Vol 4 | Issue 1 | Pages 120-125

Journal of Gastroenterology Research
ISSN: 2578-6210

Retrospective Study

DOI: 10.36959/621/604

Identification of High-Risk Individuals for Bleeding from Post-Endoscopic Variceal Band Ligation Ulceration

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Abstract

Background and aims: Endoscopic variceal band ligation (EVBL) plays an important role in management of esophageal varices for both primary prophylaxis and acute hemorrhage. However, life-threatening bleeding secondary to post-banding ulceration, whilst uncommon, can occur. This study aimed to identify rates of EVBL-induced ulcer bleeding in elective and non-elective settings, and to assess potential risk factors which contribute to this serious complication.

Method: This was a retrospective cross-sectional analysis of cirrhotic patients who underwent EVBL over a four-year period in a tertiary hospital in Australia. Differences between the bleeding group and controls were assessed using univariate analysis.

Results: 336 episodes of EVBL were identified with 19 episodes (5.6%) resulting in EVBL-induced ulcer bleeding. The mean time to re-bleeding occurred within 11 days (+/-1.36) of ligation. The incidence of EVBL-induced ulcer bleeding was 8.5% (N = 11) in the emergent setting compared to 4.0% (N = 8) in the elective setting. Factors found to significantly affect the rate of EVBL-induced ulcer bleeding included previous history of variceal bleeding (OR 2.91, p = 0.0333), presence of high-risk stigmata on endoscopy (OR 7.83, p = 0.016) and lower hemoglobin at time of initial endoscopy (mean 88.58 vs. 107.5, p = 0.0012). Unlike previous studies, proton pump inhibitor (PPI) use was not protective in reducing the risk of post EVBL-ulcer bleeding (OR 1.39, p = 0.62).

Conclusion: Strategies to address these risk factors should be adopted prior to endoscopic band ligation to minimise the risk of EVBL-ulcer bleeding. Consideration should also be given to investigating whether PPI use among this high-risk group confers any benefit.

Keywords

Liver cirrhosis, Esophageal varices, Endoscopy, Gastrointestinal hemorrhage, Ulcer

Introduction

Bleeding from gastroesophageal varices is a common complication of cirrhosis with associated portal hypertension and remains one of the leading causes of death in this population [1]. An estimated half of all patients with cirrhosis will have gastroesophageal varices and the rate of variceal hemorrhage is estimated to range between 5-15% per year [2]. Early endoscopic intervention is a routine part of acute gastroesophageal variceal hemorrhage management as only 50% of patients stop bleeding spontaneously, with high re-bleeding rates without definitive therapy [3]. Endoscopic variceal band ligation (EVBL) has been demonstrated to be the most effective form of endoscopic therapy for management of esophageal varices in the acute setting, while also playing a role in primary prophylaxis where medical therapy with beta blockers is contraindicated, or fails [4,5].

In general, EVBL is considered safe with relatively few complications, of which minor transient dysphagia and pain are most common. The sequence of healing of a varix thathas been banded include strangulation by the band itself, followed by variceal thrombosis occurring with ischemic necrosis. Following this, a shallow ulcer forms, which usually heals within two weeks, resulting in fibrosis of the submu-

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Accepted: November 18, 2020

Published online: November 20, 2020

Citation: Reji R, Buckley NS, Chin J, et al. (2020) Identification of High-Risk Individuals for Bleeding from Post-Endoscopic Variceal Band Ligation Ulceration. J Gastroenterol Res 4(1):120-125

cosa. However, if the rubber band is prematurely detached (prior to venous thrombosis) marked alteration of the mucosa and resultant ulceration may occur with the potential for re-bleeding [6,7].

While the reported incidence of bleeding from post-EVBL ulcers is low at 2.3-7.3%, the mortality rate associated with this complication is between 23-52% [8]. Currently, there is a paucity of literature identifying clear risk factors which can be optimized to reduce rates of EVBL-related ulcer bleeding but given the high mortality rate, further exploration is warranted. It has been demonstrated that previous variceal hemorrhage, severity of liver disease, coagulopathy, concomitant hepatocellular carcinoma and presence reflux esophagitis increases the risk [4,8-10]. The latter has been identified as a potentially modifiable target with the use of proton pump inhibitor (PPI) therapy. However, the role of these drugs in negating the risk by means of acid suppression and therefore promoting mucosal healing remains controversial [8,10].

The aim of this study was to determine the rates of post-EVBL ulcer bleeding in both an elective and non-elective setting. The study aimed to assess potential risk factors including Model for End-Stage Liver Disease (MELD) score, Child-Turcotte-Pugh (CTP) score, platelet and hemoglobin count, reflux esophagitis, presence of hepatorenal syndrome, spontaneous bacterial peritonitis or hepatic encephalopathy and PPI use.

Methods

Study population

We conducted a retrospective study that included 329 episodes of EVBL performed at a tertiary level hospital. All patients who underwent endoscopic variceal band ligation (EVBL) at Fiona Stanley Hospital from the period of May 1st 2015 to February 28th 2019 were identified through retrospective review of the data collected via the endoscopy database, ENDOBASE. Patients were included if they were aged more than 18 years and had band ligation of esophageal varices in either the acute and/or elective setting. The 'EVBL-induced ulcer bleed' group were defined as those who had presentations to hospital with clinical evidence of gastrointestinal bleeding and had endoscopic evidence of bleeding from post-EVBL ulcers with no other cause of digestive bleeding to account for symptoms. The 'control' group were defined as subjects who did not have any episodes of re-bleeding, or those who were found to have bled from a source other than post-EVBL ulcers endoscopically (such as mucosal tears, gastro-esophageal variceal bleeding from another site, or gastric antral vascular ectasia). Subjects who died within 48 hours of EVBL were excluded on the basis that this was too short an interval to determine that their bleeding was the result of post-EVBL ulceration.

The EVBL procedures conducted in this center were performed by consultant gastroenterologists or advanced trainees under supervision. The 'Speedband Superview Super 7™ Multiple Band Ligator' (Boston Scientific) was the device used for all cases included in this study.

A number of variables including age, sex, etiology and severity of liver disease, indication for EVBL (prophylaxis vs. acute hemorrhage), previous esophageal variceal bleed, concomitant hepatocellular carcinoma (HCC) or Portal Vein Thrombus (PVT) and other features of decompensation at time of procedure (ascites, hepatic encephalopathy) were examined. Data was gathered through retrospective review of the medical records or relevant laboratory based and radiologic investigations. The baseline characteristics of all subjects are displayed in Table 1. Both CTP and MELD Scores were used as indicators of severity of disease at time of EVBL. MELD score of each subject was calculated using laboratory data taken within three months of time of endoscopy. Data of PPI, antiplatelet and anticoagulant use at the time of EVBL was collected in order to assess the influence of these variables on the rates of bleeding from post-EVBL ulceration. Endoscopic findings collected from the endoscopyat time of EVBL, included the number and grade of varices, as well as the presence of concomitant reflux esophagitis. The presence of high-risk stigmata such as red wale sign, nipple sign, cherry red spots and fibrin plug were recorded from when the initial EVBL was performed. The outcome with respect to mortality in the two groups ('EVBL-induced ulcer bleed' and 'Controls') was also analyzed. Ethical approval for this study was granted by the Research and Ethics Committee in Fiona Stanley Hospital.

Statistical analysis

Univariate analysis was used to compare between the control and bleeding groups. Analysis was performed using GraphPad PRISM software. Associations between categorical variables were assessed using Fisher's exact test to generate an odds ratio (OR). Continuous variables were assessed using Unpaired t-test. Statistical significance was defined as two-sided P-values < 0.05.

Results

A total of 640 endoscopy records were reviewed and of those, 160 subjects were identified to have had EVBL of esophageal varices during the study period. From these, a total of 336 episodes of EVBL were identified. Baseline characteristics of subjects are displayed in Table 1. 19 episodes of EVBL resulting in post-EVBL ulcer bleeding were identified (an incidence of 5.46%). The mean time to re-bleeding occurred 11 days (+/- 1.36) after the initial EVBL. Of the 336 episodes of EVBL, 129 episodes (38%) were performed in the emergent setting for management of acute gastrointestinal hemorrhage. The incidence of EVBL-induced ulcer bleeding was 8.5% (N = 11) in those with EVBL performed in the emergent setting compared to 4.0% (N = 8) in the elective setting. The mean age for subjects in the non-bleeding EVBL (control) group was 56 years (+/- SEM 2.64) in comparison to a mean age of 53 years (+/- SEM 0.65, p = 0.66) in the EVBL-induced ulcer bleeding group. Male subjects accounting for 69% of the control group and 79% in the EVBL-induced ulcer bleeding group. The mean MELD score was higher in the EVBL-induced ulcer bleeding group when compared to the control group (15.6 +/- 0.25 vs. 13.3 +/- 1.28, p = 0.19).

Clinical characteristics of both groups of subjects are sum-

Table 1: Baseline characteristics of all subjects (SD = standard deviation; SEM = Standard Error of the Mean; MELD = Model for End-Stage Liver Disease; N = population size).

Characteristics	EVBL-induced Ulcer Bleed	Control	P-value
N	19	317	
Age (mean +/- SD, SEM)	55.6 (+/- 11.5, 2.64)	56 (+/-11.5), 0.646	0.66
Male sex (N, %)	15 (79%)	220 (69%)	0.38
MELD score (mean +/- SD, SEM)	13.8 (+/- 5.6, 1.28)	15.6 (+/- 4.4, 0.247)	0.19
Child-Turcotte-Pugh Score (N, %)			
A	6 (33%)	112 (42%)	
B	6 (33%)	91 (34%)	
C	6 (33%)	64 (24%)	
Etiology of Cirrhosis (N, %)			
Alcoholic liver disease	8 (42%)	86 (27%)	
Non-alcoholic fatty liver disease	5 (26%)	50 (16%)	
Viral	0	38 (12%)	
Alcoholic liver disease and Viral	5 (26%)	88 (28%)	
Others	1 (5%)	9 (3%)	
Non-Cirrhotic	0	14 (4%)	

Table 2: Clinical characteristics of all subjects.

	EVBL-induced ulcer bleed (N, %)	Control (N, %)	Odds Ratio	Confidence Interval	P-value
PPI use	12 (71%)	201 (63%)	1.39	1.46-10.85	0.62
High risk stigmata	14 (88%)	143 (47%)	7.83	2.05-35.05	*0.0016
Previous variceal bleed	13 (68%)	135 (36%)	2.91	1.15-7.63	*0.03
Antiplatelets	3 (16%)	26 (8%)	2.1	0.61-6.83	0.22
Anticoagulants	18 (6%)	0	-	-	0.61
Indication for EVBL					
Elective	8 (42%)	198 (63%)	0.43	0.93-5.77	
Acute hemorrhage	11 (58%)	118 (37%)	2.32	0.17-1.08	0.09
Endoscopic Findings					
Number of varices (mean)	2.82	2.79			0.89
Number of bands (mean)	3.26	2.9			0.27
Reflux Esophagitis	15 (5%)	1 (5%)	1.06	0.10-6.20	> 0.99
Comorbidities					
Hepatic encephalopathy	4 (21%)	44 (15%)	1.49	0.52-4.48	0.51
Spontaneous bacterial peritonitis	0	10 (3%)			> 0.99
Hepatorenal syndrome	1 (5%)	6 (2%)	2.85	0.24-19.51	0.34
Portal vein thrombus	2 (11%)	37 (12%)	0.85	0.19-3.26	> 0.99
Ascites	9 (47%)	123 (43%)	1.19	0.49-3.08	0.81

*Significant association with an increased risk of re-bleeding.

*Significantly increased risk of EVBL-induced ulcer bleeding.

marized in Table 2. Univariate analysis was performed which identified several factors which were significantly associated with increased risk of bleeding. Subjects with a history of previous variceal bleeding were found to have a significantly increased risk of EVBL-induced ulcer bleeding (OR 2.91, p = 0.0333). The presence of high-risk stigmata on endoscopy such as red wale sign, cherry spot, white nipple sign and platelet plug was also found to have a significant association with an increased risk of re-bleeding (OR 7.83, p = 0.016). Analysis of laboratory values, which are summarized in Table 3, revealed no significance difference in the platelet count, INR, bilirubin or creatinine levels within the groups. Howev-

Table 3: Laboratory values of all subjects (INR = International Normalised Ratio).

	EVBL-induced ulcer bleed (Mean +/- SD)	Control (Mean +/- SD)	P-value
Hemoglobin	88.58 (+/- 18.92)	107.50 (+/- 24.80)	*0.0012
Albumin	30.58 (+/- 5.97)	32.24 (+/- 6.48)	0.28
Platelet count	153.20 (+/- 111.5)	121.50 (+/- 73.44)	0.08
Creatinine	91.53 (+/- 42.82)	82.67 (+/- 39.35)	0.35
INR	1.46 (+/- 0.30)	1.44 (+/- 0.56)	0.88
Bilirubin	65.79 (+/- 80.37)	41.99 (+/- 52.37)	0.07

*This group had significantly lower hemoglobin counts compared to the control group.

er, low hemoglobin was found to be a significant risk factor leading to EVBL-induced ulcer bleeding. This group had significantly lower hemoglobincounts compared to the control group (mean 88.58 vs. 107.5, p = 0.0012).

Mortality

Three subjects from the EVBL-induced ulcer bleeding group died within 21 days of re-intervention, with a 21-day mortality rate of 16%. Two of these three subjects had recurrent bleeding from their EVBL-induced ulcer. The overall 12-month mortality for subjects with EVBL-induced ulcer bleeding was 26% vs. 22% (p = 0.51) in the control group.

Discussion

Our study has demonstrated once again that while the incidence of hemorrhage from post-EVBL ulceration remains low at 5.46%, the 21-day mortality is high at 16%. This is consistent with results from other studies where the incidence of this complication was reported to be up to 7.3% [8]. Given the implications of this complication, it is imperative to identify factors that may predispose patients to bleeding.

Our analysis also shows that the presence of high-risk stigmata at the time of initial banding was a risk factor for bleeding from post-EVBL ulcers. These have been well established as risk factors for esophageal variceal hemorrhage and even early re-bleeding post band ligation but prior to this had not previously been studied with regards to its influence on the risk of post-EVBL ulceration bleeding [11-13]. These findings suggest that subjects with more fragile mucosa at time of band placement are more likely to experience early band slippage and therefore bleed from the underlying ulcers. Additionally, the more fragile mucosa may also require a longer period to heal. The best approach to optimizing this risk factor remains to be determined and requires further investigation.

A history of previous esophageal variceal hemorrhage is another factor that was identified with association for an increased risk of bleeding. This has been reported previously with respect to re-bleeding after EVBL and following the treatment of gastric varices with Histoacryl injection sclerotherapy [14,15]. This may be due to the fact that these subjects represent a cohort with higher underlying portal pressures and, therefore, are at an inherently increased risk of variceal bleeding, which was also suggested by Duenas, et al. [8].

We found that subjects presenting with post-EVBL ulceration bleeding had significantly lower hemoglobin levels than the control group at time of index endoscopy. Mostafa, et al. similarly found anemia to be an independent predictor of re-bleeding following EVBL [16]. This may be related to having a prior hemorrhage but the exact relationship between this laboratory finding and bleeding from post-EVBL ulcers has yet to be elucidated.

There have been a number of other studies that found the presence of reflux esophagitis to be a factor increasing the risk of bleeding from post-EVBL ulceration [10,17]. PPIs are the most potent agents available to suppress gastric acid secretion thereby promoting mucosal healing and stabilizing clot formation in the setting of gastrointestinal bleeding [18]. They are commonly used following variceal ligation and it has been suggested that not administering PPIs in the setting of EVBL is a risk factor for post-procedural bleeding [4]. However, our study along with many others, demonstrates that PPI administration from the time of band ligation does not reduce the risk of bleeding from post-EVBL ulcers [8,9,16,19,20]. Two randomized control trials (RCT) comparing pantoprazole to placebo in the setting of EVBL noted a marked reduction in the size of post-banding ulcers on second look endoscopy. Despite this, neither identified a difference in mortality or rates of re-bleeding from these ulcers [16,19]. Retrospective studies examining PPI use in the both the elective and emergent EVBL setting also found no significant difference in these outcomes [9,20]. This suggests that gastric acid reflux has a lesser influence on bleeding risk in this particular setting and other factors as mentioned above are more significant. Other authors have examined the use of PPIs in the setting of gastric variceal obliteration with sclerotherapy, a method which can also lead to post-intervention mucosal ulceration. They were unable to identify any significant difference in rates of bleeding but merely suggested that the interval for re-bleeding may be longer in the PPI group [21]. Use of these medications is also not without risk, and concerns have been raised about inappropriate use in the cirrhotic population [22]. It has been well documented that prolonged administration of this class of drugs is associated with osteoporosis, pneumonia, hepatic encephalopathy and spontaneous bacterial peritonitis [9,23]. Furthermore, once commenced, PPI are commonly inappropriately continued without review on ongoing indication. Therefore, our study contributes to the growing body of evidence, which suggests there is little utility in co-administration of PPIs at time of band ligation in terms of improving the rates of bleeding from post EVBL-ulcers.

Unlike prior studies, severity of liver disease (CTP or MELD

score) in this group was not associated with a significant difference in rates of bleeding from post-EVBL ulcers [8,17]. This may be due to unavailable information in seventy-eight patients, which resulted in a lack of statistical power to show significance. However, this study demonstrated a trend towards a higher MELD score in the bleeding cohort. In another series, a low prothrombin index and a high AST to Platelet Ratio Index (APRI) score were found to be predictive of post-EVBL hemorrhage [10]. However, we did not find a significant relationship between these variables. Similarly, we did not find a statistically significant difference with regard to common laboratory tests such as international normalizes ratio (INR) or prothrombin index (PT). This is not surprising as it is increasingly recognized that these conventional coagulation tests are not particularly accurate or representative of the true underlying coagulation status in cirrhotic patients, which is a complex relationship involving various deficiencies in procoagulant and anticoagulant factors [24,25]. Further, emerging studies evaluating more accurate investigative tests such as thromboelastography will help to shed some light on this complex interplay [26].

The limitations of this study primarily lie in its retrospective nature. We were unable to ascertain definitive duration of PPI use for all subjects and so could not draw conclusions regarding timing of therapy that may impact the risk of bleeding. Additionally, the endoscopies were performed and reported by a number of different proceduralists (with varying levels of endoscopy experience) over the four-year period. The number of patients who experienced post-EVBL ulcer bleeding in our cohort was relatively low, as this is a low incidence complication. The analysis therefore may be underpowered to look for statistically significant differences in certain variables. Despite this, our findings are largely consistent with the other existing literature that has examined bleeding from post-EVBL ulcers [8,10]. Future prospective studies investigating risk factors for post-EVBL ulceration bleeding would have to involve multiple centers and a standardizedendoscopy pro-forma utilized to overcome these limitations.

Conclusion

Post-EVBL ulcer bleeding remains an uncommon complication of endoscopic banding but with high mortality rate. Subjects with high risk endoscopic stigmata at time of index procedure and those with previous variceal hemorrhage have an increased incidence of post-EVBL ulcer bleeding. A higher degree of caution should therefore be used amongst this patient cohort. Given the pre-existing links between PPI use and reduction of risk, future studies should be carried out to investigate if they can improve outcomes in this specific high-risk group.

Disclosure Statement

The authors have no conflicts of interest to disclose.

Acknowledgements

We would like to thank Dr. Seán Ó'Riordán who provided guidance on the statistical analysis. All other authors contributed to the data collection and writing of this paper.

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DOI: 10.36959/621/604