The efficiency of sucralfate in corrosive esophagitis: A randomized, prospective study

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Background/aims: Background / aims: Ingestion of a chemical agent is a serious problem, and several treatment protocols to prevent stricture formation have been proposed. We conducted a randomized prospective study to evaluate the effectiveness of oral intensive sucralfate plus conventional therapy compared to conventional therapy alone. Methods: Fifteen patients with stage 2b and 3 corrosive esophagitis admitted to our gastroenterology, general surgery and intensive care units between 2004 and 2007 were included. Patients were divided into two groups. The patients in the first group (n=8) received intensive sucralfate therapy plus conventional therapy, while the other group (n=7) received only conventional therapy. We performed upper endoscopic procedures on days: 0, 21, 45, 90 and 180 to identify the emergent complications. Results: In the first group, only one patient had stricture formation, allowing passage of a 9.2 mm endoscope and causing no dysphagia, on day 45. There was no progression in the stricture on follow-ups at the 3rd and 6th months. In the second group, 6 patients had stricture formation causing narrowing and dysphagia. Conclusions: Intensive sucralfate therapy may decrease the frequency of stricture formation in patients with advanced corrosive esophagitis. Further studies with large groups of patients are required to confirm our findings.

Key words: Corrosive esophagitis, esophagitis, esophageal stricture, sucralfate, intensive therapy

INTRODUCTION

Exposure to chemical agents is a serious problem in different age groups. While ingestion occurs as an accidental exposure in children, adult exposure is mostly intentional, although it may also occur as an accident. In adults, corrosive esophagitis is usually seen in the 2nd and 3rd decades. The consequences of ingestion are more devastating if it occurs intentionally. In underdeveloped and developing countries like ours, the adult population can ingest accidentally, since chemical agents are sold in ordinary bottles without any precautions and, furthermore, these toxic agents can be preserved in refrigerators by the families (1). According to one study, among the people who ingested chemical agents in our country, 83.7% of males and 61% of females ingested them accidentally (2). Ingestion of chemical agents can cause extensive damage to the upper gastrointestinal tract, which may re-
result in perforation and death. In the acute phase, perforation and necrosis of the esophagus may occur, while long-term complications may be stricture formation, antral stenosis or development of esophageal carcinoma. After corrosive esophagitis, the risk of developing esophageal carcinoma is 1000-3000 times higher than in the normal population (3). Today, the aim of therapy in corrosive esophagitis is to avoid development of perforation, fibrosis and stricture formation. Stricture formation can be prevented by suppressing fibrosis and scar formation (6). In Grades 1 and 2a corrosive esophagitis, stricture formation is rarely seen, whereas it is common in Grades 2b and 3 esophagitis (4). In caustic injuries, the role of the gastroenterologist is limited: to prevent stricture formation in the early phase and dilation of the narrowing segments if strictures occur. Since stricture formation occurs as a result of fibrosis and inflammation, the aim of the medical treatment must be to decrease the inflammatory reaction. The outcome with the current medical treatment protocols is still poor in advanced-grade esophagitis. Despite medical treatment, stricture develops in 70 to 100% of the patients with Grades 2b and 3 corrosive esophagitis (7, 8).

Sucralfate (sucrose octasulfate complex) forms a physical barrier between harmful agents and gastrointestinal (esophagus, stomach and rectal) mucosa (9, 10). The well-known effects of this agent are decreasing inflammatory response and increasing mucus and prostaglandin productions. Sucralfate also improves mucosal healing and tends to adhere to the ulcerated mucosa 6-7 times more than to the normal mucosa (11, 12).

The aim of this study was to determine the effectiveness of intensive oral sucralfate therapy against stricture formation in advanced corrosive esophagitis.

**MATERIALS AND METHODS**

Fifteen consecutive adult patients with Grade 2b and Grade 3 corrosive esophagitis, who were admitted to the gastroenterology, general surgery and intensive care units between 2004 and 2007, were enrolled. The patients with perforation on admission were excluded from the study. We diagnosed the perforation with fluoroscopic imaging after oral administration of a mixture of low molecular weight opaque and sterile saline in patients with a clinical picture suspicious for perforation. Patients were divided into two groups as Group 1 or 2 by their order of admission. Group 1 included 8 patients (4 men, 4 women) and Group 2 included 7 patients (4 men, 3 women). We classified the patients based on the grades of the damage but not the contents of the chemical agents. All cases were admitted to the hospital in the first 12 hours after ingestion, and we observed damage to all segments of the esophagus at the first endoscopy.

Both groups received parenteral antibiotics (extended spectrum antibiotic for 7 days), parenteral proton pump inhibitor (omeprazole 40 mg iv twice a day) and steroid therapy (12). The patients in the first group also received intensive sucralfate therapy. Sucralfate was administered in the following pattern: 10 cc (2 g) sucralfate was given every 2 hours for the first 3 days. In the following 21 days, patients received 10 cc sucralfate every 2 hours between 08:00 am to 12:00 pm and every 4 hours between 12:00 pm to 08:00 am. The oral sucralfate therapy was continued for another 45 days as 10 cc 4 times a day. In the first 3 days, both groups were allowed to take only fluids (water, juice and milk) orally and were also given parenteral hydration and nutrition. In Group 1, oral fluids were given prior to sucralfate administration. Patients did not report any adverse reactions due to sucralfate therapy.

The patients were kept in the intensive care unit for 24 hours for close monitoring. They were then transferred into normal rooms for follow-up. There were no serious complications such as death, sepsis, perforation or hemorrhage in either group.

Patients were followed up for 6-24 months. Endoscopic procedures were performed on days 0, 21, 45, 90 and 180 in both groups. We used endoscopic classification, as shown in Table 1 (13). The endoscopists were blind to the group allocations and the severity of the damage of the gastrointestinal mucosa before treatment. We performed frequent endoscopies for dilatation procedure in patients who developed stricture. Patients who underwent surgery were excluded from follow-up.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Endoscopic Findings</th>
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<tbody>
<tr>
<td>1</td>
<td>Edema and erythema</td>
</tr>
<tr>
<td>2A</td>
<td>Hemorrhage, erosions, blisters, ulcers with exudates</td>
</tr>
<tr>
<td>2B</td>
<td>Circumferential ulceration</td>
</tr>
<tr>
<td>3</td>
<td>Multiple deep ulcers with brown, black, or gray discoloration</td>
</tr>
<tr>
<td>4</td>
<td>Perforation</td>
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</tbody>
</table>

Table 1. Endoscopic classification in corrosive esophagitis (13)
Data are expressed as medians with interquartiles. Mann-Whitney U test and chi-squared test were used to assess significant differences between values in various groups of patients, where appropriate. A value of \( p < 0.05 \) was considered statistically significant. Data were analyzed using the SPSS for Windows (version 9.05; SPSS, Inc., Chicago, Illinois, USA).

RESULTS

The characteristics of the patients such as age, gender and grade of esophagitis are shown in Table 2.

In Group 1, there were 4 males and 4 females, with a mean age of 33.5 years (24-52). Of these patients, 3 had Grade 2b esophagitis and 5 had Grade 3 esophagitis. Group 2 included 3 females and 4 males, with a mean age of 31.8 years (20-55). Three patients had Grade 2b and 4 patients had Grade 3 esophagitis. In Group 1, only one patient had stricture formation, which allowed passage of a 9.2 mm endoscope, but the patient did not have dysphagia as a symptom on day 45. Stricture was at the second physiologic narrowing of the esophagus. There was no progression in stricture diameter in the follow-up endoscopies performed in the 3rd and 6th months. In the second group, 6 of the 7 patients (85%) had dysphagia as a symptom, and esophagographies with barium swallow were performed where strictures were demonstrated. Only 1-2 mm barium passage was shown through the narrowed segments. This difference was statistically significant (\( p < 0.001 \)). In Group 2, 2 patients had only one stricture in the esophagus and 2 patients had multiple strictures. Length of the strictures ranged from 2 to 4 cm. Endoscopic dilation was performed for the treatment. The narrowed segments were dilated using plastic dilators with diameters of 7 mm to 15 mm. In 3 of the 7 patients who did not respond to the endoscopic dilation, surgical treatments were required. After treatment, the healed esophagus mucosa of the patients were not normal in either group in the proper sense, with signs of damage seen. In addition, during endoscopy, the peristaltic movements of the esophagus were seen as irregular. No relationship was found in either group between the type of the chemical agent digested and the grade of the damage. The gastric damage seen during the endoscopic procedures was variable. Sucralfate was not found to be efficacious in preventing stricture formation in gastric lesions in our study since there was no difference between groups in the progression of gastric lesions or the number of patients in whom surgical procedures were required because of antral stricture.

The content of chemical agents ingested had no impact on the healing process or stricture formation since these agents were similar in both groups.

DISCUSSION

Corrosive esophagitis is a serious problem that occurs after accidental or suicidal ingestion of household bleaches, drain cleaners, sodium hydroxide, and hydrochloric acid. In a study conducted by Atug et al., it was found that lye at pHs<11.5 had no damaging effects on the esophagus mucosa, whereas lye at pHs≥1.5 caused liquefaction necrosis (5).

Many experimental pharmacological agents have been used to improve mucosal healing and prevent stricture formation in corrosive esophagitis. Pharmacological agents such as steroids, penicillamine, heparin, indomethacin, epidermal growth factor, gamma interferon, N-acetylcysteine, estrogen, progesterone, antibiotics, and their combinations are used to suppress inflammation and collagen synthesis, and to prevent fibroplasia and stricture formation. Despite the decrease in stricture formation in these experimental studies, the rate of stricture formation seen in advanced-grade corrosive esophagitis is still 70-100% (6-8, 14-20). Although the experimental studies have documented the efficiency of multiple agents, the current treatment protocol in corrosive esophagitis is still restricted to steroid, antibiotics and neutralization of the caustic agent in the early phase (13, 21-24).

The experimental studies have shown that steroids can decrease stricture formation (13). Howell et al. (25) showed that administering steroids in Grade 2 and Grade 3 corrosive esophagitis decreased stricture formation. In another study, the combination therapy of steroid and antibiotics in Grade 2 and Grade 3 esophagitis decreased the frequency of stricture formation (26).
In addition to the medical therapies, endoscopic procedures are also performed in caustic injuries. Evrard et al. (27) proposed that self-expanding metal stents (SEMS) prevent stricture formation in a limited number of patients with corrosive esophagitis. They observed migration of SEMS in 50% of cases and extracted them without any complications.

Sucralfate is known to have multiple beneficial effects in the ulcerated gastrointestinal mucosa. It increases the synthesis and release of prostaglandins, enhances mucosal cell regeneration and epidermal growth factor binding capacity, healing, and re-epithelialization, and stimulates angiogenesis resulting in enhanced microvascularization and circulation in the tissue. Control of the inflammation might decrease fibrosis and stricture formation. The physical barrier feature of sucralfate is to diminish inflammatory reaction and improve mucosal healing (9, 10, 28). Sucralfate is a hypophilic agent, and absorption in the gastrointestinal tract is very poor. Sucralfate does not cause any systemic adverse reactions (30). The studies about the usage of sucralfate in corrosive esophagitis are case reports. In one of them, in a patient with Grade 2a esophagitis, it was shown that administering sucralfate four times a day prevented stricture formation (31). Temir et al. (32), in their experimental study, showed that by giving sucralfate twice a day, stricture formation was prevented, but no mention was made in that study of the grade of the esophageal damage.

Taal et al. (33) found positive radioactivity in the esophagus in 24 of 26 patients with radiation esophagitis 2 hours after administering technetium 99m-labeled sucralfate. Tytgat et al. (11) discovered that polymerized sucralfate molecules have 6-7 times more affinity to the ulcerated mucosa than the normal mucosa. In another study, Roark (34) reported that sucralfate adhered to the ulcerated tissue in four and stopped bleeding in three of the four patients with ulcers appearing after sclerotherapy. In addition, before beginning this study, in the endoscopic procedures performed 2 hours after sucralfate administration in patients with esophageal ulcers of any etiology, we observed coverage of the ulcerated mucosa. We planned this study in light of these studies and our observations.

In the literature, we found case reports about sucralfate therapy in corrosive esophagitis. Reddy et al. (31) showed that sucralfate treatment given four times daily in Grade 2a esophagitis prevented stricture formation. Temir et al. (32) found significant results in preventing stricture formation in caustic injuries with the administration of sucralfate twice daily, but this study also gave no information about the grades of the caustic injuries.

We were also inspired by the treatment approach used in epidermal burns. It is important to prevent contact between the inflamed tissues to maintain normal anatomy as much as possible. Thus, fingers are dressed separately during the treatment of skin burns of the hand (35). The esophageal lumen is known to be collapsed between swallowing periods while it opens like a pipe during swallowing (36). We hypothesized that sucralfate would adhere to the inflamed and ulcerated mucosa and prevent contact between the opposite esophageal walls. We expected that sucralfate might function as a coverage for the damaged tissue, which would help the healing process with better outcomes.

In our study, although we found no symptomatic strictures in the first group, there were strictures in six of the seven patients in the second group, with a significant difference between the two groups (p<0.001). There was only one patient in the first group who had stricture formation without dysphagia, which allowed the passage of a 9.2 mm endoscope and did not necessitate dilation in the following 24-month observation period.

The significant result of this study is beyond our expectations. We are aware of some of the limitations in our study, such as the number of patients. The small number of the patients may have contributed to these unexpectedly good results. Further studies based on large cohorts are required to confirm our findings.

We recommend intensive high-dose sucralfate therapy in advanced-grade corrosive esophagitis to enhance mucosal healing and prevent stricture formation.

REFERENCES
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