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Secondary prophylaxis of esophageal variceal treatment: Endoscopic sclerotherapy, band ligation and combined therapy - long-term results

Özofagus varislerinde sekonder profilaksi: Endoskopik skleroterapi, band ligasyonu ve kombine tedavi: Uzun dönem sonuçlar

Sedef KURAN, Dilek OĞUZ, Erkan PARLAK, Mehmet ASİL, Bahattin ÇİÇEK, Mesut KILIÇ, Selçuk DİŞİBEYAZ, Burhan ŞAHİN

Gastroenterology Clinic, Türkiye Yüksek İhtisas Hospital, Ankara

Background/aims: *To evaluate the long-term results of endoscopic sclerotherapy and endoscopic band ligation in secondary prophylaxis on variceal eradication and to evaluate the effectiveness of endoscopic sclerotherapy and endoscopic band ligation combination in resistant cases.* ***Methods:*** *The results of the patients who underwent endoscopic sclerotherapy (n=47 31M/16F, 49.9±16.1 years) and endoscopic band ligation (n=72 56M/16F, 46.6±14.1 years) were compared. The results of patients whose varices could not be eradicated who were treated with endoscopic band ligation and combined endoscopic sclerotherapy (combined group, n=62 49M/13F, 48.8±12.7 years) are also given. Patients were evaluated for portal hypertension etiology, Child score, fundal varices-portal hypertensive gastropathy presence according to first and last endoscopic findings, varices eradication, rebleeding, recurrence and complication rates.* ***Results:*** *181 patients were followed for 35.2± 25.6 (6-123) months. Varices eradication and recurrence rates were 93.6% and 44.7% for endoscopic sclerotherapy, and 90.3% and 47.2% for endoscopic band ligation (p>0.05). The number of sessions for eradication were 6.6±4.0 and 2.5±1.6 for endoscopic sclerotherapy and endoscopic band ligation groups, respectively (p<0.05). Rebleeding rates were 16.3% for endoscopic sclerotherapy and 6.1% for endoscopic band ligation (p>0.05). In the combined group, although the rebleeding rate was 34.4%, which was as expected significantly higher than that of endoscopic sclerotherapy and endoscopic band ligation, variceal eradication and the recurrence rates were 82.3% and 50.0%, similar to endoscopic sclerotherapy and endoscopic band ligation, and the number of sessions for eradication was 6.8±3.5.* ***Conclusions:*** *Endoscopic band ligation is the most suitable method for varices eradication, but there is a group of patients resistant to endoscopic band ligation. In this patient group, the addition of endoscopic sclerotherapy to endoscopic band ligation was a suitable and effective technique in order to achieve variceal eradication.*

Key words: Esophageal varices, band ligation, sclerotherapy

Amaç: *Bu çalışmada özofagus varislerinin sekonder profilaksisinde endoskopik skleroterapi ve endoskopik band ligasyon tedavilerinin uzun dönem sonuçlarının karşılaştırılması yapıldı ve endoskopik band ligasyona resistan olgularda kombine tedavinin etkinliği değerlendiridi.* ***Yöntem:*** *Endoskopik skleroterapi (n=47 31E/16K, yaş=49.9±16.1yıl) ve endoskopik band ligasyon (n=72 56E/16K, yaş=46.6±14.1yıl) yapılan olgular eradikasyon, rekürrens, eradikasyon için gerekli seans sayısı ve tekrar kanama (rebleeding) oranları açısından karşılaştırıldı. Tek başına endoskopik band ligasyon ile varisleri eradike edilemeyen olgular, endoskopik skleroterapi ile kombine edildiklerinde (kombine grup, n=62 49E/13K, yaş=48.8±12.7 yıl) elde edilen oranlar da ayrıca değerlendirildiler. Hastalar ayrıca portal hipertansiyon etiyolojileri, child skorları, ilk ve son endoskopideki fundal varis-PHG bulguları ve komplikasyon oranları açısından karşılaştırıldırıldılar.* ***Bulgular:*** *181 hasta ortalama 35.2± 25.6 (6-123) ay takip edildi. Varis eradikasyon oranları ve rekurrens oranları endoskopik skleroterapi için %93.6, %44..7, endoskopik band ligasyon için %90.3, %47.2 olarak bulundu (p>0.05). Eradikasyon için gereken seans sayısı endoskopik skleroterapi ve endoskopik band ligasyon için sırası ile 6.6±4.0, 2.5±1.6 (p<0.05) idi. Tekrar kanama oranları endoskopik skleroterapi için %16.3, endoskopik band ligasyon için %6.1 olarak bulundu (p>0.05). Kombine grup ayrıca değerlendirildiğinde tekrar kanama oranı beklenildiği üzere endoskopik skleroterapi ve endoskopik band ligasyon gruplarından daha fazla olmakla birlikte (%34.4) eradikasyon oranı ve rekürrens oranları endoskopik skleroterapi ve endoskopik band ligasyona benzer şekilde sırası ile %82.3, %50.0 ve eradikasyon için gerekli seans sayısı 6.8±3.5 olarak bulundu.* ***Sonuç:*** *Varis eradikasyonu için en uygun metod endoskopik band ligasyondur. Ancak endoskopik band ligasyona dirençli bir grup hasta vardır. Bu çalışma sonucuna göre endoskopik band ligasyona resistan varis eradikasyonunda endoskopik skleroterapi ile kombine tedavinin etkin bir yöntem olduğunu düşünüyoruz.*

Anahtar kelimeler: Özofagus varisleri, band ligasyon, skleroterapi

Address for correspondence: Sedef KURAN
Dikmen Cad. 220/A No: 17 Dikmen, 06450 Ankara, Turkey
Phone: +90 312 483 38 45 • Fax: +90 312 442 32 64
E-mail: sedefozdal@hotmail.com

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INTRODUCTION

Complications of portal hypertension rank among the top leading causes of death worldwide (1). Variceal bleeding is the most severe outcome of portal hypertension and esophageal varices develop in 50-60% of patients with cirrhosis (2). Approximately 30% of patients with cirrhosis and portal hypertension bleed from esophageal varices (3). The source of bleeding in patients with cirrhosis is the esophageal varices in 60-90% of the cases (4, 5). The mortality rate from variceal bleeding is around 20-30% and may exceed 50% in some series (6, 7). Patients who have no treatment after their first bleeding episode have a 60% risk of re bleeding (6).

Endoscopic sclerotherapy (ES) and band ligation (EBL) are the endoscopic treatment modalities for both active variceal bleeding and for secondary prophylaxis. Both treatment modalities have their advantages and disadvantages. ES causes some important complications such as deep esophageal ulcers, bleeding from ulcers, esophageal strictures, pleural effusions and mediastinitis (8). EBL has fewer complications and eradicates varices more quickly than ES (9).

There have been some approaches to combine ES and EBL in order to increase benefits of both techniques. Generally, the combined strategy has not been shown to be more effective than EBL alone (10).

In this study we compared the results of ES and EBL. Our strategy was to eradicate varices with EBL first. But there is a group of patients with varices resistant to eradication with EBL and this stiuation cannot be predicted at the beginning of the treatment. We used the combined method in this patient group and evaluated their results as well.

MATERIALS AND METHODS

From January 1991 to November 2001, 181 patients who were followed up for more than six months and registered properly were included in our study to assess long-term results. Cases with fundal or gastric variceal bleedings, left-sided portal hypertension or patients who died during the first bleeding episode were not included in the study. In our center a varices eradication program is performed for secondary prophylaxis. Treatment is performed every three weeks until varices eradication is achieved, after which endoscopy is repeated every three to six months or in cases of bleeding recurrence. All patients are given propranolol orally during the secondary prophylaxis follow-up period with doses adjusted according to heart rates. Endoscopic treatments are performed either by a gastroenterologist or gastroenterology fellows. EBL has been performed in our center since 1996; previously all patients were treated with ES. During the EBL era, ES has been performed only in patients with acute variceal bleeding or in patients who had previous EBL, but who had small varices which could not be aspirated into the band and a stigmata of bleeding (i.e. red spot sign).

Thus, three patient groups were formed in our study: Patients who had either ES and EBL alone and patients who had ES and EBL in combination in different sessions, which was termed as the combined group. Our strategy was to eradicate varices with EBL first.

Endoscopic sclerotherapy and EBL were performed without premedication on either an inpatient or outpatient basis. Olympus XQ20, 1T20 and Pentax EG2940 diagnostic endoscopes were used for ES and EBL. ES was performed with intravariceal or paravariceal injections in the distal 5 cm of the esophagus using 1% polidocanol (Aethoxysclerol; Kreussler-Pharma) with 23 gauge sclerotherapy needle. EBL was performed using single band (Steigmann Goff-cleardye endoscopic ligator set) or multiband ligator set.

Varix size was graded according to Japanese Research Society for Portal Hypertension classification from 1-3 (11). Grade 1 varices were described as varices which collapsed with inflation of the esophagus with air. Grade 2 varices did not collapse with inflation and did not occlude the lumen. Grade 3 varices were large and occluded the lumen. Edema, submucosal petechial areas, and snake-like appearance of the stomach were described as portal hypertensive gastropathy (PHG). Varices were accepted as eradicated if they dissappeared (optimal sclerosis) or if grade 1 varices were achieved and the varix appearance continued for two consecutive endoscopic sessions. Appearance of new varices necessitating therapy after eradication was termed as recurrence, and bleeding after first therapy was termed as rebleeding. Last endoscopic findings in registration reports were evaluated and last variceal states of patients were given.

Patients were evaluated according to etiology of portal hypertension, Child score, presence of gastric and fundal varices, and PHG. After treatment, response to treatment, rebleeding rates, recurrences and complications (deep ulcer formation causing delay in treatment, bleedings from ulcers requiring treatment, strictures or any other complications) were evaluated.

All patients provided informed consent to the procedure and the Gastroenterology Clinical Council approved the study.

Statistical Analysis

Statistical Package for Social Sciences (SPSS v 11.0.0) for Windows was used for statistical analysis. Chi-square, independent sample T-tests, and one-way ANOVA tests were used to compare variables. Findings were expressed as mean±standard deviation; p values less than 0.05 were accepted as statistically significant.

RESULTS

One hundred and eighty-one (137 male, 44 female; mean age=45.5±15 years) patient registration reports were examined for long-term results. One hundred and forty patients were cirrhotic and 41 non-cirrhotic. They were followed-up 35.2±25.6 (6-123) months. Sixty-seven of 140 (47.8%) cirrhotic patients were Child A, 56 (40%) Child B, and 17 (12.2%) Child C. Fifty-five (30.4%) patients were admitted to our hospital with active variceal bleeding determined endoscopically. Others were either referred to our hospital for therapy after first bleeding or with massive bleeding history without any bleeding source other than varices. ES, EBL and combined therapy were performed to 47 (26%), 72 (39.8%) and 62 (34.2%) patients, respectively. Characteristics of patients are given in Table 1.

Table 1. Patient characteristics

Median age (years)	45.5±15
Sex ratio M/F, n (%)	137 (75.7) / 44 (24.3)
Follow-up period (months)	35.2±25.6 (6-123)
Etiology of portal hypertension, n (%)	
Cirrhotic portal hypertension	140 (77.4)
Chronic viral hepatitis	76 (42)
Cryptogenic	45 (24.9)
Alcohol	14 (7.7)
Autoimmune	4(2.2)
Wilson disease	1 (0.6)
Non-cirrhotic portal hypertension	41 (22.6)
Portal vein thrombosis	25 (13.8)
Hepatoportal sclerosis	16 (8.8)

Varices eradication rates were 93.6% in ES group and 90.3% in EBL group (p>0.05). The eradication ratio was found as 82.3% in the combined group. The number of treatment sessions required to achieve varices eradication was significantly less in the EBL group when compared to ES (2.5±1.6 vs 6.6±4.0). The number of sessions to achieve eradication in the combined group was 6.8±3.5. Rebleeding was seen most frequently in the combined group (34.4%) and the least in the EBL group (6.1%). There was no significant difference between ES and EBL groups for rebleeding [16.3% vs 6.1% (p>0.05)]. If patients were divided as cirrhotic or non-cirrhotic, rebleeding rates in cirrhotic patients in the ES and EBL groups were not significantly different. In the combined group, however, rebleeding ratios of cirrhotic patients were higher than in the ES and EBL groups, as expected. The lowest rebleeding ratio was seen in non-cirrhotic EBL patients, which was significantly lower than in non-cirrhotic ES patients (p<0.05). Varices eradication rates, number of treatment sessions to achieve eradication, recurrence rates, time period for recurrences, and rebleeding rates in cirrhotic and non-cirrhotic patients are shown in Table 2 for ES and EBL and in Table 3 for the combined group.

Table 2. Response to treatment in ES and EBL groups

	Varices eradication n (%)	**Number of sessions for eradication**	**Recurrences n (%)**	**Time period for recurrences (months)**	**Rebleeding n (%)**
ES (47)	44 (93.6)	6.6±4.0	21 (44.7)	21.8±18.1 (6-66)	7 (16.3)
Cirrhotic	34 (94.4)	6.7±4	15 (41.7)	25±20.3 (6-66)	4 (12.5)
Non-cirrhotic	10 (90.9)	6.3±4.1	6 (54.5)	14±7.4 (8-28)	3 (27.3)*
EBL (72)	65 (90.3)	2.5±1.6	34 (47.2)	18.4±13.4 (6-67)	4 (6.1)
Cirrhotic	49 (92.5)	2.5±1.7	26 (49.1)	19.2±14.3 (6-67)	4 (8.3)
Non-cirrhotic	16 (84.2)	2.5±1.3	8 (42.1)	16.9±15.5 (6-60)	0 (0)*
P value (Total)	NS	**<0.05**	NS	NS	NS

ES: Endoscopic sclerotherapy. EBL: Endoscopic band ligation. *Statistically significant

Table 3. Response to treatment in combined group

	Varices eradication n (%)	Number of sessions for eradication	Recurrences n (%)	Time period for recurrences (months)	Rebleeding n (%)
Combined	51 (82.3)	6.8±3.5	31 (50.0)	16.4±13.9 (6-60)	21 (34.4)
Cirrhotic	40 (78.4)	6.6±3.5	22 (43.1)	16.9±15.5 (6-60)	18 (36.0)
Non-cirrhotic	11 (100)	7.9±3.2	9 (81.8)	15.3±9.8 (6-36)	3 (27.3)

Some factors (portal hypertension etiology, Child score) were investigated for relation with variceal recurrences, but no statistically significant relation between them was determined (p>0.05) (Table 4).

Table 4. Possible factors related with recurrences

	Recurrence(+)	Recurrence(-)	P value
Etiology			
Cirrhotics	63 (45%)	77 (55%)	NS
Non-cirrhotics	23 (56.1%)	18 (43.9%)	
Child Score			
A	29 (43.3%)	38 (56.7%)	NS
B	27 (48.2%)	29 (51.8%)	
C	7 (41.2%)	10 (58.8%)	

Patients were compared according to PHG and fundal varices development and their complication ratios. No significant differences between groups were found if development of fundal varices and PHG was considered (PHG and fundal varices development rates in ES, EBL and combined groups were 19%, 12.8%; 11.9%, 12.5%; and 16.1%, 14.5%, respectively).

One hundred and seventy-seven of 181 had data recorded for ulcerations, bleedings from ulcerations requiring treatment and stricture formation. Ulcer ratios and bleedings from ulcerations were found to be statistically significant between groups. The lowest ulceration rate was found in the EBL group (30.9%) and the highest in the combined group (62.9%). There was no significant difference between groups regarding stricture formation. There was a significantly lower complication ratio in the EBL group (37.7%) if we evaluated overall complications (Table 5). Complications for the combined group are given in Table 6.

Table 5. Complications according to ES and EBL groups

	ES n (%)	EBL n (%)	P value
Development of PHG	8 (19)	8 (11.9)	NS
Development of fundal varices	6 (12.8)	9 (12.5)	NS
Ulcer	22 (47.8)	21 (30.9)	<0.05
Bleeding	11 (23.9)	5 (7.2)	<0.05
Stricture	3 (6.5)	4 (5.8)	NS
Total complications	28 (60.9)	26 (37.7)	<0.05

ES: Endoscopic sclerotherapy. EBL: Endoscopic band ligation. PHG: Portal hypertensive gastropathy

Table 6. Complications in combined group

Complications	Combined n (%)
Development of portal hypertensive gastropathy	9 (16.1)
Development of fundal varices	9 (14.5)
Ulcer	39 (62.9)
Bleeding	8 (12.9)
Stricture	0 (0)
Total complications	40 (64.5)

There was a significant increase in fundal varices and PHG ratios according to the first and last endocopic findings of all patients (p<0.05) (Table 7).

Table 7. First and last endoscopic findings

	First	Last	P value
Fundal varices ratio	47.5%	64.2%	<0.05
PHG ratio	36.7%	75.4%	<0.05

PHG: Portal hypertensive gastropathy

DISCUSSION

In this study, we found that varices eradication ratios for ES and EBL methods did not significantly differ, but the number of sessions needed for eradication, complications and rebleeding rates were lower in the EBL group than in the ES group. The patients in the combined group had a similar but slightly lower eradication ratio than in ES and EBL groups; the number of sessions needed for eradication was similar to ES.

Since this study was not a prospective and randomized study it was not suitable to compare

combined patients with ES and EBL patients. We thus compared the results of ES and EBL alone and gave the results of the combined group separately. Our goal was to give our long-term results for ES and EBL and to evaluate the efficiency of our protocol for varices eradication especially in resistant cases.

There are multiple studies in the literature comparing ES and EBL. Combined treatment has also been compared in the literature with band ligation or sclerotherapy alone. Eradication rates using single and multiple band ligation for EBL have been compared in the literature (12). In our treatment groups, we found varices eradication ratios as 93.6%, 90.3% and 82.3% in the ES, EBL, and combined groups, respectively. We did not find any difference in varices eradication rates between ES and EBL, and the eradication rate for the combined group was also similar to that of ES and EBL. Varices eradication ratios between cirrhotic and non-cirrhotic patients were also not different. According to the literature, varices eradication rates were between 55-56% to 93-97% for ES and EBL, respectively, and there was no significant difference (13). There have been many modalities for combined therapy. Synchronous or metachronous methods have been performed. Band ligation or sclerotherapy, or both, were compared with combined therapy. According to randomized trial results, there were generally no significant differences in eradication rates between these treatment choices (8, 14-16).

In our patient groups, the number of sessions required to achieve varices eradication was found significantly less in the EBL group compared to the ES group (2.5±1.6 vs 6.6±4.0). The number of sessions to achieve eradication in the combined group was also similar to that of ES (6.8±3.5). This result was similar to the literature (13). Recurrences and time period for recurrences were found as 44.7% and 21.8±18.1 months in the ES group; 47.2% and 18.4±13.4 months in the EBL group, and 50.0% and 16.4±13.9 months in the combined group, also not statistically significant. We did not find any difference in recurrences between cirrhotics and non-cirrhotics. Recurrence rates as reported in the literature were very different. Stiegmann et al. found recurrence rates in ES and EBL groups as 50% and 33%, respectively, and the difference was not significant (17). Masci et al. found less recurrences than Stiegmann (27% to 32% for ES, EBL), and the difference was also not significant (18). But according to the results of Hou, Sarin, and Baroncini, EBL had a higher recurrence ratio than ES (19-21). For combined groups, very different results for recurrences are reported. Metachronous treatment modality shows fewer recurrences than synchronous methods according to meta-analysis reports (13, 22). Since these were prospective studies, their combined groups of patients were selected randomly. It is possible to have patients who could be easily treated only by EBL in such groups. But in our study, we performed combined treatment for resistant cases, so our recurrence rate for the combined group was higher than in the literature.

Our rebleeding rates were 16.3%, 6.1%, and 34.4% in the ES, EBL and combined groups, respectively. We found the lowest rebleeding ratio in the EBL group, and the highest in the combined group. The above-mentioned explanation regarding the combined group (they were resistant and difficult cases probably with high portal pressure) is also true in rebleeding. In the literature, rebleeding ratios for ES and EBL were different. Rebleeding rates were generally lower with EBL than ES, sometimes reaching statistical significance (17, 19-21, 23, 24). Rebleeding rates were lower in metachronous combined therapies than in ES or EBL in studies comparing combination therapy with ES or EBL (8, 25, 26).

Child score and varices column size were important predictive factors for the first variceal bleeding (27). We did not find any significant relation between Child score and recurrences. It could be explained that for variceal recurrences, factors other than Child score alone, like portal pressure, hepatic venous pressure gradient (28) and presence and effectiveness of other collaterals, were important as well.

There was a significant increase in fundal varices and PHG ratios. There was no significant relation between treatment modalities and the fundal varices or PHG development. Although there was an increase in fundal varices and PHG ratios, we did not observe any fundal varice or PHG bleeding in these patients.

We found ulcer and bleeding ratios significantly low in the EBL group. During the follow-up period, we did not observe any esophageal perforation or hematoma. We did not find significant differences in stricture formation, which was not consistent with the literature. Overall complication

ratios were lower in the EBL group, which did not concur with the literature (13).

It was not possible to estimate response of a patient to varices eradication treatment from the beginning. Severity of portal hypertension and progression of disease show differences among patients. According to today's guidelines for secondary prophylaxis of variceal bleeding in cirrhosis, the method of first choice is band ligation. Sclerotherapy is the second choice and recommended if band ligation is not possible (21). Randomized trial reports show that band ligation resulted in less rebleeding, mortality and local complication rates (29, 30). EBL was seen as the most suitable method for varices eradication in our study as well. But there was a patient population resistant to EBL which could not be estimated at the beginning. In this study, we found that the addition of ES to patients who were resistant to EBL was suitable. Although these patients had high rebleeding rates, their varices eradication rates were similar to those of the EBL and ES patient groups. EBL and ES combination in our study was a successful means to eradicate resistant varices.

In conclusion, we found esophageal variceal eradication rates and recurrences similar in ES, EBL and combined groups in both cirrhotics and noncirrhotics. But EBL eradicates varices more quickly, with less complications and a lower rebleeding ratio than ES. In EBL-resistant varices, it is suitable to combine ES with EBL. According to our results, esophageal varices eradication increases the incidence of fundal varices and PHG, but we did not observe any increase in bleeding from these sources. Our treatment protocol for varices eradication could be advised as a reasonable and practical treatment modality (Figure 1).

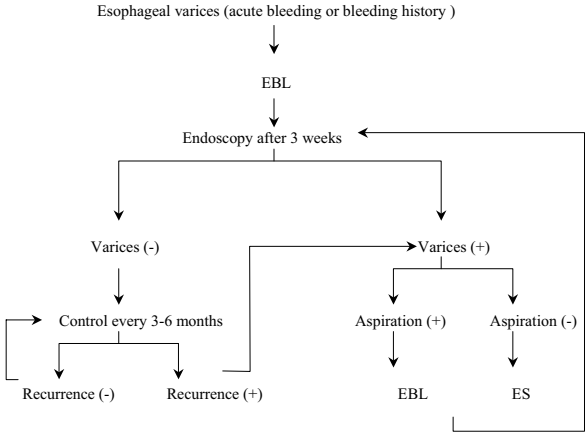

Figure 1. Varices eradication program in our clinic

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