Cyanoacrylate versus Vasoactive Therapy in Control of Post-Banding Ulcer Bleeding

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Abstract: Background: Bleeding related to post-banding ulcer is a rare, but severe complication. Aim of the work: We aimed to compare cyanoacrylate injection with octreotide vasoactive drug in controlling of postbanding ulcer bleeding. Patients&methods: This study was performed on fifty patients, with liver cirrhosis either bilharzial, post viral or mixed based on histopatholgy done at initial work up diagnosis before bleeding. Patients were presenting with upper GI bleeding caused by post-banding ulcer diagnosed by upper gastrointestinal endoscoy. Patients were subjected to history taking, thorough clinical examination, laboratory, radiological investigations, Child Pugh classification to assess the severity of liver disease and endoscopic intervention in the form of banding ligation for varices or cyanoacrylate injection for post-banding ulcer bleeding. After resuscitative measures, 25 patients were treated with 0.5 ml cyanoacrylate diluted with 0.5 ml lipiodol injected in the esophageal varix just below bleeding post-banding ulcer (group 1), 25 patients were treated with octreotide 50 microgram IV bolus and then 50 microgram IV infusion hourly for 48 hours (group 2). Results: The bleeding control was 88% in the group1 compared with 56% in the group 2 ($P<0.05$). The recorded complications: pyrexia, bacteremia, dysphagia were found more in cyanoacrylate (group 1) ($P<0.05$), nausea and diahrrea were more in octreotide (group 2) but not statistically significant (>0.05). All patients with uncontrolled bleeding in both groups were managed with TIPS. Conclusion: Endoscopic management with cyanoacrylate injection for bleeding post-banding variceal ulcers is more effective, but associated with more complications. Further studies on larger scale of patients is recommended to compare cyanoacrylate injection with other modalities of treatment of postbanding ulcer bleeding to determine the optimum way to stop bleeding with least complications.

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Introduction

Acute esophageal variceal bleeding is a severe and vital complication threatening cirrhotic patients' lives. The most important predictor of bleeding is the size of varices, with the highest risk of first bleeding (15% per year) occurring in patients with large varices. Other predictors of bleeding are decompensated cirrhosis (Child-Pugh B/C) and the endoscopic presence of red wale marks (**Garcia-Tsao et al., 2007**).

The most frequent cause of the bleeding is variceal rupture. Despite improvements in prognosis after variceal bleeding over the past two decades, the 6-week mortality rate remains high, ranging from 15 to 30%. Patients die from uncontrolled bleeding, early rebleeding, infection, or renal failure within the first weeks of a bleeding episode. Poor hepatic function, severe portal hypertension with a hepatic venous pressure gradient (HVPG) >20 mmHg, and active bleeding at endoscopy are independently associated with poor prognosis. (**Thabut et al., 2007**).

First-line treatment includes resuscitation, prophylactic antibiotic therapy, the combined use of vasoactive drugs (started as soon as possible), and an endoscopic procedure. Reconstitution of blood volume should be done cautiously to maintain the haematocrit between 25 and 30%. Terlipressin, somatostatin, or octreotide can be used, and drug therapy is maintained from 48 hours to 5 days. Ligation is the endoscopic treatment of choice in bleeding oesophageal varices; in gastric varices, obturation with cyanoacrylate is preferable. Uncontrolled bleeding should be an indication for a salvage transjugular intrahepatic portosystemic shunt (TIPS). In patients with Child-Pugh score A, shunt surgery might be an alternative to TIPS. (**Thabut et al., 2007**).

Trials have demonstrated that endoscopic variceal ligation (EVL) is an effective method to prevent variceal bleeding (**Khuroo et al., 2005**). However, early recurrent bleeding after EVL (rebleeding occurring between 24 hours and 14 days after the operation) is fatal, and is mainly due to early spontaneous slippage of rubber bands leaving the unhealed ulcer. (**Li et al., 2006**).

There is no data or guidelines concerning endoscopic control of ligation ulcers. Furthermore,

there is no data or guidelines on whether endoscopic band ligation (EBL) should be restricted to in-patients. (**Florian et al., 2010**).

Bleeding related to post-banding ulcer is a rare, but severe complication. The proposed predictive factors should be looked for and minimized before variceal ligation (**Vanbiervliet et al., 2010**). Until now, there has been no general consensus on the risk factors and measures to prevent early rebleeding.

Endoscopic variceal ligation is superior to sclerotherapy because of its lower rebleeding and complication rates. It consists of the placement of elastic bands on varices to occlude varix and causes thrombosis, this causes necrosis of the mucosa and the band falls off in few days leaving a superficial mucosal ulceration that heals within 2-3 weeks and eventually scars (**Stiegmann et al., 1988**).

In case of premature detachment of the rubber band before variceal thrombosis, marked ulceration of the mucosa can be seen.This explain the rebleeding episodes from esophageal ulcers following EVL (**Mishin et al., 2010**). Predictors for bleeding related to post-banding ulcer include: previous upper variceal digestive bleeding, peptic esophagitis, high platelet ratio index (APRI) score and low prothrombin index (**Bambha et al., 2008**).

The management of this complication is very critical and so difficult and surgical interference may be needed if general condition of the patient is suitable. The most important and common methods of management are endoscopic including: self-expanding metal stents; Ankaferd blood stopper (ABS) (**Mishin et al., 2010**).

Ankaferd blood stopper (ABS) is haemostatic agent. The major advantages of ABS appear to be the ease of use and lack of side effects (**Ozaslan et al., 2010**). ABS is a standardized mixture of the plants, becoming an effective alternative hemostatic medicine for gastrointestinal bleedings that are resistant to conventional anti-hemorrhagic measurements. (**Yavuz et al., 2011**).

Intravariceal injection of N-butyl-2-cyanoacrylate is widely used for the hemostasis of bleeding gastric varices, but not routinly for esophageal variceal hemorrhage because of various complications such as pyrexia, bacteremia, deep ulceration, and pulmonary embolization. Cyanoacrylate injection for esophageal variceal ligation induced ulcer bleeding in cirrhotic patients was used and found effective to control the bleeding from these ulcers. It is noteworthy that esophageal sinus can be developed as a rare late complication of endoscopic cyanoacrylate obliteration therapy (Eun Kyoung Kim et al., 2011).

Octreotide has emerged as vasoactive treatment of choice in the control of active variceal bleeding (**Gotzsch et al., 2008**). Octreotide reduced splanchnic blood flow and hepatic venous pressure in cirrhotic patients.Comparing terlipressin and octreotide combined with EVL showed them to be equally safe and effective therapeutic agents in patients with acute esophageal variceal bleeding. The high risk factors related to early rebleeding were poor liver function and advanced hepatocellular carcinoma (**Cho et al., 2006**). The therapeutic scheme of emergency EVL plus octreotide was a more cost-effective one for controlling acute esophageal variceal bleeding (**Zhang et al., 2006**).

TIPS may be indicated if all above modalities of treatment failed (**Garcia et al., 2007**). Uncontrollable variceal hemorrhage is best treated with transjugular intrahepatic porto-systemic shunt (TIPS) creation (**Hubmann et al., 2006**).

This procedure involves establishment of a direct pathway between the hepatic veins and the portal veins to decompress the portal venous hypertension that is the source of the patient's hemorrhage. The procedure is technically challenging, especially in critically ill patients, and has a mortality of 30%-50% in the emergency setting, but has greater than 90% effectiveness in controlling bleeding from gastroesophageal varices (**Kalva et al., 2009**).

Patients and Methods

The study included 50 patients (30 males and 20 females, age range was 36-55 years, (42.5 ± 10.4) attending the outpatient and inpatient clinic of the Hepatology Department-National Liver Institute-Menoufiya University in the period from December 2009 to May 2011.

The patients included in this study were presenting with upper gastrointestinal (Gl) bleeding caused by post-banding ulcer after variceal band ligation. This post-banding ulcer bleeding was diagnosed by upper Gl endoscopy under conscious sedation after resuscitation measures performed within 12 hours after hemorrhage without other causes of digestive bleeding.

All patients underwent variceal band ligation where six band ligations were placed (Cook, Six Shooter Saeed Multi-Band Ligator MBL-6, Wilson-Cook Medical, Winston-Salem, NC). No gastric varices were seen during endoscopy. Patients were classified into two groups, each 25 patients. First group of patients (cyanoacrylate group) (25 patients) (14 males and 11 females) were treated with a mixture of N- butyl-2-cyanoacrylate (Histoacryl; B-Braun Surgical GmbH, Melsungen, Germany) and lipiodol (Laboratoire Guerbet, Aulnay-Sous-Bois, France). This mixture was injected into the bleeding varix just below the bleeding post-banding ulcer with

a 21-gauge injector needle with a dead space of 0.8 ml (Injector Force, NM-200L-0821, Olympus Optical Co., Ltd., Tokyo, Japan). Each injection consisted of 0.5 ml of Histoacryl and 0.5 ml of lipiodol mixture and about three injections were required to arrest the bleeding according to the number of bleeding ulcers.

Cyanoacrylate is monomer that rapidly undergoes polymerization and contract with living tissue changing to hard material causing obliteration of varix (**Rengstorff and Binmoeller, 2004**).

Second group of patients (octreotide group) (25 patiets) (16 males and 9 females) presented with bleeding from post-banding ulcers and diagnosed by endoscopy were treated by giving a bolus of 50 microgram octreotide IV immediately and then 50 microgram per hour for next 48 hours. Octreotide is safe and has few reported side effects (**Orley et al., 2001**).In both groups of patients, control of bleeding and complications were recorded. Patients who were still bleeding were managed with TIPS.

The study was approved by the local ethical committee in university hospital and informed consent was obtained from the patients.

All patients were subjected to full history taking, thorough clinical examination and the following investigations: abdominal ultrasound, Laboratory investigations including hepatic transaminases (AST and ALT), albumin, total and direct bilirubin, and alkaline phosphatase.These tests were measured using lntegra-400 (Roche-Germany). Prothrombin concentration was done by Fibrintimer (Dade Behring-Germany). Complete blood cell counts were measured by Sysmix K-21 automatic cell counter (Japan). Serum α fetoprotein (AFP) was measured by an automated chemiluminescences using ACS-180SE (Chiron,Diagnostic-Germany).

Hepatitis C virus (HCV) and hepatitis B virus (HBV) antibodies were assayed by EIA (COBAS-Amplicore, Germany). HCV-RNA and HBV-DNA levels were analyzed by reverse transcriptase polymerase chain reaction (RT-PCR) using a commercial kit (Roche Diagnostic, Branchburg, NJ-Germany) according to the manufacturer's instructions. These viral markers were already done before and retrieved from patient files.

Ultrasound guided liver biopsy was performed, at initial work up diagnosis before bleeding episodes, by liver biopsy gun for all patients and histological grading and staging were performed using a modified Knodell scoring. Fibrosis score from 0-6, 0=no fibrosis, 1-2=portal fibrosis (mild fibrosis), 3-4=bridging fibrosis (moderate fibrosis) and 5-6=cirrhosis (advanced fibrosis) (**Ishak et al., 1995**). Endoscopic variceal ligation was done after resuscitation and stabilization for variceal bleeding and follow up endoscopy for elective EVL was scheduled to obliterate varices.During bleeding episodes which found to be attributable to post-banding ulcer, patients underwent cyanoacrylate injection below bleeding ulcer or octreotide infusion after being assigned randomly into two groups.

Statistical analysis:

The data were statistically analyzed using SPSS computer program version 11, data were expressed as mean ± SD and differences between groups were analyzed by t-test, while chi square test was used to compare categorical variables P value <0.05 was considered statistically significant.

3. Results

Table (1): Distribution of studied patients according to etiology of liver disease

Etiology	Cyanoacrylate group (n=25)		Vasoactive group (n=25)		X^2	P
	No.	%	No.	%		
Bilharzial group	3	12%	4	16%	3.45	>0.05
Viral hepatitis (HCV &/or HBV)	7	28%	8	32%		
Mixed bilharzial and VH (B&C)	15	60%	13	52%		

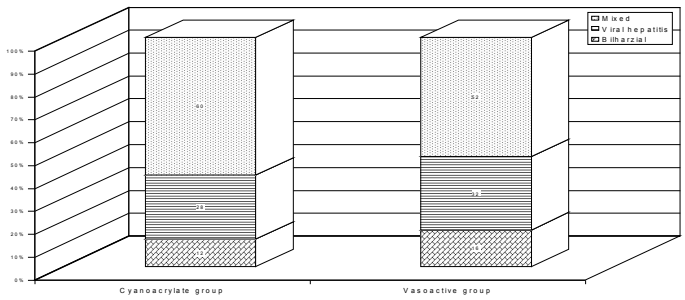

Fig. (1): Distribution of studied patients according to etiology of liver disease

Table (2): Laboratory data in both groups

Lab. data	Cyanoacrylate group (n=25)	Vasoactive group (n=25)	*t*	P
AST (U/L)	72.0 ± 26.38	78 ± 34.24	*1.04*	>0.05
ALT (U/L)	75.0 ± 35.31	87.0 ± 50.31	*1.37*	>0.05
T. Bil. (mg/dL)	3.4 ± 2.67	3.69 ± 2.94	*0.50*	>0.05
Albumin (g/dL)	2.97 ± 0.89	2.93 ± 0.66	*0.25*	>0.05
Proth. Conc (%)	62.94 ± 6.11	61.20 ± 7.39	*1.27*	>0.05

Table (3): Distribution of studied patients according to Child-Pugh classification

Child class.	Cyanoacrylate group (n=25)		Vasoactive group (n=25)		X^2	P
	No.	%	No.	%		
Child A	9	36%	7	28%	4.67	>0.05
Child B	9	36%	8	32%		
Child C	7	28%	10	40%		

Table (4): Bleeding control in relation to severity of liver disease.

Child class.	Cyanoacrylate group		Vasoactive group		*p*
	No.	%	No.	%	
Child A	8/9	88.8%	6/7	85.7%	>0.05
Child B	8/9	88.8%	5/8	62.5%	>0.05
Child C	6/7	85.7%	3/10	30%	<0.05

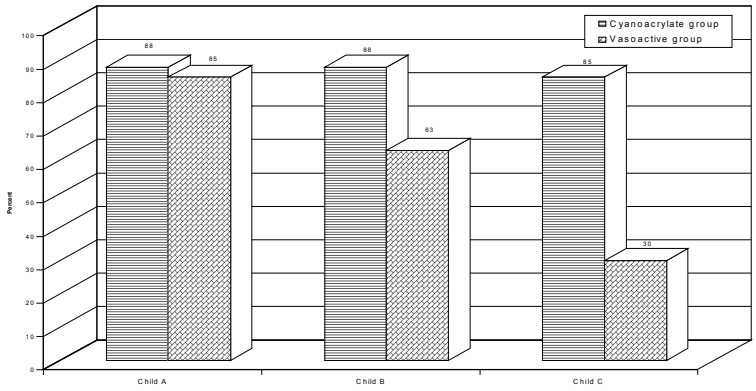

Fig. (2): Bleeding control in relation to severity of liver disease.

Table (5): Comparison of mortality between studied groups

	Cyanoacrylate group (n=25)		Vasoactive group (n=25)		X^2	P
	No.	%	No.	%		
Mortality	1	4%	2	8%	2.87	>0.05

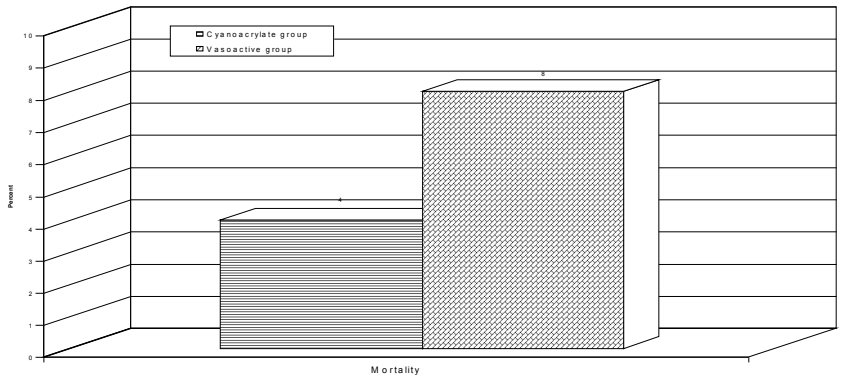

Fig. (3): Comparison of mortality in studied groups

Table (6): Side effects and complications in the studied groups

Complications	Cyanoacrylate group (n=25)		Vasoactive group (n=25)		X^2	P
	No.	%	No.	%		
Dysphagia	15	60%	0	-	21.43	<0.001
Pyrexia	10	40%	0	-	12.5	<0.001
Bacteremia	8	32%	0	-	9.5	<0.05
Sinus formation	1	4%	0	-	1.02	>0.05
Nausea	0	-	2	8%	2.08	>0.05
Diarrhea	0	-	2	8%	2.08	>0.05

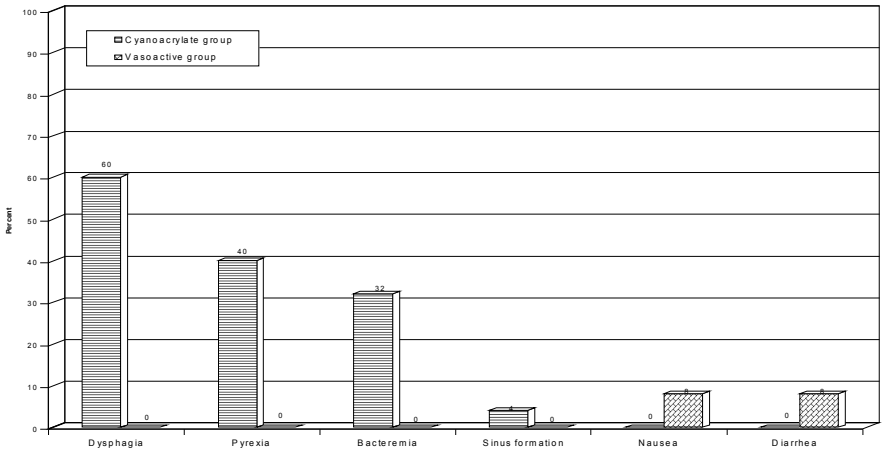

Fig. (4): Side effects and complications in the studied groups

Table (7): Control of bleeding in the studied group

	Cyanoacrylate group (n=25)		Vasoactive group (n=25)		X^2	P
	No.	%	No.	%		
Control of bleeding	22	88%	14	56%	6.35	<0.05

The control of bleeding in cyanoacrylate group was statistically significant when compared with vasoactive group.

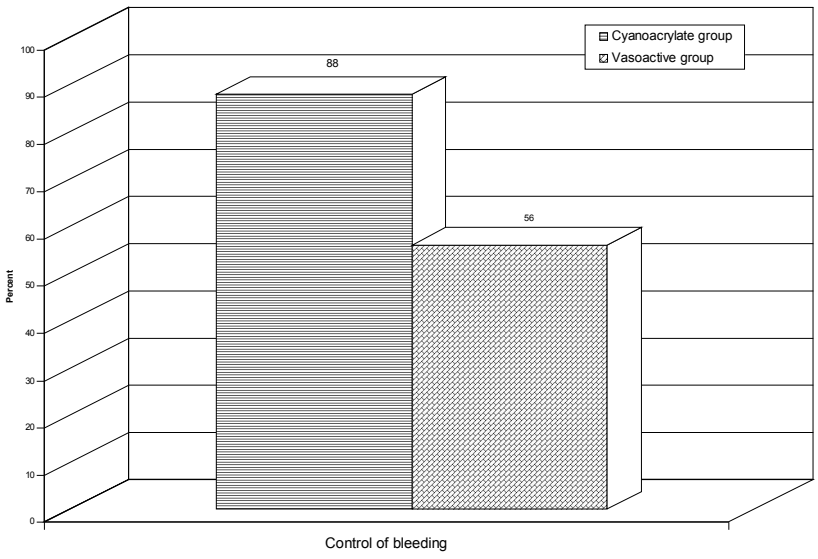

Fig. (5): Control of bleeding in the studied group (pls remove fig 1-4 and leave fig 5)

4. Discussion

The proposed predictive factors for early rebleeding should be looked for and minimized before variceal ligation. Low prothrombin index, high APRI score, previous upper variceal digestive bleeding appeared to be predictive factors of bleeding in relation to post-banding ulcer (**Vanbiervliet et al., 2010**). Endoscopic therapy is typically avoided during acute bleeding in patients who have platelet counts <50,000/mm^3 or international normalized ratios (INRs) >1.5. Therefore, transfusions of products are often given to correct these coagulation indices prior to endoscopic therapy. The only factor that was significantly associated with postbanding bleeding was Child-Pugh classification (Child-Pugh class A/B 4.3% vs Child-Pugh class C 17.0%; P=0.017) (**Vieira et al., 2009).**

The risk of bleeding from treatment-induced ulceration is lower after elective endoscopic band ligation (EBL) than after emergency intervention. Elective EBL should be done until all varices are eradicated. An excessive application of ligation bands should be avoided **(Florian et al., 2010**).

Our patients developed bleeding from an esophageal ulcer formed after an elective variceal banding. There is a paucity of data on the incidence of bleeding from such ulcers. Results from secondary prophylaxis trials for esophageal variceal bleed showed that bleeding from postbanding ulcers is relatively uncommon (**Pena et al., 2005**); (**Lo et al., 2000**). A study done by Pena et al. (n=80) showed that four of the 20 rebleeding cases were due to bleeding esophageal ulcers. Similarly, a study done by Lo and colleauges (n=122) showed that seven of the 71 rebleeding episodes were due to esophageal ulcers.

Evidence on the management of an active esophageal postbanding ulcer bleed remains lacking. In our practice, intravariceal injection of Histoacryl is often used to arrest active bleeding from such ulcers. However, it remains to be determined whether this is the optimum treatment modality.

In this study, the control of bleeding in cyanoacrylate group was 88% in comparison to octreotide group (vasoactive therapy) which was 56% (P<0.05). The same results as regards treatment by cyanoacrylate was in agreement with a study done by (**Kim et al., 2011**).

In this study, bleeding control in relation to the severity of liver disease in both studied groups has no significant difference in Child A and Child B patients. In Child A 88% in cyanoacrylate group vs 85% in vasoactive group (P>0.05); in Child B was 88% in cyanoacrylate group vs 63% in vasoactive group (P>0.05), but in Child C, the control of bleeding showed statistically significant difference between cyanoacrylate group and vasoactive group, 85% and 30% respectively (P<0.05). Histoacryl was superior to cotreotide in controlling of bleeding in child C and overall. The bleeding was life threating and it's control was considered a life saving.

As regards the mortality, in cyanoacrylate group there was 1 patient Child C died due to the presence of multiple post-banding ulcers with uncotrollable bleeding, this patient had hepatorenal syndrome.In vasoactive group there were 2 patients Child C died due to uncontrollable bleeding, both had liver cell failure.

With regard to the complications, there was a statistically significant difference between cyanoacrylate group and vasoactive group regarding the following: dysphagia: 15 out of 25 patients (60%) in cyanoacrylate group and 0% in vasoactive group (P<0.05). This dysphagia was transient and improved gradually in a few days post injection. Pyrexia: in 10 out of 25 patients (40%) in cyanoacrylate group and 0% in vasoactive group (P<0.05). Bacteremia: in 8 out of 25 patients (32%) in cyanoacrylate group and 0% in vasoactive group (P<0.05). bactremia was teated successfully with third generation cephalosporin. Sinus formation: in 1 patient in cyanoacrylate group and none in vasoactive group (>0.05). Nausea: 0% in cyanoacrylate group and 2 patients in vasoactive group (8%) (>0-05). Diarrhoea: 0% in cyanoacrylate group and 2 patients in vasoactive group (8%) (>0.05).

There are several modalities in treatment of variceal bleeding and controlling bleeding from post-banding ulcers including cyanoacrylate injection, vasoactive therapy, ABS, placement of esophageal metal stent, TIPS, surgical vasoligation and liver transplantation. The most cheap and available measures are cyanoacrylate injection and vasoactive therapy.

Cyanoacrylate injection is superior in comparison to vasoactive therapy because it is simple, cheap, available in most centers and more effective in controlling the post-banding ulcer bleeding .Other modalities are expensive, not available in all centers. Recently Tuncer et al reported a patient with a fundal variceal hemorrhage that was effectively treated with 6 ml of ABS. Immediate hemostasis was achieved in 18 seconds without any further treatment. Control endoscopy was performed on day 5 that revealed clean surface fundal varices and a successful variceal obscuration by cyanoacrylate injection that was performed subsequently (**Tuncer et al., 2010**).

Similarly, in a case report by Ozaslan et al, a patient with alcoholic cirrhosis who developed severe bleeding during an elective EBL session due

to immediate band slippage underwent endoscopic topical application of ABS, which was then associated with the cessation of the hemorrhage (**Ozaslan et al., 2010**). Although both of these reports seem to be encouraging, further controlled randomized studies are required to validate the effectiveness of ABS in the therapy of gastroesophageal varices.

Esophageal metal stent is expensive and needs endoscopist with experience in it.TIPS is expensive and not available in many centers.Liver transplantation is expensive and not available in most of centers as it needs more experience and advanced facilities.

Conclusion

Endoscopic management by cyanoacrylate injection for bleeding post-banding variceal ulcers is more effective than octreotide vasoactive therapy in controlling the bleeding but associated with more complications. Further studies are recommended to compare different treatment modalities in post-banding ulcer bleeding to determine the optimum modality to arrest the bleeding with least complications.

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