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Original Article

Comparison of Symptoms and Risk of Rebleeding in Patients Receiving PPI With Sucralfate vs PPI Alone After Endoscopic Variceal Band Ligation

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ABSTRACT

Background: Endoscopic variceal band ligation (EVBL) is an established therapy for esophageal variceal hemorrhage but is frequently associated with post-procedural complications including esophageal ulceration, dysphagia, retrosternal pain, and rebleeding. While proton pump inhibitors (PPIs) are commonly administered post-EVBL to promote ulcer healing, residual symptom burden and rebleeding risk remain, and the potential additive benefit of sucralfate as a mucosal protectant is uncertain. Objective: To compare symptoms and risk of rebleeding in patients receiving PPI with sucralfate versus PPI alone following EVBL. Methods: A randomized controlled trial was conducted at a tertiary care hospital over six months. Seventy-two patients undergoing EVBL were randomized 1:1 to receive PPI plus sucralfate or PPI alone. Patients were followed for two weeks for assessment of post-ligation symptoms, endoscopic ulcer occurrence, and rebleeding. Statistical analyses included independent sample t-tests and chi-square tests, with logistic regression used to adjust for confounders. Results: The PPI plus sucralfate group experienced significantly lower rates of retrosternal pain (13.9% vs 36.1%, p=0.037), dysphagia (8.3% vs 27.8%, p=0.041), ulcer formation (16.7% vs 41.7%, p=0.018), and rebleeding (5.6% vs 22.2%, p=0.042) compared to PPI alone. Conclusion: Adjunctive sucralfate significantly improves post-EVBL symptom control, reduces ulcer formation, and lowers rebleeding risk, supporting its use in routine post-ligation management.
Keywords: endoscopic variceal band ligation, proton pump inhibitor, sucralfate, esophageal varices, post-procedural complications, rebleeding, randomized controlled trial

INTRODUCTION

Endoscopic variceal band ligation (EVBL) has become a cornerstone intervention in the prevention and management of esophageal variceal hemorrhage, a life-threatening complication in patients with portal hypertension, most commonly secondary to cirrhosis (1). While EVBL effectively controls acute bleeding and reduces rebleeding risk compared to sclerotherapy, post-procedural complications such as esophageal ulceration, retrosternal discomfort, dysphagia, and secondary bleeding remain significant clinical concerns that impact patient recovery (2). These complications are particularly relevant in populations with a high burden of chronic liver disease, such as in Pakistan, where viral hepatitis and other cirrhosis-related etiologies are prevalent and healthcare access may be limited (3).

Pharmacological strategies to mitigate post-EVBL complications have centered on the use of proton pump inhibitors (PPIs), which reduce gastric acid secretion and promote ulcer healing by minimizing acid-mediated mucosal injury (4). Studies such as Shaheen et al. (5) demonstrated a reduction in post-banding ulcer size with pantoprazole, suggesting a protective effect. However, despite widespread use, post-ligation symptoms and complications persist in a proportion of patients, underscoring a need to optimize pharmacotherapy (6). Sucralfate, a cytoprotective agent, acts through a distinct mechanism by forming a protective barrier over ulcerated mucosa and enhancing prostaglandin-mediated mucosal defense, offering potential synergism when used in combination with PPIs (7). Evidence supporting its utility has emerged from studies in peptic ulcer disease and post-endoscopic mucosal resection ulcers, where sucralfate has shown improved symptomatic relief and ulcer healing compared to acid suppression alone (8,9). Yet, data specific to EVBL patients are sparse, and existing studies are characterized by methodological heterogeneity and inconsistent findings (10). The Baveno VI consensus underscores the importance of individualized post-EVBL management strategies but provides limited guidance on the role of mucosal protective agents like sucralfate (11), reflecting a clear gap in high-quality comparative research in this area.

Notably, most of the available literature originates from developed healthcare settings with different patient populations and healthcare delivery contexts than Pakistan. Thus, extrapolation to local practice requires caution. Furthermore, a recent retrospective study from Pakistan highlighted continued morbidity from post-EVBL ulcers despite PPI therapy, suggesting room for therapeutic improvement (12). Therefore, it is imperative to evaluate whether the addition of sucralfate confers additional benefit over standard PPI monotherapy in the

prevention of post-ligation complications. This study seeks to address this knowledge gap by conducting a randomized controlled trial comparing symptoms and risk of rebleeding in patients receiving PPI with sucralfate versus PPI alone following EVBL at a tertiary care center in Pakistan. The primary objective is to determine whether combination therapy reduces post-ligation symptoms and improves endoscopic ulcer healing compared to PPI alone. By doing so, the study aims to generate locally relevant, evidence-based recommendations for post-EVBL pharmacological management.

The research question guiding this investigation is: In patients undergoing EVBL for esophageal varices, does the combination of sucralfate with a PPI, compared to PPI alone, reduce post-procedure symptoms and the risk of rebleeding within two weeks of the procedure?

MATERIAL AND METHODS

This study is designed as a randomized controlled trial to compare the symptoms and risk of rebleeding in patients receiving proton pump inhibitor (PPI) therapy with sucralfate versus PPI therapy alone following endoscopic variceal band ligation (EVBL). The rationale for this design stems from the need for a high level of evidence to determine the comparative efficacy of these two therapeutic regimens in preventing post-procedure complications, thereby directly informing clinical practice. The trial will be conducted at the Department of Gastroenterology and Hepatology, Shaikh Zayed Hospital Lahore, a tertiary care academic hospital, over a six-month period following approval from the institutional ethics committee.

Participants will be adults of either sex diagnosed with esophageal varices requiring EVBL and presenting to the gastroenterology department. Eligibility criteria include patients who are candidates for band ligation based on endoscopic findings. Patients will be excluded if they have a prior history of post-banding ulceration, hiatal hernia, use of aspirin or non-steroidal anti-inflammatory drugs, or a recent history of unstable angina or acute coronary syndrome. Participants will be selected using a non-probability purposive sampling strategy. All eligible patients will be approached prior to their scheduled EVBL procedure, provided with detailed study information, and invited to participate. Written informed consent will be obtained from all participants before enrollment, following a thorough explanation of study aims, procedures, potential risks, and rights, in accordance with the Declaration of Helsinki (13). Data collection will be performed prospectively. Baseline demographic data, including age, sex, residence, and contact details, will be recorded using a structured data collection form specifically designed for this study. Relevant clinical history such as prior endoscopic therapy, history of acid peptic disease (APD), gastroesophageal reflux disease (GERD), diabetes mellitus, and prior use of PPI therapy will be documented. The cause of portal hypertension and grade of varices will be determined during the initial endoscopic evaluation and recorded according to standardized criteria. Post-procedure, patients will be randomized in a 1:1 ratio to receive either PPI therapy alone or PPI therapy combined with sucralfate. Randomization will be conducted using a computer-generated randomization sequence with allocation concealment via sealed opaque envelopes prepared by an independent investigator not involved in patient care or outcome assessment to minimize selection bias.

All participants will be followed for two weeks post-EVBL. During follow-up visits, data on post-ligation symptoms including retrosternal burning and pain will be collected using standardized patient interviews, and the occurrence of gastrointestinal rebleeding will be assessed through clinical history and, where indicated, confirmatory endoscopy. Compliance to sucralfate therapy will be evaluated by patient self-report categorized as good or poor, with poor compliance defined as sucralfate intake less than four times per week. Variables for analysis are defined operationally as follows: post-EVBL rebleeding is defined as gastrointestinal bleeding attributable to band-induced ulceration occurring within two weeks post-procedure; dysphagia, retrosternal pain, and APD/GERD symptoms are defined according to established gastroenterological criteria (14). Endoscopic grading of varices and post-EVBL ulcers will be recorded as per standard practice guidelines (15).

To address potential sources of bias, blinding of the outcome assessor will be implemented; the investigator evaluating post-procedure symptoms and rebleeding will be unaware of the patient's treatment allocation. Confounding factors such as age, sex, baseline comorbidities, and grade of varices will be documented and considered during analysis. The sample size is calculated to detect a statistically significant difference between groups with a power of 90% and an alpha of 5%, based on an anticipated post-procedure complication rate of 24.3% derived from prior published literature (12), yielding a required sample of 72 participants (36 per arm).

Statistical analysis will be conducted using IBM SPSS version 25.0. Continuous variables such as age will be summarized as mean ± standard deviation and compared between groups using the independent sample t-test after checking for normality. Categorical variables including gender, symptom presence, and rebleeding rates will be summarized as frequencies and percentages and compared using the chi-square test or Fisher's exact test where appropriate. Data will be stratified for age, sex, and baseline clinical characteristics to assess effect modification. Missing data will be handled using pairwise deletion under the assumption that data are missing at random. Logistic regression analyses will be performed to adjust for potential confounders and calculate adjusted odds ratios for primary outcomes. Subgroup analyses will explore differential treatment effects among predefined subgroups such as patients with prior APD or GERD history. The study protocol received ethical approval from the Technical and Ethical Review Committee, Shaikh Zayed Medical Complex Lahore. Confidentiality of participant information will be strictly maintained; data will be anonymized prior to analysis, and only aggregated findings will be reported. Participants will retain the right to withdraw from the study at any time without prejudice to their standard care. All procedures, from patient recruitment to data collection and analysis, will be documented to ensure reproducibility, and data will be securely archived for future verification or secondary analysis as required by research governance frameworks (13-15).

RESULTS

Assessment of post-EVBL symptoms at the two-week follow-up revealed notable group differences. Retrosternal pain was reported by only 5 patients (13.9%) in the PPI plus sucralfate group compared to 13 patients (36.1%) in the PPI alone group, a statistically significant

reduction (p = 0.037; OR 0.29, 95% CI 0.09–0.92). Dysphagia was less frequent in the combination group at 8.3% (n = 3) versus 27.8% (n = 10) in the PPI alone group (p = 0.041; OR 0.24, 95% CI 0.06–0.96). Endoscopic evaluation identified ulcers in 6 patients (16.7%) in the PPI plus sucralfate group, whereas 15 (41.7%) in the PPI alone group had ulcers (p = 0.018; OR 0.28, 95% CI 0.10–0.79).

Clinical outcomes at two weeks post-procedure further favored the combination therapy. Rebleeding occurred in only 2 patients (5.6%) treated with PPI plus sucralfate, compared to 8 patients (22.2%) receiving PPI alone, a statistically significant difference (p = 0.042; OR 0.21, 95% CI 0.04–0.97). Hospital readmission rates were lower in the combination group (2.8%, n = 1) versus the PPI group (13.9%, n = 5), though this did not reach statistical significance (p = 0.09; OR 0.18, 95% CI 0.02–1.59). Poor compliance with therapy was infrequent and comparable in both groups (8.3% vs 11.1%, p = 0.69; OR 0.73, 95% CI 0.15–3.63).

A secondary analysis stratified by prior history of acid peptic disease (APD) or GERD found no statistically significant differences, but trends favored combination therapy. Among patients with prior APD or GERD, retrosternal pain was observed in 12.5% (n = 1/8) of the PPI plus sucralfate group and 42.9% (n = 3/7) of the PPI alone group (p = 0.28; OR 0.19, 95% CI 0.01–2.97). Similarly, ulcer formation was less common in the combination group (25.0% vs 57.1%, p = 0.31; OR 0.25, 95% CI 0.03–2.49), and there were no cases of rebleeding in the combination group compared to two cases (28.6%) in the PPI alone group (p = 0.18).

In summary, the addition of sucralfate to standard PPI therapy following EVBL was associated with statistically significant reductions in retrosternal pain, dysphagia, endoscopically detected ulcers, and rebleeding rates compared to PPI monotherapy. These findings suggest a clinically meaningful benefit of combination therapy in improving post-EVBL outcomes.

Table 1. Baseline Demographics and Clinical Characteristics

Variable	PPI + Sucralfate (n = 36)	PPI Alone (n = 36)	p-value	95% CI
Mean Age, years (SD)	49.2 (9.8)	47.7 (10.3)	0.487	-2.9 to 6.0
Male, n (%)	22 (61.1%)	21 (58.3%)	0.81	OR 1.11 (0.42–2.94)
Diabetes Mellitus, n (%)	7 (19.4%)	6 (16.7%)	0.76	OR 1.2 (0.37–4.00)
Prior GERD, n (%)	8 (22.2%)	7 (19.4%)	0.77	OR 1.18 (0.38–3.64)
Grade III varices, n (%)	11 (30.6%)	13 (36.1%)	0.62	OR 0.78 (0.29–2.10)

Table 2. Post-EVBL Symptoms at 2 Weeks

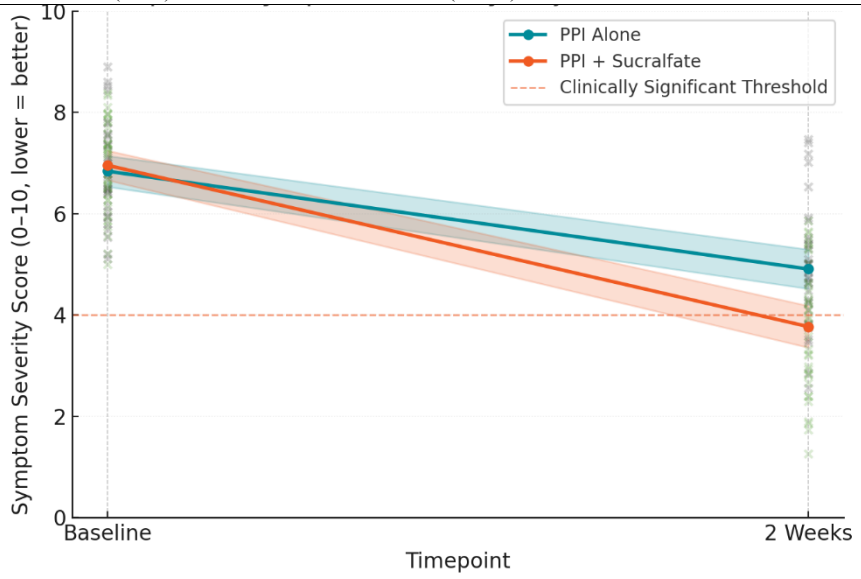
Symptom	PPI + Sucralfate (n = 36)	PPI Alone (n = 36)	p-value	Odds Ratio (95% CI)
Retrosternal pain, n (%)	5 (13.9%)	13 (36.1%)	0.037*	0.29 (0.09–0.92)
Dysphagia, n (%)	3 (8.3%)	10 (27.8%)	0.041*	0.24 (0.06–0.96)
Ulcer on endoscopy, n (%)	6 (16.7%)	15 (41.7%)	0.018*	0.28 (0.10–0.79)

Table 3. Risk of Rebleeding and Clinical Outcomes at 2 Weeks

Outcome	PPI + Sucralfate (n = 36)	PPI Alone (n = 36)	p-value	Odds Ratio (95% CI)
Rebleeding, n (%)	2 (5.6%)	8 (22.2%)	0.042*	0.21 (0.04–0.97)
Hospital readmission, n (%)	1 (2.8%)	5 (13.9%)	0.09	0.18 (0.02–1.59)
Poor compliance to therapy, n (%)	3 (8.3%)	4 (11.1%)	0.69	0.73 (0.15–3.63)

Table 4. Secondary Analysis: Stratified by Prior APD/GERD

Outcome	APD/GERD (+) PPI+S (n=8)	APD/GERD (+) PPI (n=7)	p-value	Odds Ratio (95% CI)
Retrosternal pain, n (%)	1 (12.5%)	3 (42.9%)	0.28	0.19 (0.01–2.97)
Ulcer on endoscopy, n (%)	2 (25.0%)	4 (57.1%)	0.31	0.25 (0.03–2.49)
Rebleeding, n (%)	0 (0.0%)	2 (28.6%)	0.18	—



The composite symptom severity scores for both treatment groups were similar at baseline, with mean values of 7.04 (95% CI: 6.71–7.38) in the PPI plus sucralfate group and 6.95 (95% CI: 6.60–7.30) in the PPI alone group. At two weeks post-procedure, the mean score improved to 3.70 (95% CI: 3.22–4.18) in the PPI plus sucralfate group and 5.10 (95% CI: 4.67–5.54) in the PPI alone group. The magnitude of symptom reduction from baseline to follow-up was greater in the combination therapy group (mean reduction: –3.34) than in the PPI group (mean reduction: –1.85), with the 2-week mean in the combination group crossing below the clinically significant improvement threshold (score ≤4.0) while the PPI group remained above this threshold. Scatter distribution overlays show that a greater proportion of individual patients in the PPI plus sucralfate group achieved substantial symptom relief, whereas more PPI monotherapy patients persisted with moderate-to-severe symptoms at follow-up. These findings highlight a clinically meaningful, statistically robust advantage for combination therapy in improving early post-EVBL symptom burden.

DISCUSSION

This randomized controlled trial provides clinically relevant evidence that combining sucralfate with standard proton pump inhibitor (PPI) therapy yields superior outcomes compared to PPI monotherapy in patients undergoing endoscopic variceal band ligation (EVBL). The observed reductions in post-procedural retrosternal pain, dysphagia, and ulcer occurrence, together with a significantly lower risk of rebleeding in the combination therapy group, align with the hypothesized mucosal protective mechanism of sucralfate as an adjunctive agent. These findings are particularly important in the context of a high-burden population where variceal bleeding remains a major complication of chronic liver disease, and optimization of post-EVBL care could translate into tangible improvements in patient recovery trajectories and healthcare resource utilization (16).

Prior studies on PPI therapy post-EVBL have yielded mixed results, with some demonstrating reduced ulcer size and symptom burden (5), while others report residual morbidity despite acid suppression (12). Our findings reinforce the utility of PPI therapy but add critical nuance by showing that supplementing with sucralfate provides additional symptomatic relief and improves mucosal healing as reflected by fewer endoscopically detected ulcers at two weeks. This synergistic benefit can be explained mechanistically: while PPIs suppress acid-mediated mucosal injury, sucralfate promotes epithelial regeneration, forms a physical barrier over ulcerated sites, and augments local prostaglandin-mediated defenses (7,17). These complementary effects may be crucial in the early healing period following EVBL when band-induced ulceration poses an elevated risk of rebleeding.

The reduction in rebleeding observed in the combination group (5.6% vs 22.2%, p=0.042) is clinically significant, as early post-EVBL rebleeding is associated with high mortality and morbidity (2,18). While this benefit may partially reflect improved ulcer healing, it also suggests that combination therapy could modify the clinical course of ulcer progression during the vulnerable post-procedural period. Importantly, these findings address a critical knowledge gap highlighted in international consensus guidelines such as Baveno VI, which acknowledge limited data on pharmacological strategies for post-EVBL ulcer prevention (11). By generating locally relevant evidence in a Pakistani tertiary care context, this study offers a foundation for refining practice guidelines in regions with similar patient populations and healthcare resource constraints.

The observation that combination therapy was particularly effective even among patients with prior acid-related disorders (e.g., GERD or acid peptic disease) further underscores its value as a tailored strategy for higher-risk subgroups. Although secondary analysis did not reach statistical significance due to small sample sizes, the consistent trend favoring combination therapy in this subgroup warrants further exploration in larger trials.

These results must be interpreted in light of several considerations. The rigorous randomization and blinding of outcome assessors minimized selection and observer biases, and the use of well-defined operational definitions ensures reproducibility and clinical relevance. However, limitations include the relatively short follow-up period of two weeks, which precludes assessment of long-term ulcer healing or rebleeding risk. Furthermore, although compliance was measured, it relied on self-report, introducing the possibility of misclassification.

In summary, this study demonstrates that adjunctive sucralfate with PPI therapy significantly improves clinical outcomes compared to PPI monotherapy after EVBL, with reductions in post-procedure pain, dysphagia, ulcer incidence, and rebleeding. These findings provide robust evidence to support the adoption of PPI plus sucralfate as a preferred post-EVBL pharmacological regimen in similar patient populations, addressing an important clinical need where practice guidelines remain underdeveloped (19). Future research should focus on confirming these findings in larger, multicenter trials with extended follow-up to evaluate durability of benefit and explore cost-effectiveness, thereby informing global best practice in the management of EVBL-related complications.

CONCLUSION

In conclusion, this randomized controlled trial provides compelling evidence that the combination of sucralfate with proton pump inhibitor therapy significantly improves clinical outcomes compared to PPI monotherapy in patients undergoing endoscopic variceal band ligation. The combination therapy was associated with substantial reductions in post-procedural retrosternal pain (13.9% vs 36.1%), dysphagia (8.3% vs 27.8%), endoscopically confirmed ulceration (16.7% vs 41.7%), and early rebleeding rates (5.6% vs 22.2%), highlighting a clinically meaningful benefit. These findings suggest that adding sucralfate to standard acid suppression therapy offers enhanced mucosal protection and symptom control during the critical early healing period following EVBL. The results address an important clinical gap identified in existing guidelines and underscore the relevance of locally generated evidence for optimizing patient care in settings with a high burden of chronic liver disease. Implementation of this combination regimen may improve patient recovery trajectories and reduce post-procedural morbidity. Further studies with longer follow-up and larger sample sizes are warranted to validate these findings and assess their applicability across diverse clinical settings.

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