Introduction

The increased number of acidic gastroesophageal reflux episodes in the postprandial period is at odds with the intuitive idea of meals buffering gastric acid. The concept of a postprandial proximal gastric acid pocket (PPGAP) solved this apparent paradox. In 2001, Fletcher et al. (1) showed the presence of acid at the gastroesophageal junction that is not neutralized by food. In the following years, other groups also clearly demonstrated that gastric acid is not uniformly spread in the stomach in the postprandial period (2-6).

The PPGAP is thought to be a reservoir of non-neutralized acid surrounding the gastroesophageal junction that enables the occurrence of postprandial acidic reflux events when the distal stomach is alkaline due to meal’s buffering effect (5). Interestingly, some researchers demonstrated that the refluxate may be more acidic than distal gastric content, thus corroborating the PPGAP as the source of these acidic postprandial reflux events (1-5).

The effect of oral sucralfate on postprandial proximal gastric acid pocket

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Background: A postprandial proximal gastric acid pocket (PPGAP) that escapes neutralization by food was demonstrated in volunteers and gastroesophageal reflux disease (GERD) patients. It is elusive; however, if this acid layer is morphologically best conceptualized as a real pocket or a film. This study aims to analyze the effect of oral sucralfate administration on PPGAP to shed some light on PPGAP morphology and treatment.

Methods: Twenty-six patients (mean age 51 years, 19 females) were studied. A pull-through pH monitoring was performed from 5 cm below the lower border of the lower esophageal sphincter (LES) to the actual border in increments of 1 cm, in a fasting state, 10 min after a fatty meal and 10 min after oral sucralfate administration. PPGAP was defined by an acid reading (pH <4) in the proximal stomach between non-acid segments distally (food) and proximally (proximal pH transition point). Standard 24 h pH monitoring was performed for objective characterization of GERD. The protocol was approved by local ethics committee.

Results: PPGAP was not found in 15 patients and these were excluded from the post-sucralfate analysis. After sucralfate, PPGAP increased in length in 5/11 (45%) patients; decreased in 2/11 patients (18%). In 3/11 (27%) patients PPGAP disappeared; in 1/11 (9%) PPGAP length remained equal.

Conclusions: In conclusion, sucralfate altered PPGAP in more than 90% of the patients, supporting the theory of an acid film. Sucralfate is, however, not an adequate treatment for PPGAP.

Keywords: Acid pocket; gastroesophageal reflux; sucralfate; pH monitoring

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gastric motor activity in the postprandial period and food components partitioning in the stomach (1).

The existence of acid at the gastroesophageal junction after meals modified our current understanding about gastroesophageal junction diseases. For instance, PPGAP may represent an alternative explanation for epithelial damage at the gastroesophageal junction in individuals that gastroesophageal reflux disease (GERD) could not be diagnosed by routine work-up (7). Some authors also believe that PPGAP may have an intrasphincteric and even intraesophageal component, behaving like a film, not a pocket (5). The pocket theory implies that, after meals, a volume of unbuffered acid floats on top of the non-acid chyme. The film theory suggests that unbuffered acid remains as an acid layer attached to the acid-secreting mucosa whereas meals are localized in the central area of gastric lumen.

This study attempts to expand current knowledge about PPGAP, especially on the morphological aspect (film vs. pocket). The rational basis for using sucralfate to determine PPGAP tridimensional structure was the hypothesis that mucosal coating with sucralfate would probably not change acid layer configuration in case of a pocket whereas an acid film, devoid of significant volume, would more likely be modified by this drug. In addition, this study aims to assess whether sucralfate would be a suitable potential drug targeting specifically the PPGAP.

### Methods

#### Population

Twenty-six patients investigated for GERD were prospectively studied.

All patients had GERD symptoms and underwent an upper digestive endoscopy.

Exclusion criteria were previous foregut operation and denial to participate in the study.

Demographic and endoscopic data are shown in Table 1.

#### High-resolution manometry (HRM)

All patients fasted for 8 hours before the tests. All participants underwent HRM (Medtronic, Los Angeles, CA, USA) to determine lower esophageal sphincter (LES) borders.

#### pH monitoring

After HRM, all individuals underwent gastroesophageal pH studies (Alacer Biomedica, São Paulo, SP, Brazil).

Antacid medications were discontinued opportune.

The pH catheter was initially placed in the proximal stomach 5 cm below LES lower border (LESLB). A station pull-through was performed from 5 cm below LESLB in increments of 1 cm signaled by pushing the event bottom until detection of gastric-to-esophageal pH transition point or until LESUB was reached, according to classical methodology for PPGAP detection (1).

After this first pull-through in the fasting state, the sensor was replaced at the initial position (5 cm below LESLB) and the patients received a standardized fatty meal (hamburger, 11% fat and chocolate milk, 3% fat). The pull-through was identically repeated 10 minutes after food intake was finished.

Patients with a detected PPGAP received 2 g/10 mL of oral sucralfate suspension (Sucrafilm®, EMS, Brazil) and underwent a third pull-through for PPGAP detection 10 minutes after administration of the mucosal coating agent.

After the protocol for PPGAP evaluation, all individuals completed conventional ambulatory 24-hour pH monitoring.

#### PPGAP assessment

PPGAP was defined by the presence of an acid reading (pH <4) in a segment of the proximal stomach between nonacid segments distally (food) and proximally (gastric-to-esophageal pH transition point) (8) (Figure 1). PPGAP length and position relative to LESLB were recorded postprandially and after sucralfate.
Ethics

The protocol was approved by the Institutional Review Board of Federal University of Sao Paulo (13473013.6.0000.5505) and was conducted in accordance with the Helsinki Declaration of 1964 (revised 2008). Informed consent was obtained from all individuals.

The authors are responsible for the manuscript and no professional or ghost writers were hired.

Results

Esophageal manometry and pH monitoring

Esophageal manometry parameters and prolonged ambulatory pH monitoring results are expressed in Table 2.

Gastric pH

Four patterns previously described of gastric acidity (9) were identified: permanent alkaline stomach in 4 out of 26 patients (15%); no PPGAP detected in 5 out of 26 (19%); permanent acid stomach (no buffering effect of food) in 6 out 26 (23%) and PPGAP present in 11 out of 26 (43%) (Figure 2).

PPGAP

PPGAP was detected in 11 out of 26 (43%) patients. Intraspincteric extension of the PPGAP was noticed in 3 out of 11 (27%) cases.

After sucralfate, PPGAP disappeared (or it was displaced distally beyond detection) in 3 out of 11 patients (27%) and was unaltered in 1 of the 11 (9%). PPGAP length increased in 5 out of 11 (45%) of the individuals and a decrease in 2 out of 11 (18%). After sucralfate, intraspincteric extension of the PPGAP disappeared in patients with this finding previously but it was present de novo in 1 out of 11 (9%).

Table 2

<table>
<thead>
<tr>
<th>Variables</th>
<th>Data</th>
</tr>
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<tbody>
<tr>
<td>High-resolution manometry data</td>
<td></td>
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<tr>
<td>% hypotonic LES</td>
<td>17/26 (65.4%)</td>
</tr>
<tr>
<td>LES basal pressure (mmHg)</td>
<td>7.1 (2.8–20.3)</td>
</tr>
<tr>
<td>% short LES</td>
<td>21/26 (80.8%)</td>
</tr>
<tr>
<td>LES length (mm)</td>
<td>20 [18–26]</td>
</tr>
<tr>
<td>Dissociation between HPZ intrinsic and extrinsic components</td>
<td>14/26 (53.8%)</td>
</tr>
<tr>
<td>Distance between LES and crural diaphragm (mm)</td>
<td>16.5 (9.2–29)</td>
</tr>
<tr>
<td>Distal esophageal wave amplitude (mmHg)</td>
<td>60.8 (49.4–92.9)</td>
</tr>
<tr>
<td>pH monitoring data</td>
<td></td>
</tr>
<tr>
<td>Abnormal esophageal acid exposure (at 5 cm above LES)</td>
<td>21/26 (80.8%)</td>
</tr>
<tr>
<td>DeMeester score</td>
<td>37 (12.6–48.1)</td>
</tr>
</tbody>
</table>

Data are expressed as median and interquartile ranges. LES, lower esophageal sphincter; HPZ, high pressure zone.
Figure 2 Acidity patterns in the proximal stomach: (A) no acid in the proximal stomach; (B) lack of acid buffering by meal; (C) no acid pocket detected; (D) postprandial acid pocket present. Dotted vertical bars represent pull-through in increments of 1 cm. Horizontal red bar represents pH = 4. Proximal pH sensor depicted in the top and distal in the bottom.

Figure 3 Acid pocket status after meal (red arrows) and after sucralfate administration (black arrows): (A) increased acid pocket length after sucralfate; (B) decrease in the acid pocket’s length after oral sucralfate; (C) acid pocket with unaltered length after the mucosal coating agent; (D) acid pocket’s extinction after sucralfate. Dotted vertical bars represent pull-through in increments of 1 cm. Horizontal red bar represents pH = 4.
sucralfate effects on PPGAP, summarized in Figure 4.

**Discussion**

Our results show that sucralfate affected PPGAP in most cases (91%) with an increase in length in almost half of the patients and a decrease/suppression in the other half.

**PPGAP morphology**

It is still controversial whether acidity at the gastroesophageal junction would be better described as an acid pocket or an acid film (6). In favor of the film concept is the presence of an intrasphincteric extension of the PPGAP measured by pH monitoring, even with an intact LES (6,10,11) or increased LES basal pressure with the use of baclofen (12). In favor of the pocket concept is the presence of a volume of acid not limited to the gastric wall as detected by magnetic resonance or scintigraphy (13,14).

Sucralfate is a sulfated aluminum salt of sucrose. This non-systemic agent does not have any acid-neutralizing effect and does not influence gastric acid secretion as well (15,16). It is a mucosal-coating agent that attaches both to injured and normal gastric mucosa (15). We theorized that mucosal coating with a non-acid substance would alter normal PPAGP morphology in case of a film. On the other hand, a tridimensional pocket would be undisturbed by mucosal coating. In our study, sucralfate altered the acid pocket in 91% of the patients favoring the presence of an acid film as an important component of the PPGAP. Furthermore, the presence of an intrasphincteric PPGAP was suppressed by sucralfate. However, the finding of an increase in length in half of the patients may suggest a dual behavior of the PPGAP as a film and a pocket.

If our individual results are carefully analyzed, an erratic response to sucralfate administration was found. Although PPGAP extinction was found only in patients GERD—and in the absence of a hiatal hernia, the presence of GERD and hiatal hernia was unpredictable in the other patterns. Interesting only is that in PPAGP increase group, 4 out of 5 were GERD patients. In this group the acid pocket continued to form after ten minutes, and sucralfate was far from able to suppress it. Intrasphincteric extension of PPGAP also does not predict sucralfate effect.

**PPGAP treatment**

A therapy directed towards PPGAP may be useful in patients with postprandial symptoms and a putative prevention of carditis and Barrett’s esophagus as a consequence of a permanently acidic environment adjacent to the esophagogastric junction (16).

Gastric acid output blocking by proton pump inhibitors has shown to decrease PPGAP volume, acidity and
symptoms but did not suppressed PPGAG (4,17-19). This may be caused by accumulation of exogenous acid from the food or small amounts of acid still secreted despite pharmacological blockage and concentrated in the PPGAP. Acceleration of gastric emptying with prokinetics seems to displace the PPGAP distally avoiding reflux of the acid within the PPGAP (4). The same effect was observed with an alginate-antacid formulation by forming a gel raft on top of the acidic layer (11). A fundoplication (9) decreases the incidence of the PPGAP by changes in gastric anatomy.

Sucralfate promoted suppression of the PPGAP in a quarter of the patients and a decrease in length in other 20%. This result is suboptimal and not different from previous described therapies. Curiously, all patients in which sucralfate extinguished PPGAP were non-refluxers without a hiatal hernia.

**Study limitations**

This study comprises a small number of patients, since PPGAP was not found to be as ubiquitous as previously described (1,2,4,6,14). A control group without sucralfate administration was not studied. This group may be argued valuable to differentiate the effect of the drug from washout of the acid. Previous studies; however, showed that PPGAP may be present even 120 minutes after a meal (12,20). Furthermore, the results of previous studies, including from our group, fill the need for a control group. The timepoint to assess whether the acid pocket was present or not was 10 minutes based on the methodology of previous studies (8). It has been shown that it may take longer to fully form; therefore our protocol may have excluded a subset of patients. The main aim of the study; however, was to investigate patients with proved PPGAP, not access the incidence of the condition.

Future studies in combination with magnetic resonance or scintigraphy may shed more light in the pathophysiology of the PPGAP as the findings of the current study are not definite proof of PPGAP spatial configuration but a modest contribution.

**Conclusions**

We conclude that the fact that sucralfate altered the PPGAP configuration in up to 91% of the patients, suggests that acidity at the gastroesophageal junction may have a film component, since a mucosal coating drug would probably not disturb an acid pocket. Also, sucralfate is not an adequate target therapy for the PPGAP.

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**Footnote**

Conflict of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The protocol was approved by the Institutional Review Board of Federal University of Sao Paulo (#13473013.6.0000.5505) and was conducted in accordance with the Helsinki Declaration of 1964 (revised 2008). Informed consent was obtained from all individuals.

**References**


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