

Review Article

Marginal Ulcers are Less Responsive to Proton Pump Inhibitors Compared to Gastric Ulcers: A Case-Control Study

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Background: Marginal ulcer is a well-known complication after gastrectomy associated surgeries. Proton Pump Inhibitors (PPIs) are commonly used to treat marginal ulcers, but their effectiveness has not been well studied. Our objective was to conduct a retrospective case-control study to assess the effectiveness of PPI treatment of marginal ulcers in comparison to gastric ulcers and elucidate the risk factors affecting healing of marginal ulcers.

Method: The study was conducted at Minneapolis Veteran Affairs medical center from year 2000 to 2018. Patients with ulcers diagnosed at endoscopy who were treated with PPIs and had a follow-up endoscopy were included.

Results: A total of 20 patients with marginal ulcers aged matched with 50 gastric-ulcer patients were included in the study. There was no statistically significant difference between baseline characteristics of the two groups. When compared to gastric ulcers, patients with marginal ulcers were significantly less responsive to PPIs (Odds Ratio=0.14; 95% CI 0.04-0.49, p=0.02). Age, H pylori status, NSAIDs use, smoking status, alcohol use, diabetes and cardiovascular diseases were not independent risk factors affecting healing of marginal ulcers.

Conclusion: Marginal ulcers are less responsive to PPI compared to gastric ulcers, and about 50% of marginal ulcers will not heal with PPI treatment. Our study is limited by sample size. Further studies with large sample size are warranted to further investigate effective medical treatments for marginal ulcers and to identify risk factors impeding ulcer healing.

Keywords: Marginal Ulcer; Anastomotic Ulcer; Ulcer Healing; Proton Pump Inhibitors

Abbreviations

PPIs: Proton Pump Inhibitors; NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; VA: Veterans Affairs

Introduction

Marginal ulcer is a well-known complication after gastrectomy. It is defined as an ulcer within 3 cm of the gastrojejunostomy site [1]. The incidence of marginal ulcer ranges from 0.6% to 25% [2], and depends on the types of surgery creating the gastrojejunostomy sites. Most of the ulcerations develop within 2 years after surgery [1,3,4]. The underlying mechanism for the development of marginal ulcer has not been clearly defined. The reported etiologies are abundant, including NSAIDs use, smoking, technical problems at the gastrojejunostomy site causing ischemia, foreign body such as suture materials, and *Helicobacter pylori* infection [3,4]. Marginal ulcerations have been treated anecdotally as gastric ulcerations by using Proton Pump Inhibitors (PPIs). Despite broad application of PPIs in marginal ulcers, few data are available regarding its effectiveness in treating marginal ulcers. We aim to conduct a retrospective case-control study to 1) assess the effectiveness of PPI treatment of marginal ulcers in comparison to gastric ulcers; and 2) to elucidate the risk factors affecting healing of marginal ulcers.

Methods

We identified the study populations - patients with marginal ulcers diagnosed on endoscopy, by searching ICD-9 and -10 codes of "Gastrojejunal Ulcer" in Provision database at Minneapolis Veteran Affairs (VA) Medical Center from year 2000 to 2018. We identified patients with biopsy-proven gastric ulcers (controls) by searching SNOMED Code 63000 "Stomach Ulcer" in the VA pathology database from year 2000 to 2018. For all patients, we excluded those who were not treated with PPIs and/or had no follow-up endoscopy to check for ulcer healing. Each marginal ulcer patient was age-matched with two to three controls by +/- 2 years of age. For control groups, we also excluded those who had missing endoscopy reports.

For each patient, we reviewed endoscopy reports, as well as associated electronic health records to abstract clinical data. We extracted data on patient demographics, risk factors of ulcer disease, PPI dosages, endoscopy indications, and endoscopy findings before and after PPI treatment.

The primary outcome was the proportion of ulcer healing diagnosed on follow up endoscopy. We defined ulcer healing as 1) decreasing ulcer size, or 2) resolving ulceration on follow-up endoscopy comparing to initial endoscopy. The proportion of ulcer

healing was compared for patients with marginal ulcers versus gastric ulcers using χ^2 or Fisher exact tests. $P < .05$ was considered statistically significant for all comparisons.

The secondary outcome of interest was potential risk factors affecting healing of marginal ulcers. We identified potential risk factors as *H. pylori* infection, active smoking, chronic steroids use, anticoagulation use, diabetes, coronary artery disease or peripheral artery disease. Data were analyzed using logistic regression. The study was approved by The Minneapolis VA Medical Center Institutional Review Board.

Results

Among the 480 pathology reports and 728 endoscopy reports retrieved, a total of 20 patients with marginal ulcers and 50 patients with gastric ulcers were included in the study. The baseline characteristics of participants were shown in Table 1. Among patients with marginal ulcers, the average age was 66 years and 85% were men. 40% of the patients with marginal ulcers were smokers and 60% had chronic Nonsteroidal Anti-inflammatory Drugs (NSAIDs) use. The most common surgeries were Roux-en-Y gastric bypass (45%), followed by Billroth II (25%) and Whipple's procedure (20%). The most common surgical indications were obesity (30%), followed by peptic ulcer disease (20%) and malignancies (20%).

There was no clinical or statistically significant difference between patients with marginal ulcers comparing to those with gastric ulcers. Of the patients with marginal ulcers treated with PPIs, only 11/20 (55%) demonstrated ulcer healing on follow-up endoscopies. Nearly all patients (98%, 49/50) with gastric ulcers treated with PPIs demonstrated ulcer healing on follow-up exams. When compared to gastric ulcers, patients with marginal ulcers were significantly less responsive to PPIs in healing ulcers (Odds Ratio=0.14; 95% CI 0.04-0.49, $p=0.02$). PPI dosages, ulcer size, endoscopy indications, NSAIDs use, smoking status, alcohol use, diabetes and cardiovascular diseases were not independent risk factors affecting healing of marginal ulcers (Table 2).

Discussion

Marginal ulceration at the site of the Gastrojejunal anastomosis is a well-known complication in patients after gastrectomy surgeries. Although the marginal ulceration has been treated anecdotally with PPI administrations among the gastroenterologists and bariatric surgeons, there is little information on the responsiveness of marginal ulcerations to PPI treatment. Previous studies were mostly done by bariatric surgeons focusing on using prophylaxis PPIs to prevent marginal ulcer formation after Roux-en-Y gastric bypass [1-4].

The present study focused on PPI treatment in existing marginal ulcerations, and included not only Roux-en-Y gastric bypass surgeries, but also Billroth I/II surgeries and Whipple's procedures. Furthermore, all our patients had gastrectomy surgeries more than six years ago, which suggest the studied marginal ulcers are likely chronic ulcerations rather than newly formed ulcers as reported in previous literatures.

The underlying mechanisms for the development of marginal ulcerations have not been fully elucidated. The etiology is likely multifactorial with ischemia potentially playing a major role in the

Table 1: Baseline characteristics of the participants.

Baseline Characters	Marginal Ulcers (N=20)	Gastric Ulcers (N=50)
Age		
Mean (Std Dev)	66.1 (10.6)	66.3 (10.2)
Gender n, (%)		
Male	17 (85)	48 (96)
Current Smoking Status n, (%)		
Yes	8 (40)	18 (36)
Heavy Alcohol Use n, (%)		
Yes	4 (20)	11 (22)
NSAIDs use n, (%)		
Yes	12 (60)	31 (62)
H Pylori Infection n, (%)		
Yes	0 (0)	4 (8)
Comorbidities n, (%)		
Diabetes	6 (30)	15 (30)
Cardiovascular diseases	7 (35)	16 (32)
Endoscopy Indications n, (%)		
Asymptomatic	1 (5)	5 (10)
Iron deficiency anemia	2 (10)	12 (24)
Epigastric pain/dyspepsia/Nausea/Vomiting	6 (30)	14 (28)
Gastrointestinal bleeding	11 (55)	19 (38)
Proton pump inhibitor regimen n, (%)		
40 mg twice daily	16 (80)	32 (64)
40 mg daily/20 mg twice daily	3 (15)	17 (34)
20 mg daily	1 (5)	1 (2)
Ulcer size n, (%)		
0-10 mm	13 (65)	27 (54)
11-19 mm	3 (15)	8 (16)
≥ 20 mm	2 (10)	11 (22)
Unknown	2 (10)	4 (8)

Std Dev: Standard Deviation

Table 2: Potential Risk Factors Affecting Healing of Marginal Ulcers.

Potential Risk Factors	Odds Ratio	95% Confidence Intervals	P-Value
Gastrointestinal bleeding	2.19	0.36-13.22	0.42
PPI 40 mg twice daily	1.29	0.14-11.54	0.25
Ulcers > 20 mm	0.8	0.04-14.89	0.2
Heavy Alcohol Use	3	0.25-35.33	0.85
Active Smoker	0.71	0.12-4.32	0.75
NSAIDs Use	1.4	0.23-8.46	0.88
Diabetes (Yes)	2	0.27-14.70	1
Cardiovascular Disease (Yes)	2	0.27-14.70	1

pathogenesis [2]. Notably, 55% of patients with marginal ulcers in our study responded to PPI treatment, which is higher than we expected. This high PPI responsive rate can likely be explained by the unique veteran populations our study focused on, whom tend to be

older, have more comorbidities, and more likely on chronic aspirin or non-steroidal anti-inflammatory medications comparing to general populations.

Our study is unique as this is the first case-control study to assess the effectiveness of PPI in treating existing marginal ulcerations in veterans. Previously, Schulman et al. [5] have reported their experience in treating marginal ulcers with opened PPI capsules vs. intact capsules, and concluded that opened capsules reduce time to healing compared with intact capsules for marginal ulceration. However, their primary interest was to compare opened vs. intact capsules in treating marginal ulcers, rather than the overall effectiveness of PPI in healing marginal ulcerations.

There are several limitations of this study. First, the small sample size precluded us to obtain sufficient data to elucidate any associations between potential risk factors and healing of marginal ulcerations. Second, the unique characteristics of the veteran population precluded us to generalize our study results. Third, the retrospective nature of the study increased the possibility of selection bias.

Conclusion

In conclusion, PPI administrations can potentially heal more than half of the chronically existing marginal ulcerations in the veteran populations. However, our sample size was too small to adequately

assess the effectiveness of PPI in treating marginal ulcerations. Further studies with large sample size are warranted to further investigate the effective dosage and duration of PPI for marginal ulcerations and to identify risk factors impeding ulcer healing.

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