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Esophageal variceal ligation for acute variceal bleeding: Results of three years' follow-up

Akut varis kanaması için özofagus varis ligasyonu: 3 yıllık takip sonuçları

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Background/aims: *Endoscopic variceal ligation is widely accepted as the optimum endoscopic treatment for esophageal variceal hemorrhage. However, the rebleeding course and long-term outcome of patients with esophageal variceal hemorrhage after ligation have been poorly defined. Therefore, we conducted a long-term follow-up study to delineate the outcome of ligation.* ***Methods:*** *Twenty-one liver cirrhotic patients with endoscopically proven esophageal variceal hemorrhage were treated by endoscopic variceal ligation. These patients received regular follow-up and detailed clinical assessment of at least 24 months.* ***Results:*** *Twenty-one eligible patients were followed up for a mean of 44.45 months (range 33.5-64 months). The mean number of sessions required to obtain eradication was 3.57±1.99 (range 1-8). Esophageal varices could be obliterated within 11.57±6.8 weeks (range 3-30). The percentage of variceal recurrence during follow-up was 57.14% (12/21) after endoscopic variceal ligation. Recurrence were observed in a mean of 34 months (median 29 months). Rebleeding from esophageal varices appeared in four patients (19.04%). The appearance rates of portal hypertensive gastropathy and fundal gastric varices after varice obliteration were found to be 45.45% (5/11) and 25% (3/12), respectively.* ***Conclusions:*** *Based on the results of long-term follow-up of endoscopic variceal ligation, although the percentage of variceal recurrence was high, endoscopic ligation achieved variceal obliteration faster and in fewer treatment sessions. Furthermore, endoscopic variceal ligation had a lower rate of rebleeding and of development of fundal gastric varices, but high portal hypertensive gastropathy.*

Keywords: Variceal hemorrhage, band ligation, liver cirrhosis, complication

Amaç: *Endoskopik varis ligasyonu özofagus varis kanaması için optimum endoskopik tedavi olarak yaygın kabul görmektedir. Ancak, ligasyon sonrası özofagus varis kanamalı hastaların yeniden kanama ve uzun süreli takip konusunda yeterince veri azdır. Bu nedenle ligasyonun seytini göstermek için uzun süreli takip çalışması planladık.* ***Yöntem:*** *Endoskopik olarak ispatlanmış özofagus varis kanaması olan ve endoskopik varis ligasyonu ile tedavi edilmiş karaciğer sirozlu yirmi bir hasta çalışmaya alındı. Bu hastalar 24 ay boyunca düzenli olarak takip edildi ve ayrıntılı klinik değerlendirme yapıldı.* ***Bulgular:*** *Uygun 21 hasta 44.45 ay (erim 33.5-64 ay) takip edildi. Eradikasyon sağlamak için gerekli ortalama oturum sayısı 3.57±1.99 (erim 1-8) idi. Özofagus varisi 11.57±6.8 haftada (erim 3-30) oblitere edildi, endoskopik varis ligasyonu sonrası takip sırasında varis nüks oranı %57.14 (12/21) idi. Nüks ortalama 34. ayda (ortanca 29 ay) gözlendi. Özofagus varisinden yeniden kanama 4 hastada (%19.04) görüldü. Varis obliterasyonundan sonra portal hipertansiv gastropati ve fundal varis ortaya çıkma oranı sırasıyla %45.45(5/11) ve %25 (3/12) idi.* ***Sonuç:*** *endoskopik varis ligasyonun uzun süreli takip sonuçlarına göre, varis nüksü oranı yüksek olmasına rağmen; endoskopik ligasyon daha az tedavi oturumunda ve daha hızlı varis obliterasyonu sağladı; ve endoskopik varis ligasyonunun daha az yeniden kanama ve fundal gastrik varis oranı vardı; fakat portal hipertansif gastropati oranı yüksekti.*

Anahtar kelimeler: Varis kanaması, band ligasyonu, karaciğer sirozu, komplikasyon

INTRODUCTION

Acute bleeding from esophageal varices is a major problem in patients with cirrhosis of the liver, and is associated with a 30-50% risk of death and an early rebleeding rate of 40-60% within 7 to 10 days of a controlled index episode (1-2). This early rebleeding indicates that a correct therapeutic approach should be aimed not only at arresting the acute variceal bleeding episode but also at preventing an early variceal bleeding. The risk of recurrent bleeding approaches 70% by two years after the index bleed (3). Each bleeding episode is associated with a 30% mortality rate (3). Thus, urgent

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treatment of the acute hemorrhage and steps to prevent rebleeding are essential.

Different therapeutic methods have been used in the treatment of this complication (4). However, so far none of them have shown a clear benefit over the other. Endoscopy is indicated to diagnose and treat the acute bleeding with either band ligation or sclerotherapy. Other therapies include vasoactive drugs (e.g., octreotide, vasopressin, terlipressin), balloon tamponade, and transjugular intrahepatic portosystemic shunting (TIPS). Emergency surgical procedures such as surgical portosystemic shunts or transection of the esophagus and the availability of liver transplantation have further increased the therapeutic options available to the physician treating this disorder (4). Generally, patients whose endoscopic procedures fail to control the bleeding should undergo emergency TIPS, if feasible. Beta-blockers have been shown to be of value in preventing both the first episode of bleeding in patients with varices (index bleed) and rebleeding (4). At a recent consensus meeting, it was concluded that pharmacologic therapy is an important option in the treatment of portal hypertension (5). For the treatment of acute variceal bleeding vasopressin plus nitroglycerin, terlipressin, and somatostatin and its analogues were recommended (6).

The aims of this retrospective trial were to investigate the efficacy and rebleeding rate of endoscopic variceal band ligation (EVL), the duration of follow-up and estimation of post-EVL complications in the treatment of an acute episode of variceal bleeding in cirrhotic patients.

MATERIALS AND METHODS

All adult cirrhotic patients with an episode of upper gastrointestinal bleeding (hematemesis or melena or both) were admitted to the emergency service, and underwent endoscopy as soon as they had been resuscitated. A total of 21 patients who were followed-up for at least 24 months were enrolled in the trial. Patients were admitted to our hospital if they had active variceal bleeding at endoscopy (spurting or oozing from esophageal varices) or if they had nonbleeding varices but evidence of blood with no other potential source of gastrointestinal bleeding. Our admission protocol included the patients with less than 24 hours' elapsed time between the occurrence of hematemesis or melena (or both) and the emergency endoscopy, and cirrhosis documented either on the basis of a liver biopsy performed during a previous admission or typical laboratory, clinical and ultrasonographic findings. The patients who were excluded from the trial presented with the following conditions: admission to the hospital from other medical centers with vasoactive therapy (17 patients) or Sengstaken-Blakemore tube (none); previously administered sclerotherapy (21 patients); gastric fundal variceal bleeding (3 patients); concomitant hepatoma (3 patients) or another tumor, or upper gastrointestinal tract bleeding from causes not related to the varices (5 patients); or the development of serious side effects that required the discontinuation of therapy; and pregnancy (none). Information about alcohol abuse was obtained from all the patients, and tests for hepatitis B and C viruses and autoimmune markers in the serum were also performed. The severity of liver disease was classified according to Child's classification. The esophageal varices gradings were made as follows: 1= disappeared with air insufflation; 2= did not disappear with air insufflation; 3= occluded more than one-third of esophageal lumen.

Endoscopic Ligation

Patients underwent ligation at the first endoscopy session or within the next 24 hours. After local application of lidocaine, an endoscope (model GIF X-Q 20 Olympus Optical, Tokyo) was introduced, and the ligation was carried out by placing a single or multiple rubber band over a varix each time the endoscope was inserted. As many bands as possible (average, 3 to 5 bands, with fewer in later sessions) were placed in the lower 5 to 7 cm of all variceal columns (vertical veins). Each residual varix was ligated distally and proximally to accelerate obliteration. Patients underwent regular EVL without drug therapy such as beta-blockers until variceal obliteration.

Follow-up

Patients were followed up from January 1992 to until May 1998. Endoscopic ligation was performed every three weeks until the varices were obliterated or were reduced to a size of grade 1. In the latter instance, it was impossible to apply more bands because of the small size of the varices. Patients were asked to record all symptoms, such as hematemesis, melena, chest pain, fever, and dysphagia. The presence of ulcers, esophagitis or strictures was noted on endoscopic examination. After the varices had been obliterated or reduced in size to grade 1, patients underwent endoscopy

every three months until the end of follow-up. If varices recurred and became larger or grade 2 in size, repeated ligation to obliterate was done. Patients were advised to refrain from consuming alcohol and from taking nonsteroidal antiinflammatory drugs, beta-blockers, histamine H2 blockers, or proton-pump inhibitors.

Bleeding

Any patient who had overt upper gastrointestinal bleeding during the study was admitted to the hospital and underwent endoscopy of the upper gastrointestinal tract within 24 hours to determine the source of bleeding. Bleeding from esophageal varices was diagnosed if active bleeding or a clot was seen on endoscopy and if there was evidence of recent bleeding in a patient with an esophageal varice and no other visible mucosal lesion. Bleeding was considered to have arisen from gastric varices if active bleeding or clot was seen on endoscopy or if there was evidence of recent bleeding in a patient with a gastric varix and the bleeding had no other possible cause. Bleeding was considered to be caused by portal hypertensive gastropathy if distinct lesions of the gastric mucosa were present and there was no evidence of bleeding from esophageal, gastric, or ectopic varices. Bleeding was considered to be caused by esophageal ulcers as a result of band ligation if there was active bleeding or if there was an adherent clot on the esophageal ulcer.

Management of Upper Gastrointestinal Tract Bleeding

All episodes of upper gastrointestinal tract bleeding were managed with supportive therapy, including transfusions of blood and emergency ligation. Other complications of liver disease, such as hepatic encephalopathy and spontaneous bacterial peritonitis, were managed according to standard protocols.

Statistical Analysis

Quantitative data were expressed as means (±SD) or as medians. The recurrence of varices was calculated by the Kaplan-Meir method.

RESULTS

The were 21 eligible patients who underwent endoscopic variceal ligation. The patients' characteristics are shown in (Table 1). The 21 patients were followed up for a mean of 44.45 months (range 33.5-64 months). The etiologies of these patients were as follows: 10 patients viral cirrhosis; 5 patients portal vein thrombosis; 4 patients cryptogenic cirrhosis; and 2 patients alcoholic cirrhosis. The average age of the patients was 43.90 years (range 20-64) and 71.42% were males. Thirteen of 21

Table 1. Patients' characteristics

Patient	Age (year)	Sex	Etiology	Child's Classification	Grade of Varix	Follow of time (months)	Number of Sessions	Obliteration time (weeks)	Portal Hypertensive Gastropathy*	Fundal Varices*
1	60	F	Viral Cir.(C;ı	A	3	54	1	3	(+)	(-)
2	41	M	PVT	A	3	46	3	9	(-)	(-)
3	41	F	Cry. Cir.	A	3	39	3	9	(-)	(-)
4	45	F	Cry. Cir.	C	2	38.5	2	6	(-)	(-)
5	34	F	PVT	A	3	52	1	3	(+)	(+)
6	50	M	Alc. Cir.	B	3	37	8	24	(+)	(+)
7	47	M	PVT	A	3	40.5	4	14	(+)	(+)
8	29	F	PVT	A	3	49	8	30	(-)	(-)
9	40	M	Viral Cir.(C;ı	B	3	52.5	3	9	(-)	(+)
10	47	M	Viral Cir.(C;ı	B	3	36.5	5	15	(+)	(+)
11	52	M	Viral Cir.(B;>	B	3	36	5	15	(+)	(-)
12	64	M	Cry. Cir.	C	3	39.5	3	12	(+)	(+)
13	55	M	Viral Cir.(C;)	A	3	64	2	6	(+)	(-)
14	20	F	PVT	A	2	35	2	6	(-)	(+)
15	62	M	Viral Cir.(B;)	A	3	60.5	6	18	(+)	(-)
16	26	M	Viral Cir.(C;)	B	3	42.5	3	9	(-)	(-)
17	26	M	Cry. Cir.	B	3	36.5	2	6	(-)	(-)
18	48	M	Viral CİT.(B;)	A	3	33.5	4	12	(-)	(-)
19	44	M	Viral Cir.(B;)	A	3	39	3	15	(-)	(-)
20	48	M	Alc. Cir.	A	3	58.5	2	6	(-)	(-)
21	43	M	Viral Cir.(B;)	A	3	43.5	5	15	(+)	(+)

Viral Cir.: viral cirrhosis; C: viral hepatitis C; B: viral hepatitis B; PVT: portal vein thrombosis; Cry. Cir.: cryptogenic cirrhosis; Alc. Cir.: alcoholic cirrhosis. (*) Initial endoscopic examination findings. (+): present; (-): absent

patients were Child's class A, whereas there were 6 patients in Child's class B liver cirrhosis and 2 patients in Child's class C liver cirhosis.

All of the patients had recently bled from esophageal varices. At the time of treatment, 4 of 21 patients (19.04%) were actively bleeding. They were all treated acutely with EVL and had repeated treatments with the long-term goal of variceal eradication. Hemostasis rates at the first endoscopic session were 100%. Obliteration of the varices was achieved in all patients with 3.57±1.99 (range 1-8) endoscopy sessions over a period of 11.57±6.8 weeks (range 3-30 weeks). Varices recurred in a mean of 34 months after the initial obliteration (Figure 1) and could be obliterated again in a mean of 1.91±1.37 (range 1-5) sessions by repeated ligation over a period of 5.75±4.13 weeks (range 3-15 weeks). First variceal recurrence was seen in 12/21 (57.14%) patients and was managed by repeated EVL. Second recurrences were rare (3/21) during follow-up. At the same time, these three patients also had exhibited third variceal recurrence.

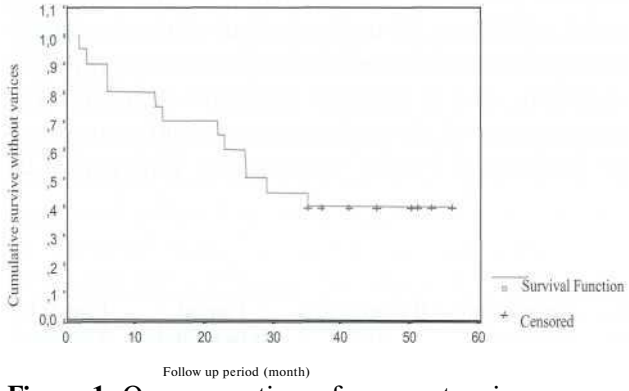

Figure 1. Occurrence time of recurrent varices

During the study period, rebleeding from esophageal varices occurred in four patients (19.04) (patients 8, 12, 20 and 21). The first patient's bleeding was observed twice in the first month and was from post-ligation variceal ulcer. The other patients' bleedings occurred after 29 months, 25 months and 39 months, respectively. They were managed with supportive therapy, including transfusions of blood and EVL. There was no mortality due to gastrointestinal bleeding during the follow-up period.

In initial endoscopic examination, 19 of 21 patients had 3rd degree esophageal varices and the other two patients had 2nd degree (Table 1). Ten patients had portal hypertensive gastropathy. In five patients (5/11, 45.45%), it developed after EVL. Nine patients had fundal varices. After EVL, we observed the development of fundal varices in three patients (3/12, 25%).

No serious complications resulted from variceal ligation (Table 2). Transient retrosternal pain, fever, and dysphagia developed in 23.8%, 23.8%, and 4.76% of the patients, respectively. Post-ligation variceal ulcers, generally superficial, developed in 15 (71.42%) patients; esophagitis developed in seven (33.33%) patients; esophageal diverticula developed in one patient (4.76%); and post-ligational variceal ulcer bleeding in one (4.76%).

Table 2. Complications related to endoscopic variceal ligation

Complications	n(%)
Retrosternal pain	6 (23.8)
Fever	6 (23.8)
Dysphagia	1 (4.76)
Postligation variceal ulcer	15 (71.42)
Esophagitis	7 (33.33)
Diverticula	1 (4.76)
Bleeding	1 (4.76)

DISCUSSION

Twenty-one patients with esophageal variceal bleeding were enrolled. Many patients admitted for variceal bleeding have a previous history of bleeding and have received previous sclerotherapy or ligation, or both. Therefore, only 21 patients were eligible for this study.

Endoscopic variceal ligation is an effective endoscopic technique and it was initially introduced by Steigniann in 1986 (7). This procedure involves the placement of rubber "O-rings" on variceal columns which are suctioned into a hollow cylinder that is attached to the tip of the endoscope. Placement of the bands causes venous obstruction, mucosal inflammation, necrosis, and formation of scars. The sloughing of varices then forms ulcers. The healing of these ulcers promotes fibrosis and eventual variceal obliteration (8). Unlike sclerotherapy, which uses chemicals to arrest bleeding, EVL stops bleeding by physically constricting the varix at or near the site of bleeding (9). As a result, EVL lacks adverse systemic effects. Complications associated with the procedure include dysphagia, esophageal strictures, and transient chest discomfort (8). In our study retrosternal pain, fever, and dysphagia developed in 23.8%, 23.8%, and 4.76% of the patients, respectively. Severity of these

complications was mild and transient. The most frequent complication that we encountered was post-ligation variceal ulcer (15/21 patients, 71.42%) (Table 2). Moreover, we noted the case that developed esophageal diverticula after EVL.

Lo et al. (10) conducted a prospective, randomized trial comparing sclerotherapy with EVL in 120 patients with active esophageal variceal bleeding. The study showed that both sclerotherapy and EVL could effectively stop active variceal bleeding; however, EVL was more effective in decreasing the incidence of rebleeding from esophageal varices with fewer complications (10). We determined a rebleeding rate of 19.04%.

Laine et al. (11) conducted a meta-analysis of results from randomized clinical trials that compared sclerotherapy to EVL. Their study suggested that EVL had equal efficacy to injection sclerotherapy in the treatment of acute variceal bleeding, with lower rates of rebleeding, mortality and complications (11). Also, fewer treatment sessions were needed with EVL than with sclerotherapy to achieve variceal obliteration, which has favorable economic implications (11). In light of these findings, EVL may be a more reasonable choice than sclerotherapy in the treatment of active bleeding varices.

Often, bleeding from esophageal varices is the major contributory factor of the death of patients with portal hypertension (12). Mortality for the first variceal bleed is approximately 20% for patients with mild impairment (Child's A cirrhosis) and 60% or higher for severe impairment (Child's C patients) (3). Undisputedly, further treatment is needed to reduce the risk of bleeding and mortality in these patients. There was no mortality due to gastrointestinal bleeding during the follow-up period in our study.

Endoscopic variceal ligation is another alternative to pharmacologic therapy for the primary prophylaxis of variceal bleeding. Sarin et al. (13) compared EVL to propranolol. The study concluded EVL to be safe and more effective than propranolol in lowering the risk of bleeding (13). Endoscopic variceal ligation has been found to be comparable, if not better, than propranolol in the primary prevention of variceal bleeding. Additionally, there are several advantages to EVL over pharmacological treatment (12). Ligation may be considered for patients in whom beta-blockers are contraindicated or not tolerated (12).

Patients surviving a first variceal bleed have a high risk of rebleeding and death. Most patients will experience a rebleed within the first few weeks after the first variceal bleed. Therefore, further treatment is needed to reduce the risk of rebleeding (14). Both sclerotherapy and beta-blockers decrease the risk of mortality and rebleeding. Both methods also have a similar effect on survival. Although sclerotherapy is associated with less episodes of rebleeding than beta-blockers, it is associated with a higher risk of complications (15).

Endoscopic sclerotherapy or band ligation is commonly used to eradicate varices. Both methods are effective. However, as mentioned earlier, band ligation has advantages over sclerotherapy. Many experts believe that band ligation should be the treatment of choice for variceal eradication.

In the present study, obliteration of the varices was achieved in all patients with 3.57±1.99 (range 1-8) endoscopy sessions over a period of 11.57±6.8 weeks (range 3-30 weeks). These findings were similar to the literature. Varices can usually be obliterated after 4-5 endoscopic sessions given over a period of 3-6 months (8). Rebleeding during this period is not indicative of endoscopic treatment failure. However, other therapeutic interventions should be considered in cases of variceal rebleeding associated with hypovolemic shock or two instances of rebleeding varices associated with a decrease in hemoglobin of >2 g/dl (8). In cases of recurrent bleeding despite adequate endoscopic treatment or varices that are difficult to eradicate by endoscopy, TIPS or shunt surgery should be considered.

The strong difference in rebleeding rate in favor of rubber banding is probably the consequence of several factors: The number of treatment sessions required to achieve variceal eradication was significantly smaller with banding (2.5-4.1 sessions) than with sclerotherapy (2.9 to 6.5 sessions) in all 12 trials reporting these data except one (19). In the present study it was estimated that the mean number of sessions required to obtain eradication was 3.57±1.99 (range 1-8). In most studies, this corresponded to a shorter time to achieve eradication. We have shown that esophageal varices could be obliterated within 11.57±6.8 weeks (range 3-30). Decreasing such time reduces the "vulnerable phase" of endoscopic treatments (i.e., the time when the risk of rebleeding is decreased but still exists due to the incomplete eradication of varices).

In addition, the number of clinically significant complications was generally lower in patients treated with banding (29). Esophageal stenosis after banding was reported as 2% by Masci et al. (27), whereas its incidence after sclerotherapy ranged between 0 and 33%; the incidence of bleeding from treatment-induced ulcers was lower with banding in all studies but one (16). Finally, the incidence of septic complications (pulmonary infections, spontaneous bacterial peritonitis) and of fatal complications was also lower in patients undergoing rubber band ligation, although the difference with sclerotherapy was small (29). In view of these results, rubber band ligation has become the endoscopic treatment of choice for the prevention of recurrent bleeding from esophageal varices (30).

It is unclear whether banding ligation is followed by a higher rate of variceal recurrence in comparison with sclerotherapy. Of the seven trials that give such information, variceal recurrence was slightly more frequent after sclerotherapy than banding in three and more frequent after banding in four, with a difference reaching statistical significance in two (16, 20-22, 25-27). In the seven studies, recurrences ranged between 8% and 48% after banding, and between 2% and 50% after sclerotherapy (28). We have found that recurrence occurred in a mean of 34 months and the recurrence rate was determined as 57.14% (Figures 1).

Interpretation of these results is complicated by the different lengths of follow-up in the studies and by differences in the definitions of variceal recurrence. Meta-analysis shows no significant difference between treatments (POR, 1.31; 95% CI 0.89-1.94) (28). At any rate, in recent years several combinations of treatments have been proposed to reduce the recurrence rate of varices after band ligation. In two studies, banding was compared with a regimen consisting of band ligation plus simultaneous sclerotherapy (31,32). The combined treatment was superior to banding alone in one and showed no advantage in the other (31,32). In another study, banding was compared with a sequential therapy with initial banding followed by low-dose sclerotherapy after varices were reduced to small residual cords (33). The combined treatment significantly reduced both variceal recurrence and rebleeding. In a further study, a comparison was made between banding alone and banding followed by microwave coagulation of the lower esophagus, leading to mucosal fibrosis (34). Variceal recurrence was observed in 15 of 25 (60%) patients treated with banding alone and in four of 25 (16%) of those treated with the combined regimen ($p = 0.03$) (34). In conclusion, it is still unclear whether variceal recurrence is more frequent after banding than after sclerotherapy. The clinical value of combined treatments to reduce variceal recurrence rates after banding is unknown.

Another issue on which conflicting data .exist is the influence of sclerotherapy and rubber band ligation on the development of portal hypertensive gastropathy, whereas the two techniques seem to have an equally limited effect on gastric varices (32,35,36). According to our study the appearance rates of portal hypertensive gastropathy and fundal gastric varices after varice obliteration were found as 45.45% (5/11) and 23.07% (3/13), respectively.

In conclusion, band ligation is a safe and effective treatment of esophageal variceal bleeding. Although variceal recurrence was high, the rebleeding rate was not high in our study. Our data shows that EVL is an effective and safe treatment modality. Because EVL has a high incidence of the development of portal hypertensive gastropathy, a combination of pharmacological treatments such as beta-blockers or nitrates should be evaluated as a preventative measure.

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