REVIEWS

Diagnosis, management and prophylaxis of bleeding related to post-esophageal variceal band ligation ulcer in cirrhotic patients

Talles Bazeia Lima,* Giovanni Faria Silva, Fernando Gomes Romeiro

Botucatu Medical School, São Paulo State University (UNESP), Botucatu, Brazil

Received: May 21, 2018 **Accepted:** June 24, 2018 **Online Published:** July 3, 2018
DOI: 10.5430/crim.v5n3p23 **URL:** https://doi.org/10.5430/crim.v5n3p23

ABSTRACT

Esophageal varices develop in half of cirrhotic patients. Endoscopic variceal band ligation is the current treatment for acute bleeding and applicable for primary and secondary prophylaxis. However, there is a risk of complications, including ligation-induced ulcer bleeding. The aim of this study is to review the current diagnosis, management and prophylaxis of bleeding related to post-esophageal variceal band-ligation ulcers in cirrhotic patients. PubMed and Google Scholar were searched for English language articles about the theme. The main findings were that Child-Pugh class C, higher model of end-stage liver disease, emergency ligation, presence of hepatocellular carcinoma, peptic esophagitis and bacterial infection were reported as the most important risk factors for post-banding ulcer hemorrhage. There are few studies with proton pump inhibitors and sucralfate showing size reduction of post-banding ulcers. Many treatment modalities have been used to control post band ulcer bleeding, such as band local injection of epinephrine or cyanoacrylate, balloon tamponade, stent placement and ligation of the ulcerated bleeding site. However, the optimal management remains uncertain. The principal conclusions of the study were that post-banding ulcer bleeding is potentially life-threatening and must be suspected in the presence of hematemesis, melena or anemia after endoscopic variceal band ligation (EVL). Predictors of rebleeding must be assessed and controlled as much as possible before band ligation. The post-banding treatment with proton pump inhibitors or sucralfate seems advisable, in particular for high-risk patients. Further investigation and new approaches are still required to achieve optimal management of this complication.

Key Words: Esophageal varices, Gastrointestinal bleeding, Advanced endoscopy, Ligation, Esophageal injury

1. INTRODUCTION

Endoscopy is paramount in the management of patients with liver disease and esophageal varices caused by portal hypertension. Esophageal varices occur in 50% of patients with cirrhosis,[1] and despite the fact that the outcome of variceal bleeding has improved, the mortality rate still reaches 20% at 6 weeks.[2] Endoscopic variceal band ligation (EVL) has been recommended as the best treatment for obtaining hemostasis in acute bleeding. Furthermore, it is also performed for prophylaxis of recurrent bleeding and even before the first episode when the patient is insensitive to β-blockers.[3,4] The procedure aims to obliterate the perforating veins that connect the submucosal varices to extra-esophageal collaterals in the esophageal palisade zone. For

*Correspondence: Talles Bazeia Lima; Email: tallesbazeialima@gmail.com; Address: Department of Internal Medicine, Division of Gastroenterology – São Paulo State University (UNESP), Botucatu Medical School. Av. Prof. Mário Rubens Guimarães Montenegro, s/n. Rubião Jr. District Zip Code 18 608 917. Botucatu, State of São Paulo, Brazil.

most patients, it leads to the formation of shallow ulcers that heal in two weeks, without substantial blood loss.[5]

Once EVL is performed, the rubber ring remains attached to the esophageal wall for 3 to 7 days. Some complications can occur, such as heartburn, chest pain, transient dysphagia, odynophagia, stricture formation, worsening of portal hypertensive gastropathy and bacteremia.[6] Moreover, another significant complication is rebleeding after EVL, which may be caused by either post-banding ulcers or variceal hemorrhage. When band ligation detachment occurs before variceal thrombosis, the original vessels can be exposed inside a post-banding ulcer and these patients can suffer massive bleeding. There are no guidelines concerning endoscopic control of ligation ulcers whereas few studies have evaluated the risk of complications from them, with contradictory results. Acid suppression or muco-protectants can be considered for adjunctive therapy for EVL, but few data exist on their efficacy.

Post-banding ulcer hemorrhaging must be suspected in the presence of hematemesis, melena or anemia after EVL. Thus, measures to reestablish hemodynamic parameters must be taken to prepare the patient for a new upper endoscopy. There are different therapies that can be adopted to control or even avoid this type of hemorrhage.

This work aims to review how to identify, treat and decrease the risk of bleeding related to post-esophageal variceal ligation ulcers in cirrhotic patients. Predictors of rebleeding, physiopathological and epidemiological aspects are also presented.

2. METHODS

PubMed and Google Scholar were searched for English language articles using the key words "esophageal varices", "gastrointestinal bleeding", "advanced endoscopy", "ligation" and "esophageal injury".

3. RESULTS & DISCUSSION

3.1 Epidemiology

In most of the prior studies on complications following EVL, the global rate of rebleeding is about 15% within 5 days whereas the mortality is 14% within 6 weeks.[2,7–9] However, bleeding after EVL can be caused by either variceal hemorrhage or post-banding ulcers.[10] The studies evaluating the rate of bleeding after EVL are few and contradictory. According to the American Society for Gastrointestinal Endoscopy (ASGE), bleeding caused by post-banding ulcers occurs in up to 3% of cases, although this rate may be higher,[11–15] reaching up to 13.5%,[16] irrespective of the prior EVL indication (prophylactic or therapeutic procedures). When the EVL indication is considered, rebleeding occurs more frequently after emergency than elective ligation.[17,18] Although uncommon, the mortality rate is up to 52%, mainly due to infectious complications.[19]

Our group is conducting a controlled prospective trial aiming to analyze outcomes after treatment of osteoporosis or osteopenia in cirrhotic patients (119 subjects) with esophageal varices. Until now only 17 patients required 26 EVL sessions (Child-Pugh classes A, B and C were 6, 10 and 1, respectively). Sixteen of them were submitted to elective procedures and just one patient needed to receive an emergency procedure, 5 days after the last EVL, allowing us to control the hemorrhage successfully. Therefore, in this preliminary evaluation there was only one case of bleeding after EVL out of 26 follow-up exams (3.84%), in agreement with prior studies, showing that elective EVL is a safe procedure and that bleeding after EVL is less common than in emergency EVL (non-published data).

3.2 Risk factors

Poor liver condition (Child Pugh C class or high model of end-stage liver disease - MELD score) has been previously identified as a bleeding predictor in cirrhotic patients submitted to EVL.[7,18,20] In addition, prior variceal digestive bleeding, high platelet ratio index (APRI score), peptic esophagitis and low prothrombin index are also deemed bleeding risk factors after early spontaneous slippage of the EVL rubber band.[19] However, it remains controversial whether coagulation status predicts bleeding after EVL.

In a prospective study performed to evaluate the efficacy of primary and secondary prophylaxis with EVL in 150 cirrhotic patients (49% Child-Pugh A, 28% Child B and 23% Child C), levels of factor V, fibrinogen, D-dimer, C and S proteins, von Willebrand factor were assessed, as well as thromboelastography. These parameters did not differ between the cases of bleeding and the other patients.[14] Additionally, a retrospective study of 148 cirrhotic patients also showed that the international normalized ratio (INR) does not reflect the variceal hemorrhage risk.[21]

Considering the physiopathology of the variceal bleeding, portal vein tumor thrombus (PVTT) and hepatocellular carcinoma (HCC) are predictors of rebleeding after EVL. The tumor compression and the portal thrombosis increase the variceal pressure, leading to the bleeding. A recent retrospective study showed a high rate of rebleeding after EVL (39.3%) in patients with HCC and PVTT despite initial hemostasis, with a median overall survival of only 36 days. Child-Pugh classes A and B as well as low α-fetoprotein-L3 levels were associated with longer overall survival.[22]

Patients with cirrhosis and variceal hemorrhage are fre-

quently stricken by bacterial diseases. This complication was already reported as a risk factor for rebleeding in a prior retrospective study, which included 96 individuals who received elective or emergency EVL. The authors reported a bleeding rate of 20% within 14 days after EVL,[20] but the bleeding source was not mentioned.

Elective EVL has a lower risk of bleeding than emergency ligation.[17,18] In elective procedures, higher MELD score and reflux esophagitis were associated with significant EVL-induced ulcer hemorrhage.[23]

The number of rubber bands applied per patient seems to have no correlation with rebleeding in most trials.[8] A prospective study showed that the placement of more than six bands per session was not associated with better outcomes but rather with prolonged banding, increased procedure time and more misfired bands.[24] On the other hand, in a study by Petrasch et al., patients with bleeding events at ligation sites had received more ligation bands. Since the number of post-banding ulcers would be higher, one can infer that applying more ligation bands may also be a risk factor for rebleeding events.[17]

In a Mayo Clinic study, the interbanding interval $\geq$ 3 weeks, adjusted for age, sex, and Child-Pugh class increased the likelihood of not rebleeding, suggesting that longer interbanding intervals are better.[8] On the other hand, some authors advocate that EVL sessions should be repeated at 1- to 2-week intervals until complete obliteration of all varices. It can be achieved in about 90% of patients, but only after 2-4 sessions.[25]

A prior study using endoscopic ultrasonography (EUS) showed that larger paraesophageal varices were associated with higher rates of post-EVL bleeding.[26] However, this association is still controversial. In a review article, the authors postulated that paraesophageal varices and other extra-esophageal vessels may reduce the portal pressure and prevent variceal recurrence according to branching patterns.[27]

3.3 Prophylaxis of ulcer bleeding after esophageal band ligation

Scientific evidence on this kind of prophylaxis is still lacking. Even so, some drugs have been studied and may be considered for adjunctive therapy for EVL, as follows.

3.3.1 *Gastric acid secretion inhibitors*

EVL leads to mechanical obliteration of esophageal varices, entrapping only the mucosal and submucosal venous channels but leaving the muscle layer unaffected, thus causing only superficial ulcers that heal by fibrosis. It is thought that acid suppression contributes to early healing of these ulcers because even physiological acid exposures may delay the recovery process. Considering that gastroesophageal reflux disease has a high prevalence (64%) in cirrhotic patients and portal hypertension,[28] some authors claim that acid suppression therapy should be started after EVL to decrease the risk of bleeding. However, whether or not proton pump inhibitors (PPI) use can decrease the risk of bleeding after EVL is still under investigation.

In 2005, a randomized, placebo-controlled trial of 44 individuals with cirrhosis undergoing EVL as secondary prophylaxis showed that pantoprazole (40 mg IV post-EVL, then 40 mg orally for 9 days) decreased the post-banding ulcer size. The study did not demonstrate any relationship between the use of PPI and the risk of post procedural hemorrhage.[29] Similar results were found in a Korean trial in 2008.[30]

In 2012, Hidaka et al. reported that long-term administration of PPI decreased the risk of treatment failure after EVL. However, the subjects (n = 21 and 22 in the rabeprazole and placebo groups, respectively) were included only after endoscopic statement of post-EVL ulcer healing; so the PPI effect on active post-banding ulcers was not evaluated.[31]

In 2013, another randomized controlled study compared 5 days of intravenous PPI (pantoprazole 40 mg or omeprazole 40 mg) versus intravenous vasoconstrictors (somatostatin 250 mg/h or terlipressin 1 mg/6 h) after EVL in 118 individuals with cirrhosis and acute variceal bleeding. The number and the width of the esophageal ulcers were higher in the vasoconstrictor group than in the PPI group, but no significant difference in esophageal ulcer bleeding was found between the treatments.[32]

In a retrospective cohort study, 505 cirrhotic patients who received primary prophylactic EVL were included. Post-EVL bleeding was defined as bleeding after prophylactic EVL within 8 weeks, diagnosed by the presence of melena, hematemesis or hemoglobin decrease higher than 2.0 g/dl, always followed by endoscopy confirmation. Only 14 patients developed bleeding (2.8%), whereas multivariate logistic analysis showed that not administrating PPI was associated with bleeding after prophylactic EVL. Among the limitations of this study, it did not evaluate the changes of the post-banding ulcer size by endoscopy. Moreover, it did not assess long-term outcomes after EVL and the subjects received different types of PPI.[33]

The use of PPI has increased worldwide because of their easy access, low cost, safety profile and effectiveness in inhibiting acid secretion. This class of drugs can be considered an adjunctive therapy after EVL to prevent post-banding ulcers bleeding, as previously established. However, some caution is still needed when using these drugs on advanced cirrhosis.

Recent data suggest that acid secretion is already reduced in cirrhotic individuals due to hypertensive gastropathy. Since all PPI are metabolized in the liver by cytochrome CYP450, the dosages of the most available PPI should be reduced in these patients.[34] Moreover, acute hepatitis due to PPI use was previously related,[35] while gastric acid suppression can increase the risk of community-acquired pneumonia[36] and spontaneous bacterial peritonitis in advanced cirrhosis.[37–39]

3.3.2 *Sucralfate*

Sucralfate is a complex of disaccharide sugar, sulfate, sucrose and aluminum. It is considered a cytoprotective agent because it improves growth factors and favors angiogenesis, granulation tissue formation and epithelization. It exerts antibacterial activity and is capable of promoting prostaglandins production. In addition, it inhibits cell apoptosis and the production of oxygen free radicals after injuries, which are key factors in tissue healing. Moreover, sucralfate can attach to exposed proteins, binding to the ulcers and protecting their surface from further injuries by acid and pepsin. The drug inhibits pepsin in the presence of stomach acid and binds to bile compounds, preventing or treating several gastrointestinal diseases.[40] Sucralfate is a safe drug and has no significant interactions with other drugs because it is only minimally absorbed and is excreted in urine, free of liver metabolism. The most common side effects, such as constipation and dizziness, are rare.

Sucralfate has been used to promote healing of sclerotherapy-induced esophageal ulcers.[41] The advent of rubber band ligation raised the hypothesis that patients treated with sucralfate following EVL would have fewer and smaller post-banding ulcers, thus decreasing chest pain, dysphagia and rebleeding. In 1994, Nijhawan et al. randomized 30 patients undergoing elective EVL to receive either sucralfate or placebo, but found no differences in healing between the groups.[42] Compared with antacid therapy, sucralfate allowed faster post-EVL ulcer healing in a group of 45 randomized cirrhotic patients.[43] Vanbiervliet et al. analyzed predictive factors of hemorrhage related to post-banding ulcer and did not find any benefits from sucralfate usage for bleeding prevention, despite the low number of subjects evaluated.[19]

In 2011, a randomized, double-blinded, placebo-controlled trial included 31 patients who received sucralfate after EVL (1 gram every 6 hours for 2 weeks). The placebo group was also composed of 31 patients. In this study, sucralfate decreased the occurrence and the size of post-banding ulcers ($p < .05$). None of the patients experienced post-banding ulcer rebleeding.[44]

Unfortunately, there are no studies comparing sucralfate versus PPIs in the healing of esophageal band ulcers. Theoretically, acid suppression could limit sucralfate polymerization. Only one retrospective study analyzed the combination of PPI plus sucralfate and octreotide in post-banding ulcer treatment, but not all the subjects used sucralfate. Among 991 banding sessions and 23 post-banding ulcer bleeding events, only six were effectively treated with octreotide infusion + PPI +/- sucralfate.[18] Perhaps this combination of drugs merits future studies.

3.3.3 *Other drugs*

The prophylactic role of nonselective β-blockers was well established in the Baveno VI Consensus. Ligation plus nadolol and sucralfate was better than ligation alone for preventing variceal recurrence and bleeding. There were fewer episodes of post EVL ulcer bleeding in the patients' group receiving triple therapy, though the difference was not significant. Since it was not clear when these episodes of bleeding occurred, it is not possible to know how many of them were caused by post EVL ulcer bleeding.[15]

Simvastatin can decrease portal pressure and improve hepatocellular function.[45,46] A multicenter double-blind trial included 158 cirrhotic subjects receiving standard prophylaxis (band ligation and β-blocker). Within 10 days of the hemorrhage episode, individuals were stratified by Child-Pugh class and randomly assigned to groups taking simvastatin (69 subjects receiving 20 mg/day during the first 15 days, 40 mg/day after that) or placebo (n = 78). They were followed for 2 years, but simvastatin did not reduce all-cause rebleeding. Unfortunately, the authors did not mention the incidence of post EVL ulcer bleeding, and the incidence of rhabdomyolysis was higher than expected.[47]

Somatostatin is a vasoconstrictor that is known for reducing portal pressure. A double-blind randomized controlled trial with 61 patients compared EVL plus somatostatin versus EVL plus placebo for controlling acute variceal bleeding. The primary endpoint was treatment failure within 5 days, defined as: hematemesis $\geq$ 2 h after starting the therapy, 3-gram drop in hemoglobin, or death (the incidence of post EVL ulcer bleeding was not specified). However, somatostatin infusion associated with EVL did not achieve any advantage for controlling the variceal bleeding or reducing mortality.[48]

Octreotide, a synthetic analogue of somatostatin, decreases portal pressure and collateral blood flow inside variceal vessels. It also increases lower esophageal sphincter pressure and inhibits acid gastric and pepsin secretion.[49] In theory, it may also help prevent rebleeding from post banding ulcers. However, there is a lack of scientific evidence about this effect, and the same can be said of somatostatin.

3.4 Diagnosis & management

Post-banding ulcers are considered the bleeding source when they are clearly bleeding (spurting or oozing from the ulcer bed) or if they have stigmata of recent hemorrhage (presence of protruding vessel, adherent clot, pigmented elevation or a red spot at the ulcer base) during the endoscopic evaluation. Examples of post-banding ulcers are shown in Figure 1.

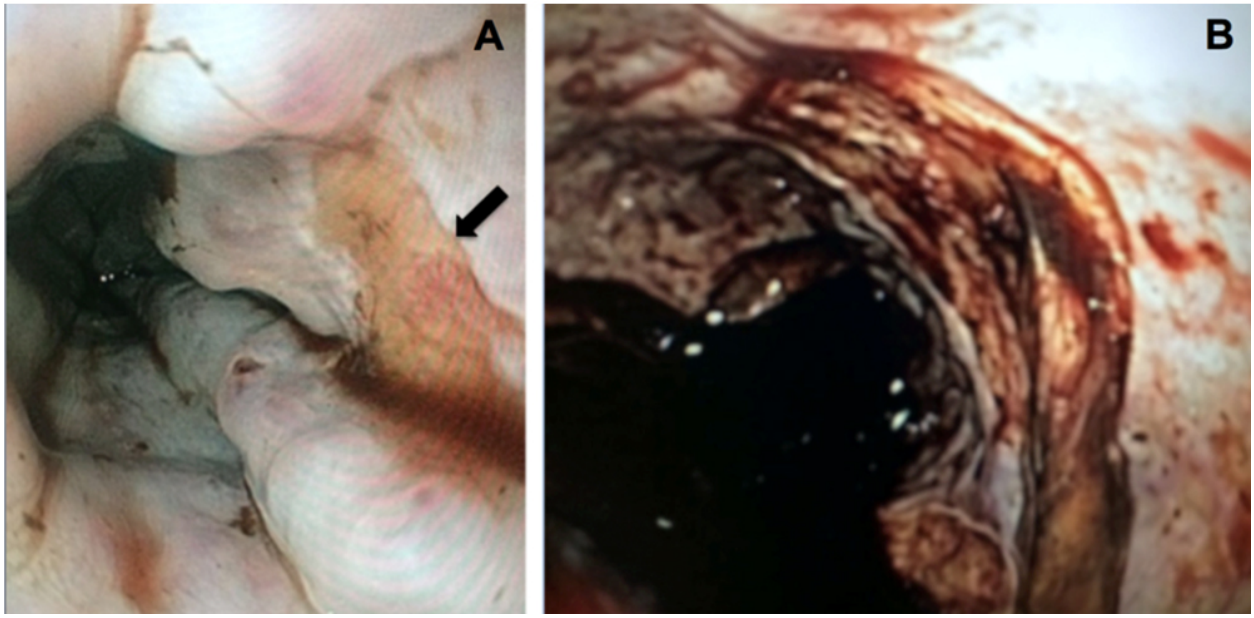

Figure 1. Post-esophageal variceal band ligation ulcers in two different cirrhotic patients
A: A small superficial ulcer (black arrow). B: A large oozing ulcer.

Even before the endoscopic exam, the presence of hematemesis, melena, hematochezia or hemoglobin decrease without an identifiable source of upper gastrointestinal hemorrhage (such as gastric antral vascular ectasia, non-variceal upper gastrointestinal bleeding, gastro-esophageal variceal hemorrhage) constitutes a sign of recurrent variceal bleeding. After EVL, the mean time to the occurrence of post-banding ulcer bleeding is variable, ranging from 8.7 to 13.5 days, according to some authors.[18,19,50] The main goal of the initial approach of a patient with suspected variceal bleeding include severity assessment and identification of the hemorrhage source.[51]

Active hemorrhagic varices are a challenge and the best strategy for management of post-banding ulcer bleeding remains undefined. Clinical management must be implemented before endoscopy for any variceal bleeding in cirrhotic patients, including post-banding ulcer bleeding. Airway protection in the presence of significant hematemesis in patients who are unable to protect their airway is vital.[51] At the same time, adequate intravenous lines must be prepared for infusions of crystalloids and blood transfusions to maintain hemodynamic stability achieving hemoglobin concentration of approximately 7 to 8 g/dl. Transfusions of platelets and/or fresh frozen plasma must be performed for individuals with severe thrombocytopenia or coagulopathy. Prophylactic antibiotics (oral or intravenous quinolone, or intravenous ceftriaxone) must be given for 7 days or until the hemorrhage had been resolved. Terlipressin, octreotide, somatostatin or vasopressin must be started according to the American Society for Gastrointestinal Endoscopy guidelines.[4] Patients must be continuously monitored throughout the treatment procedures. Ideally, upper endoscopy must be accomplished as soon as the first measures have taken place and the patient is hemodynamically stabilized.[51] Ideally, it must be done within 12 hours.[25]

When bleeding after EVL occurs due to variceal recurrence, new ligations should be accomplished at or around the hemorrhage source.[16] However, when the hemorrhage occurs due to a post-banding ulcer, different endoscopic therapies may be adopted, including cyanoacrylate injection, placement of fully covered self-expanding metallic stents and rescue therapies, such as balloon tamponade, transjugular intrahepatic portosystemic shunt (TIPS) and surgical shunts. Unfortunately, most reports on this issue are limited to case studies.

Endoscopic injection of cyanoacrylate is a available therapy for controlling esophageal variceal hemorrhage in Child-Pugh C cirrhotic patients.[52–54] However, there is a lack of

data on cyanoacrylate injection for post-banding ulcer hemorrhaging. Moreover, despite being rare, cases of cerebral embolism were reported following cyanoacrylate-lipiodol injection.[55,56] Until now, the only case of death probably caused by venous embolism in our endoscopy unit occurred during cyanoacrylate injection performed to control gastric variceal bleeding (non-published data).

The self-expandable metallic stent (SEMS) is a promising endoscopic therapy that can be employed to contain bleeding in cases of refractory variceal esophageal hemorrhage as an alternative to balloon tamponade. The stent can be maintained for as long as 2 weeks, enabling some liver function improvement until the establishment of further treatment measures.[57] Since SEMS is still not available worldwide, data on post EVL ulcers bleeding are scarce. The first report in English regarding life-threatening hemorrhage from postbanding esophageal ulcer successfully treated by SEMS was published in 2010. The patient presented massive hemorrhage from an esophageal ulcer eigth days after successful band ligation, which was performed to treat a variceal bleeding.[58] Another report of SEMS placement for post-EVL ulcer bleed was after liver transplantation. The patient had had melena eigth days after the surgery (22 days after a prior band ligation). Post EVL ulcers and oozing bleeding were found and the authors performed endoscopic sclerotherapy with sodium tetradecyl sulfate. Since the hemorrhage was not controlled, SEMS was successfully placed.[59]

The balloon tamponade is proposed as a "bridge" to definitive therapy in cirrhotic patients with copious or refractory esophageal variceal hemorrhage. The Sengstaken-Blakemore tube is the most used, providing bleeding control rates of up to 90%.[60] It can also be employed to treat post-banding ulcer bleeding from uncontrolled massive bleeding with hemodynamic instability.[19] However, there are risks of complications in 20%-60% of the cases, including esophageal rupture, aspiration pneumonia, asphyxia resulting from balloon migration, esophageal ulcers, arrhythmia, chest pain and necrosis of the tongue, the nose or the lips.[61] A multicenter randomized controlled trial showed that the balloon tamponade (n = 15) were less effective than self-expandable, covered, esophageal metal stents (n = 13) for the temporary control of copious or refractory esophageal acute bleeding from esophageal varices in cirrhotic patients.[62] More studies on this issue would be interesting to confirm this result.

The Baveno VI workshop recommends early TIPS with expanded polytetrafluoroethylene-covered stents within 72 h for individuals with esophageal variceal hemorrhage at high risk of treatment failure (e.g. Child-Pugh C < 14 points or Child-Pugh class B with active bleeding). However, TIPS and surgical shunts are not indicated for patients with poor liver function and/or PVTT. As previously mentioned in this review, a retrospective study on interventions for post-banding ulcer hemorrhage evaluated 991 banding sessions (663 for prophylaxis and 328 for variceal bleeding treatment). Six out of 23 cases of post-banding ulcer bleeding were effectively controlled with pharmacological therapy alone (octreotide infusion + PPI +/- sucralfate). Five out of these six subjects were not actively hemorrhage during the endoscopy. Initial endoscopic approach was effective in 10 of 14 subjects, and was performed by different techniques (band ligation of ulcerated hemorrhage source, epinephrine injection or hemoclip placement). Even so, endoscopic treatment failed in 4 cases of patients who presented substantial hemorrhaging. In three of them the bleeding was then stopped by TIPS placement. Two subjects with massive hemorrhage were directly submitted to TIPS placement successfully. It is worth noting that 2 subjects with severe hemorrhaging died before TIPS placement (one had failed to stop bleeding at endoscopic intervention and the other was still bleeding despite the/a balloon tamponade). According to this study, patients with post-banding ulcer hemorrhage without active bleeding observed during upper endoscopy can be treated only with drugs. Furthermore, endoscopic treatment can be successful in cirrhotic subjects with active bleeding, however TIPS placement should be considered early in cases of substantial hemorrhaging caused by post-banding ulcers.[18]

Several endoscopic therapies have been suggested to replace EVL. Variceal clipping (n = 19) has been shown to be as effective as EVL (n = 21) in the management of acute esophageal variceal bleeding. One of the main advantages would be that variceal clipping could avoid mucosal ulceration, as occurs after EVL, thus reducing the risk of a subsequent hemorrhage.[36] Similar results have been related with detachable endoloops, but the risk of snare slippage during the procedure and the possibility of subsequent ulcer formation were not fully evaluated.[64] Despite its high cost, hemospray might also be useful in achieving hemostasis for post-banding bleeding.[65] Overall, these new approaches must be well evaluated in randomized clinical trials.

4. CONCLUSIONS

Despite the fact that post-banding ulcer hemorrhaging is not a common complication after EVL, it is a noteworthy cause of mortality. Child-Pugh class C status, high MELD score, emergency ligation, presence of HCC plus PVTT, peptic esophagitis and bacterial infection are the most important risk factors for this type of bleeding. Whenever possible, all of them must be assessed and controlled before prophylactic variceal ligation.

Given the nonthreatening nature of interventions based on oral drugs, the post-banding treatment with PPI or sucralfate seems advisable. There are more studies of PPI than sucralfate showing reduction of post-banding ulcers size, but there is a lack of evidence that these medications reduce the bleeding risk. The studies are heterogeneous and with small samples. There is no study comparing PPI versus sucralfate. On the other hand, the use of PPI by subjects with decompensated cirrhosis is a debatable issue.

Post-banding ulcer bleeding should always be suspected in the presence of hematemesis, melena, hematochezia or hemoglobin decrease within the first two weeks after EVL. A new upper endoscopy must be realized as soon as hemodynamic stability is achieved. Many treatment modalities have been used to control post-EVL bleeding, including medical therapy (PPI, sucralfate, vasoactive drugs), band ligation of the ulcerated bleeding site, local injection of epinephrine or cyanoacrylate, balloon tamponade and other therapies such as hemoclip or stent placement. TIPS and surgical shunts can be considered in cases of recurrent bleeding as a "bridge" to liver transplantation or within 72 h (ideally < 24 h) for patients with esophageal variceal bleeding at high risk of treatment failure. However, the optimal management of this complication remains uncertain. New approaches for controlling acute variceal bleeding are being developed to replace EVL, such as variceal clipping, detachable endoloops and hemospray, but further investigation is still required.

ACKNOWLEDGEMENTS

The authors are grateful for the financial support received from the Sao Paulo Research Foundation (FAPESP) grant No. 2016/07117-9.

CONFLICTS OF INTEREST DISCLOSURE

The authors declare that they have no competing interests.

REFERENCES

[1] Garcia-Tsao G, Bosch J. Management of Varices and Variceal Hemorrhage in Cirrhosis. N Engl J Med. 2010; 362: 823-32. PMid:20200386. https://doi.org/10.1056/NEJMra0901512

[2] D'Amico G. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. Hepatology. 2003; 38: 599-612. PMid:12939586. https://doi.org/10.1053/jhep.2003.50385

[3] Kamath PS, Mookerjee RP. Individualized care for portal hypertension: Not quite yet. J Hepatol. 2015; 63: 543-45. PMid:26150255. https://doi.org/10.1016/j.jhep.2015.07.001

[4] Hwang JH, Shergill AK, Acosta RD, et al. The role of endoscopy in the management of variceal hemorrhage. Gastrointest Endosc. 2014; 80: 221-27. PMid:25034836. https://doi.org/10.1016/j.gie.2013.07.023

[5] Hou MC, Lin HC, Kuo BI, et al. The rebleeding course and long-term outcome of esophageal variceal hemorrhage after ligation: comparison with sclerotherapy. Scand J Gastroenterol. 1999; 34: 1071-6. PMid:10582755. https://doi.org/10.1080/00365529975002 4841

[6] Elwakil R, Al Breedy AM, Gabal HH. Effect of endoscopic variceal obliteration by band ligation on portal hypertensive gastroduodenopathy: endoscopic and pathological study. Hepatol Int. 2016; 10: 965-73. PMid:26932843. https://doi.org/10.1007/s12072-016-9711-z

[7] Bambha K, Kim WR, Pedersen R, et al. Predictors of early rebleeding and mortality after acute variceal haemorrhage in patients with cirrhosis. Gut. 2008; 57: 814-20. PMid:18250126. https://doi.org/10.1136/gut.2007.137489

[8] Harewood GC, Baron TH, Song LM. Factors predicting success of endoscopic variceal ligation for secondary prophylaxis of esophageal variceal bleeding. J Gastroenterol Hepatol. 2006; 21: 237-41. PMid:16460480. https://doi.org/10.1111/j.1440-1746.2006.04169.x

[9] Lo GH, Lai KH, Cheng JS, et al. Emergency banding ligation versus sclerotherapy for the control of active bleeding from esophageal varices. Hepatology. 1997; 25: 1101-4. PMid:9141424. https://doi.org/10.1002/hep.510250509

[10] Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding. A meta-analysis. Ann Intern Med. 1995; 123: 280-7. PMid:7611595. https://doi.org/10.7326/0003-4819-123-4-199508150-00007

[11] Sarin SK, Lamba GS, Kumar M, et al. Comparison of endoscopic ligation and propranolol for the primary prevention of variceal bleeding. N Engl J Med. 1999; 340: 988-93. PMid:10099140. https://doi.org/10.1056/NEJM199904013401302

[12] Schmitz RJ, Sharma P, Badr AS, et al. Incidence and management of esophageal stricture formation, ulcer bleeding, perforation, and massive hematoma formation from sclerotherapy versus band ligation. Am J Gastroenterol. 2001; 96: 437-41. PMid:11232687. https://doi.org/10.1111/j.1572-0241.2001.03460.x

[13] Schepke M, Kleber G, Nürnberg D, et al. Ligation versus propranolol for the primary prophylaxis of variceal bleeding in cirrhosis. Hepatology. 2004; 40: 65-72. PMid:15239087. https://doi.org/10.1002/hep.20284

[14] Vieira da Rocha EC, D'Amico EA, Caldwell SH, et al. A prospective study of conventional and expanded coagulation indices in predicting ulcer bleeding after variceal band ligation. Clin Gastroenterol Hepatol. 2009; 7: 988-93. PMid:19410018. https://doi.org/10.1016/j.cgh.2009.04.019

[15] Lo GH, Lai KH, Cheng JS, et al. Endoscopic Variceal Ligation Plus Nadolol and Sucralfate Compared With Ligation Alone for the Prevention of Variceal Rebleeding: A Prospective, Randomized Trial. Hepatology. 2000; 32: 461-65. PMid:10960435. https://doi.org/10.1053/jhep.2000.16236

[16] Stiegmann GV, Goff JS, Michaletz-Onody PA, et al. Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. N Engl J Med. 1992; 326: 1527-32. PMid:1579136. https://doi.org/10.1056/NEJM199206043262304

[17] Petrasch F, Grothaus J, Mössner J, et al. Differences in bleeding behavior after endoscopic band ligation: a retrospective analysis. BMC

Gastroenterol. 2010; 15: 10-5. https://doi.org/10.1186/1471-230X-10-5

[18] Tierney A, Toriz BE, Mian S, et al. Interventions and outcomes of treatment of postbanding ulcer hemorrhage after endoscopic band ligation: a single-center case series. Gastrointest Endosc. 2013; 77: 136-40. PMid:23062759. https://doi.org/10.1016/j.gie.2012.08.031

[19] Vanbiervliet G, Giudicelli-Bornard S, Piche T, et al. Predictive factors of bleeding related to post-banding ulcer following endoscopic variceal ligation in cirrhotic patients: a case-control study. Aliment Pharmacol Ther. 2010; 32: 225-32. PMid:20412065. https://doi.org/10.1111/j.1365-2036.2010.04331.x

[20] Yang MT, Chen HS, Lee HC, et al. Risk factors and survival of early bleeding after esophageal variceal ligation. Hepatogastroenterology. 2007; 54: 1705-9. PMid:18019699.

[21] Hshieh TT, Kaung A, Hussain S, et al. The international normalized ratio does not reflect bleeding risk in esophageal variceal hemorrhage. Saudi J Gastroenterol. 2015; 21: 254-8. PMid:26228370. https://doi.org/10.4103/1319-3767.161646

[22] Kawai T, Yashima Y, Sugimoto T, et al. Emergency endoscopic variceal ligation following variceal rupture in patients with advanced hepatocellular carcinoma and portal vein tumor thrombosis: a retrospective study. World J Surg Oncol. 2016; 24: 14-52. https://doi.org/10.1186/s12957-016-0802-z

[23] Sinclair M, Vaughan R, Angus PW, et al. Risk factors for band-induced ulcer bleeding after prophylactic and therapeutic endoscopic variceal band ligation. Eur J Gastroenterol Hepatol. 2015; 27: 928-32. PMid:25951490. https://doi.org/10.1097/MEG.0000000000000387

[24] Ramirez FC, Colon VJ, Landan D, et al. The effects of the number of rubber bands placed at each endoscopic session upon variceal outcomes: a prospective, randomized study. Am J Gastroenterol. 2007; 102: 1372-6. PMid:17437506. https://doi.org/10.1111/j.1572-0241.2007.01211.x

[25] Garcia-Tsao G, Sanyal AJ, Grace ND, et al. Practice Guidelines Committee of the American Association for the Study of Liver Diseases; Practice Parameters Committee of the American College of Gastroenterology. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology. 2007; 46: 922-38. PMid:17879356. https://doi.org/10.1002/hep.21907

[26] Leung VK, Sung JJ, Ahuja AT, et al. Large paraesophageal varices on endosonography predict recurrence of esophageal varices and rebleeding. Gastroenterology. 1997; 112: 1811-6. PMid:9178670. https://doi.org/10.1053/gast.1997.v112.pm9178670

[27] Kakutani H, Hino S, Ikeda K, et al. Prediction of recurrence of esophageal varices-special reference to a role for endoscopic ultrasonography. Hepatol. 2005; 33: 259-66. PMid:16226914. https://doi.org/10.1016/j.hepres.2005.09.003

[28] Ahmed AM, al Karawi MA, Shariq S, et al. Frequency of gastroesophageal reflux in patients with liver cirrhosis. Hepatogastroenterology. 1993; 40: 478-80. PMid:8270239.

[29] Shaheen NJ, Stuart E, Schmitz SM, et al. Pantoprazole reduces the size of postbanding ulcers after variceal band ligation: A randomized, controlled trial. Hepatology. 2005; 41: 588-94. PMid:15726658. https://doi.org/10.1002/hep.20593

[30] Boo GB, Oh JC, Lee BJ, et al. The effect of proton pump inhibitor on healing of post-esophageal variceal ligation ulcers. Korean J Gastroenterol. 2008; 51: 232-40. PMid:18516002.

[31] Hidaka H, Nakazawa T, Wang G, et al. Long-term administration of PPI reduces treatment failures after esophageal variceal band ligation: a randomized, controlled trial. J Gastroenterol. 2012; 47: 118-26. PMid:21947706. https://doi.org/10.1007/s00535-011-0472-0

[32] Lo GH, Perng DS, Chang CY, et al. Controlled trial of ligation plus vasoconstrictor versus proton pump inhibitor in the control of acute esophageal variceal bleeding. J Gastroenterol Hepatol. 2013; 28: 684-9. PMid:23278466. https://doi.org/10.1111/jgh.12107

[33] Kang SH, Yim HJ, Kim SY, et al. Proton Pump Inhibitor Therapy Is Associated With Reduction of Early Bleeding Risk After Prophylactic Endoscopic Variceal Band Ligation. Medicine (Baltimore). 2016; 95: 2903. PMid:26937932. https://doi.org/10.1097/MD.0000000000002903

[34] Lodato F, Azzaroli F, Di Girolamo M, et al. Proton pump inhibitors in cirrhosis: tradition or evidence based practice? World J Gastroenterol. 2008; 14: 2980-85. PMid:18494046. https://doi.org/10.3748/wjg.14.2980

[35] Romero-Gómez M, Otero MA, Suárez-García E, et al. Acute hepatitis related to omeprazole. Am J Gastroenterol. 1999; 94: 1119-20. PMid:10201510. https://doi.org/10.1111/j.1572-0241.1999.01119.x

[36] Sarkar M, Hennessy S, Yang YX. Proton-pump inhibitor use and the risk for community-acquired pneumonia. Ann Intern Med. 2008; 149: 391-8. PMid:18794558. https://doi.org/10.7326/0003-4819-149-6-200809160-00005

[37] Chang SS, Lai CC, Lee MT, et al. Risk of spontaneous bacterial peritonitis associated with gastric Acid suppression. Medicine (Baltimore). 2015; 94: 944. PMid:26039135. https://doi.org/10.1097/MD.0000000000000944

[38] Huang KW, Kuan YC, Luo JC, et al. Impact of long-term gastric acid suppression on spontaneous bacterial peritonitis in patients with advanced decompensated liver cirrhosis. Eur J Intern Med. 2016; 32: 91-5. PMid:27139916. https://doi.org/10.1016/j.ejim.2016.04.016

[39] Lo EAG, Wilby KJ, Ensom MHH. Use of proton pump inhibitors in the management of gastroesophageal varices: a systematic review. Ann Pharmacother. 2015; 49: 207-19. PMid:25583938. https://doi.org/10.1177/1060028014559244

[40] Masuelli L, Tumino G, Turriziani M, et al. Topical use of sucralfate in epithelial wound healing: clinical evidences and molecular mechanisms of action. Recent Pat Inflamm Allergy Drug Discov. 2010; 4: 25-36. PMid:19832693. https://doi.org/10.2174/187221310789895649

[41] Roark G. Treatment of postsclerotherapy esophageal ulcers with sucralfate. Gastrointest Endosc. 1984; 30: 9-10. https://doi.org/10.1016/S0016-5107(84)72284-X

[42] Nijhawan S, Rai RR. Does post-ligation oesophageal ulcer healing require treatment? Lancet. 1994; 343: 116-7. https://doi.org/10.1016/S0140-6736(94)90844-3

[43] Yang WG, Hou MC, Lin HC, et al. Effect of sucralfate granules in suspension on endoscopic variceal sclerotherapy induced ulcer: analysis of the factors determining ulcer healing. J Gastroenterol Hepatol. 1998; 13: 225-31. PMid:10221828. https://doi.org/10.1111/j.1440-1746.1998.tb00642.x

[44] Sakr MA, El-Atty Hamed WA, El Gafaary MM, et al. Role of Sucralfate in Promoting Healing of Post Band Variceal Ulcer. Advances. 2011; 4: 7-14.

[45] Abraldes JG, Albillos A, Ba-ares R, et al. Simvastatin lowers portal pressure in patients with cirrhosis and portal hypertension: a randomized controlled trial. Gastroenterology. 2009; 136: 1651-8. PMid:19208350. https://doi.org/10.1053/j.gastro.2009.01.043

[46] Zafra C, Abraldes JG, Turnes J, et al. Simvastatin enhances hepatic nitric oxide production and decreases the hepatic vascular tone

in patients with cirrhosis. Gastroenterology. 2004; 126: 749-55. PMid:14988829. https://doi.org/10.1053/j.gastro.2003.12.007

[47] Abraldes JG, Villanueva C, Aracil C, et al. Addition of Simvastatin to Standard Therapy for the Prevention of Variceal Rebleeding Does Not Reduce Rebleeding but Increases Survival in Patients With Cirrhosis. Gastroenterology. 2016; 150: 1160-70. PMid:26774179. https://doi.org/10.1053/j.gastro.2016.01.004

[48] Kumar A, Jha SK, Mittal VV, et al. Addition of Somatostatin After Successful Endoscopic Variceal Ligation Does not Prevent Early Rebleeding in Comparison to Placebo: A Double Blind Randomized Controlled Trial. J Clin Exp Hepatol. 2015; 5: 204-12. PMid:26628838. https://doi.org/10.1016/j.jceh.2015.06.001

[49] Imperiale TF, Birgisson S. Somatostatin or octreotide compared with H2 antagonists and placebo in the management of acute nonvariceal upper gastrointestinal hemorrhage: a meta-analysis. Ann Intern Med. 1997; 127: 1062-71. https://doi.org/10.7326/0003-4819-127-12-199712150-00002

[50] Chen WT, Lin CY, Sheen IS, et al. MELD score can predict early mortality in patients with rebleeding after band ligation for variceal bleeding. World J Gastroenterol. 2011; 17: 2120-5. PMid:21547132. https://doi.org/10.3748/wjg.v17.i16.2120

[51] Kapoor A, Dharel N, Sanyal AJ. Endoscopic Diagnosis and Therapy in Gastroesophageal Variceal Bleeding. Gastrointest Endosc Clin N Am. 2015; 25: 491-507. PMid:26142034. https://doi.org/10.1016/j.giec.2015.03.004

[52] Ljubicić N, Bisćanin A, Nikolić M, et al. A randomized-controlled trial of endoscopic treatment of acute esophageal variceal hemorrhage: N-butyl-2-cyanoacrylate injection vs. variceal ligation. Hepatogastroenterology. 2011; 58: 438-43. PMid:21661410.

[53] Cipolletta L, Zambelli A, Bianco MA, et al. Acrylate glue injection for acutely bleeding oesophageal varices: A prospective cohort study. Dig Liver Dis. 2009; 41: 729-34. PMid:19362522. https://doi.org/10.1016/j.dld.2009.02.006

[54] Ribeiro JP, Matuguma SE, Cheng S, et al. Results of treatment of esophageal variceal hemorrhage with endoscopic injection of n-butyl-2-cyanoacrylate in patients with Child-Pugh class C cirrhosis. Endosc Int Open. 2015; 3: 584-9. PMid:26716117. https://doi.org/10.1055/s-0034-1392600

[55] Abdullah A, Sachithanandan S, Tan OK, et al. Cerebral embolism following N-butyl-2-cyanoacrylate injection for esophageal postbanding ulcer bleed: a case report. Hepatol Int. 2009; 3: 504-8. PMid:19669253. https://doi.org/10.1007/s12072-009-9130-5

[56] Sée A, Florent C, Lamy P, et al. Cerebrovascular accidents after endoscopic obturation of esophageal varices with isobutyl-2-cyanoacrylate in 2 patients. Gastroenterol Clin Biol. 1986; 10: 604-7. PMid:3781162.

[57] McCarty TR, Njei B. Self-expanding metal stents for acute refractory esophageal variceal bleeding: A systematic review and meta-analysis. Dig Endosc. 2016; 28: 539-47. PMid:26845490. https://doi.org/10.1111/den.12626

[58] Mishin I, Ghidirim G, Dolghii A, et al. Implantation of self-expanding metal stent in the treatment of severe bleeding from esophageal ulcer after endoscopic band ligation. Dis Esophagus. 2010; 23(7): E35-8. PMid:20731698. https://doi.org/10.1111/j.1442-2050.2010.01090.x

[59] Choudhary NS, Puri R, Saigal S, et al. Innovative Approach of Using Esophageal Stent for Refractory Post-Band Ligation Esophageal Ulcer Bleed Following Living Donor Liver Transplantation. J Clin Exp Hepatol. 2016; 6(2): 149-50. PMid:27493462. https://doi.org/10.1016/j.jceh.2016.01.003

[60] Terés J, Planas R, Panes J, et al. Esophageal tamponade for bleeding varices. Controlled trial between the Sengstaken-Blakemore tube and the Linton-Nachlas tube. Gastroenterology. 1978; 75: 566-9. PMid:361485.

[61] Pinto-Marques P, Romãozinho JM, Ferreira M, et al. Esophageal perforation–associated risk with balloon tamponade after endoscopic therapy. Myth or reality? Hepatogastroenterology. 2006; 53: 536-9. PMid:16995456.

[62] Escorsell À, Pavel O, Cárdenas A, et al. Esophageal balloon tamponade versus esophageal stent in controlling acute refractory variceal bleeding: A multicenter randomized, controlled trial. Hepatology. 2016; 63: 1957-67. PMid:26600191. https://doi.org/10.1002/hep.28360

[63] Yol S, Belviranli M, Toprak S, et al. Endoscopic clipping versus band ligation in the management of bleeding esophageal varices. Surg Endosc. 2003; 17: 38-42. PMid:12364992. https://doi.org/10.1007/s00464-002-9033-1

[64] Naga MI, Okasha HH, Foda AR, et al. Detachable endoloop vs. elastic band ligation for bleeding esophageal varices. Gastrointest Endosc. 2004; 59: 804-9. https://doi.org/10.1016/S0016-5107(04)00361-X

[65] Ibrahim M, Lemmers A, Devière J. Novel application of Hemospray to achieve hemostasis in post-variceal banding esophageal ulcers that are actively bleeding. Endoscopy. 2014; 46: 263. PMid:24906091. https://doi.org/10.1055/s-0034-1365112