Rates of Recurrent Variceal Bleeding Are Low with Modern Esophageal Banding Strategies: A Retrospective Cohort Study

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Abstract:

Background: Variceal bleeding has a high rate of mortality and recurrence. Endoscopic band ligation (EBL) is the established standard of care for secondary prevention of variceal bleeding.

Objective: To determine the long-term re-bleeding rate of an EBL protocol similar to current society guidelines.

Design: We conducted a retrospective cohort study at a tertiary care center of all patients with a history of a variceal bleed who underwent an aggressive band ligation protocol.

Interventions: At the time of sentinel bleed, all varices, regardless of size, were ligated. EBL was then repeated every 2 weeks until stabilization, and all visible varices were ligated. The interval between banding sessions then increased.

Main Outcome Measurements: The incidence of re-bleeding was calculated as the time between clinical stabilization after the sentinel event until data censoring, which occurred at time of re-bleed, death, transplant, or loss-to-follow up. Gastric variceal bleeding was a secondary endpoint.

Results: N=176 patients were treated with aggressive EBL, and followed for a median of 16 months (range, 3 months – 6.9 years). The 6 month incidence of re-bleeding was 2.3%, the 12 month incidence was 3.4%, and the 2 year incidence was 4.6%. Overall,

aggressive EBL was well-tolerated. One patient died during follow up secondary to a gastric variceal bleed.

Conclusions: Aggressive EBL yields a low rate of re-bleeding when compared to standard practice. Secondary prophylaxis with aggressive EBL should be a consideration for patients following a sentinel bleeding event.

Key Words: Band ligation, variceal bleeding, secondary prophylaxis

Introduction:

Bleeding from esophageal varices is associated with significant morbidity and mortality, with previous studies reporting a mortality rate of up to 50% after a first bleed and up to 30% after each bleed thereafter. Patients have an 80% chance of recurrent bleeding during the two years following a sentinel bleeding event without modern interventions.[1] [2] However, more recent data suggest lower mortality rates in the modern era. [3, 4] Eradication of esophageal varices reduces both morbidity and mortality. [5-7]

Several modalities are available for secondary prevention of variceal bleeding – pressure reduction with non-selective beta blockers, endoscopic sclerotherapy, endoscopic band ligation (EBL), and placement of transvenous intrahepatic portosystemic shunt (TIPS). Of these, EBL plus pharmacologic beta-blockade is the standard of care [8] given its greater efficacy compared to pharmacologic therapy alone [9] and its lower adverse event rate when compared to sclerotherapy. [10-12] TIPS is another option that improves outcomes in the setting of an acute variceal bleeding episode, particularly in patients with Child's B and C cirrhosis [13, 14].

EBL is used to reduce the mortality from esophageal variceal re-bleeding, however, death rates among patients undergoing standard EBL remain elevated, and reported re-bleeding rates range from approximately 10% [15] to greater than 50% [16, 17].

Although EBL plus beta-blockers are one modality for secondary prevention of variceal bleeding, few studies have evaluated rates of re-bleeding with banding protocols based on

current societal guidelines, particularly in patients who do not have Child's B or C cirrhosis. In particular, which types of varices to target with EBL, and the optimal time interval between banding procedures remains a source of ongoing debate. The most recent American Association for the Study of Liver Diseases (AASLD) and American College of Gastroenterology (ACG) guidelines suggest banding all varices until eradication is achieved, followed by repeat EGD every 3-6 months to check for variceal recurrence [18], although some data suggest no benefit to shorter follow up intervals [19]. In real world clinical practice, controversy remains regarding which varices should be targeted for eradication. Studies of the natural history of varices demonstrate that large varices are at higher risk of bleeding when compared to smaller varices, however, any size varix has the potential to bleed [2, 20-22].

At our tertiary care center, we implemented a band ligation protocol with recommendations similar to current AASLD/ACG guidelines. Patients were recommended to receive band ligation of any visible esophageal varix with frequent EGD until eradication of varices is achieved. We sought to characterize the risk of recurrent esophageal variceal bleeding and death with current band ligation strategies. We further theorized that the current banding protocol would be well tolerated, with few severe adverse events. This report assesses the outcomes of a retrospective cohort of patients treated over the long-term with a band ligation protocol similar to current AASLD/ACG recommendations.

Methods:

Study setting: Northwestern Memorial Hospital is an 800-bed academic tertiary care center with 125 intensive care unit beds and a busy liver transplantation program.

Case Definition: All patients with an initial esophageal variceal bleed treated with band ligation who were followed for at least two months post-ligation were eligible for study inclusion. Patients were deemed to have primary failure of therapy if they re-bled within five days of initial endoscopy, and were included in the study after the primary bleeding episode was stabilized.

Modern EBL protocol: Fiber optic videoscopes (Pentax) and band ligation devices (Saeed Multi-band Ligator from Cook Endoscopy) were consistent throughout the entire study period. At the time of the sentinel variceal bleed, all visible varices, regardless of grade, were treated with band ligation. Varices were graded in the following manner. Trace varices were defined as small, dilated veins less than 5 mm at the level of the surrounding tissue. 1+ varices were small, dilated veins less than 5 mm slightly protruding into the esophageal lumen. 2+ varices were dilated veins greater than 5 mm protruding into the esophageal lumen, but not obstructing the lumen. 3+ varices were large, tortuous dilated veins greater than 5 mm protruding into, but not obstructing, the lumen. 4+ varices were large, tortuous dilated veins protruding into the lumen and nearly causing obstruction.

After the initial banding, patients were referred for repeat endoscopy, which was scheduled 1-3 weeks after stabilization. Patients were then rescheduled every 1-3 weeks

until varices were small (1+) or obliterated (trace or no varices seen on endoscopy). Once the size of the varices stabilized, the recommended time interval between endoscopy sessions was then increased to every 1-2 months to every 4-5 months and finally to every 6 to12 months, provided the patient's varices remained stable [11]. Surveillance every 6-12 months was maintained indefinitely. All varices with the potential for banding, regardless of size, were ligated.

Case Identification: To identify all patients with a history of esophageal variceal bleeding, we searched relevant ICD-9 codes for a broad range of diagnoses potentially associated with esophageal varices, and identified a cohort of 176 consecutive patients who underwent aggressive endoscopic band ligation and were followed for greater than two months at our tertiary care center during the study period, from 12/31/1997 - 12/31/2005. Clinical data were extracted through chart review.

Variceal bleeding definition: Variceal bleeding was defined as clinically significant bleeding with evidence of bleeding varices on endoscopy, a decline in hemoglobin with endoscopic evidence of bleeding varices, or a of at least 3 gm/dl in hemoglobin with varices present on endoscopy and no other obvious bleeding source. Initial bleeding was defined as the first bleed prior to initiation of the modern banding protocol. Recurrent bleeding was defined as a variceal bleed as above after an initial bleed. If the patients re-bled within two weeks of initial endoscopy, they were considered to have failed initial therapy. They were included in the survival analysis starting after their sentinel bleeding

event was fully treated and stabilized. Re-bleeding events evaluated at outside hospitals were included when reported and data were available.

Data extraction: Data were collected via manual chart review. Variables extracted included: demographic data, including gender and age, clinical data including underlying diagnosis of liver disease, Child-Pugh score when available, MELD score, concurrent use of beta-blockers, complete blood counts, biopsy results, magnetic resonance imaging and ultrasound results, and endoscopy information, including number of banding sessions, number of bands placed at each session, date of procedure, and varix size and number. The underlying liver disease for each patient could include more than one diagnosis. Outcome data were collected for all patients, and included recurrent esophageal variceal bleeding, gastric variceal bleeding, vital status, liver transplantation, placement of transvenous intrahepatic portosystemic shunt (TIPS) or splenorenal shunt, or loss to follow-up. In re-bleeding patients, more than one outcome was recorded.

Data analysis: The results of the study were then analyzed using SAS version 9.2.1 (SAS Institute, Cary, NC). T-test and Chi-squared test were used as appropriate, and The Kaplan-Meier method was used to estimate the cumulative incidence of re-bleeding. Data were censored at the time of death, the last clinic or endoscopy visit, liver transplantation, a TIPS or splenorenal shunt placement, or if they were noted to have a re-bleeding episode.

Ethical Considerations: Institutional Review Board Approval was obtained prior to study initiation and data analysis.

Results:

We identified 176 patients with a history of esophageal variceal bleeding who underwent serial band ligation during the study period (**Figure 1**). Participants were followed for a median of 16 months (range, 3 months to 6.9 years). The majority of patients in our study were men (65.3%), and the mean age of patients at the start of the banding protocol was 56.8 years.

The underlying diagnoses of liver disease in our cohort included (patients may be in more than one category): hepatitis C infection 33% (59), alcoholic liver disease 28% (51), hepatitis B infection 12% (21), cryptogenic cirrhosis 12% (21), hepatocellular carcinoma 14 (8%), NAFLD 10 (6%) , portal vein thrombosis 4% (8), primary biliary cirrhosis 4% (8), primary sclerosing cholangitis 3% (6)3% (5) autoimmune hepatitis 3% (5), Budd-Chiari syndrome 1% (2), 1 transplant rejection 0.5% (1), other 17/176, 10% (17), unknown 0.5% (1).

The majority of patients (80.1%) had biopsy-proven or imaging suggestive of cirrhosis; (96 with biopsy-proven and 45 with imaging suggestive of cirrhosis), and a MELD score of 11-20 (51.7%) (**Table 1**). Fourteen patients (8.0%) had a diagnosis of hepatocellular

carcinoma. The majority of patients (67.6%) received concurrent beta-blocker therapy for risk reduction. Complete follow up was available for 85.2% (150/176) of patients.

The median time to repeat EGD after initial variceal bleed was 18 days (IQR, 13-32 days). The cumulative incidence of re-bleeding was 2.3% at 6 months, 3.4% at one year, and 4.6% at 2 years (**Figure 2**). Total eradication of varices with no recurrence of any varices of sufficient size to be targeted with banding (trace or no varices only) was achieved in 96/176 patients (54.5%). Seven patients in the cohort had recurrent variceal bleeding. Three of these patients with recurrent bleeding achieved total eradication and four did not (p=1.0). The median number of EGD required for total eradication was 4 (IQR, 3-6), with a minimum of 1 and a maximum of 17 sessions.

Of note, three patients developed recurrent bleeding between 5 and 14 days following initial band ligation. Two of the three received emergent TIPS, and one received repeat band ligation followed by transplantation four days later. These patients were not included in the cohort analysis, because all three had less than one month of follow up following the sentinel bleeding event.

Six patients (85.7%) with a re-bleeding episode were receiving beta-blocker therapy in addition to band ligation for secondary prophylaxis. The only variable significantly associated with re-bleeding in univariate analysis was underlying diagnosis of primary biliary cirrhosis (2/8, p=0.034). There was a trend toward an increased rate among patients with cryptogenic cirrhosis, however, the association was not statistically

significant (2/18, p=0.17). There was no association between hepatocellular carcinoma and re-bleeding (p=0.52) or between portal vein thrombosis and re-bleeding (p=1.0).

Three patients who re-bled survived for a prolonged period after re-bleeding events: One had a minor esophageal variceal re-bleeding event with no subsequent episodes and two patients underwent TIPS procedures with no recurrence of bleeding. Two of the three patients who survived the rebleeding event did not follow up for banding procedures according to the recommended time intervals (See **Table 2** for detailed description of all patients with recurrent bleeding).

Of the seven patients who re-bled, four (57%) did not achieve total eradication of varices and ultimately died or were transferred to hospice care (**Table 2**). One patient died from an acute bleeding event from gastric varices; one patient had metastatic hepatocellular carcinoma, one patient had end-stage renal disease and refused hemodialysis, and one had a minor esophageal re-bleeding event and was subsequently transferred to hospice care for management of end stage liver disease.

In total, 26 patients (14.8%) died, including four patients who rebled as detailed above. Causes of death included: hepatocellular carcinoma (8), sepsis (4), adverse events of end-stage liver disease (4), GI cancer other than hepatocellular carcinoma (2), gastric variceal bleed (1), complications following a hip fracture (1), end-stage renal disease (1), breast cancer (1), unknown (4). No patients died from a recurrent esophageal bleeding episode.

Of the remaining 154 patients in the cohort, 78 (51%) survived without recurrent bleeding. Thirty-eight cases (25%) eventually underwent liver transplant without any intervening episodes of re-bleeding. A small proportion of cases (2.8%, 5/176) survived until TIPS or splenorenal shunt placement. Seven (5%) cases suffered a recurrent variceal bleed (**Table 2**). Twenty-six patients (14.8%) were lost to follow up; these patients did not differ significantly from the rest of the cohort.

The banding protocol was well tolerated overall. Among patients followed for at least three months following the sentinel bleeding episode, one patient developed minor bleeding following banding, and required overnight hospitalization for observation. The patient was discharged the following day and did not require blood transfusion or repeat banding. One patient was unable to tolerate EGD due to anxiety surrounding the procedure and thus did not complete the banding protocol due to procedural intolerance. No other immediate adverse events were identified. Two patients developed gastric variceal bleeding after EBL and included one death.

Discussion:

A modern EBL banding protocol similar to current AASLD/ACG guidelines[18], resulted in low rates of recurrent bleeding when compared to historically-reported rate in a real-world setting. Our study demonstrated an overall re-bleeding rate in a real-world clinical practice over a 2-year period of 4.6%, which is markedly lower than previous reports with standard clinical practice [4, 15, 16, 23-29]. Other studies suggest a re-bleeding rate of 17.2% during the first 12 months following sentinel bleed among patients

undergoing band ligation in conjunction with beta-blockers for secondary prevention[30], although more recent data suggest that recurrent bleeding may be much lower with modern banding protocols [19].

In our real-world effectiveness study, EBL for secondary prevention had recurrent bleeding rate of only 4.6% over a prolonged period. Further, patients who did not complete follow up at the recommended intervals and patients with poor prognostic factors (i.e. portal vein thrombosis, end-stage renal disease, hepatocellular carcinoma) were included in the analysis, improving the robustness and generalizability of our findings. Given the high mortality rate associated with variceal bleeding [31, 32], a 10-15% reduction in re-bleeding episodes may translate into improved long-term patient outcomes.

Although EBL has consistently been shown to reduce re-bleeding rates in patients with esophageal varices, [30] few studies have examined how the band ligation strategy affects rates of recurrent bleeding. In clinical practice, many centers only band esophageal varices that are grade 3-4 in size, however, our group banded all varices, regardless of size, based on prior work showing that all varices, regardless of size, have the potential to bleed [2]. This strategy is in line with current guidelines, which put an emphasis on achieving total eradication of all varices [18], and is similar to other recent reports suggesting low rates of recurrence with modern band ligation protocols [19].

The majority of patients (6/7, 85.7%) who developed a re-bleeding episode were also receiving beta-blockers, a rate that was not statistically significant compared to patients who did not develop re-bleeding (p=0.43). Current AASLD/ACG guidelines recommend both EBL and beta-blockers in combination as the optimal secondary prevention strategy [18], however, beta-blockers are poorly tolerated by many patients, and thus long-term compliance with these medications may be difficult. In our cohort, the use of beta-blockers in addition to band ligation for secondary prophylaxis may be a marker of higher than average risk of recurrent bleeding, as physicians caring for high-risk patients may more strongly reinforce the need for multi-modal approaches to secondary bleeding prevention.

Recently, TIPS has emerged as a potential alternative to band ligation for prevention of recurrent bleeding [13]. TIPS may reduce the portosystemic pressure gradient in more than 90% of patients, however, complications of the procedure may include worsening of hepatic encephalopathy and thus the risks must be weighed against the benefits, particularly in patients with less severe liver disease. Multiple randomized controlled trials have compared the use of TIPS to endoscopic therapy for refractory or recurrent variceal bleeding [33-35], and results are mixed, with some suggesting a benefit to early TIPS [36] and others suggesting that band ligation is superior [34]. A recent meta-analysis demonstrated decreased bleeding with TIPS, but similar rates of mortality in both groups [37]. Further, the incidence of hepatic encephalopathy was nearly twice as high in the patients who received TIPS. Thus, although early TIPS may be a consideration, band ligation plus beta-blockers remain an important mode of prevention

among patients suffering from an initial variceal bleeding event.

A relatively small number of patients in our cohort (5/176) received TIPS or shunting, despite studies demonstrating the effectiveness of TIPS in patients with advanced liver disease and acute variceal bleeding [13]. An additional two patients received TIPS for management of early recurrent bleeding. The relatively low incidence of TIPS placement in our cohort may be because many of the patients in this cohort, despite having a history of varices, did not have Child's B or C cirrhosis. The use of TIPS may also be increasing in clinical practice in recent years, as additional studies suggest a benefit in patients with Child's B or C cirrhosis [13, 14]. However, many of the patients included in this cohort would have been excluded from TIPS, due to complicated underlying medical conditions.

Because of concerns of increasing portal pressures leading to worsening of gastric varices and morbidity and mortality from gastric bleeding episodes, [38-40] there has been concern that targeting all esophageal varices during EBL procedures might paradoxically worsen clinical outcomes in a subset of patients with existing gastric varices. However, in our cohort of 176 patients, only two patients developed gastric variceal bleeding. One of these patients developed a fatal bleeding event from a gastric variceal bleed, which is a catastrophic event. However, overall the cohort had very low rates of recurrent bleeding, suggesting that the benefit of banding all varices may outweigh the risks of gastric variceal bleeding. Reassuring was the low rate of bleeding events from gastric varices, which was less than 2% in the entire cohort.

Data regarding non-bleeding complications of band ligation, such as pain and nausea, may not be recorded in the clinical chart, and were not collected. Thus, we are not able to comment on these quality-of-life considerations.

Our study was limited by not having control patients who did not receive the banding protocol. Thus, we used estimates from other clinical trials for comparison of secondary prophylaxis strategies. Due to our lack of contemporary controls, the improved outcomes in this study may be due to temporal changes in patient care as opposed to use of a specific band ligation strategy. Further, the retrospective nature of our study meant that some data points may have been lost. Although the vast majority of the patients included in this cohort followed at our center, and we included results from outside facilities when available, it is possible that some recurrent bleeding episodes were missed if the patient followed up elsewhere. The modern protocol was implemented at only at a single institution, which may have increased the treatment effect. Further, because the hospital was a tertiary care center, the adjunctive services and patient population may have differed from those available in other facilities. However, because all patients, even those with additional risk factors for bleeding were included in the study, our data are likely representative of real-world re-bleeding rates with a modern band ligation strategy. We also included patients who followed up after longer-than-recommended intervals, in accordance with real world practice, thus improving the generalizability of our findings.

Conclusions:

The low rates of recurrent variceal bleeding in our cohort may suggest a benefit to utilizing a modern banding protocol among patients following a sentinel variceal bleeding event, with a goal of achieving total eradication of all varices. The banding protocol may be used to stabilize patients prior to transplantation, or used for long-term prevention in patients with stable liver disease. While additional randomized studies looking at different banding protocols are needed to further illuminate the utility of this strategy, we offer preliminary data that banding protocols similar to those in the current AASLD/ACG guidelines may improve outcomes in patients following variceal bleeding episodes.

Conflicts of Interest:

All authors have no conflicts of interest to report.

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Table 1. Baseline Characteristics of Cohort

	Total Cohort (N=176)	Non-Re-bleeders (N=169)	Re-bleeders[A] (N=7)
Demographics			
Mean age +/- SD	56.80 +/- 11.78	56.72 +/- 11.55	58.66 +/- 17.41
Men (%)	116 (65.9%)	112/169 (66.2%)	4/7 (57.1%)
Women (%)	60 (34.1%)	57/169 (33.7%)	3/7 (42.8%)
Biopsy or Imaging-defined Cirrhosis	140 (79.6%)	136/169 (82.8%)	4/7 (57.1%)
Beta Blocker Therapy			N/A
Yes	119 (67.6%)	113/169 (66.8%)	6/7 (85.7%)
No	57 (32.4%)	56/169 (33.1%)	1/7 (14.2%)
MELD Score			
0-10	62/176 (35.2%)	59/169 (34.9%)	3/7 (42.9%)
11 20	91/176 (51.7%)	88/169 (52.1%)	3/7 (42.9%)
21-30	13/176 (7.4%)	12/169 (7.1%)	1/7 (14.2%)
Unknown	10/176 (5.7%)	10/169 (5.9%)	0/7 (0%)
Total Number EGD			
Median, IQR	5.5 (4,8)	5 (4,8)	6 (6,8)
Total Number of Bands Placed	15 (9,24)	14 (9,24)	22 (18,27)
Outcomes			
Length of Follow Up			
Median, in months	15.9 (IQR, 8.1,35.2)	16.2 (IQR, 8.4,35.3)	9.1 (IQR, 4.2,14.8)
Alive without re-bleeding and still in EBL protocol	78 (44.3%)	78	-
Re-bleeding Event [A]	7 (4.0%)	-	7
Lost to Follow Up	26 (14.8%)	26	-
Transplantation	38 (21.6%)	38	-
TIPS or shunt placement	5 (2.9%)	5	-
Died [B]	26 (14.8%)	22	4[C]

A Includes both esophageal and gastric variceal re-bleeders.

B Includes one patient who suffered a fatal re-bleeding event. Patients in this category may have more than one outcome (ie, death and re-bleeding event).

C One patient died secondary to a re-bleeding event. Three patients died or were transferred to hospice care secondary to other medical problems.

Table 2. Details of Re-bleeders

	Clinical Data	Endoscopy Details	Outcomes and notes
1	62-year-old male with underlying metastatic hepatocellular carcinoma.	Total of 7 EGD during study inclusion, with 1-5 bands placed during each session. Highest varix grade recorded size 2.	Patient with underlying metastatic hepatocellular carcinoma. Received protocol for six months prior to transfer to hospice.
2	30 year-old female with primary biliary cirrhosis and stage 2-3 fibrosis.	Total of 6 EGD with 33 bands placed. Highest varix grade recorded grade 2.	Survived recurrent bleeding event and subsequently had TIPS placed without further bleeding episodes and ultimately liver transplantation one year later.
3	56-year-old male with HBV, HCV, and alcoholic liver disease and cirrhosis. Repeatedly non-compliant with follow up.	Total of 6 EGD during the study period and 18 bands, patient not compliant with usual follow up. Multiple grade 2 and 3 varices present on multiple EGD.	Developed minor re-bleeding episode two years after initiating protocol. Ultimately transferred to hospice care.
4	82 year-old male with cryptogenic cirrhosis and end-stage renal	Total of 8 EGD during the study period with 22 bands placed. Highest	Developed re-bleeding episode 8 months after initiating protocol and then

	failure.	varix grade noted size 2.	refused ongoing dialysis, and died secondary to renal failure.
5	75 year-old female with primary biliary cirrhosis.	Total of 5 EGD during the study period with 5 bands placed. Highest varix grade noted size 2 until recurrent bleeding episode when size 3 found.	After recurrent bleed, received TIPS placement with no further episodes.
6A	66 year-old female with cryptogenic cirrhosis and GAVE syndrome. Child's class B when entered the protocol.	Received 6 EGD and 6 bands during the study period. Highest varix grade recorded size 2.	Patient with cryptogenic cirrhosis, Child's C. Ultimately died secondary to bleeding from a gastric ectasia.
7A	42 year-old male with alcoholic cirrhosis. Child's class C when he entered the protocol.	Received 10 EGD during the study period; developed bleeding from gastric varices during the 3rd EGD. Highest varix grade noted size 3.	Patient with alcoholic cirrhosis with marked fibrosis noted. Developed oozing from gastric varices one month into the protocol, and then did not have any subsequent re-bleeding episodes in one year of follow up.

A Recurrent bleeding episode secondary to a gastric variceal bleed.

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Figure 1 Legend.

Flow diagram showing the outcomes of the 176 patients included in the cohort.

Figure 2 Legend.

Kaplan Meier Curve showing cumulative incidence of re-bleeding during the study period. 95-percent confidence intervals are shown. Data were censored at the time of variceal rebleeding, or after death, liver transplantation, or TIPS placement.