ORIGINAL RESEARCH ARTICLE

Endoscopic variceal ligation in primary and secondary prevention of variceal bleeding: a retrospective study in Digestive Endoscopy Unit, University Hospital Joseph Raseta Befelatanana, Antananarivo, Madagascar

Chantelli Iamblaudiot Razafindrazoto[1,2*] , Nitah Harivony Randriamifidy[1,2], Jolivet Auguste Rakotomalala[2,3], Sedera Radoniaina Rakotondrasoa[2], Behoavy Mahafaly Ralaizanaka[2,4], Henintsoa Rakotoniaina[1,2], Antsa Fihobiana Randrianiaina[1,2], Mialitiana Rakotomaharo[1,2], Domoina Harivonjy Hasina Laingonirina[1,2], Sonny Maherison[1,2], Anjaramalala Sitraka Rasolonjatovo[1,2], Andry Lalaina Rinà Rakotozafindrabe[1,2], Tovo Harimanana Rabenjanahary[1,2], Soloniaina Hélio Razafimahefa[4,5] and Rado Manitrala Ramanampamonjy[1,2]

Abstract

Introduction Endoscopic variceal ligation (EVL) is a crucial procedure for the primary and secondary prevention of variceal bleeding. The objective of this study was to evaluate the efficacy and tolerability of EVL in the prevention of variceal bleeding.

Methods This was a retrospective, single-center study over 8 years, from January 2013 to December 2020, including all patients who came for EVL in primary or secondary prevention.

Results Fifty-seven patients (male/female: 39/18) were included. The mean age of the patients was 40.02 ± 12.32 years (range: 19–68). Portal hypertension was secondary to cirrhosis in 13 patients (22.8%) and to a non-cirrhotic cause in 44 patients (77.2%). EVL was indicated for primary and secondary prevention in 5.3% and 94.7%, respectively. All patients had received propranolol with a mean daily dose of 108.07 ± 38.52 mg (extremes: 80–160). Eradication of varices was achieved in 33 patients (57.9%) with an average of 3.06 ± 0.70 sessions (extremes: 1–5) and an average duration of 10.12 ± 6.21 months (extremes: 1–24). Ten patients (17.5%) had variceal bleeding, and one patient (1.8%) died. There was no significant difference between patients with cirrhotic and non-cirrhotic portal hypertension in terms of varices eradication, variceal bleeding, and mortality. Gender (*HR*: 37.18; *CI*: 0.14–18.4; $p = 0.009$) and the number of previous bleeds (*HR*: 1.34; *CI*: 1.01–1.80; $p = 0.041$) were independent predictors of variceal bleeding during EVL. Dysphagia (73.7%) and retrosternal pain (78.9%) were the main adverse events after ligation.

Conclusion EVL is an efficient technique to eradicate varices. Its tolerance is good with post-ligation signs that are rapidly regressive.

Keywords Endoscopic variceal ligation, Variceal bleeding, Efficacy, Safety, Madagascar

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*Correspondence:
Chantelli Iamblaudiot Razafindrazoto
iamblaudiotchantelli@yahoo.com
Full list of author information is available at the end of the article

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Introduction

Esophageal variceal bleeding is a major cause of morbidity and mortality in patients with cirrhotic and non-cirrhotic portal hypertension (PH) in developing countries [1, 2]. Endoscopic variceal ligation (EVL) is a crucial treatment for acute variceal bleeding [3]. The use of non-selective beta-blockers (NSBBs) or EVL is recommended for primary prevention of variceal bleeding in patients with large and medium esophageal varices [4, 5]. The combination of EVL and NSBBs (propranolol or nadolol, with carvedilol as an alternative) is a standard approach to rebleeding prevention [6]. EVL also plays an important role in the primary and secondary prevention of variceal bleeding [6]. In developed countries, this technique has been commonly used since the 1980s and reported in various guidelines [1, 6]. Some sub-Saharan data and a previous Malagasy study had found convincing results on the eradication of varices [1, 7, 8]. Few patients could benefit from this endoscopic technique because of its high cost. The aim of this study was to evaluate the efficacy and safety of EVL in Malagasy patients who had benefited from this procedure in primary and secondary prevention.

Patients and methods

Study design and participants

This was a retrospective and single-center study conducted in Gastroenterology Unit, University Hospital Joseph Raseta Befelatanana, Antananarivo, Madagascar, from January 2015 to December 2018. We included all patients treated EVL in primary or secondary prevention. Patients who had stopped after a single session of EVL without endoscopic control were excluded. The parameters studied were as follows: gender, age, comorbidities, previous bleeding, jaundice, ascites, splenomegaly, grade of varices, red signs, Child–Pugh class, propranolol dose, number of sessions, interval between sessions, follow-up time, varices eradication, bleeding rate during the procedure, mortality, and adverse events.

Endpoints

The primary endpoints were varices eradication rate, variceal bleeding rate, and mortality during the protocol. Safety was judged on the occurrence of immediate post-ligation adverse events.

Definitions

A diagnosis of cirrhosis was based on the results of non-invasive liver examination (clinical, biological, hepatobiliary ultrasound, and degree of fibrosis). Alcoholic etiology of cirrhosis was retained on the basis of an alcohol consumption of more than 20 g/day in women and 40 g/day in men for at least 10 years and without any other etiologies found. Viral and autoimmune etiology of cirrhosis was retained in view of the positivity of viral markers and anti-tissue autoantibodies.

Hepatosplenic schistosomiasis diagnostic criteria were as follows: the presence of splenomegaly, the presence of periportal fibrosis, the presence of radiological and/or endoscopic evidence of PH, and positive schistosomiasis serology.

The diagnosis of portal thrombosis was made by hepatic doppler ultrasound and/or abdominal CT scan.

Variceal bleeding was retained by the association of several criteria: evidence of PH and the presence of esophageal varices with red signs or recent bleeding (hematemesis and/or melena).

Eradication of varices was defined by the disappearance of esophageal varices or the existence of grade 1 fibrous varices.

Description of EVL and management of variceal bleeding

EVL consisted of the placement of rubber rings on variceal columns, which are sucked into a plastic hollow cylinder attached to the tip of the endoscope by an experienced senior endoscopist. Ligation was started at the lower end of the esophagus and proceeded upwards in a spiral fashion. The average number of rubber bands was five (extremes 2–5). Olympus® Q160 video endoscope and a rechargeable multiband system (Euroligator) were used. EVL sessions were performed under general anesthesia with propofol administered intravenously in a patient fasting for at least 6 h. Induction dose was 2.5 to 3 mg/kg. The maintenance dose was done by a bolus of propofol of 25, 50, or 100 mg, intermittently as judged by the anesthesiologist, depending on the clinical (hemodynamic parameters) and sedation level of the patient. After the ligation, the patients were kept in hospital for 24-h monitoring and systematically put on nefopam infusion and paracetamol every 8 h associated with a proton-pump inhibitor.

Patients with variceal hemorrhage between EVL sessions were hospitalized and supportively cared according to a standardized protocol of the gastroenterology unit. Propranolol was continued in all patients during hospitalization, maintaining the dose before bleeding. EVL was continued at discharge in all patients until eradication of esophageal varices.

Statistical analysis

Statistical analyses were performed using SPSS (Inc., Chicago, IL, USA version 25). Quantitative variables were expressed as mean and standard deviation (SD), while qualitative variables were expressed as frequency and percentage. The chi-square (χ^2) test or Fisher's exact test, when appropriate, was used for the comparison of

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for qualitative variables between cirrhotic PH and non-cirrhotic PH. Continuous variables in both groups were compared using the paired *t*-test. In case of a skewed distribution, the Mann-Whitney *U*-test was used for the comparison of continuous variables. The cumulative probability of patients who experienced bleeding was assessed by Kaplan-Meier curves. Multivariate Cox proportional hazard models were used to detect independent predictors of variceal bleeding. All *p*-values were two-sided, with values < 0.05 considered statistically significant.

Results

Clinical and endoscopic characteristics of our patients

Fifty-seven patients were included in this study. Portal hypertension was secondary to cirrhosis in 13 patients (22.8%) and a non-cirrhotic cause in 44 patients (77.2%). Thirty-nine patients (68.4%) were male. The overall mean age of the patients was 40.02 ± 12.32 years, with extremes from 19 to 68 years. The mean age was significantly lower in patients with non-cirrhotic PH compared with those with cirrhosis (30 vs 50.23, $p < 0.001$). Alcohol (38.46%) and hepatitis B virus (30.77%) were the main etiologies of cirrhosis. Hepatic schistosomiasis (90.91%) and portal thrombosis (9.09%) were the causes of non-cirrhotic PH. Grade III varices occupied the 96.49% of patients ($n = 55$), and 38.6% ($n = 22$) had red signs. For patients with cirrhosis, the mean Child–Pugh score was 8.38 ± 2.29. All patients were on beta-blocker (propranolol) before EVL (mean dose: 108.07 ± 38.52 mg/day) including 37 patients (64.91%) on 80 mg/day and 20 (35.09%) on 160 mg/day. EVL was indicated for primary prevention in 5.3% of patients and secondary prevention in 94.7% of cases. The overall mean number of EVL sessions was 2.40 ± 1.03 (range 1–5). The mean interval between EVL sessions and the mean duration of follow-up were 1.30 ± 0.46 months (range 1–2) and 6.28 ± 6.54 months (range 1–24), respectively. There was no significant difference between the characteristics of cirrhotic and non-cirrhotic patients, except for age, the presence of jaundice and splenomegaly, and daily dose of propranolol. The clinical and endoscopic characteristics of the patients are shown in Table 1.

Efficacy and safety of EVL

Eradication of esophageal varices was achieved in 33 patients (57.9%). The average number of sessions and the average duration to achieve eradication were 3.06 ± 0.70 sessions (extremes: 1–5) and 10.12 ± 6.21 months (extremes: 1–24), respectively. Ten patients (17.5%) had variceal bleeding during the follow-up period, and one patient (1.8%) died. There was no significant difference between cirrhotic and non-cirrhotic patients in terms

of eradication rate, variceal bleeding rate, and mortality (Table 2). The number of EVL sessions was significantly higher in patients with variceal bleeding compared with those without bleeding (3.30 ± 0.82 vs 2.21 ± 0.98; $p = 0.002$). The probability of variceal bleeding was determined using Kaplan-Meier survival curves (Fig. 1). Male gender (*HR*: 37.18; *CI*: 0.14–18.4; $p = 0.009$) and number of previous bleeds (*HR*: 1.34; *CI*: 1.01–1.80; $p = 0.041$) were independent predictors of variceal bleeding during EVL (Table 3). Dysphagia (73.7%) and retrosternal pain (78.9%) were the main adverse events after ligation that resolved very quickly.

Discussion

Esophageal variceal bleeding is one of the most important causes of morbidity and mortality in patients with parenchymal liver disease and portal hypertension. Endoscopic treatment is one of the recommended therapeutic armamentariums for primary prevention of variceal bleeding in patients at high risk of bleeding and has become the gold standard for the management of bleeding esophageal varices. Once the initial bleeding episode is controlled by endoscopic treatment, there is a significant risk of rebleeding. Patients who survive the bleeding episode require repeated endoscopic treatments until the varices are obliterated to prevent recurrence [4–6, 9].

We conducted a retrospective study evaluating the efficacy of EVL in patients with cirrhotic or non-cirrhotic PH in primary and secondary prevention followed in Endoscopy Unit, University Hospital Joseph Raseta Befelatanana, Antananarivo, Madagascar. This study remains fundamental because it allowed us to determine the eradication rate, the number of sessions for varices eradication, and the rate of variceal bleeding in our center. Nevertheless, this study had several limitations. The retrospective, monocentric nature, and the relatively small size of our sample constituted these main limitations.

The study population consisted mainly of 90.91% non-cirrhotic PH patients. Madagascar is known to be an endemic area for *Schistosoma mansoni* bilharzia, which explains the high prevalence of PH secondary to schistosomiasis [1, 2, 10]. Our results are consistent with some African literature where schistosomiasis was the primary cause of PH [11, 12]. Age has been considered an important risk factor for varicose rebleeding [9]. In the present study, the overall mean age was 40.02 years. This mean age was significantly higher in the cirrhotic PH group compared to those in the non-cirrhotic PH group.

In our series, secondary prevention of variceal bleeding occupied the totality of the indication for EVL (94.7%). This finding can be explained by two reasons. The first reason was that the technical platform did not allow us to perform EVL in the context of acute variceal

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Table 1 Clinical and endoscopic characteristics of patients

Variables	Total (*N* = 57)	Cirrhotic PH (*N* = 13)	Non-cirrhotic PH (*N* = 44)	*P*-value
Gender, male, *n* (%)	39 (68.40)	10 (76.90)	29 (65.9)	0.45
Mean age ± SD (years)	40.02 ± 12.32	50.23 ± 11.50	37.00 ± 10.94	< 0.001
Hypertension, yes/no	7/50	2/11	5/39	0.70
Diabetes, yes/no	3/54	1/12	2/42	0.65
Number of previous bleeds, mean ± SD	2.88 ± 2.56	3.23 ± 2.00	2.77 ± 2.71	0.58
1/2/ ≥ 2	9/21/22	0/7/6	9/14/16	0.276
Jaundice, yes/no	17/40	9/4	8/36	< 0.001
Splenomegaly, yes/no	37/20	5/8	32/12	0.02
Stage 1/2/3/4/5	1/13/11/7/5	1/4/0/0/0	0/9/11/7/5	0.016
Ascites, yes/no	14/43	5/8	9/35	0.19
Grade 1/2/3	3/5/6	1/1/3	2/4/3	0.37
Causes of cirrhotic PH, *n* (%)				
Alcohol	5 (8.80)	5 (38.46)	-	-
Hepatitis B virus	4 (7.00)	4 (30.77)	-	-
Hepatitis C virus	1 (1.80)	1 (7.69)	-	-
Alcohol/hepatitis B virus	1 (1.80)	1 (7.69)	-	-
Autoimmune hepatitis	2 (3.50)	2 (15.39)	-	-
Causes of non-cirrhotic PH, *n* (%)				
Hepatosplenic schistosomiasis	40 (70.20)	-	40 (90.91)	-
Portal thrombosis	4 (7.00)	-	4 (9.09)	-
Grade of esophageal varix III/II	55/2	13/0	42/2	0.43
Red signs, yes/no	22/35	5/8	17/27	0.99
Child–Pugh score, mean ± SD	8.38 ± 2.29	8.38 ± 2.29	-	-
Child–Pugh class, A/B/C	3/8/2	3/8/2	-	-
Dose de propranolol (mg/jour), mean ± SD	108.07 ± 38.52	86.15 ± 22.19	114.55 ± 40.08	0.02
Propranolol dose (mg/day), 80/160	37/20	12/1	25/19	0.02
Indication for EVL, *n* (%)				
Primary prevention	3 (5.30)	0 (0.00)	3 (6.80)	0.33
Secondary prevention	54 (94.70)	13 (100.00)	41 (93.20)	
Number of sessions, mean ± SD	2.40 ± 1.03	2.31 ± 1.03	2.43 ± 1.04	0.71
Time between EVL sessions (months), mean ± SD	1.30 ± 0.46	1.31 ± 0.48	1.30 ± 0.46	0.93
Follow-up time (months), mean ± SD	6.28 ± 6.54	7.69 ± 7.27	5.86 ± 6.33	0.38

PH Portal hypertension, *EVL* Endoscopic variceal ligation, *SD* Standard deviation

Table 2 Efficacy and tolerance of EVL in our patients

Variables	Total (*N* = 57)	Cirrhotic PH (*N* = 13)	Non-cirrhotic PH (*N* = 44)	*P*-value
Varices eradication, *n* (%)	33 (57.90)	8 (56.80)	25 (61.50)	0.76
Number of sessions for eradication, means ± SD	3.06 ± 0.70	3.00 ± 0.54	3.08 ± 0.76	0.79
Time for eradication, means ± SD	10.12 ± 6.21	11.88 ± 6.22	9.56 ± 6.23	0.37
Variceal bleeding, *n* (%)	10 (17.50)	4 (30.80)	6 (13.60)	0.15
Death, *n* (%)	1 (1.80)	0 (0.00)	1 (2.30)	0.58
Tolerance				
Dysphagia, *n* (%)	42 (73.70)	13 (100.00)	29 (65.90)	0.01
Retrosternal pain, *n* (%)	45 (78.90)	13 (100.00)	32 (72.70)	0.03
Perforation, *n* (%)	1 (1.80)	0 (0.00)	1 (2.30)	0.58

PH Portal hypertension, *SD* Standard deviation

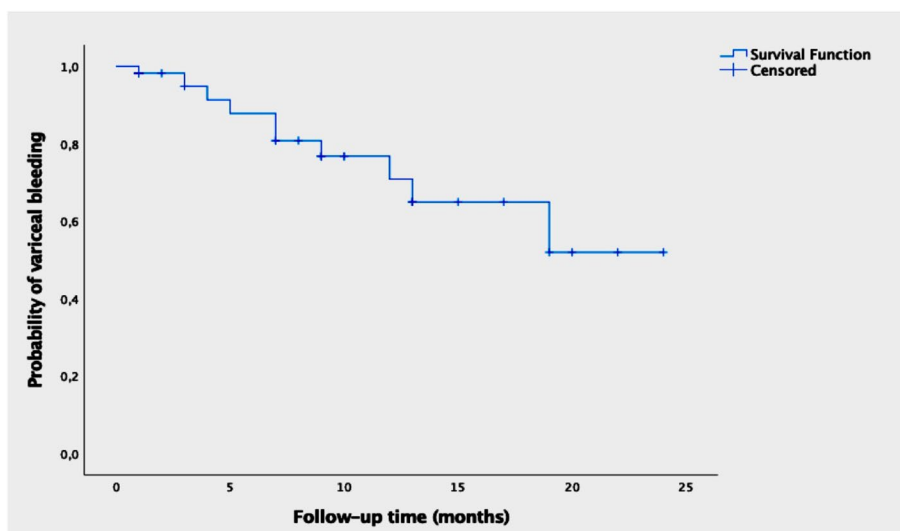Razafindrazoto *et al. Egyptian Liver Journal* (2023) 13:60

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Fig. 1 Probability of variceal bleeding was determined using Kaplan-Meier survival curves

Table 3 Predictive factors of variceal bleeding during EVL

Variables	Multivariate		
	HR	CI (95%)	*p*-value
Age (years) (< 35 vs ≥ 35)	1.62	0.14–18.4	0.696
Gender (male vs female)	37.18	2.50–553.40	0.009
Number of previous bleeds	1.34	1.01–1.80	0.041
Splenomegaly (yes vs no)	0.99	0.13–7.80	0.995
Ascites (yes vs no)	0.71	0.09–5.80	0.753
Jaundice (yes vs no)	0.22	0.03–1.70	0.144
Red signs (yes vs no)	0.16	0.02–1.60	0.124
Cirrhosis vs non-cirrhosis	5.08	0.37–70.10	0.224
Number of EVL sessions (< 3 vs ≥ 3)	0.05	0.0001–220	0.487
Interval between EVL sessions (months) (1 vs 2)	1.20	0.22–6.70	0.836

EVL Endoscopic variceal ligation, *HR* Hazard ratio, *CI* Confidence interval

hemorrhage, unlike in other African countries [3, 7, 8, 13]. The second reason was that patients came to hospital in the majority of cases only after an episode of hemorrhage, and the diagnosis of PH is often made at this time.

Several studies had shown that EVL is effective and safe, requires few sessions to eradicate varicose veins, and significantly reduces the rate of recurrent bleeding. Varices eradication in this study was achieved in 57.9% of patients with an average of 3.06 endoscopy sessions. There was no significant difference in patients with cirrhotic and non-cirrhotic PH. Our eradication rate was similar to those reported in the sub-Saharan literature (50% in Senegal and 62.5% in Mali) [7, 8]. However, this eradication rate remains largely inferior to those of the Maghrebian and Western literature where eradication varies from 79 to 100 [3, 9, 13–15]. This difference can be explained by our technical platform. In our study and the other sub-Saharan African studies, the reusable ligation kit was used, allowing only a maximum of 5 elastics to be dropped, whereas in Western countries, they use precise and efficient kits (Multiple Band Ligator) allowing a maximum of 8 elastics to be dropped. In addition, the average number of elastic bands recommended is 5 to 8 bands per session, whereas it is 2 to 5 per session in our study [1, 16]. In our series, patients required an average of 3 endoscopy sessions with an interval of 4 to 8 weeks to achieve eradication of varicose veins. Several authors had reported the same result. Khattak et al. had observed that the majority of these patients obtained complete eradication after 3 sessions of ligation [17]. Lahbabi et al. had reported obliteration of varices in 89.6% of patients with 3 ± 1.99 sessions of ligation [3]. Lo et al. required an average of 3.3 sessions at 3–4-week intervals to achieve varices obliteration [18]. Patch et al. required a median of 2 sessions using 2-week intervals, while Sarin et al. required an average of 3.2 sessions with 1-week intervals [19, 20]. There are varying views regarding the timing of EVL sessions. We have followed a flexible 4- to 8-week interval for our EVL sessions, whereas some prefer a weekly or biweekly schedule and others a bimonthly schedule [21, 22].

In our study, 10 patients (17.5) had experienced variceal bleeding. The rate of bleeding was higher in patients with cirrhosis (30.8%) compared with patients with noncirrhotic PH (13.6%) but without a statically significant difference. The two population groups are probably

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not similar in terms of severity of portal hypertension because the mean number of previous bleeding episodes was higher in the cirrhosis group than in the noncirrhotic PH group (3.23 ± 2.00 vs. 2.77 ± 2.71). A Chinese study had reported a bleeding rate of 15%, similar to our study [23]. Nevertheless, the rate of variceal bleeding is variable in the literature, ranging from 5 to 29% [7, 8, 13, 21, 23–28]. Guo et al. had found that variceal rebleeding was significantly higher in patients who received endoscopic sessions > 3 times compared with those who received sessions ≤ 3 times (61.5% vs 17.5%, $p < 0.001$) [29]. This finding was verified in our patients where the number of EVL sessions was significantly higher in patients with variceal bleeding compared with those without bleeding (3.30 ± 0.82 vs 2.21 ± 0.98; $p = 0.002$). In our series, male gender (*HR*: 37.18; *CI*: 0.14–18.4; $p = 0.009$) and number of previous bleeding (*HR*: 1.34; *CI*: 1.01–1.80; $p = 0.041$) were independent predictors of variceal bleeding during EVL. We found that the predictive factors were different in each of the studies [29–31]. The population was different in each study explaining this finding. EVL is an effective treatment option for the prevention of recurrent variceal bleeding. However, the efficacy of elastic ligation is significantly increased by the addition of β-blocker therapy [5, 6]. Other treatment modalities such as splenectomy/EVL or EVL/sclerotherapy could also be considered in selected clinical scenarios [2, 9].

As in our study, other authors had also reported the adverse effects after ligation, such as dysphagia and retrosternal pain [1, 7, 8, 23].

Conclusion

This study demonstrates the feasibility and efficacy of EVL to eradicate esophageal varices and reduce variceal rebleeding. Its tolerance is good even if there are post-ligature signs which are rapidly regressive. The improvement of the technical platforms remains at least necessary to improve our results.

Declarations

Ethics approval and consent to participate

This study was ethically and scientifically approved by Ethic Committee of University Hospital Joseph Raseta Befelatanana, with a waiver for informed consent as all patients were de-identified. All study procedures were conducted in accordance with the Declaration of Helsinki. All authors had access to the study data and reviewed and approved the final manuscript before submission.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1] Unity of Gastroenterology, University Hospital Joseph Raseta Befelatanana, Antananarivo, Madagascar. [2] Faculty of Medicine, University of Antananarivo, Antananarivo, Madagascar. [3] Unity of Hepato-Gastroenterology, University Hospital Mahavoky Atsimo, Mahajanga, Madagascar. [4] Unity of Hepato-Gastroenterology, University Hospital Andrainjato, Fianarantsoa, Madagascar. [5] Faculty of Medicine, University of Fianarantsoa, Fianarantsoa, Madagascar.

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