Optimality of 2-week Versus 4-week Intervals in Secondary Prophylaxis of Bleeding by Endoscopic Esophageal Variceal Ligation

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Background and study aim: There is a constant debate about the most appropriate intervals between endoscopic variceal ligation (*EVL*) sessions that can help achieve variceal obliteration with minimal complications. This study aims to compare 2-weekly and 4-weekly EVL schedule as regards achieving variceal obliteration and prevention of recurrent variceal bleeding.

Methods: This study included 204 patients with first attack variceal bleeding randomly allocated in two groups; group I: included 102 patients who underwent 2-weekly *EVL* schedule and group II: included 102 patients who underwent 4-weekly *EVL* schedule. Both groups were followed up till either obliteration or recurrence of bleeding occurred.

Results: Group I had significantly higher rate of variceal obliteration at both week 8 (17.5 % vs 0 % P < 0.001) and in week 12 (40 % vs 6.2 % P < 0.001). The overall rate of rebleeding was higher in group II (9.8 % vs 21.6 % p < 0.001). There were no significant differences between the studied groups as regards any of the post banding symptoms, complication, and rehospitalization.

Conclusion: The two weekly *EVL* schedule can help achieve variceal obliteration in shorter duration than 4 weekly schedule and lower overall rate of rebleeding without any significant increase in the post banding symptoms, complication and rehospitalization.

INTRODUCTION

Three modalities of treatment are available for esophageal varices (*EVs*): primary prophylaxis (preventing first bleeding episode), acute bleeding management, and secondary prophylaxis (preventing recurrent bleeding). There is a high risk of recurrent attack of bleeding in patients who survive after acute variceal haemorrhage. Most of these patients will rebleed within 2 years with a 33 % mortality rate **[1]**. Reducing risk of variceal rebleeding is essential and should be started as soon as the initial hemorrhage is controlled **[2]**.

Recommended treatment for preventing secondary variceal hemorrhage includes nonselective beta-blockers alone or in combination with endoscopic variceal ligation (*EVL*). Trans-jugular intrahepatic portosystemic shunt (TIPS) may be considered in patients rebleed despite nonselective beta-blockers and *EVL*. In terms of endoscopic therapy, *EVL* is superior to sclerotherapy and is the most preferred and safe method **[3]**.

Repeated *EVL* every 1 – 4 weeks is recommended for secondary prophylaxis of variceal bleeding until variceal obliteration **[4]**. However, the optimal *EVL* time interval is a point of debate among many endoscopists **[5]**. Variable time interval between *EVL* sessions ranging from 1 to 8 weeks until variceal eradication has been evaluated in various studies **[6]**.

This study aimed to determine the optimum interval between band ligation sessions done to manage variceal bleeding, the interval that achieves the balance between the benefit of rapid eradication of esophageal varices and risk of complications due to frequently repeated sessions.

PATIENTS AND METHODS

The study was conducted in Tropical medicine department, Zagazig University Hospitals in period between November 2018 and November 2020. Two hundred and four patients with liver cirrhosis and portal hypertension, (diagnosed by clinical, sonographic and laboratory data), recently admitted with first episode of acute upper gastrointestinal bleeding, diagnosed with *EVs* by upper GI endoscopy, and successfully had a first session of *EVL* were included in this study.

Patients were randomly allocated into two groups; Group I: underwent *EVL* sessions every 2 weeks till obliteration of *EVs* and Group II: underwent *EVL* sessions every 4 weeks till obliteration of *EVs*.

Exclusion criteria; Patients < 18 years, patients with platelet count < 40×10^9/L, patients who didn't give consent to participate in the study, patients with decompensated cirrhosis (Child C), patients who missed one scheduled *EVL* session, patients with any cause of bleeding other than esophageal varices (fundal varices or portal hypertensive gastropathy), patients who had sclerotherapy during the bleeding episode, patients on anticoagulant therapy, patients who acquire any other disease or take any drug affecting the outcome within the time of the study, patients with grade I *EVs*, and previous TIPS or surgery for treatment of portal hypertension.

Patient assessment

All patients were subjected to:

- Full history taking.
- Thorough clinical examination.
- Laboratory studies included liver and kidney function tests, complete blood count and coagulation profile.
- Calculating Child-Pugh scoring **[7]**.
- Pelviabdominal ultrasound using Mindray diagnostic ultrasound system (DC-N2), with attention to criteria of cirrhosis in ultrasound **[8]**.
- Upper GI endoscopy (PENTAX VIDEO) for performing *EVL*, using endoscopic ligating device. The patients were positioned on their left lateral position, with head supported on a small firm pillow to remain in a comfortable neutral position and a bite guard in their mouth. Sedation was received and the tip of endoscope was lubricated and checked for being functioning, regarding image quality, air and water, suction, and tip angulations. Then endoscope was introduced gently and under vision.

EVs were shown as tortuous bluish cords running longitudinally within the esophagus and covered with mucosa. The number of cords, the grade of *EVs* and red wale signs were detected. *EVs* were graded into 4 grades (grade I, II, III, and IV) according to Paquet's classification **[9].**

Patients were followed up for the following:

- The total time till eradication of *EVs*.
- Number of sessions needed till eradication.
- Mean time of each session.
- The post banding symptoms: dysphagia, odynophagia, heart burn, dyspepsia, nausea, and vomiting.
- Hospitalization (cause and duration)
- Fever (cause of fever should be investigated)
- Endoscopic findings seen in every session of follow up especially the development of post-banding ulceration.

The patients were followed up till obliteration of *EVs* or occurrence of severe complications that lead to interruption of the schedule of banding especially variceal bleeding.

Statistical analysis

All data were collected, tabulated, and statistically analyzed using SPSS 20.0 for windows (IBM Inc., Chicago, IL, USA). Continuous quantitative data were expressed as the mean ± SD & median (range), and qualitative data were expressed as an absolute frequency (number) & relative frequency (percentage). Continuous variables were checked for normality by using Shapiro-Wilk test. Independent samples Student's t-test was used to compare between two groups of normally distributed variables while Mann Whitney U test was used for non-normally distributed variables. Kruskal Wallis H test was used to compare between more than two groups of non-normally distributed variables. Categorical data were compared using Chi-square test or Fisher's exact test when appropriate. All tests were two sided . P- value <0.05 was considered statistically significant (S),

p-value <0.001 was considered highly statistically significant (HS), and p-value >0.05 was considered statistically insignificant (NS).

RESULTS

A total of 204 cirrhotic patients with *EVs* were included in the study. The mean age was about 49.66 ± 10.73 patients. Male represented about 62.7 % of all patients. Included patients were Child class A (34.3 %) and Child class B (65.7 %). There were no significant differences between two groups as regard clinical, sonographic and laboratory data at beginning of study (Table 1).

Table 2 showed endoscopic data of 2 groups starting from the first *EVL* session done during the bleeding episode and all through the following seven sessions till obliteration of *EVs* was achieve. It showed that starting from the second session, group II (4-weekly schedule) showed significantly higher grade of *EVs* than group I until the fifth session (2^{nd} session x^2=10.75 p=0.013, then 20.66 p < 0.001in 3^{rd} one, 31.69 p < 0.001 in 4^{th} and finally 24.24 p < 0.001 in 5^{th} session). Comparison between the studied groups in the last two sessions revealed no significant difference as regards *EVs* grade. However, by the last endoscopy session the *EVs* in group II started to show significantly higher rate of risky signs (0% in group I vs 18. 2% in group II p = 0.045).

Comparison between the studied groups as regards the frequency of post banding ulcer revealed that group I had significantly the higher frequency and this was evident from the second to the fourth session as seen in table 2 (2^{nd} session 46.1 % in group I vs 19.6 % in group II p < 0.001), (3^{rd} session 14.3 % in group I vs 4.1 % group II p = 0.013) and finally (4^{th} session 12.2 % in group I vs 0 % in group II p = 0.01).

Table 2 also shows that there was no significant difference between the studied groups as regards rebleeding in the session by session follow up. However, in table 4 the overall rate of rebleeding was higher in group II (9.8 % vs 21.6 % p < 0.001).

As regard *EVs* obliteration, group I had significantly higher rate of *EVs* obliteration at both week 8 (17.5 % vs 0 % P < 0.001) and in week 12 (40 % vs 6.2 % P < 0.001). Time needed till *EVs* obliteration was high significantly shorter in biweekly group (9.92 ± 2.97 weeks in group I & 19.64 ± 5.76 in group II). There were no significant differences between the two studied groups as regards any of the post banding symptoms, complication, and rehospitalization (Table 3). Variceal rebleeding was the most common cause of hospitalization among patients in both groups (Table 4).

Table (1): Comparison between group I and group II regarding demographic, clinical, and laboratory data.

		Group I n=102	Group II n= 102	P value
Age (yrs.) mean ± SD		49.72 ± 10.68	49.60 ± 10.78	0.9 (NS)*
Gender	**Male**	68 (66.7%)	60 (58.8%)	0.2 (NS)†
	Female	34 (33.3%)	42 (42.2%)	
Liver size	**Shrunken**	22 (21.6%)	26 (25.5%)	0.747 (NS)†
	Average	70 (68.6%)	68 (66.7%)	
	Enlarged	10 (9.8%)	8 (7.8%)	
Encephalopathy	**Absent**	50 (49%)	60 (58.5%)	0.373 (NS)†
	Grade I	32 (31.4%)	26 (25.5%)	
	Grade II	20 (19.6%)	16 (15.7%)	
Ascites	**No**	72 (70.6%)	70 (68.6%)	0.12 (NS)†
	Mild	24 (23.5%)	30 (29.4%)	
	Moderate	6 (5.9%)	2 (2%)	
Child	**A**	40 (39.2%)	30 (29.4%)	0.14 (NS)†
	B	62 (60.8%)	72 (70.6%)	
AST		54.64±10.61	55.43±11.44	0.622 (NS)*
ALT		69.94±15.94	82.62±47.75	0.673 (NS)*
Bilirubin		1.18±0.61	1.19±0.39	0.88 (NS)*
Albumin		3.55±0.69	3.56±0.68	0.662 (NS)*
Hemoglobin		11.51±0.87	11.41±1.29	0.55 (NS)‡
WBC's		7.41±2.06	8.03±4.09	0.805 (NS)*
Platelets		101.96±33.19	104.82±58.50	0.247(NS)*
INR		1.45±0.33	1.43±0.34	0.648 (NS)*
Creatinine		1.23±0.58	1.22±0.55	0.857 (NS)*
BUN		72.72±51.33	70.79±50.35	0.936 (NS)*

* Mann-Whitney U test
† Chi-square test
‡ Independent samples student's t- test
P value ≥0.05 is statistically non-significant

Table 2: Comparison between the studied groups as regards endoscopic findings throughout the whole period of the study.

		group I n=102		group II n=102		P value
		N	%	N	%	
Initial endoscopy session		n=102		n=102		
EVs grade	**Grade II**	10	9.8%	22	21.6%	0.765*
	Grade III	43	42.2%	40	39.2%	
	Grade IV	49	48%	40	39.2%	
Risky signs		32	31.4%	34	33.3%	0.063*
Second endoscopy session		n=102		n=102		
EVs grade	**Grade I**	6	5.9%	2	2%	0.013 (S)*
	Grade II	70	68.6%	62	60.8%	
	Grade III	22	21.6%	38	37.3%	
	Grade IV	4	3.9%	0	0%	
Risky signs		6	5.9%	4	3.9%	0.517(NS)*
Post banding ulcer		47	46.1%	20	19.6%	<0.001(HS)*
Re-bleeding		0	0%	0	0%	1(NS)*
Third endoscopy session		n=98		n=98		
EVs grade	**Obliterated**	7	7.1%	2	2%	<0.001 (HS)*
	Grade I	22	22.4%	4	4.1%	
	Grade II	59	60.2%	70	71.4%	
	Grade III	10	10.2%	22	22.4%	
Risky signs		4	4.1%	2	2%	0.683(NS)*
Post banding ulcer		14	14.3%	4	4.1%	0.013(S)*
Re-bleeding		0	0%	0	0%	1(NS)*
Fourth endoscopy session		n=82		n=88		
EVs grade	**Obliterated**	16	19.5%	14	15.9%	<0.001(HS)*
	Grade I	30	36.6%	4	4.5%	
	Grade II	36	43.9%	68	77.3%	
	Grade III	0	0%	2	2.3%	
Risky signs		2	2.4%	4	4.5%	0.683(NS)*
Post banding ulcer		10	12.2%	0	0%	0.001(S)*
Re-bleeding		0	0%	2	2.3%	0.498(NS)*
Fifth endoscopy session		n=64		n=66		
EVs grade	**Obliterated**	9	14.1%	16	24.2%	<0.001(HS)*
	Grade I	30	46.9%	6	9.1%	
	Grade II	25	39.1%	42	63.6%	
	Grade III	0	0%	2	3%	
Risky signs		0	0%	2	2.9%	0.497 (NS)*
Post banding ulcer		4	6.2%	4	9.1%	0.744 (NS)*
Re-bleeding		1	1.6%	4	6.1%	0.366 (NS)*
Sixth endoscopy session		n=51		n=44		
EVs grade	**Obliterated**	22	43.1%	18	40.9%	0.784 (NS)*
	Grade I	9	17.6%	6	13.6%	
	Grade II	20	39.2%	20	45.5%	
Risky signs		0	0%	2	4.5%	0.212 (NS)*
Post banding ulcer		2	3.9%	0	0%	0.497 (NS)*
Re-bleeding		4	7.8%	6	13.6%	0.506 (NS)*
Seventh endoscopy session		n=24		n=22		
EVs grade	**Obliterated**	16	66.7%	14	63.6%	0.573 (NS)*
	Grade I	4	16.7%	2	9.1%	
	Grade II	4	16.7%	6	27.3%	
Risky signs		0	0%	4	18.2%	0.045 (S)*
Post banding ulcer		0	0%	0	0%	1 (NS)*
Re-bleeding		4	16.7%	6	27.3%	0.484 (NS)*

* Chi-square test

P value ≥0.05 is statistically non-significant

P value <0.05 is considered statistically significant

P value <0.001 is considered statistically highly significant

EVs, Esophageal varices

Table 3: Comparison between the studied groups as regards rate of eradication, total time, and number of sessions needed for eradication.

	Group I n=102		Group II n=102		P value
	N	%	N	%	
Eradication rate					
4 weeks	3	2.9%	0	0%	0.246 (NS)*
8 weeks	14	17.5%	0	0%	<0.001 (HS)*
12 weeks	20	40%	6	6.2%	<0.001 (HS)*
Total time					
	Mean ± SD		Mean ± SD		
Days in hospital	5.36±1.81		6±1.67		0.367 (NS)†
Time till obliteration (weeks)	9.92±2.97		19.64±5.76		<0.001 (HS)†
Total number of endoscopy sessions	4.98±1.46		5.07±1.91		0.896 (NS)†
Time of each session (min)	9.74±1.08		9.66±1.23		0.556 (NS)†

* Chi-square test
† Mann-Whitney U test
P value ≥0.05 is statistically non-significant
P value <0.001 is considered statistically highly significant

Table 4: Comparison between the studied groups as regards post banding symptoms, hospitalization rate, and causes of hospitalization.

	Group I n=102		Group II n=102		P value
	N	%	N	%	
Post banding symptoms					
Dysphagia	48	47.1%	38	37.3%	0.156 (NS)*
Odynophagia	44	43.1%	32	31.4%	0.082 (NS)*
Heart burn	36	35.3%	28	27.5%	0.227 (NS)*
Fever	20	19.6%	20	19.6%	1.000 (NS)*
Hospitalization	20	19.6%	28	27.5%	0.07 (NS)*
Causes of hospitalization					
Re-bleeding	10	9.8%	22	21.6%	0.003 (S)*
Chest infection	6	5.9%	6	5.0%	1 (NS)*
UTI	4	3.9%	2	2%	0.683 (NS)*
SBP	4	3.9%	6	5.0%	0.517 (NS)*

* Chi-square test
P value ≥0.05 is statistically non-significant
P value <0.05 is considered statistically significant
UTI, Urinary Tract Infections; *SBP*, Spontaneous Bacterial Peritonitis.

DISCUSSION

This study aimed at determining the optimum interval between band ligation sessions done to manage variceal bleeding, the interval that achieves the balance between the benefit of rapid eradication of *EVs* and risk of complications due to frequent repeated sessions.

Patients were randomly allocated into two groups, with a total number of 204 (102 patients in each group). The patients were referred to endoscopy unit for control of the first attack of varices bleeding. Group I: 68 males and 34 females have undergone *EVL* sessions every 2 weeks till obliteration of *EVs* and Group II: 60 males and 42 females have undergone *EVL* sessions every 4 weeks till obliteration of *EVs.*

This study showed no significant differences between the two groups as regard age, sex, clinical findings as well as laboratory and sonographic data. Most of included cases in both groups were Child B classification (60.8 % in group I and 70.6 % in group B) which agree with Butt et al., who stated that most of their patients presented with first attack variceal bleeding was Child-Pugh class B or C (84%) **[10]**.

Most patients in our study denied previous history of endoscopic evaluation until this time when they presented with first variceal bleeding attack. This delay can be caused by the hesitation of both patients and health care providers to refer their patients to endoscopic evaluation when they are still well compensated in Child grade A. This hesitation may be because both patients and health care providers would consider endoscopy to be risky, expensive, and invasive. Hence, the importance of non-invasive diagnostic methods for *EVs* was stated by the Baveno VI and VII consensus **[11,12]**, to avoid referring patients to unnecessary endoscopic evaluation and detect patients at high risk of *EVs* before they bleed and assign them for primary prophylaxis with *EVL*.

In the present study, there was no significant differences between both groups as regard initial endoscopic evaluation (grade of *EVs* as well as presence of risky signs). This means that the two groups were comparable to each other and the absence of a third factor manipulating the final results is assured.

Comparison between the two groups in the later endoscopy sessions showed that group II had significantly higher grade of *EVs* starting from second till the fifth session. This means that there was a delay in the obliteration of *EVs* in this group enhancing the risk of rebleeding among those patients. However, there were no significant differences between the studied groups as regards neither rebleeding nor risky signs all through period of follow up except in the final endoscopy session when group II showed significantly higher rate of risky signs on *EVs*. The rate of variceal rebleeding in the session by session (follow up) showed no significant differences between two groups. However, overall rate of variceal rebleeding was higher in group II. This agreed with Sheibani et al., who discovered that increasing the time interval between follow up endoscopy sessions led to increase in the rate of variceal rebleeding in between sessions **[13]**.

In our study, the most common causes of post-banding rehospitalization were re-bleeding, chest infection, urinary tract infections and spontaneous bacterial peritonitis among which variceal rebleeding was the most common cause of hospitalization in those patients. It is also worth saying that there was no significant difference between both groups as regard causes of hospitalization. In contrast, a case-control study by Harewood et al., compared patients in whom *EVs* rebleeding developed with those who did not rebleed. The median interval between banding sessions in the rebleeding group was 2 weeks. This disagreement may be because all patients in our study fall in the interquartile range of interval between *EVL* sessions of non-bleeders according to Harewood et al **[14]**.

This study showed significantly higher rate of post-banding ulcer in group I patients noted starting from second to forth session. The decision to apply band ligation in patients with observed post-band ulcers in their follow up endoscopy sessions, was tailored according to the evaluation done by the endoscopist (regarding the number and depth of the ulcers), the more the depth and the more the ulcers were scattered, the more the decision to proceed was hindered. Moreover, the technique of banding was modified to be applied away from the edges of the pre-existing post-band ulcers. This significantly higher rate of post banding ulcer was not associated with any significant increase in the rate of rebleeding in those patients neither in the session by session follow up nor in the overall rate. On the contrary, the overall rate of rebleeding was higher in group II, the group with lower rate of post-banding ulcer. It was also worth noticing that the rate of different post banding symptoms like; dysphagia, odynophagia, heart burn or fever was also found to be insignificantly different in both groups this mean that this higher rate of post banding ulceration in group I had no specific symptoms in most instances. This finding comes in line with Sheibani et al., who stated that , there were no significant increase in the proportion of patients developing post band complication after 1 week or 2 week of *EVL* **[13]**. In another study by Wang et al., there was a significant increase of adverse events in the Monthly group than in Biweekly group **[15]**.

In the current study regarding to eradication rate of *EVs*, there was no significant difference between both groups at 4 weeks and there was a high significant difference at 8 and 12 weeks with higher eradication rate in group I than in group II. Our findings are consistent with Sheibani et al, and Wang et al, who said that the shorter the interval between sessions, the faster the eradication of varices **[13,15]**. Similarly, most recommendation for primary prophylaxis, endoscopy with *EVL* should be repeated every 1 to 2 weeks until *EVs* obliteration **[16]**. In contrast, a study done by Yoshida et al., stated that *EVL* every two months was better for total *EVs* eradication **[17]**. British Society of Gastroenterology guideline recommended interval of 2 – 4 weeks for *EVL* **[18]**. However, these recommendations are based on older randomized trials of sclerotherapy, intervals employed in prior ligation trials, and retrospective observational studies of ligation **[16,19]**.

In the present study, the mean number of sessions needed for *EVs* eradication in group I was 4.98 ± 1.46 and in group II was 5.07 ± 1.91 with no significant difference in between which partially agree with a study conducted in Morocco by Villanueva et al., showed that number of session needed for variceal obliteration was from 1 to 8 sessions (mean 3) **[20]**. In another study by Wang et al., the mean number of sessions was 3.6 sessions to achieve *EVs* eradication for each patient **[21]**. Similarly, our findings were supported by a study by Alvi et al., and Khattak et al., in which majority of patients achieved complete eradication after 3 sessions or 4 session of band ligation **[22,23]**. In contrast, Shrestha et al.**,** reported that *EVs* were eradicated after 2 sessions of band ligation and about 24 % of patients required just 1 session of *EVL* **[24]**. None of the patients in our study achieved *EVs* eradication after 1 session only.

This study has some limitations; it was a single-center study, and the sample size was relatively small. *EVL* is operator dependent. The endoscopist' experiences may have an impact on successful *EVs* eradication and complication after *EVL*. Also, patients not followed up after *EVs* eradication for detection of variceal recurrence. Large-scale multicenter trials are needed to confirm our results and to detect the optimal interval between *EVL* sessions.

In conclusion, the two weekly *EVL* schedule can help achieve *EVs* obliteration in shorter duration than 4 weekly schedule and lower overall rate of rebleeding without any significant increase in the post banding symptoms, complications, or rehospitalization.

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Conflict of interest

None declared.

Ethical consideration

Permission and official approval to carry out the study was obtained. All patients signed a written informed consent before inclusion into this study and the institutional ethical committee at Zagazig University, Faculty of Medicine approved the study (ZU-IRB #4084/15-10-2017). The study protocol conforms with the ethical guidelines of the 1975 Declaration of Helsinki.

HIGHLIGHTS

- Cirrhotic patients after their first variceal hemorrhage have a risk (> 60 %) of recurrent bleeding within 1 year, and mortality from each rebleeding episode is roughly 20%.
- First-line therapy for the prevention of recurrent variceal hemorrhage is the combination of traditional NSBBs or carvedilol and EVL.
- The optimal time interval for EBL sessions remains without consensus owing to the limited evidence.
- Secondary preventive measures are administered to reduce variceal rebleeding, thereby improving patient survival and clinical outcome.

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