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Endoscopic banding ligation compared with sclerotherapy for the treatment of esophageal varices

Özefagus varislerinin tedavisinde endoskopik band ligasyonu ve skleroterapinin etkinliklerinin karşılaştırılması

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SUMMARY: *Injection sclerotherapy of bleeding esophageal varices is undoubtedly beneficial but it is associated with a substantial local and systemic complication rate and variceal rebleeding is common during the treatment period before variceal obliteration is achieved. Endoscopic banding ligation, a different form of endoscopic treatment for esophageal varices, may be safer. We compared the effectiveness and safety of the two techniques. Among the patients in whom variceal eradication was achieved, there was no significant difference between the two groups in mean time of variceal eradication and number of sessions although ligation therapy offered shorter eradication time [3,4 (1-4) months vs 2,4 (1-4,5) months respectively, p > 0.05] and in fewer sessions [4,5 (1-7) vs 5,6 (1-18) respectively, p> 0.05)] than sclerotherapy. Rebleeding tended to be less with banding ligation than sclerotherapy [four patients (10%) vs nine patients (32%) respectively, p< 0.05] There was no difference in survival between the groups. Complications were less common in the ligation group [two patients (4,6%) vs seven patients (25%) respectively, p< 0.05]. In the patients with cirrhosis who have esophageal varices, banding ligation is a safe and effective technique which obliterates varices quickly and with a lower rebleeding rate than injection sclerotherapy.*

Key words: Esophageal varices, sclerotherapy, banding ligation

ÖZET: *Özefagus varislerinin endoskopik skleroterapi ile tedavisinde başarılı sonuçlar alınmakla birlikte lokal ve sistemik komplikasyonlara ve kanama tekrarına sıkça rastlanmaktadır. Endoskopik band ligasyonu özofagus varisi tedavisinde geliştirilen diğer bir tekniktir ve daha güvenli bir yöntem olabilir. Biz bu çalışmada iki tedavi yönteminin etkinlik ve güvenilirliğini karşılaştırdık. İstatistiksel olarak anlamlı bir fark bulunmamakla birlikte, band ligasyonu ile tedavi edilen hastalarda varis eradikasyonu skleroterapi uygulanan hastalara göre daha kısa zamanda [Sırasıyla 3,4 (1-4) ay ve 2,4 (1-4, 5) ay, p>0.05] ve daha az seansda elde edildi [Sırasıyla 4,5 (1-7) ve 5,6 (1-18), p>0.05]. Tekrar kanama oranı band ligasyonu yapılan grupta daha düşüktü [Sırasıyla 4 hasta (% 10) ve 9 hasta (% 32), p<0.05]. Hayatta kalma süreleri bakımından her iki grup arasında anlamlı fark yoktu. Ligasyon yapılan grupta komplikasyon oranı skleroterapi yapılan guruba göre daha düşüktü [Sırasıyla 2 hasta (% 4,6) ve 7 hasta (% 24)]. Özefagus varisi olan karaciğer sirozlu hastalarda endoskopik band ligasyonu istatiksel olarak anlamlı olmamakla birlikte skleroterapiye göre daha çabuk ve etkili bir varis eradikasyonu sağlayan güvenli bir yöntemdir. Ayrıca, bu yöntemde tekrar kanama ve komplikasyon gelişme olasılığı skleroterapiye göre anlamlı olarak daha düşüktür.*

Anahtar sözcükler: Özofagus varisleri, skleroterapi, band ligasyonu

Bleeding esophageal varices account for up to 30% of patients with major upper gastrointestinal hemorrhage (1) and are associated with mortality rates of 15% to 40% (2, 3). Patients with bleeding esophageal varices have a higher rebleeding rate, more transfusion requirements, longer lenght of hospitalisation and greater risk of death than do patients bleeding from nonvariceal sites (4). Endoscopic injection sclerotherapy is of proven benefit in the management of esophageal varices and in the long term prevention of recurrent bleeding (5, 6). Nevertheless, the use of endoscopic sclerotherapy is associated with a rebleeding rate of up to 50% in many trials (7). Sclerotherapy is also associated with various local and systemic complications that may limit its effectiveness, and in a large retrospective study, 50% of cases had complications (8). Therefore endoscopic ligation was developed in an attempt to provide a treatment at least as effective as sclerotherapy but with fewer adverse effects (9, 10). Initial studies showed the safety and efficacy of this method and a multicentre randomised controlled trial has confirmed these findings (11). We report here a single centre study comparing endoscopic ligation and sclerotherapy for the treatment of esophageal varices.

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Table 1. Baseline characteristics of patients with cirrhosis and bleeding esophageal varices treated by endoscopic ligation and sclerotherapy.

Characteristics	*Ligation (n=50)*	*Sclerotherapy (n=28)*
Mean age	55 (18-77)	42 (16-80)
Sex (M/F)	39/11	16/12
Aetiology		
Viral cirrhosis	37	20
Alcoholic cirrhosis	3	1
Alcoholic+Viral cirr.	4	2
Criptogenic cirrhosis	2	5
Portal venous thromb.	4	-
Child-Pugh score		
A	18	7
B	23	13
C	9	8
No (%) of previous bleeding	39 (78)	28 (100)
Grade of varices at the index endoscopy		
4	44	23
3	5	3
2	1	2

MATERIALS AND METHODS

Selection of patients:

Seventy-nine patients admitted within ten days of upper gastrointestinal haemorrhage from esophageal varices to our gastroenterology clinic were enrolled in the trial. Patients were excluded from the study if they had contraindication to endoscopy, previous operative treatment for esophageal varices, expected survival of less than six months and symptoms of esophageal dysfunction. Previous treatment with balloon tamponade, vasopressin or beta-adrenergic antagonist agents did not disqualify patients but the use of these procedures was not permitted during the trial. Variceal haemorrhage was defined as active bleeding from an esophageal varix visible on endoscopy, the presence of a blood clot over an esophageal varix with no other endoscopically observed source of bleeding or the presence of large esophageal varices, blood in the stomach and no other bleeding lesion. Twenty eight patients were treated with sclerotherapy and 50 patients with ligation.

Technique of endoscopic sclerotherapy and endoscopic band ligation:

A sedative agent (midazolam or diazepam) was given before endoscopy at the discretion of the investigator. At each endoscopic session the size of varices, the presence of fundal gastric varices and portal hypertensive gastropathy were assessed. Variceal size was estimated or compared with an object of known size as follows; grade 1; < 3 mm, grade 2; 4 to 6 mm, grade 3; 7 to 10 mm, grade 4; > 10 mm or large enough to fill the esophageal lumen completely. Injection sclerotherapy was perfomed as previously described (5), with 1 percent polidocanol (Aetoxysclerol 1%) as sclerosant. The injections were intravariceal which begun at or near the gastroesophageal junction and delivered up to 2 ml of sclerosant at each site. No more than 20 ml of sclerosant was injected during each session. Injections were placed within the lower 10 cm of the esophagus. In patients who were actively bleeding , the bleeding varix was injected first if it was identifiable. The injections were then continued as in the case of patients not actively bleeding. In patients with active variceal haemorrhage at the time of endoscopy, we used vasoconstrictor therapy, balloon tamponade or both when haemostasis could not be achieved.

Endoscopic variceal banding (EBL) was done as described by Stiegmann et al (11) with an endoscopic ligating device. Varices were ligated with single elastic O rings applied to the end of an endvieweing endoscope with an outer adapter (Bard Intervention Products, USA). While the overtube (25 cm long and 25 mm wide) was used in the first 20 patients, it was not used in the last 30 patients. In the last 30 patients, the ligation device was inserted separately for each banding (i.e., six times for six bandings).Varices were ligated individually with a single elastic O ring starting at or just below the gastroesophageal junction and continuing cephalad to 10 cm or more above that junction. All individual varices were ligated at least once per treatment and larger varices were often ligated twice at separate points, one caudad and one cephalad. No more than eight individual ligations were performed during sessions of elective treatment. In patients bleeding actively, ligations were performed at or around the site of bleeding to control haemorrhage. Additional varices were than ligated as in patients with upper gastrointestinal haemorrhage that required endoscopy and was associated without bleeding.

Endoscopic examination was perfomed every week in the sclerotherapy group and every three or two

Table 2. Control of bleeding, recurrent bleeding and eradication of esophageal varices

Characteristics	*Ligation (n=50)*	*Sclerotherapy (n=28)*	*p*
No (%) of patients actively bleeding at index endoscopy	4 (8)	5 (18)	
No (%) of these with active bleeding controlled	4 (100)	4 (80)	
No (%) of patients with rebleeding	4 (8)	9 (32)	(*)
No (%) of rebleeding	4	19	
Site of rebleeding			
Esophageal varices	3	19	
Portal hypertensive gastropathy	1	-	
Mean time for variceal eradication (month)	3, 4 (1-4)	2, 5 (1-4, 5)	
Treatment sessions to eradication	4, 5 (1-7)	5, 6 (1-18)	
No (%)of patients with complications	2 (4, 6)	7 (25)	(*)
No (%) of complications resulting death	-	-	
Cause of death			
Liver failure	4	-	
Bleeding	-	9	
Survival (%)			
6 months	(100)	(100)	
12 months	(94)	(92)	
18 months	(92)	(88)	

(*) $p<0.05$

weeks in the ligation group until variceal obliteration was achieved and then 3, 6 and 12 months later or whenever rebleeding occured. All patients received sucralfate 1 g q.i.d. by mouth and famotidine 20 mg b.i.d until variceal obliteration was confirmed. The outcomes assessed were control of active variceal bleeding, time to the obliteration of varices, frequency of variceal rebleeding, occurence of complication and mortality. Control of active variceal haemorrhage was defined as the absence of upper gastrointestinal bleeding (ie; stable vital signs and hematocrit and the absence of hematemesis) for 12 hours after treatment. Rebleeding was defined as a fall in hematocrit of more than 5%. The source of rebleeding was identified as esophageal varices, gastric varices, portal hypertensive gastropathy or treatment induced esophageal ulceration.

Student's t test was used for the analysis of continuous variables and X^2 test was used for discrete variables. Kaplan-Meier analysis was used to examine the time to death. The log-rank test was used to determine whether times to outcomes were different between groups.

RESULTS

Seventy eight patients were screened over a 30 month period. The baseline characteristics of the two groups are shown in Table 1.

Control of variceal haemorrhage:

Active haemorrhage was found at index endoscopy in four patients (8%) in the band ligation group and five patients (18%) in the sclerotherapy group. Fourty two banding treated patients and 28 sclerotherapy treated patients had had previous upper gastrointestinal haemorrhage. Haemostasis of active variceal haemorrhage at 12 hours was achieved in all patients in both groups and both treatments were equally effective in the control of active haemorrhage (Table 2). Among patients in whom variceal eradication was achieved, there was no significant difference between the two groups in the mean time of variceal eradication and number of sessions [3,4 (1-4) months vs 2,4 (1-4,5) months respectively in the ligation and sclerotherapy group, $p>0.05$ and 4,5 (1-7) vs 5,6 (1-18) sessions respectively in ligation and sclerotherapy group, $p>0.05$]. The mean number of

bands required to obliterate the varices was 13 (4-27). Variceal rebleeding occurred more often in the sclerotherapy group [four patients (8%) in the ligation group vs nine patients (32%) in sclerotherapy group, $p<0.05$]. The site of recurrent bleeding was most often an esophageal varix. Treatment induced recurrences of bleeding due to occurred ulceration in one patients in the ligation group (2%) and two patients in the sclerotherapy group (7%). Overall 4, rebleeds occured in the banding ligation group (10%) and 19 in the sclerotherapy group (32%) ($p< 0.05$).

Complications:

Complication rates were 4,6 % in the ligation group (two patients) and 25% in the sclerotherapy group (seven patients) ($p<0.05$). The most common complication after sclerotherapy was esophageal ulceration. Deep esophageal ulcers were more frequent after treatment with sclerotherapy [in 11 patients in the sclerotherapy group (39%) compared to one (2,5%) in the ligation group ($p<0.05$)]. Infection related complications resulting from treatment occurred in four patients (17.5%) in the sclerotherapy group [Transient fewer was occured in 4 patients (14%), and septic arthritis in one patient (3,5%)]. Reflux esophagitis occurred in 1 patient (3,5%). No patients developed an esophageal stricture required dilation during the study period in either treatment group and aspiration pneumonia occured in one patient (2%) in the ligation group. Transient retrosternal discomfort or dysphagia were observed in nearly all patients treated with ligation but were not in sclerotherapy group.

Survival:

The overall rate of survival was higher in patients treated by ligation than in those treated by sclerotherapy, but there was no significant difference in survival between groups. While liver failure was the most common cause of death in the ligation group, variceal bleeding was the only cause in the sclerotherapy group (Table 2). Cumulative survival of band ligation and sclerotherapy groups at months 6, 12 and 18 were 100% , 94% , 92% and 96% , 92% , 88% respectively, $p>0.05$.

DISCUSSION

Endoscopic ligation of esophageal varices is a technique developed by Stiegmann in an attempt to provide an endoscopic treatment for esophageal varices (9, 10). Ligation of varices is based on the widely used technique of band ligation of hemorrhoids. The mucosa and submucosa of the esophagus are ensnared, leading to strangulation, sloughing and eventual fibrosis with obliteration of varices.

The first randomized trial comparing sclerotherapy and ligation was published in 1992 by Stiegmann et al (11) and showed statistical differences in favor of ligation for two variables: complications and survival. In this study the survival advantage of ligation may have been attributable to a lower rate of complications combined with a trend toward less rebleeding in the ligation group. No statistical differences were noted for cessation of active bleeding, transfusion requirements or length of hospitalisation.

Our trial has shown that variceal banding ligation has some advantages over intravariceal injection sclerotherapy. Recurrent bleeding was less common in the patients treated by endoscopic ligation than in those treated by sclerotherapy. (10% vs 32% , $p< 0.05$). The incidence of recurrent bleeding in our study was lower than that in other reports (13-16). The most likely reason for the lower rebleeding rate in the banding ligation group was the more rapid and effective eradication of varices with that method. Stiegman et al. (11) also reported a lower rebleeding rate in the eradication of varices. Recurrent bleeding may result from varices not yet eradicated. Recurrence of esophageal varices following initial eradication [four patients in the banding (8%) and four (18%) in the sclerotherapy group] emphasized the need for continued follow up. Experimental studies in dogs have shown that endoscopic variceal ligation results in shallow ulcer formation at the site of each ligation and that mucosal and submucosal layers (including variceal channels) are ablated and replacement with dense scar tissue covered by squamous epithelium (12). Recurrence of, varices is minimised because there is no place for them to recur.

An important finding of Stiegmann et al (11) was a lower incidence of complications in the banding ligation group and our results confirmed this finding. The definition of complications in trials of endoscopic variceal therapy has varied and some workers believe that esophageal ulceration is an inevitable consequence of sclerotherapy (3, 5, 13, 17). Although ulceration was found in a high proportion of patients in the banding group, the ulcers were small and rarely associated with

symptoms. In the banding ligation group the ulcers were mucosal defects at the site of previously applied bands; Stiegmann et al. did not classify these as complications (11). In our series deep esophageal ulcers were more frequent after treatment with sclerotherapy [in 11 patients in the sclerotherapy group (39%) compared to one (2.5%) in the ligation group ($p<0.05$)]

Esophageal stricture was not seen in either groups in our study. Stiegmann et al. found a high frequency (12%) of esophageal strictures in the sclerotherapy group. The lower stricture rate in our trial may be attributable to routine prophylactic use of sucralfate in both groups following endoscopy; this treatment decreases the frequency of stricture formation after sclerotherapy (18). Sucralfate may also reduce rebleeding from treatment related ulceration (19).

Infection related complications associated with treatment occurred in five patients (17.5%) in the sclerotherapy group (transient fever in four patients and septic arthritis in one patient). Bacteremia may trigger infectious complications in patients treated by sclerotherapy. Aspiration pneumonia was detected in one patient treated with banding ligation (2.4%). The lower pulmonary complication rate in band ligation may be attributable to the use of overtube preventing tracheal aspiration but there were no pulmonary complications in the last 30 patients of our ligation group who were treated without an overtube. This evidence contradicts with the opinion that an overtube prevents pulmonary complications (10-12).

Mortality rates were low and survival rates were similar in both of our treatment groups. In our study, the difference in survival rates between ligation and sclerotherapy groups at 6, 12 and 18 months was less than 5% and not significant ($p>0.05$). Less frequent recurrence of bleeding and fewer infection related complications seem the likely explanation for the higher (but not significant) rate of survival among patients in the ligation group.

We conclude that endoscopic ligation is superior to sclerotherapy in the treatment of esophageal varices and that the benefit of endoscopic ligation in this trial resulted in part from less frequent recurrences of bleeding, fewer complications and greater tolerance of the procedure.

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