonly for the symptomatic treatment of pain, but the results have been variable[2-7]. Hypotheses regarding pathogenesis can be divided into two groups : those that ascribe it to a disturbance in gastric motillity and those that ascribe it to an imbalance in acid secretion[8, 9]. Infusing acid into the stomach of ulcer patients was reported to lead to gastric pain in early reports[10-12]. However, later studies have failed to demonstrate pain despite infusion of large quantities of highly acidic solutions. Thus, the role of acid in eliciting gastric

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pain is less clear than was previously supposed. However, in recent reports, cimetidine has been found to be effective in providing symptomatic relief of pain in patients with ulcer-like functional dyspepsia[6, 7], suggesting that symptoms in these patients may be related to gastric acid. There was no significant correlation between pain and acid secretion in functional dyspepsia. In order to test this hypothesis, we carried out a single blind cross over study to determine whether gastric acidification produced symptoms in patients with ulcer-like functional dyspepsia.

MATERIALS AND METHODS

1. Subjects

Twelve patients having ulcer-like functional dyspepsia were studied. Seven healthy subjects were studied and served as the control group. All had upper gastrointestinal endoscopies. The patients must have had pain or discomfort centered in the upper abdomen which lasted for three months or a longer period of time. Upper abdominal pain must be the predominant complaint and three or more of the following were necessary; pain that was well localized in the epigastrium, relieved by food, relieved by antacids and/or H2 blockers, occurring before meals or when hungry, wakens the patients from sleep at times, or periodic pain with remission and relapses. None of the patients had a history of biliary tract disease esophagitis, ulcer disease, or change in bowel habits. There was no endoscopic evidence of esophagitis, gastric or duodenal ulcer disease. Of the 12 patients studied, 5 men and 7 women, age raneed from 30 to 72 years. The control group consisted of 7 healthy subjects, 3 men and 4 women, and their age ranged from 25 to 48 years (Table 1).

Table 1. Characteritics of Patients with Ulcer-like Dyspepsia and Control Subjects

	Ulcer-like FD[a]	Control
No	12	7
Sex(M/F)	5/7	3/4
Age(yr)		
Mean±SD	41.0±3.7	36.0±5.6
histologic finding	normal(3) CSG[b](7) metaplastic gastritis(2)	normal(7)

[a] FD : functional dyspepsia
[b] CSG : chronic superficial gastritis

2. Study Design

After overnight fasting, the patients underwent upper fiberoptic endoscopy under light anesthesia, consisting of 2% lidocaine spray to the back of the throat and hyoscine-N-butylbromide intramuscularly. After endoscopic examination, a nasogastric sump tube was passed and its tip positioned in the dependent portion of the gastric antrum under fluoroscopic guidance. No premedication was given. Two solutions (0.1N HCl and normal saline), prepared in advance and coded were administered through the sump tube in a randomized, single blind technique. Two hundred mililiters, 10ml/min, of these solutions were infused continuously for 20 minutes. A total of 200ml of each solution was infused over a period of 20 minutes followed by a rest period of 10 minutes before instillation of the next solution. Subjects were asked in 5-minute intervals to indicate whether abdominal pain developed, exacerbated or improved, and whether the pain was similar to the usual in terms of site, severity and character. The test was considered positive only when similar pain was previously experienced and the pain lasted for at least 5 minutes. If positive, then the infusion was discontinued.

RESULTS

1. Responses to acid or saline

Of 12 patients, 5 developed pain during the acid infusion that was similar to their usual pain in term of intensity or severity (41.7%) (Fig. 1). No patient experienced pain on saline infusion. Using Fishers exact test, this difference was statistically significant ($p<0.05$). Patients who showed positive response to acid infusion did not differ from those with negative reponse in terms of age, duration of disease or type and severity of symptoms. In patients who showed a positive response to acid

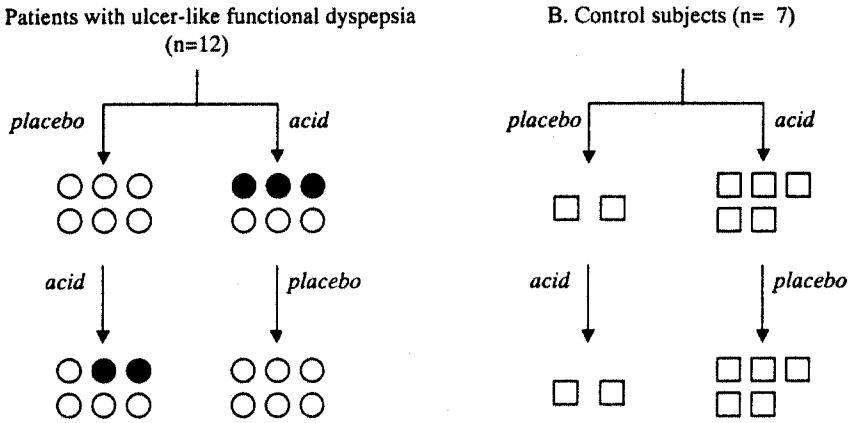

Fig. 1. A. of 12 patients with ulcer-like functional dyspepsia, 5 patients developed pain during the acid infusion and no patient developed symptoms on saline infusion in a randomized single blind technique
B. None of the control subjects showed positive response during acid or saline infusion in a randomized single blind technique($p<0.05$).
○; patient with ulcer-like functional dyspepsia who showed negative response during acid or saline infusion
●; patient with ulcer-like functional dyspepsia who showed positive response during acid or saline infusion
□; control subject who showed negative response during acid or saline infusion

infusion, the pain occurred within 5 minutes of starting the infusion.

None in the control group showed positive response during acid or saline infusion. The difference in the responses to acid infusion between the patients and the control group was statistically significant ($p<0.05$) (Fig. 2).

DISCUSSION

Most patients diagnosed as having dyspepsia do not have a chronic peptic ulcer or any recognized anatomicopathologic entity; thus, they are classified as having functional dyspepsia. As a working definition, especially patients with ulcer-like dyspepsia have symptoms that prompt a physician to believe an ulcer may be present, but no ulcer is found on evaluation[13]. The prevalence of ulcer-like functional dyspepsia ranged from 20-30% and annual incidence of over 1%[14]. It is at least twice as common as peptic ulcer disease. Ulcer-like functional dyspepsia is not only common but costly, because it often results in empric treatment intended to control gastric acidity including antacid or H_2 receptor blocker. Because treatment of this chronic disorder has been inadequate, studies of the pathogenesis are important. Peptic ulcer disease is considered to be closely related to gastric acid secretion. It has been postulated that acid oozing through altered mucosa produces abdominal pain[15]. Two questions need to be considered: Is gastric acid secretion abnormal in ulcer-like functional dyspepsia, and does acid bathing of the mucosa ever cause symptoms? Gastric acid secretion was not increased in patients with ulcer-like dysyepepsia, and there were no differences in acid secretion between patients with typical ulcer-like functional dyspepsia[16]. Most studies have confirmed that acid secretion is normal in patients with ulcer-like functional dyspepsia[17]. In fact, negative correlation between peak acid secretion and severity of symptoms has been reported[18]. It is uncertain if hydrochloric acid bathing of the mucosa causes symptoms, even in the presence of peptic ulcer. Early studies by Palmer and Pickering confirmed that duodenal ulcer pain is related to gastroduodenal acidity. Palmer[10] instilled acid into the

stomach or duodenum in peptic ulcer patients whose last episode of pain occurred within the last 24 hours. Typical ulcer pain occurred in 314 out of 324 instances. Up to 600ml 0.5% hydrochloric acid (0.135N) was given. However, in some instances, it took more than one hour before pain occurred. Bonney and Pickering[11] instilled up to 300ml 0.1N hydrochloric acid into the stomach of peptic ulcer patients during days when they experienced spontaneous ulcer pain. In eight out of nine cases, pain was reproduced. Pain was not induced by similar amounts of normal saline. Kang et al reported that 33% of patients with duodenal ulcer experienced pain during infusion of 10mmol of hydrochloric acid over five minutes. Of those who did not experience pain after the first 10mmol of acid, 21% developed pain when an additional 10mmol of acid was given[19].

In a study by Bates et al[20], an injection of pentagastrin does lead to increased reports of epigastric pain in patients with non-ulcer dyspepesia. Misra[21] et al study showed that 22% of patients with non-ulcer dyspepsia developed pain on acid infusion. These patients did not develop pain during infusion with similar or even greater volume of saline, suggesting that pain was due to acidic pH and not due to volume distension of the stomach. Acid may be of importance in the genesis of symptoms in these patients as suggested by the pain induced due to acid infusion which was similar to the usual pain experienced by these patients. But, there are little data on direct instillation of acid in ulcer-like functional dyspepsia. In our study, 41.7% of the patients experienced pain during infusion of 0.1N of hydrochloric acid within five minutes. We included the patients with ulcer-like functional dyspepsia only. This explains why more of our patients experienced pain than others have reported under similar circumstances. The pathogenesis of ulcer pain in the remaining 58.3% of patients remains unclear. Altered gastroduodenal motility or spasm are other factors that may contribute to the pathogenesis of pain. Wilson[22] had observed that pain in the duodenal ulcer was associated with sustained contraction of the duodenal bulb. Ruffin[23] found that duodenal ulcer pain was invariably related to delay of gastric evacuation or spasm at the ulcer site. Texter[8] et al reported that ulcer pain was accompanied by increased intraluminal pressure and delayed emptying time, while relief of pain accompanied resumption of gastric evacuation. But these were, at most, minor factors and further studies are required in this area.

In conclusion, our findings suggest that gastric acid plays a role in the genesis of symptoms in some patients with ulcer-like functional dyspepsia, even though the clinical significance of these observation remains to be tested. Patients, in whom the pain is related to acid, may be expected to respond to treatment with H_2 receptor anatagonists. Obviously, a correlation of therapeutic efficacy of H_2 receptor anatagonists to the results of acid infusion would be interesting.

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