

Original Article

Outcome of Post Esophageal Variceal Band Ligation with Sucralfate and Proton Pump Inhibitor vs. Proton Pump Inhibitor Alone in Cirrhotic Patients

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ABSTRACT

Introduction: Endoscopic band ligation is the mainstay of treatment in bleeding varices in cirrhosis. Subsequent bleeding from the band ulcers is a possible complication. Proton pump inhibitors and Sucralfate are commonly used post band ligation and often in combination. The aim of the study was to identify the advantage of combining Sucralfate to proton pump inhibitor in reducing the number and size of band ulcers.

Materials and Methods: This was an open label comparative study conducted in a tertiary level hospital of Nepal. Patients with cirrhosis after band ligation were included. Eligible patients were randomized into a proton pump inhibitor alone (Group A) or proton pump inhibitor and sucralfate group (Group B) and they underwent upper gastrointestinal endoscopy after two weeks. Baseline parameters, number and mean size of band ulcers were compared.

Results: A total of 58 patients, 29 in each group, were evaluated. The baseline characteristics were comparable. EBL was done for bleeding varices in 51.7% and as primary prophylaxis in the rest of them. All the patients had band ulcers after two weeks. The mean size of the largest ulcer was 1.62 ± 0.72 and 1.10 ± 0.60 ($p=0.78$) respectively in group A and B. Low albumin was significantly associated with OR of 8.7 (95% CI:1.68-44.99) for the formation of multiple (more than two) ulcers ($p=0.01$).

Conclusions: The ulcer formation was universal after band application. The addition of sucralfate did not offer more benefits in terms of the number and mean size of the ulcer. Low albumin was the independent predictor for multiple ulcer formation.

Keywords: Band ligation; Band Ulcer; Esophageal varices; Proton pump inhibitors; Sucralfate

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INTRODUCTION

Portal hypertension is the pathophysiologic basis for the formation of oesophageal varices in cirrhosis.¹ Bleeding from varices occurs in about 30% of patients with varices and carries a mortality risk of 15%-30% per episode.² Endoscopic sclerotherapy (ES) was the standard of care until the introduction of more effective endoscopic band ligation (EBL) technique in 1986.^{3,4} Post-EBL bleeding was reported up to 7.7% in one study.⁵ Once there is EBL ulcer bleeding, the management can be challenging and the mortality can reach as high as 52%.⁶

The EBL ulcers heal faster than post-sclerotherapy ulcers.⁷ Use of either proton pump inhibitors (PPI) or mucoprotectant like Sucralfate can reduce the ulcer size and its numbers.⁸ A combination of PPI and sucralfate are often used post banding although the evidence for the benefit of such combination is still not clear. The aim of this study was to find out if the addition of sucralfate to PPI would lead to faster healing of the EBL ulcers in terms of its number and size leading to fewer ulcer related complications.

MATERIALS AND METHODS

This was a hospital based open label randomized study conducted in one of the tertiary referral hospitals of Nepal. The study was conducted in the Gastroenterology and Hepatology Unit of Bir Hospital from May to December 2018. Ethical approval was taken from the institutional review board of the institute. The trial was registered in the UMIN database as UMIN-000035296 (<https://www.umin.ac.jp/ctr/>). Data collection was started after the Institute Review Board (IRB) approval. Patients more than 18 years and less than 65 years, who underwent EBL either as primary or secondary prophylaxis were included in the study after informed consent. Patients presenting with fundal varices, having endoscopically confirmed pre-existing oesophageal ulcers and with co-morbidities like diabetes, bleeding disorders, heart failure, chronic kidney disease and malignancy were excluded. Clinical, epidemiological, laboratory and endoscopic data were collected at the time of randomization and during follow up.

Eligible patients were randomized into a PPI alone group (Group A) or PPI plus sucralfate group (Group B). A sealed envelope method was used for randomization. All of them underwent a variceal band ligation procedure using a multi-band ligator device with six set rubber bands attached to the distal end of the gastroscope. The number of bands applied depending upon the number and size of varices with a maximum number of bands applied in a session to be six. The patient was observed for any post procedural chest pain that was assessed subjectively and graded as no, mild, moderate and severe described by the patient as follows-Mild: chest pain that could be tolerated, Moderate: could be tolerated in between and Severe: awoken the patient from sleep and need medication.

Patients in group A were given Tab pantoprazole 40 mg twice daily for 14 days where as patients in group B were prescribed syrup Sucralfate 10 ml four times daily in addition to pantoprazole for the same duration. All patients were inquired by telephone at the end of one week regarding post banding bleeding (haematemesis and/or melena), chest pain (mild, moderate and severe) and

dysphasia. At the end of two weeks, all the patients were assessed clinically. Upper gastrointestinal endoscopy was done to assess the presence of EBL ulcers, number of ulcers and the size of ulcers. The size of the largest ulcer was measured using the measurement of opened standard biopsy forceps which was taken as 5mm.

The primary outcome was to compare the incidence of EBL ulcers, their number and mean size of the largest ulcer in both the groups. The secondary outcome was to find the incidence of post EBL chest pain, bleeding or death due to any cause within two weeks of the procedure. We also aimed to find out if there were any predictors of multiple ulcers (>2).

The sample size was calculated using the incidence of EBL ulcer in the study done by Mohamed Amin Sakr et al⁹ who used sucralfate to reduce the incidence of post EBL ulcers, where 12 patients (38.7%) in the study group developed post-band ulcers versus 23 patients (74.2%) in the control group. It was calculated that a total 58 patients (29 in each arm) would be required for the analysis with an alpha error at 0.05 and the power of study at 80%. The participants were randomized using sealed envelopes containing either group A or group B inside. Both treating physicians and the patients knew about the treatment being offered to them.

We used intention-to-treat analysis for all efficacy analyses, analyzing all participants who underwent randomization. Continuous variables were expressed as mean \pm standard deviation (SD) and categorical variables as numbers and frequencies. Categorical variables were compared using the χ^2 test and continuous variables with independent t test. Bi variate and multivariate analysis were carried out to assess the degree of association between the formation of multiple ulcers (>2) and the above-mentioned variables. All statistical analyses were performed using the SPSS 20.0 statistical package.

RESULTS

A total of 58 patients were included in the study with 29 in each group (fig. 1).

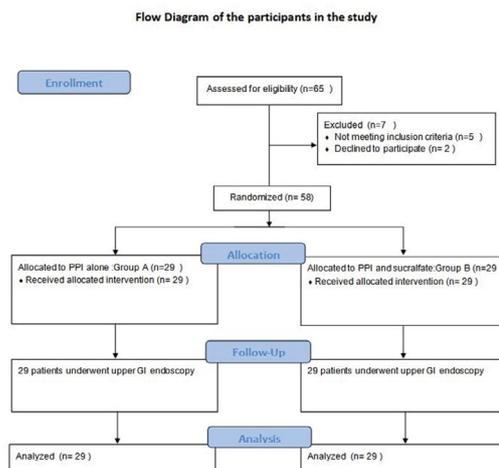


Figure 1: Participant flow chart as per CONSORT guideline

The study period was of eight months commencing from May 2018 and ended in December 2018 after the fulfillment of sample size. The baseline demographic and lab parameters were comparable in both the arms (Table 1).

Table 1: Baseline characteristics in the study groups (n=58)

Variables (Mean ± SD)	Group A (PPI alone) n=29	Group B (PPI + Sucralfate) n=29	p-value
Age	45.48 (± 6.78)	44.93 (± 8.4)	0.56
Sex (male)	25 (86.21%)	26 (89.7%)	1.0
Bleeder	16 (55.2%)	12 (41.4%)	0.29
Etiology - Alcohol	27 (93.1%)	27 (93.1%)	1.0
Child Pugh			
A	0	2 (6.9%)	0.34
B	16 (55.2%)	17 (58.6%)	
C	13 (44.8%)	10 (34.5%)	
Albumin	2.84 ± 0.41	2.97 ± 0.65	0.37
Bilirubin	4.9 ± 3.2	4.3 ± 3.2	0.78
INR	1.64 ± 0.45	1.59 ± 0.22	0.62
Hb	9.3 ± 1.7	10.05 ± 0.89	0.06
Creatinine	1.15 ± 0.72	1.1 ± 0.6	0.78
CTP score	9.5 ± 1.8	8.9 ± 1.5	0.16
APRI, Median(IQR)	2.3 (1.70, 3.75)	2.3 (1.20, 3.30)	0.56*
MELD	18.24 ± 4.6	17.24 ± 3.67	0.36
Upper GI endoscopy findings			
No of varices	3.93 ± 0.25	3.97 ± 0.18	0.56
No of Bands applied	5.52 ± 0.7	5.62 ± 0.6	0.56

*Mann-whitney test

The mean age of the patients was 45.48 ± 6.78 years and 44.93 ± 8.4 years in the study groups A and B. There was male predominance with 87.9% out of total. Almost half of the patients received the esophageal band ligation for the secondary prophylaxis i.e. as a part of the treatment for the bleeding. The alcohol was the most common etiology of chronic liver disease in 93.1 % followed by Hepatitis B and Non-alcoholic Steatohepatitis. Most of the patients were in either Child B or Child C class. The mean albumin was 2.84±0.41 mg/dl and 2.97±0.65 mg/dl (p=0.37) in the study groups A and B respectively. The bilirubin, prothrombin time with international normalized ration (INR), Aspartate aminotransferase to platelet ratio index (APRI) and model for end-stage liver disease (MELD) scores were comparable.

On upper gastrointestinal endoscopy, all the patients have large varices with red color signs. Most of them had more than three varices and the mean number of bands applied were 5.52 ± 0.7 and 5.62±0.6 in group A and B respectively (Table 1). All the patients were called for follow up at the end of two weeks. The patients in both groups have similar incidences of chest discomfort and bleeding complication. One patient in each group had post band ulcer related bleeding and both were managed conservatively with hospital admission, intravenous octreotide, and blood products. There was no mortality for two weeks in any of the groups.

All patients had at least one band ulcer (fig. 2) at the end of two weeks. There were 2.79±0.97 and 2.76±0.63 number of ulcers in groups A and B respectively. The mean size of the largest ulcer was 1.62 ± 0.72 cm and 1.10 ± 0.6 cm (p=0.78) in groups A and B respectively and the difference was not statistically significant (Table 2). The group A had more than three ulcers compared to group B (20.71% vs 10.5%) but it did not reach statistical significance, p=0.34 (fig. 3).



Figure 2: Representative band ulcer in the study

Comparison of No of ulcer in two groups

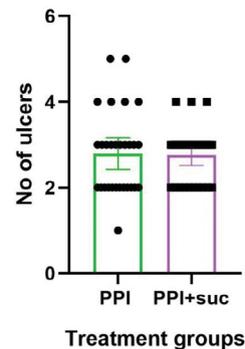


Figure 3: Comparison of number of ulcers in both the groups

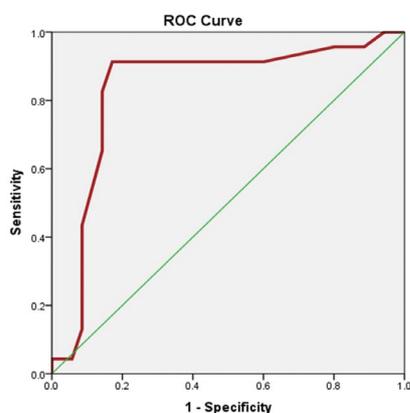
Table 2 : Upper GI endoscopic findings on follow up at the end of two weeks

Variables (Mean ± SD)	Group A, n=29	Group B, n=29	p value
1	1 (3.4%)	0	0.34
2	12 (41.4%)	10 (34.5%)	
3	10 (34.5%)	16 (55.2%)	
4			
5			
Size (largest ulcer)	1.62 (± 0.72)	1.10 (± 0.6)	0.78
Chest pain	6 (20.7%)	7 (24.1%)	0.75
EBL ulcer bleeding	1 (3.4%)	1 (3.4%)	1.0

Table 3: Bi-variate and multivariate analysis for the formation of multiple (>2) ulcers

Variables	Crude Odds ratio (OR)	p value	Adjusted OR With 95% CI	p value
Group (Sucralfate)	1.54 (0.54-4.45)	0.42	-	-
Platelet < 150 lac/cc	1.26 (0.30-5.30)	0.75	-	-
APRI >2.2	1.73 (0.59-5.01)	0.30	-	-
INR >1.7	1.06(0.26-4.26)	0.94	-	-
MELD >10	1.68 (1.35-208)	1.00	-	-
Albumin < 2.8 mg/dl	11.12 (2.26-54.77)	0.001	8.7 (1.68-44.99)	0.01
CTP score > 9	3.68 (1.18-11.47)	0.020	2.1 (0.60-7.23)	0.24

Low albumin <2.8 mg/dl and CTP score >9 were significantly associated with the formation of multiple ulcers on bi-variate analysis however only low albumin reached statistical significance with OR of 8.7 (95% CI:1.68-44.99) (Table 3). The regression model was fit (p value for Hosmer Lemeshow test =0.75) with a significant Omnibus test value of p=0.001. When the ROC curve was analyzed for the serum albumin and the formation of multiple ulcers, the AUROC was 0.83 with a statistically significant p value <0.001, 95 % CI:0.72-0.95(fig. 4).

**Figure 4: Receiver-operator characteristics (ROC) curve for serum albumin to predict the formation of multiple band ulcers.**

The best cut off value of albumin from the ROC co-ordinates of the curve was 2.85 mg/dl with a sensitivity of 91.3% and specificity of 83.0% for the prediction of multiple ulcers.

DISCUSSION

The most common etiology of chronic liver disease in our study was alcohol (93.1%). It was different from the Korean study¹⁰ where alcohol was etiology in only 38.6% and 51.1% had hepatitis B infection. In another study by Sakr et al⁹ from Egypt, hepatitis C was the major cause in 96.8% followed by schistosomiasis but not alcohol. The alcohol predominance in our study can be explained due to the higher number of male patients in our study. The male population are likely to consume more alcohol in our culture. In a study done previously in our institute, alcohol was the main etiology for chronic liver disease.¹¹

EBL has become the mainstay of the management of esophageal varices in chronic liver disease.¹² The use of PPI has been shown to decrease the EBL related bleeding in a retrospective study by Kang SH et al¹⁰ where 14 out of 505 patients developed post EBL bleeding and in the multivariate analysis not administering PPIs (OR 8.2, p=0.002) was associated with bleeding. The role of sucralfate in ulcer healing was done mainly for the sclerotherapy related ulcers and has shown to be effective.¹³ This is the first of its kind of study where we have tried to combine PPI and sucralfate for the treatment of band ulcers.

In our study, all the patients had at least one ulcer at the end of two weeks. It is consistent with the finding that ulcer formation is not the complication but the part of the natural history in the esophageal band ligation.¹⁴ The ulcer formation is the universal process that eventually heals by fibrosis and thus helps in the obliteration of the varices. A study by Sakr et al⁹ where the patients were subjected to endoscopy at two weeks, only 56.4% had ulcers unlike our results. Whether the predominant etiology that was alcohol in our study has resulted in delayed ulcer healing or there are other factors contributing to slow healing of ulcers needs to be analyzed further.

There were no statistically significant differences in the number and the size of the ulcer in both the study groups. The PPI alone group had more than three ulcers compared to the other group. The number and size of the ulcer have been taken as the surrogate marker for the risk of bleeding in our study since the sample size would have been very high if we had taken the incidence of post EBL bleeding. There are however no prospective studies to confirm that the increased number and larger ulcers will translate clinically into more incidences of bleeding complications.

The use of PPI had shown to be effective in reducing the size of ulcer in a randomized trial where the mean size of ulcer was 37 mm² and 82 mm² in the group with pantoprazole 40 mg vs placebo (p<0.01).¹⁵ Similarly the use of sucralfate has also been shown to decrease the incidence as well as the mean size of post band ulcers; incidence : 38.7% in sucralfate group vs 74.2% in the control group (p= 0.005) and mean size: 2.7 mm ± 1.2 vs 3.8mm ± 1.7 (p=0.043) respectively.⁹ This finding was not reproduced in our study when we used the combination of both pantoprazole and sucralfate. The utility of using sucralfate have been questioned in other trial previously by Nijhawan et al¹⁶ where the authors showed that all the post band ulcers heal by third week irrespective of use of sucralfate. In a study by Wu CK et al,¹⁷ where the authors retrospectively evaluated 637 patients who underwent EBL with either acid suppression therapy or none, they found that adjuvant acid suppression may not change the re-bleeding rate and mortality outcome.

Since the formation of band ulcer in our study was universal unlike the previous study,⁹ we tried to find out if there are any variables associated with this occurrence by using the bi-variate and multivariate analysis. Low albumin was significantly associated with the occurrence of multiple ulcers. We took cut off of albumin as less than 2.8 as it represented the lowest threshold while calculating CTP score. The finding was similar to the study by Vanbiervliet G et al⁶ where albumin was shown to be predictor of bleeding risk along with presence of peptic esophagitis, high APRI and low prothrombin index. The low albumin can be associated with delayed ulcer healing and thus more ulcer related complications. Low albumin can also explain the universal occurrence of ulcers in our study. It also been associated with significant recurrent bleeding and mortality in peptic ulcer disease.¹⁸

There are some limitations in our study. We could not take the incidence of ulcer bleeding as the primary outcome due to limited sample size. This was single center study and was not

blinded. The compliance for the use of sucralfate was inquired at the follow up and found to be good, however it is likely that the participants might have missed or did not take the medications as advised.

CONCLUSIONS

Adding sucralfate in a patient who is already taking PPI may not offer added benefit to reduce the number and size of ulcers. It will only add to the cost of the treatment. Low albumin is the independent predictor of multiple ulcers formation after esophageal band ligation.

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