



ORIGINAL ARTICLE

Comparison of betablockers and endoscopic variceal band ligation (EVBL) for secondary prevention of variceal bleed in cirrhotics.

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ABSTRACT... Objective: To compare the efficacy of pharmacological and endoscopic procedures (band ligation) in preventing variceal bleed. **Study Design:** Randomized Control Trial. **Setting:** MU-I of Allied Hospital Faisalabad. **Period:** January to June 2020. **Material & Methods:** 80 patients were enrolled after fulfilling exclusion and inclusion criteria, divided into two groups. Group A, patients treated Carvedilol 6.25-12.5mg pulse rate of 60-70 beats per minute. Group B patients underwent repeated endoscopic procedures (band ligation), repeated every 2 weeks until obliteration of varices was achieved. Surveillance endoscopy was done one month later. Follow up was done by telephonic contact at 3 months. **Results:** In our study, mean age was 52.88+9.29 and 53.57+8.85 years in Group-A and B, 42.5%(n=17) in Group-A and 50%(n=20) in Group-B were male, 57.5%(n=23) in Group-A and 50%(n=20) female in group B, Recurrence of variceal bleeding and efficacy of drug comparison showed that 7.5%(n=3) in Group-A and 27.5%(n=11) in Group-B had a recurrence of variceal bleed while 92.5%(n=37) in Group-A and 72.5%(n=29) in Group-B had no recurrence of variceal bleed, p-value (0.01) was significant. **Conclusion:** Beta-blocker (Carvedilol) is more efficacious for preventing recurrence of variceal bleed than Endoscopic Band Ligation.

Key words: Cirrhosis, Endoscopic Band Ligation, Pharmacological Management, Prevention of Upper GI Bleed, Upper GI Bleed, Variceal Bleed.

INTRODUCTION

Cirrhosis is characterized by the formation of simultaneous fibrotic bands and regenerative nodules. Its etiology includes chronic viral infections, alcohol, drugs, autoimmunity, metabolic liver diseases and other miscellaneous disorders.¹ Cirrhosis is one of the leading causes of death in the United States.¹ It has various complications like ascites, oedema, SBP (spontaneous bacterial peritonitis), prerenal azotemia (HRS), encephalopathy, coagulopathy, upper GI bleed from esophageal varices, hepatopulmonary syndrome and Porto pulmonary hypertension.¹

Esophagus, stomach, and duodenum are various places where upper GI bleed can originate. It presents as hematemesis (bright

red color or coffee-ground), melena and/or hematochezia (fresh bleeding per rectum).^{2,3} The annual incidence of hospital admissions for upper gastrointestinal bleed in the United States is <0.1%, with a mortality of <5%-10%. Variceal hemorrhage is a dreadful problem and can cause mortality up to 20%-30% with each episode of bleeding.³

Portal hypertension resulting in esophageal variceal bleed is a dreadful complication. It causes 70% of the cases. The overall risk of upper GI bleed in cirrhotics is approximately 30% and is associated with 30-50% mortality with each event.⁴ The mortality rate from an upper GI bleed due to esophageal varices has been decreased significantly in the last couple of decades from 42% in the Graham and Smith

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study in 1981 to the 6%-12%. This reduction in mortality is caused by the availability of efficient options, such as upper GI endoscopy and EVBL, targeted pharmacological options, trans Jugular Intrahepatic Stent shunt (TIPS) and also with improvement of general measures.⁵

There is always a risk of recurrence of upper GI bleed, which carries a mortality of 33%, so there must be some treatment to prevent further episodes of variceal bleed. Secondary prophylaxis includes drugs, repeated endoscopic procedures, or their combination and the use of shunts like TIPS.⁶

Carvedilol is a beta-blocker, non-selective and has a weak anti-alpha-adrenergic activity.^{7,8} The risk of upper GI bleed recurrence due to esophageal varices has been decreased to 40%-50%, and reduction in mortality by 25%-45% is observed in cirrhotic patients treated with beta-Blocker.⁴

In Endoscopic variceal band ligation, rubber bands are applied on esophageal varices after sucking them into a rounder plastic cylinder on the tip end of the endoscope.

Although both reduce the frequency of re-bleed in patients with cirrhosis, the incidence of re-bleed with Carvedilol is 5% vs EVBL, which has an incidence of 25% in a follow-up interval of 2 years.⁹ The objective of this study was to compare and determine the efficacy of pharmacological and endoscopic esophageal variceal band ligation in the prevention of variceal bleed in patients of cirrhosis in the Pakistani population.

MATERIAL & METHODS

After obtaining approval from the ethical review committee (480/IRC/PM), this randomized control trial was conducted in MU-I of Allied Hospital Faisalabad for a 06-month duration (January to June 2020). This study aimed to compare and determine the efficacy of pharmacological and endoscopic variceal band ligation in the prevention of variceal bleed in cirrhosis patients.

The sample size was calculated using the WHO sample size calculator for two proportions, $P_1 = 5\%$

[40] and $P_2 = 25\%$. The power of the study was 80%, and the level of significance was 5%, sample size calculated as 80 (40 in each group). Eighty patients admitted in the medical unit I of Allied hospital Faisalabad fulfilling inclusion criteria (Patients of both gender and age from 18-70 years, all cirrhotic patients having upper gastrointestinal bleed due to esophageal varices diagnosed by Esophagogastroduodenoscopy within last 3 months.) and exclusion criteria, (Cirrhotic patients who have upper gastrointestinal bleed from other sources like gastric ulcer, duodenal ulcer, gastric or fundal varices and congestive gastropathy. Cirrhotic patients who have a contraindication for beta-blockers like Asthma (suggestive history), Heart block 2nd degree or higher on ECG, Peripheral arterial disease (symptoms like intermittent claudication, gangrene, pain at rest in limbs, findings of arterial insufficiency on doppler studies), were enrolled in the study. Patients were diagnosed with an acute esophageal variceal bleed based on history (hematemesis, malena and hematochezia) and esophageal varices were diagnosed after Esophagogastroduodenoscopy.

In group A, patients were given Carvedilol starting from 6.25mg once a day for one week and then increased to 12.5mg once a day to achieve a pulse rate of 60-70 beats per minute. In group B, patients underwent repeated endoscopic variceal band ligation. Endoscopic variceal band ligation was repeated every 2 weeks until obliteration of varices is achieved.⁹ Following this, a surveillance endoscopy month was repeated once a month.

Data was collected and filled on standardized proforma by Principal Investigator. Follow up was done by telephonic contact at 3 months. Our variables were initial presentation (hematemesis or malena), endoscopic findings, and recurrence of upper GI bleed in this study.

SPSS version 20 was used for entering and analysis of data. For quantitative variables like age, Mean and Standard deviation SD was calculated. Frequency and percentage were calculated for gender, the qualitative variable, recurrence of variceal bleed and efficacy of the drug. A Chi-square test was applied to compare

efficacy for both groups. A significant p-value was taken as <0.05 . Age and sex affect modulators we controlled by stratification.

RESULTS

A total of 80 cases which fulfilled the inclusion and exclusion criteria, were enrolled to compare, and determine the efficacy of pharmacological Vs variceal endoscopic, band ligation, for prevention of recurrent upper GI variceal bleed in patients of cirrhosis.

Patients were distributed according to age of the patients, In Group-A (n=15), 37.5% and (n=12) 30% in Group-B, were having age 18-50 years. 62.5% (n=25) Group-A and in Group B 70% (n=28) were 51-70 years. Mean + SD (52.88 + 9.92years) and (53.57 + 8.85 years) in A & B Groups, respectively (Table-I).

In gender distribution male were, 42.5% (n=17) in Group-A and 50% (n=20) in Group-B. female distribution was, 57.5% (n=23) in Group-A and 50%(n=20) in Group-B. (Table-II)

Recurrence of variceal bleeding and efficacy of drug comparison showed that 7.5% (n=3) in Group-A and 27.5% (n=11) in Group-B had recurrence of variceal bleed while 92.5% (n=37) in Group-A and 72.5% (n=29) in Group-B had no recurrence of variceal bleed, p value (0.01) was significant. (Table-III)

Age and sex were effect modulators and we controlled them by stratification. After stratification independent sample t-test was applied. Significant P-value was taken as $<.05$. (Table-IV & V)

Age (Years)	Group-A (n=40)	Group-B (n=40)
	Patients (%)	Patients (%)
18-50	15 (37.5%)	12 (30%)
51-70	25 (62.5%)	28 (70%)
Total	40 (100%)	40 (100%)
Mean+SD	52.88+9.29	53.57+8.85

Table-I. Age distribution (n=80)

Gender	Group-A (n=40)	Group-B (n=40)
	Patients (%)	Patients (%)
Male	17 (42.5%)	20 (50%)
Female	23 (57.5%)	20 (50%)
Total	40 (100%)	40 (100%)

Table-II. Gender distribution (n=80)

Recurrence of Variceal Bleed	Group-A (n=40)	Group-B (n=40)
	Patients (%)	Patients (%)
Yes	3 (7.5%)	11 (27.5%)
No	37 (92.5%)	29 (72.5%)
Total	40 (100%)	40 (100%)

**Table-III. Frequency of recurrence of variceal bleed and efficacy of drug (n=80)
P value: 0.01**

AGE: 18-50

Group	Efficacy		P-Value
	Yes	No	
A	1	14	0.41
B	2	10	

AGE: 51-70

Group	Efficacy		P-Value
	Yes	No	
A	2	23	0.03
B	9	19	

Table-IV. Stratification for recurrence of variceal bleed and efficacy of drug with regards to age

Male

Group	Efficacy		P-Value
	Yes	No	
A	2	15	0.30
B	5	15	

Female

Group	Efficacy		P-Value
	Yes	No	
A	1	22	0.02
B	6	14	

Table-V. Stratification for recurrence of variceal bleed and efficacy of drug with regards to gender

DISCUSSION

Cirrhosis of the liver is the 12th leading cause of death, resulting from different etiologies.¹⁰ Upper GI bleed due to varices is the most life-threatening complication of liver cirrhosis and is associated with a high mortality rate.^{11,12} The risk of bleeding from esophageal varices is 70% in incidence and has a mortality of 20-35%.¹³⁻¹⁵ Decreasing hepatic

venous pressure gradient (HVPG), a strong predictor of upper GI bleed, 20% below baseline reduces the risk of variceal bleeding.^{16,17}

At present, we have two modalities to combat: pharmacological (non-selective Betablockers, NSBB). The second is physical obliteration of vessels like band ligation or sclerotherapy (though band ligation has replaced sclerotherapy). NSBB reduce HVPG and hence are used to reduce the incidence of upper GI bleed.

In recent years, preventing variceal bleed is an active area of research, so did the comparison of different modalities available to attain this target. Currently, the prevention of re-bleed is based upon NSBB and variceal band ligation.¹⁸ We planned this study with the view to find out the most efficacious way of treating variceal bleed amongst Carvedilol and Endoscopic variceal band ligation in our setup. In our study, we saw non-selective beta-blockers were more efficacious in preventing recurrent upper GI bleed than endoscopic band ligation, as discussed earlier in results with p-value (0.01) was significant.

Carvedilol is a beta-blocker, non-selective (NSBB); it has a weak anti-alpha-adrenergic activity.⁸ It reduces the risk of variceal re-bleed by 40%-50% and a mortality of 25%-45% in cirrhotic patients.⁴ Although pharmacological measures and recurrent upper GI endoscopy reduce the frequency of re-bleed in Cirrhotics, treatment with Carvedilol has a 5% frequency of re-bleed vs EVBL frequency of 25% was observed in a follow-up interval of 2 years.⁹ These findings agree with our results. The decrease in HVPG Carvedilol (NSBB) exerts an antioxidant effect on intrahepatic vasculature and may have two-fold benefits in cirrhosis.^{19,20}

Another study²¹ showed the superiority of Carvedilol in the primary prevention of variceal bleed as compared to VBL.

A metanalysis, which gathered 32 randomized trials and 3,362 patients, showed different interventions for re-bleed or primary prophylaxis and their relation to mortality in cirrhotics at risk

of variceal development, had interesting results.⁶ It showed a combination of NSBB and EVBL is superior for the prevention of bleeding as compared to NSBB alone.⁶ Carvedilol is superior in NSBB in the prevention of re-bleed, but it has fewer benefits on decreasing mortality.⁶ The benefits of NSBB in decreasing mortality are not only due to their efficacy in preventing bleeding in comparison to EVBL, but also due to their effect on GI mobility, hence reduction in bacterial transport²² and decreasing portal pressure.⁶ Again, this metanalysis favors our study in terms of a decrease in the incidence of variceal bleed with the use of NSBB.

A study showed NSBB association with increased mortality when used in patients with ascites and SBP (spontaneous bacterial peritonitis).²³ Our study did not demonstrate any of such effects may be the shorter duration of our study.

NSBB may have more side effects in prone individuals than EVBL, which may lead to discontinuation of treatment²⁴, but in our study, we did not observe any of such discontinuations or side effects in the understudy population.

One of the important predictors of bleed from varices' is the size of the vessels which is significantly decreased using Betablockers.¹⁸ The incidence of bleed from small-sized varices is 5%/year as compared to 15%/year from a bigger vessel.²⁵

Interestingly, one of the studies which compared VBL, and placebo (beta-blocker intolerant patients) was terminated prematurely after observing three upper GI bleed incidences in the VBL arm, though there was no statistical importance of this finding.²⁶

The study also showed that 60% of patients had small varices hence concluded that VBL should be reserved for moderate to large varices, so careful selection of patients is necessary. Acid suppression during band ligation has unknown significance, so two trials with PPI (Proton Pump Inhibitors) during VBL did not significantly affect band-related complications.^{27,28}

A meta-analysis from Poynard and colleagues in 1991 analyzed, NSBB (Non-selective Beta Blockers) are effective in the prevention of the first bleed so reduce mortality among patients with cirrhosis, four studies were chosen in this analysis.²⁹⁻³³

Additionally, in another metanalysis, NSBB was found to be the first line for primary and secondary bleed prevention.^{34,35}

Cirrhotics treated with beta-blockers (Carvedilol), have better ascites control and improved child-Pugh score, so their use is associated with better life expectancy; this benefit is beyond only GI bleed control.^{36,37}

The incidence of variceal development in cirrhosis is 5-10%/year^{38,39}, so prophylaxis for their bleed is extremely important. Secondary prophylaxis aims to decrease re-bleed and hence related death.¹⁸

The findings of our study support the hypothesis that “Patients of Cirrhosis have less frequency of re-bleed with beta-blocker (Carvedilol) as compared to Endoscopic Variceal Band Ligation”. However, some other local multicenter trials may validate our results.

CONCLUSION

It is concluded that beta-blocker (Carvedilol) is more efficacious for preventing recurrence of variceal bleed compared with Endoscopic Variceal Band Ligation.

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


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AUTHORSHIP AND CONTRIBUTION DECLARATION

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2	Hina Akram	Writing manuscript.	
3	Ahmed Zeeshan Chughtai	Data collection.	
4	Muhammad Yasir Yaqoob	Data collection.	
5	M. Usman Musharaf	Data collection.	