ORIGINAL ARTICLE

Efficacy of Omeprazole Plus Sucralfate Suspension Compared to Omeprazole Alone for the Prevention of Post-endoscopic Variceal Ligation Ulcer in Cirrhotic Child-Pugh A and B Patients: A Prospective Randomized Controlled Trial

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Background: Post-endoscopic variceal ligation (EVL) ulcers represent a complication following EVL, with potential implications for mortality in cirrhotic patients. Prophylaxis against this complication typically involves either a proton pump inhibitor (PPI) or sucralfate. Limited studies have explored the combination of PPI with sucralfate suspension in the prevention of post-EVL ulcers.

Objective: The present study aimed to assess the efficacy of the combination of omeprazole and sucralfate suspension in comparison to omeprazole alone for preventing post-EVL ulcers in cirrhotic patients classified as Child-Turcotte-Pugh (CTP) A or B.

Materials and Methods: Conducted from March 2019 to December 2022, this prospective, single-center, randomized controlled trial enrolled patients diagnosed liver cirrhosis CTP A or B with esophageal varices. Systematic randomization assigned patients to either the omeprazole plus sucralfate suspension group or the omeprazole alone group. Subsequent esophagogastroduodenoscopy (EGD) was performed two weeks later to evaluate EVL ulceration using Jamwal's classification and complications.

Results: Out of the 84 initially enrolled patients, 2 in the omeprazole group were lost to follow-up. Intention-to-treat analysis (82 patients) revealed no significant differences between the combination of omeprazole plus sucralfate suspension and omeprazole alone groups in terms of EVL ulcer type (1 (2.4%) vs. 3 (7.5%) in type C, 40 (95.2%) vs. 35 (87.5%) in type D ulcer; p=0.41), EVL ulcer numbers (4.4±2.0 vs. 4±2.1; p=0.43), and percent decreasing of EVL ulcer numbers (33.3±35.8 vs. 35.7±28.8: p=0.47). No statistically significant variations in post-EVL complications were observed between the two treatment groups.

Conclusion: The present study indicates no discernible differences in post-EVL ulcer type, EVL ulcer numbers, percentage reduction in EVL ulcer numbers, and complications between the combination of omeprazole plus sucralfate suspension and omeprazole alone.

Keywords: Post EVL ulcer; Omeprazole; Sucralfate suspension; Jamwal's classification

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Esophageal varices (EV), a prominent complication associated with liver cirrhosis and portal hypertension, constitute a primary contributor to mortality. Despite persistent endeavors over the past decades, the mortality rate attributed to EV bleeding remains substantial, ranging between 15 to 20%. A contemporary standard for primary prophylaxis against EV bleeding in clinical practice is Endoscopic Variceal Ligation (EVL)[1-5]. However, the application of banding ligation on varices introduces a significant risk of complications, with post-EVL ulcers emerging as a noteworthy concern, affecting 74.2% of cases[6]. Approximately 3 to 7 days post-banding, these ulcers progress to strangulated varices due to thrombosis, ischemic necrosis, and mucosal sloughing. Notably, the majority of these ulcers heal within 2 to 3 weeks, with a resolution rate of 60% within 2 weeks and 100% within 3 weeks[7]. The severity of these ulcers, spanning from

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active bleeding to a clean or pigmented base, has been systematically classified by Jamwal et al.[8].

Numerous studies have explored strategies for preventing post-EVL ulcers, with a predominant focus on the efficacy of Proton Pump Inhibitors (PPIs)[1,2,5,9]. Meta-analyses indicate that acid suppression with PPIs effectively reduces ulcer size and significantly diminishes the incidence of bleeding. However, no statistically significant differences have been observed in mortality rates, chest pain, dysphagia, or length of stays[9,10]. Despite research demonstrating vonoprazan's superior efficacy in reducing the size of EVL ulcers compared to pantoprazole, the current drug reimbursement system still falls short in providing access to all patients[11]. Omeprazole, a commonly used PPI, has been deemed safe for administration in cirrhotic patients classified as Child-Turcotte-Pugh (CTP) A or B according to a meta-analysis[12]. Additionally, Mohammad G, et al. reported that only 60% of cirrhotic patients developed post-variceal ligation ulcers when administered pantoprazole[13]. Sucralfate, employed in the treatment of gastroduodenal ulcers, functions by creating a mucous barrier for mucosal protection from acid and gastric enzymes, and by enhancing the formation of Prostaglandin E2[6,14]. Sakr et al. demonstrated a statistically significant reduction in post-EVL ulcer rates with sucralfate compared to a placebo group[6].

Presently, there is a paucity of studies examining the combination of PPIs and sucralfate for preventing post-EVL ulcers. The primary aim of the present study is to assess the efficacy of a combination regimen comprising PPI (omeprazole) plus sucralfate suspension in comparison to PPI (omeprazole) alone for preventing post-EVL ulcers. Furthermore, the secondary objective is to evaluate the efficacy of both regimens in preventing symptoms after EVL.

Materials and Methods

Study design & population

A single-blinded, prospective, randomized controlled trial was conducted at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, spanning the period from March 2019 to December 2022. The study protocol received approval from the Khon Kaen University Ethics Committee for Human Research, adhering to the principles outlined in the Declaration of Helsinki and the International Conference on Harmonisation (ICH) Good Clinical Practice Guidelines. The trial is registered under the number HE621042. and it is also registered in the Thai Clinical Trials Registry (TCTR) under the number TCTR20190421003.

Prospective enrollment targeted patients diagnosed with liver cirrhosis classified as CTP A or B and presenting with EV as confirmed by esophagogastroduodenoscopy (EGD) who required EVL. Inclusion criteria encompassed individuals aged 18 years or older, diagnosed with cirrhosis rated as CTP score A or B resulting from various etiologies such as hepatitis B or C infection, or alcohol-related causes. Diagnosis relied on laboratory assessments (liver function test), radiological examinations (Ultrasound, CT scan, MRI), or pathological findings (liver biopsy). Mandatory criteria included the presence of EV identified during elective EGD and the necessity for EVL as part of primary prophylaxis against variceal bleeding. Furthermore, participants were required to provide informed consent to voluntarily participate in the study. Exclusion criteria included 1) history of previous EV rupture, 2) contraindications for EGD or EVL, including a platelet count below 50,000/uL, and an INR >2.5 that cannot be corrected by plasma, 3) prior treatment with sclerotherapy or EVL, 4) presence of esophageal ulcer or esophagitis before the administration of EVL, 5) recent use of PPI, H2 receptor antagonists, or sucralfate within 7 days before the commencement of the study, 6) use of anti-platelet drugs or fibrinolytic drugs within 7 days prior to the study, 7) diagnosis of Barrett's metaplasia. 8) history of previous procedures for treating acid reflux (anti-reflux procedure), 9) pregnancy or breastfeeding, 10) presence of an active severe illness with a life expectancy of less than 1 year, 11) hypersensitivity to drugs (specifically omeprazole and/or sucralfate) and current use of medications with potential drug interactions with those administered in the present study.

Procedure

Examined participants meeting the eligibility criteria underwent a comprehensive data collection process, which included gathering fundamental information such as age, gender, medical history, medication usage (including β-blocker intake), alcohol consumption history, the etiology, and severity of cirrhosis (evaluated through CTP and Model for End-stage Liver Disease [MELD] scores), as well as pertinent laboratory results. Additionally, endoscopic findings, including the number and severity grading of EV, were documented by a consensus reached among four experienced endoscopists in accordance with the Japanese Research Society for Portal Hypertension Classification[15]. The allocation of patients into two groups prior to EVL was performed through systematic randomization at a ratio of 1:1, utilizing blocks of two and four to ensure a balanced distribution.

The study group, receiving a combination of PPI and sucralfate, was administered Omeprazole (20 mg) twice daily (morning and evening before meals) along with sucralfate suspension (1 gm/5 ml) four times daily (at least 1 hour before meals—morning, afternoon, evening, and before bedtime) for a duration of 2 weeks.

The control group, exclusively receiving PPI, was administered Omeprazole (20 mg) twice daily (morning and evening before meals) for the same 2-week duration.

Both groups were required to adhere to a regimen ensuring the consumption of the medications not less than 80% of the prescribed dosage.

Endoscopic variceal ligation

Researchers scheduled EVL appointments for patients, administering general anesthesia for the procedure. Prior to the intervention, patients underwent standard pre-procedural assessments, including blood tests, electrocardiograms, and chest x-rays. During the procedure, endoscopists performed a comprehensive ligation of varices in a single session, termed complete EVL. Following EVL, the endoscopists were blinded to the treatment group. Subsequently, patients were prescribed medications according to randomization by a separate doctor.

Evaluation of studies

This assessment will occur two weeks post-EVL and will involve the following steps:

1) Verification of patients' drug compliance through the examination of the drug packaging provided to them.

2) EGD follow-up to quantify the number of EVL ulcers and categorize them according to Jamwal's classification.

3) Patient inquiry regarding symptoms experienced after EVL over a two-week period. This includes chest pain, dysphagia, nausea and vomiting, rash, and diarrhea, assessed through a tri-pod questionnaire. The assessors will be blinded to ensure impartial evaluation.

Outcomes

The principal objective was to assess the effectiveness of the combination of omeprazole plus sucralfate suspension compared to the omeprazole alone group in preventing post-EVL ulcers in patients with cirrhotic CTP A and B status. The secondary aim was to evaluate the occurrence of symptoms and complications after EVL over a two-week period.

Statistical analysis

Descriptive statistics were employed to summarize baseline demographic data, utilizing frequency, percentage. Analytic statistics were applied to assess outcome data through per-protocol analysis or intention-to-treat methods. Statistical calculations were performed using Stata version 10.1. The sample size was determined using the formula for estimating sample size in a two-sample comparison of proportions, testing the null hypothesis (Ho: p1 = p2). With a confidence level of 95%, power set at 80%, a two-sided α of 0.05, and accounting for a dropout rate of 10%, the calculated total sample size for each group was 40 patients.

Results

A total of 86 patients underwent screening for the present study. One patient was excluded due to a prescription error, and another patient was excluded because of a stroke. The remaining 84 patients were successfully enrolled and randomized, with 42 patients in each study group, as illustrated in Figure 1. Two patients in the control group were lost to follow-up, but all other patients exhibited drug compliance exceeding 80%.

Baseline demographic characteristics were comparable between both groups, with the exception of the presence of hepatocellular carcinoma (28.6% vs. 50%, p=0.047). The majority of patients were male (51.6% vs. 48.4%), had cirrhosis classified as CTP A (59.5% vs. 65%), and had a mean age of 55.8±8.8 vs. 58.3±6.5. The leading cause of cirrhosis was hepatitis C virus infection (61.9% vs. 65.5%). The most common endoscopic finding was EV F2 (57.1% vs. 67.5%), and EV with angioma was present in 52.4% vs. 52.5% of cases. The mean number of esophageal ligation rings was 6.3±2.5 vs. 6.5±2.2 (Table 1).

At the 2-week follow-up endoscopy, the majority of patients in both groups exhibited EVL ulcer type D (95.2% vs. 87.5% for combination omeprazole and sucralfate suspension vs. omeprazole alone). Some patients presented with EVL ulcer type C (2.4% vs. 7.5%), while others had no ulcer (2.4 vs. 5%), with no significant differences in ulcer type (p=0.4), the number of ulcers (4.4±2.0 vs. 4±2.1, p=0.43), and the percentage decrease in the number of EVL ulcers (33.3%±35.8% vs. 35.7%±28.8%, p=0.47) (Table 2).

Regarding post-EVL ulcer complications, there were no significant differences in chest pain (26.2% vs. 35%, p=0.38), dysphagia (33.3% vs. 42.5%, p=0.39), nausea and vomiting (4.8% vs. 10%, p=0.43), rash (0% vs. 2.5%, p=0.49), and diarrhea (4.8% vs. 5%, p=1.00). However, a trend toward decreased complications was observed with combination omeprazole and sucralfate suspension compared to omeprazole alone, as illustrated in Figure 2.

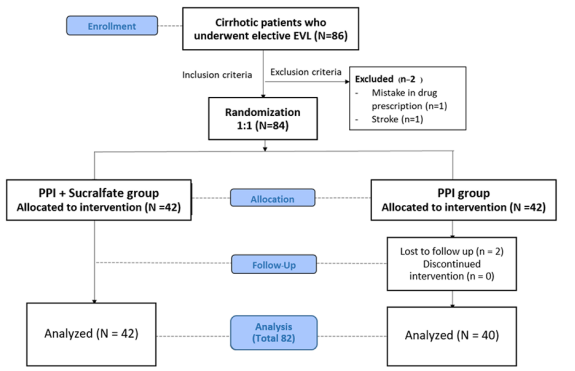

Figure 1. Consort diagram.

Table 1. Baseline characteristics of the 82 patients

Characteristics	PPI + Sucralfate (n=42)	PPI (n=40)
Gender (Male)	32 (51.6%)	30 (48.4%)
Age (years)	55.8±8.8	58.3±6.5
Body mass index (kg/m^2)	24.7±3.3	23.9±3.2
Child turcotte pugh score		
- A	25 (59.5%)	26 (65%)
- B	17 (40.5%)	14 (35%)
Cause		
- HCV	26 (61.9%)	26 (65.5%)
- HBV	5 (11.9%)	7 (17.5%)
- NASH	3 (7.1%)	2 (5%)
- Alcohol	6 (14.2%)	7 (17.5%)
MELD	12.1±4.2	11.2±3.0
Present hepatocellular carcinoma*	12 (28.6%)	20 (50.0%)
Hct (vol %)	35.1±5.7	35.5±5.1
Platelet (x103/uL)	110.3±61.4	99.7±39.4
INR	1.2±0.1	1.2±0.1
Albumin (g/dl)	3.4±0.7	3.6±0.5
Esophageal varices F stage		
- F2	24 (57.1%)	27 (67.5%)
- F3	18 (42.9%)	13 (32.5%)
Present esophageal varices angioma	22 (52.4)	21 (52.5)
Number of esophageal varices columns	3.4±0.8	3.4±1.0
Number of esophageal varices ligation rings	6.3±2.5	6.5±2.2

Data are expressed as number (percentage) or mean±SD. * Significant difference between two groups

HBV=Chronic hepatitis B virus; HCV=Chronic hepatitis C virus; Hct=Hematocrit; INR=international normalized ratio; MELD=Model for End-Stage Liver Disease; NASH=Non-Alcoholic Steatohepatitis

Table 2. Endoscopic findings on follow-up at 2 weeks

Characteristics	PPI + Sucralfate (n=42)	PPI (n=40)	P value
EVL ulcer Jamwal classification			
- No ulcer	1 (2.4%)	2 (5%)	0.41
- A	0	0	
- B	0	0	
- C	1 (2.4%)	3 (7.5%)	
- D	40 (95.2%)	35 (87.5%)	
EVL ulcer numbers	4.4±2.0	4±2.1	0.43
Percent change of EVL ulcer numbers	33.3±35.8	35.7±28.8	0.47

Data are expressed as number (percentage) or mean±SD

EVL=Esophageal varices ligation

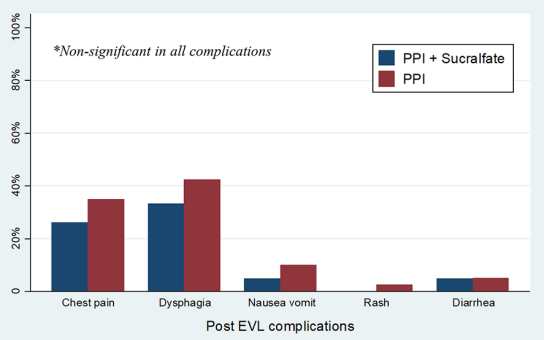

Figure 2. Compare percentage of post EVL complications in each study group

Discussion

The present study marks a significant advancement by expanding the enrolled patient population and systematically assessing post-EVL complications and the healing response following medication therapy. Although the findings reveal no statistically significant difference in the efficacy between the combination of omeprazole and sucralfate suspension and omeprazole alone in preventing post-EVL ulcers among cirrhotic patients categorized as CTP A or B, these results align with those of a preceding study[16]. Nevertheless, our study contributes additional insights into post-EVL complications and the numerical reduction of ulcers following medical intervention.

Despite the absence of discernible differences in post-EVL complications and the reduction in ulcer numbers, it is noteworthy that the study sheds light on the potential impact of acid suppression on sucralfate polymerization, suggesting a mechanism that could compromise the drug's efficacy in diminishing ulcer formation[17]. As the present study omitted patients with cirrhosis CTP C or high score of MELD (≥18), a group prone to heightened post-EVL ulcer complications due to impaired hemostasis and wound healing compared to cirrhosis CTP A or B, the risk of bleeding and other complications escalates[18-21]. Consequently, no discernible variance in the effectiveness of the combination drug versus omeprazole alone was observed.

It is particularly noteworthy that an investigation has revealed a notably higher incidence of post-EVL ulcers compared to a precedent study[6], reaching a substantial 96.34%. Despite the administration of either PPIs or sucralfate for treatment. This is due to the study's requirement for complete EVL banding, ensuring complete variceal eradication, utilizing a full band, and employing a larger ring volume than usual in the present study results in heightened esophageal tension and an increased risk of ischemia, potentially leading to numerous ulcers. However, none of the individuals manifesting these post-EVL ulcers experienced bleeding. This underscores the efficacy of PPIs or sucralfate to prevent bleeding subsequent to EVL aligning with findings from prior studies[1,2,5,9]. Consequently, the prevalence of patients with EVL ulcer types A, B, and C was limited in both study groups, thereby influencing the evaluation of the efficacy of the investigated drugs,

encompassing both combination therapy and omeprazole alone.

In terms of complications, our study indicates no statistically significant disparities between the combination therapy and omeprazole alone. This lack of significance may be attributed to the comparable number and types of ulcers observed in the primary outcome, thereby not exerting an influence on the secondary outcome. However, the observed trend towards a reduction in complications with the combination therapy compared to omeprazole alone raises intriguing possibilities, especially considering that a larger sample size might elucidate notable differences in this aspect.

Several limitations in our study. Firstly, the study is confined to a single-center trial, limiting the generalizability of the results. Secondly, the absence of ulcer size measurement in the primary outcome contrasts with prior studies. Lastly, the use of a 3-point Likert scale for the secondary outcome, while practical, may lack the precision required to distinguish outcomes accurately. Employing a well-designed questionnaire focusing on individual symptoms could potentially enhance the precision and relevance of our assessments.

Conclusion

The present study indicates no discernible differences in post-EVL ulcer type, EVL ulcer numbers, percentage reduction in EVL ulcer numbers, and complications between the combination of omeprazole plus sucralfate suspension and omeprazole alone.

What is already known on this topic?

Meta-analyses indicate that acid suppression with PPIs effectively reduces ulcer size and significantly diminishes the incidence of bleeding.

Sucralfate is enhancing the formation of Prostaglandin, leading to a significant reduction in post-EVL ulcer rates.

What this study adds?

Combining PPI with sucralfate suspension does not enhance efficacy in reducing both the number and severity of post-EVL ulcers. Additionally, there is no reduction in other complications such as chest pain, dysphagia, nausea vomiting, and diarrhea. Nevertheless, there may be a trend indicating potential benefits in reducing the incidence of these complications with this combined approach.

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Conflicts of interest

The authors declare no conflicts of interest.

References

1. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey WD. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Am J Gastroenterol 2007;102:2086-102.
2. Hwang JH, Shergill AK, Acosta RD, Chandrasekhara V, Chathadi KV, Decker GA, et al. The role of endoscopy in the management of variceal hemorrhage. Gastrointest Endosc 2014;80:221-7.
3. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology 2017;65:310-35.
4. Tripathi D, Stanley AJ, Hayes PC, Patch D, Millson C, Mehrzad H, et al. U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. Gut 2015;64:1680-704.
5. de Franchis R. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63:743-52.
6. Sakr MA, Hamed W, Gafaary MME, El-Folly RF, El-Hamamsy M. Role of sucralfate in promoting healing of post band variceal ulcer. Adv Nat Sci 2011;4:7-14.
7. Nijhawan S, Rai RR, Nepalia S, Pokharana DS, Bharagava N. Natural history of postligation ulcers. Am J Gastroenterol 1994;89:2281-2.
8. Jamwal K, Kumar M, Maiwall R, Kumar G, Sharma B, Sarin S. Post EVL (Endoscopic Variceal Ligation) ulcer bleeding: A new classification and outcomes. Gastroenterology 2017;152(5 Suppl 1):S908.
9. Zhu J, Qi X, Yu H, Su C, Guo X. Acid suppression in patients treated with endoscopic therapy for the management of gastroesophageal varices: a systematic review and meta-analysis. Expert Rev Gastroenterol Hepatol 2018;12:617-24.
10. Khawaja I, Babar M, Awan SA, Shaikh AJ, Abbasi AA. Effectiveness of proton pump inhibitor therapy in the prevention of bleeding after prophylactic endoscopic variceal band ligation. Cureus 2023;15:e33932. doi: 10.7759/cureus.33932.
11. Lashen SA, Shamseya MM, Shamseya AM, Hablass FH. Efficacy of Vonoprazan vs. Pantoprazole or non-acid suppression in prevention of post-variceal ligation ulcer bleeding in portal hypertension: A multi-arm randomized controlled trial. J Clin Exp Hepatol 2023;13:962-71.
12. Weersink RA, Bouma M, Burger DM, Drenth JPH, Harkes-Idzinga SF, Hunfeld NGM, et al. Safe use of proton pump inhibitors in patients with cirrhosis. Br J Clin Pharmacol 2018;84:1806-20.
13. Soliman GMM, Amer Y, Mostafa S. Comparative study between the efficacy of rebamipide, sucralfate and

pantoprazole in treatement of post banding variceal ulcers. Al-Azhar Assiut Med J 2015;13:28-35.
14. MIMS.com Thailand. Sucralfate: Indication, dosage, side effect, precaution [Internet]. 2024 [cited 2024 Feb 13]. Available from: https://www.mims.com/thailand/drug/info/sucralfate?mtype=generic.
15. Beppu K, Inokuchi K, Koyanagi N, Nakayama S, Sakata H, Kitano S, et al. Prediction of variceal hemorrhage by esophageal endoscopy. Gastrointest Endosc 1981;27:213-8.
16. Karki B, Shrestha R, Paudel B, Sudhamshu KC, Khadka D, Thapa S, et al. Outcome of post esophageal variceal band ligation with sucralfate and proton pump inhibitor vs. Proton pump inhibitor alone in cirrhotic patients. Nepal Med J 2019;2:209-14.
17. Lima TB, Silva GF, Romeiro FG. Diagnosis, management and prophylaxis of bleeding related to post-esophageal variceal band ligation ulcer in cirrhotic patients. Case Rep Intern Med 2018;5:23-31.
18. Ryu H, Kim TU, Yoon KT, Hong YM. Predicting the risk of early bleeding following endoscopic variceal ligation in cirrhotic patients with computed tomography. BMC Gastroenterol 2023;23:410. doi: 10.1186/s12876-023-03038-1.
19. Yang MT, Chen HS, Lee HC, Lin CL. Risk factors and survival of early bleeding after esophageal variceal ligation. Hepatogastroenterology 2007;54:1705-9.
20. Berreta J, Kociak D, Corti R, Morales G, Ortiz M, Laplacette M, et al. Predictors of intrahospitalary mortality in the upper gastrointestinal variceal bleeding due to chronic liver disease treated endoscopically. Acta Gastroenterol Latinoam 2008;38:43-50.
21. de Brito Nunes M, Knecht M, Wiest R, Bosch J, Berzigotti A. Predictors and management of post-banding ulcer bleeding in cirrhosis: A systematic review and meta-analysis. Liver Int 2023;43:1644-53.