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Prospective randomized trial: Endoscopic follow up 3 vs 6 months after esophageal variceal eradication by band ligation in cirrhosis

Wilma Debernardi Venon, Chiara Elia, Davide Stradella, Mauro Bruno, Maurizio Fadda, Claudio DeAngelis, Mario Rizzetto, Giorgio Saracco, Alfredo Marzano

Highlights

- We examine two strategies of monitoring in cirrhotics treated with variceal ligation.
- The incidence of variceal recurrence and bleeding is the same at 3 and 6 months.
- Endoscopic control at 3 months after eradication does not influence the outcome.
- Endoscopic control twice a year after variceal eradication is cost-effective.

Abstract

Background and objectives

Endoscopic variceal ligation (EVL) is recommended to treat esophageal varices (EV) in cirrhosis and portal hypertension. A program of endoscopic surveillance is not clearly established. The aim of this prospective randomized trial was to assess the most effective timing of endoscopic monitoring after variceal eradication and its impact on the patient's outcome and on the costs.

Methods

A hundred and two cirrhotic patients with esophageal varices treated by EVL were evaluated. After variceal eradication patients were randomized to receive first endoscopic control at 3 (Group 1) and 6 (Group 2) months respectively.

Results

Variceal obliteration was achieved in all patients. Variceal recurrence was observed in 28 cases at the first control (29.1%) without difference between the two groups (32% vs 29% in group 1 and 2 respectively, $p = 0.75$). The incidence of large varices is similar in the two groups (33% vs 38% respectively). Using a multivariate analysis, medical therapy with B blockers was the only independent predictor of lowest risk of variceal recurrence [OR 2.30, 95% CI (1.68–3.26)]. Bleeding related to recurrent varices occurred in 3.1% of cases and was associated with portal thrombosis. Child Pugh score ≥ 8 was the only predictor of mortality ($p = 0.0002$).

Conclusions

Recurrence of varices after banding ligation is not rare but it is associated with a low risk of variceal progression and bleeding. Accordingly, a first endoscopic control at 6 months after variceal eradication associated with a good risk stratification might be a cost-effective strategy of monitoring.

Keywords

- Portal hypertension;
- Esophageal varices;
- Bleeding;
- Band ligation

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1. Introduction

Esophageal variceal (EV) bleeding is a severe complication in the cirrhotic patient's life and represents a change in the clinical evolution of the liver disease (1) and (2). Esophageal varices are present in about 60% of patients with an end-stage cirrhosis and in about 30% of patients with compensated cirrhosis (3). About one-third of patients with cirrhosis and esophageal varices experience bleeding in the course of the disease with a 20–30% mortality rate (4). After an initial bleeding from EV, re-bleeding occurs in about 60% of the patients; for this all cirrhotic patients who survive a bleeding event have to undergo secondary prophylaxis to prevent rebleeding (5) and (6). Endoscopic Variceal Ligation (EVL) is used to prevent and treat esophageal variceal bleeding (6), (7) and (8). It has a recognized role in primary prophylaxis in naive patients with a high risk of bleeding for Child and size of varices or for intolerance to treatment with β-blockers. Current guidelines recommend EVL combined with B blockers to prevent variceal rebleeding and to reduce bleeding related mortality(5), (9), (10), (11), (12) and (13). Even though the EVL is routinely used in clinical practice and considered a safe procedure with few treatment-related complications, there are no specific guidelines regarding the technical aspects such as the number of bands placed per session or the intervals between sessions and the endoscopic surveillance after eradication. Some authors suggest that the placement of more than 6 bands at any given session is associated with a higher risk of endoscopic complications and does not reduce the time to achieve obliteration (14) and (15). An interbanding interval < 3 weeks seems to increase the risk of rebleeding (14). In our previous experience we reported that a longer interbanding interval (> 20 days) reduces the incidence of treatment-related complications and the number of missing endoscopies (14). About the endoscopic monitoring after eradication, the current indications suggest an endoscopy performed after one, three and six months from variceal eradication but the timing is variable according to the different experiences and the clinical impact of this close monitoring is also unclear (16), (17) and (18).

The main purpose of this prospective randomized study was to assess if the introduction of an early endoscopic control 3 months after variceal eradication was convenient and cost effective in order to prevent variceal recurrence and bleeding. Once the eradication was reached, the patients were randomized to receive an endoscopic control at 3 and 6 months (group 1) or only at 6 months (group 2). The impact of these different monitoring strategies on endoscopic therapy and on variceal bleeding was evaluated. The direct medical costs of the management for both groups were calculated using the Italian Health Service tariffs.

2. Materials and methods

2.1. Patients

A hundred and twelve consecutive cirrhotic patients with portal hypertension referred between January 2010 and June 2011 to our Endoscopic Operative Unit for banding ligation were included

for study. Patients with clinical evidence of advanced hepatocellular carcinoma, previous surgical or endoscopic treatment for esophageal varices, fundal varices were excluded. The study was made on 102 patients and approved by the Ethics Committee of S. Giovanni Battista Hospital. An informed consent was given by each included patient.

2.2. Methods

Patients with active esophageal variceal bleeding underwent emergent EVL or sclerosis and received iv vasoactive drugs. B-blockers were started if the patient was not treated. Patients with recent esophageal variceal bleeding underwent elective EVL. Variceal bleeding was defined as a new onset of hematemesis or melena with evidence of active bleeding from the varix or when a clot was seen adherent to a varix and no other cause of bleeding from the gastrointestinal tract was evident.

EVL was performed in primary prophylaxis in patients with high risk of bleeding from esophageal varices (Child C or small varices with red signs) and with intolerance or contraindications to use of B blockers. Among 32 patients with high risk varices, despite the use of B blockers, EVL was introduced in 17 of them waiting for liver transplant, in 6 candidates to locoregional therapy for hepatocellular carcinoma, and in 9 who needed anticoagulation therapy for portal thrombosis. In the total number of patients EVL treatment was continued so as to achieve variceal eradication.

EVL was performed with endoscopic multiband ligator (Wilson Cook Medical Inc., Winston Salem NC; Ireland) and a sedation with midazolam was used prior to endoscopy. The varices were ligated about 1–2 cm above the gastroesophageal junction applying one or two bands for each variceal column. The severity of esophageal varices was graded as F1: small, straight varices; F2: enlarged and tortuous varices (less than 1/3 of the lumen); F3: large and coil-shaped varices (more than 1/3 of the lumen) (19). The treatment scheduled involved a session every 20–30 days until variceal eradication; this timing was chosen on the basis of previous experience (14). The patients missing more than two consecutive sessions were excluded from the study.

Varices were considered eradicated when absent or venous ectasias smoothed out completely with air insufflation were found. Variceal recurrence was defined as the reappearance of varices which could be treated by new ligation.

When obliteration of varices was obtained, the patients were randomized to undergo endoscopic control after 3 and 6 months (Group 1) or after 6 months only (Group 2). The following endoscopic controls were performed every 6 months in both groups to monitor variceal recurrence (Fig. 1). Variceal eradication and variceal recurrence had to be agreed upon by two experienced endoscopists.

Fig. 1.

Trial flow chart.

2.3. Design of the study

According to the published data about the variceal recurrence after banding ligation, we hypothesized that about 45% of treated patients develop new varices during the follow up with an incidence in the first 6 months after eradication between 10 and 25% (20), (21), (22), (23) and (24).

On the assumption of a minimal 10% difference between 3 and 6 months in terms of variceal recurrence, the simple size was calculated as 46 patients in each treatment group, using a 2-side test with 80% of the study power and an alpha error of 0.05.

Randomization was done by computer and was kept in consecutively numbered opaque envelopes used when the group was assigned.

2.4. Statistical analysis

Categorical variables were compared using the χ^2 test and Fisher test when appropriate, the continuous variable using unpaired Student's *T*-test. Logistic regression was used to evaluate the relationship between the presence of variceal esophageal recurrence (no/yes = 0/1) as the dependent variable and possible predictors as the independent variables. The model was estimated using the stepwise backward method. In the multivariate analysis we used the variable that resulted in statistically significant difference in univariate examination using a non parametric analysis like the Mann–Whitney test. We performed a survival analysis between the two follow-up variables (3 vs 6 months) using the Kaplan–Meier estimates of survival, and the difference between curves was calculated with Log-Rank and Wilcoxon test. We performed a Cox (Proportional Hazard) Regression to evaluate a relationship between survival and predictors that resulted to have a significant difference in univariate analysis. A two-tailed P-value of 0.05 or less was considered significant. All analyses were performed using StatsDirect Statistical Software version 3.0.86 except for the Cox Regression, which was calculated with MedCalc version 10.2. The results were expressed as range and median. The Kappa-statistic was used for agreement analysis between observers with regard to the eradication and recurrence of esophageal varices.

3. Results

A total of 102 patients participated in the study. Six patients had to be excluded because they dropped out before reaching the eradication or had undergone liver transplantation. Therefore, ninety-six patients were treated until variceal eradication and had regular follow-up (73.02 to 91.27 months, mean survival time 82.15). Chronic viral hepatitis alone or in combination with alcohol was the most common cause of portal hypertension and esophageal varices (89%). Sixty-two patients underwent EVL for primary prophylaxis and another 34 after an episode of esophageal variceal bleeding. Twenty-four patients were actively bleeding at the time of their first EVL session.

Forty-eight patients received a first endoscopic control after 3 months from variceal eradication (Group 1) and the other 48 after 6 months (Group 2). The two groups were comparable for gender, age, etiology of cirrhosis, Child–Pugh classification and grade of the EV (Table 1). The patients treated in primary prophylaxis were not different in terms of bleeding risk from patients receiving EVL in secondary prophylaxis (Table 2). It's important to notice that one patient per group had small varices without red signs and received EVL before being treated for portal thrombosis.

Table 1.

Clinical and endoscopic characteristics of the patients at the time of first endoscopy.

	Group 1 (3 months)	Group 2 (6 months)	p
Number of patients	48	48	
Age (years)	60 (48–84)	59 (37–81)	0.91
Gender (male/female)	34/14	37/11	0.87
Etiology of portal hypertension: (n%)			
Viral	25/52%	27/56%	0.93
Alcoholic	10/21%	12/25%	0.93
Vascular disease	4/8%	1/2%	0.86
Viral + alcoholic	5/11%	6/13%	0.91
Other	4/8%	2/4%	0.75
Child–Pugh: (n/%)			
A	31/65%	24/50%	0.73
B	16/33%	18/37%	0.76
C	1/2%	6/13%	0.84
EV: (n/%)			
F1	2/4%	4/8%	0.73
F2	29/61%	32/67%	0.72
F3	17/35%	12/25%	0.87
Red signs (n/%)	31/65%	27/56%	0.88
β-blockers (n/%)	31/65%	29/61%	0.89
Diabetes mellitus (n/%)	11/23%	8/17%	0.87
Primary prophylaxis (n/%)	34/71%	28/58%	0.66
Secondary prophylaxis (n/%)	14/29%	20/42%	0.73
Actively bleeding (n/tot)	11/14	13/20	0.81

Table 2.

Distribution of risk factors of variceal hemorrhage in patients receiving EVL in primary and secondary prophylaxis.

	Primary prophylaxis (62)	Secondary prophylaxis (34)	p
Child C	4/62 (6.4%)	2/34 (5.8%)	0.94
Red wale signs on varices (RWS)	38/62 (61%)	20/34 (58%)	0.98
B blockers	32/62 (51%)	28/34 (82%)	0.002
Large varices	59/62 (95%)	31/34 (91%)	0.47
Small varices with RWS	2/62 (3.2%)	2/34 (5.8%)	0.57
Session ≥4	15/62 (24%)	3/34 (8.8%)	0.06

Variceal eradication was achieved in all treated patients. The median number of sessions of EVL required to achieve variceal obliteration was 3 ± 1.28 for the Group 1 and 2 ± 1.21 for the Group 2.

The median number of bands per session was 4 ± 1.06 for the Group 1 and 3.5±1.33 for the Group 2. The interval between sessions was 28 days for Group 1 and 30 for Group 2. Eighteen patients (18.7%), 11/48 (22.9%) in Group 1 and 7/48 (14.5%) in Group 2 received ≥ 4 sessions of EVL. The difference between the two groups for each parameter was not statistically significant (Table 3). Patients with large esophageal varices required more sessions (≥ 3) than patients with small varices to obtain eradication (22/28 vs 25/68, p = 0.0004) but the number of sessions did not influence significantly the incidence of variceal recurrence (p = 0.05). Esophageal ulcers resulting from each EVL session were found during the examination in 3% of the patients (2 in Group 1 and 1 in Group 2). In two of these patients a bleeding episode occurred within the first three weeks, before the varices could be eradicated. The bleeding originated from post-ligation ulcer caused melena and anemia but did not require endoscopic treatment. The presence of ulcers delayed the following session of banding in all cases. No stricture formation, aspiration pneumonia, or perforation occurred. Transient dysphagia was occasional.

Table 3.

Number of sessions of EVL, number of bands per session, interval between sessions in two groups of patients.

	Group 1 (48)	**Group 2 (48)**	**p**
Number of sessions of EVL required (mean)	3 (range 1–5)	2 (range 1–6)	0.97
Bands per session (mean)	4 (range 2–7)	3.5 (range 1–6)	0.96
Interval between sessions (mean)	28 (range 20–36)	30 (range 21–34)	0.25
Session ≥4	17/48	7/48	0.31

Four patients died within two months after eradication: one, a Child Pugh's C patient, in Group 1 and 3 patients (Child Pugh's B/C, 1/2 respectively) in Group 2. The mortality was unrelated to bleeding events. These patients were excluded from the analysis of variceal recurrence.

Recurrence of varices after endoscopic banding was observed in 28 cases at the first control (29.1%) without difference between the two groups (32% vs 29% in Groups 1 and 2 respectively, p = 0.753). In these patients the incidence of large varices was not different after 3 and 6 months being 5 cases out of 15 (33%) in Group 1 and 5 cases out of 13 (38%) in Group 2, suggesting a low risk of progression of EV after a new formation. When variceal recurrence was diagnosed, 10/15 patients in Group 1 and 10/13 patients in Group 2 received a new treatment of EVL at the same time of diagnosis (67% vs 77% respectively, p = 0.5) (Table 4). The kappa index regarding the interobserver agreement rate for eradication and recurrence was 0.89 and 0.85 respectively.

Table 4.

Recurrence of EV, incidence of large varices at the first control after eradication and early treatment of newly formed EV during the follow up in both groups.

	Group 1 (47)	**Group 2 (45)**	**p**
Recurrence of EV	15/47 (32%)	13/45 (29%)	0.75
Incidence of large varices	5/15 (33%)	5/13 (38%)	0.81
Early treatment of newly formed EV	10/15 (67%)	10/13 (77%)	0.45

We analyzed the incidence of EV recurrence according to the etiology of cirrhosis. Compatible with the small sample size, there were no differences when comparing the number of patients with variceal recurrence for each etiology (viral, alcohol, viral + alcohol). Similarly we did not observe any difference in the incidence of variceal recurrence in patients with viral cirrhosis when compared to alcoholic or viral + alcoholic patients (viral vs alcohol, 24/52 vs 11/22, $p = 0.80$, viral vs viral + alcohol, 24/52 vs 7/18, $p = 0.78$). Using a multivariate analysis, medical therapy with B blockers was the only independent predictor associated with a lower risk of variceal recurrence [OR 2.30, 95% CI (1.68–3.26)].

Three patients had variceal rebleeding during the follow-up: two of these have developed portal thrombosis and one advanced hepatocellular carcinoma. None of them died of variceal bleeding. No bleeding event occurred between 3 and 6 months in Group 2. There was no mortality difference between the two groups (mean survival time 42.22 months in Group 1 and 39.92 in Group 2, $p = 0.09$). Kaplan–Meier survival is presented in Fig. 2. Liver failure was the only predictor of mortality: Child Pugh's score ≥ 8 was associated with a higher risk of mortality (RR 2.49, $p = 0.0002$) as presented in Fig. 3. This explains the apparent worse survival in Group 2 in which there were more patients with advanced liver disease.

Fig. 2.

Probability of survival in each group of patients. The difference between two groups is not statistically significant ($p = 0.09$).

Fig. 3.

Survival probability related to liver failure in two groups of patients. The mortality in patients with Child Pugh's score > 8 is significantly higher (p = 0.0002).

The summary of the costs in the two treatment strategies is shown in Table 5. Medical costs sustained by health-care providers were related to visit, endoscopy and 1-day hospital stay.

Table 5.

Summary of direct costs of treatment in patients allocated to 3 months (Group 1) and 6 months (Group 2) for the first endoscopy.

Patients	**Group 1 (3 months)**	**Group 2 (6 months)**
	47 pts	**45 pts**
Endoscopy + visit	3272	3133
EVL treatment (a)	5850	4875
Total	12395 (b)	8009

a

Including the costs of 1 day hospital stay + 1 day work lost.

b

Including the costs of endoscopy + visit repeated at 6 months in all patients.

4. Discussion

The indications for EVL include primary prophylaxis, episodes of variceal bleeding and rebleeding (5) and (6). It might be considered in patients with high risk of variceal bleeding (Child C patients with small varices with red signs or Child A/B with large varices). In these patients, EVL is an alternative to β-blockers when the pharmacological treatment is contraindicated or not tolerated (25) and (26). In patients who had acute variceal hemorrhage EBL combined with β-blockers is indicated to prevent rebleeding (27) and (28). Compared with sclerotherapy, EVL is equally effective in controlling active esophageal variceal bleeding but it is associated with a lower rate of rebleeding and complications (29) and (30).

Although banding ligation has become the endoscopic treatment of choice for esophageal varices, there is still a wide disparity in technical approach and an optimal program of endoscopic surveillance is not standardized. For a long time, the discussion has been focused on the technical aspects such as the number of bands to be placed in every session and the time interval between sessions. About the first point, we know that the number of bands placed in every session does not influence the time required to achieve the variceal obliteration. Particularly, six bands per session should be the optimal cut-off number to reduce the procedure time and the side effects as dysphagia or chest pain. A higher number of bands does not reduce the time to obliteration and increases the complications (15). Our experience confirms the effectiveness of this approach. The mean number of bands per session was < 5 in all patients with a low incidence (3%) of complications. No severe dysphagia, perforation or stricture formation was encountered.

The time interval between sessions is another relevant topic. The success of EVL is closely related to the duration of time needed to reach the variceal obliteration. An interval of 2 months suggested by some authors is not feasible because associated with a high variceal bleeding rate between sessions (31). On the other hand, a too short interval (1 or 2 weeks) increases the incidence of ulcers present after every session and the risk of having to postpone the EVL because ulcers preclude the placement of bands (14) and (20). Based on our previous experience, in our current clinical practice the sessions are scheduled at 4 week intervals. With this approach we have had to defer variceal ligation in only 3% of treated patients and we observed episodes of bleeding in only 2 patients before achieving variceal obliteration.

However, an optimal surveillance program after variceal obliteration is yet to be established. Even if eradication can be obtained with ligation in more than 90% of patients, the frequency of variceal recurrence is high (20), (21), (22), (23) and (24). Since the recurrence is early reaching up to 48% within the first year in many series, some authors have suggested the need for close endoscopic control after eradication (every 3 months) through the first year of follow-up (32). The current indications recommend control of patients after 1 and 3 months after eradication (17). However, such monitoring requires significant consumption of resources and has an important impact on the quality of the patient's life (loss of working days, anxiety, discomfort). In view of this, we must consider that against a high recurrence rate, the variceal bleeding from recurrent varices is very low, increasing significantly one year after eradication (24). The rebleeding is mostly related to the ulcers post treatment and the liver reserve. Child's C patients ran a higher risk of rebleeding compared with Child A (29), (30) and (33).

The main goal of our study has been just to define the optimal timing of endoscopic control after eradication. Variceal eradication has to be documented before beginning the follow up to avoid confusion between variceal recurrence and residual varices. On reaching this step, considering that the first control after 1 month was not cost-effective (one hundred procedures to diagnose < 5% of recurrent varices), the patients were randomized to receive the first control after 3 and 6 months. We observed a relatively early recurrence of esophageal varices, around 35% in the first 6 months. This incidence is similar to the results reported by other studies in which the variceal recurrence rate

after EVL is variable from 20 to 38%, until 47% after 1 year (22), (23), (24) and (34). Only the medical therapy with B blockers appears protective against variceal recurrence when associated with EVL.

The number of patients controlled after 6 months who presented newly formed varices is not different from that of patients evaluated after 3 months. Of note is the fact that there was no significant difference between the two groups for the presence of large varices, pointing out the absence of a rapid progression of new EV. Moreover, despite early reappearance of EV, one-third of the patients in Group 1 did not undergo an early EVL retreatment; this, in part, because the banding of small varices may not be feasible in the context of scarring. None of these patients bled during the following 6 months. Thus we can assume that the early recurrence of varices is not associated with clinical events (20). The mortality in patients who received EVL for esophageal variceal bleeding appears related to severity of liver disease more than to variceal recurrence or variceal bleeding.

Costs were higher for the Group 1 than for the Group 2 strategy. In Group 1 more than 100 procedures were performed to treat 13% of the patients. The approach with the first endoscopic control after 6 months was cost-effective reducing the number of endoscopies by 45–50% whereas the incidence of bleeding and mortality was not influenced.

Summarizing, this study showed that, despite an early rate of variceal recurrence after EVL, the variceal progression rate is low and the variceal rebleeding rare. Even if preliminary, these observations seem to indicate that a close endoscopic monitoring after variceal obliteration did not add value to the outcome or treatment, did not influence the prognosis of the patient and was not cost-effective. Endoscopic control twice a year after variceal eradication might be optimal. The timing should be adapted to each patient considering several factors able to influence variceal recurrence and bleeding as liver function, the appearance of portal thrombosis or hepatocellular carcinoma and the presence of red wale markings on recurrent varices. These observations should be taken into account in the management of cirrhotic patients in everyday clinical practice.

Conflict of interest

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Corresponding author. Tel.: + 39 0116335558; fax: + 39 0116335927.

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