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A Randomized Controlled Trial Comparing Endoscopic Variceal Ligation (EVL) Alone Versus Endoscopic Variceal Ligation (EVL) Plus Non-Selective B-Blocker (Proponolol) in The Secondary Prophylaxis of Variceal Haemmorrhage.

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ABSTRACT

Background: Variceal hemorrhage is perhaps the most devastating portal hypertension-related complication in patients with cirrhosis, occurring in up to 30% of such individuals during the course of their Variceal hemorrhages occur only when there is a clinically significant portal hypertension, defined as HVPG > 12 mmHg. The 1-year rate of a first bleeding episode is 5–15% as many as 70% of the survivors have recurrent bleeding within 1 year after the index hemorrhage. Patients surviving in the first episode of variceal haemorrhages are at high-risk of recurrent bleeding, with a mortality of 33%, and thus should have secondary therapy to prevent further variceal bleeding. **Methods:** 80 haemodynamically stable patients with esophageal varices (post first bleed) were included in the study. The male : female ratio was age range was between 22-63 years and the mean age was 49.32 years. **Results:** Re-bleeding rate of EVL (Group A) was 37% rebleeding rate of EVL+Propanol (Group B) was 18%. The difference was not statistically significant. The appearance of new varices initial eradication was less in group B, this was statistically significant (P value < 0.008). Mortality in group A was 9%, while it was 43% in group B, however the results were statistically not significant. **Conclusion:** Combination therapy using β-blockers with EVL (Group B) has statistically significant benefit (P < 0.001) over endoscopic variceal ligation alone (EVL) Group A, in the secondary prophylaxis of bleeding oesophageal varices.

Keywords: Oesophageal varices, Endoscopic variceal ligation (EVL), Secondary prophylaxis, β-blockers, propanolol.

INTRODUCTION

Variceal hemorrhage is perhaps the most devastating portal hypertension-related complication in patients with cirrhosis, occurring in up to 30% of such individuals during the course of their illness. Esophageal varices are present in nearly 30% to 40% of patients with compensated cirrhosis and in 60% of those with decompensated cirrhosis.[1] Variceal hemorrhages occur only when there is a clinically significant portal hypertension, defined as HVPG > 12 mmHg.[2] The 1-year rate of a first bleeding episode is 5–15% and its risk is defined by variceal size, red signs on the varices, and severity of liver disease in patients.[3] As many as 70% of the survivors have recurrent bleeding within 1 year after the index hemorrhage.[4] Management of patients with gastroesophageal varices includes: prevention of varices (pre primary prophylaxis), primary prophylaxis to prevent the initial bleeding episode, the control of an acute hemorrhage, and the prevention of recurrent bleeding after a first episode (secondary prophylaxis). Patients surviving in the first episode of variceal haemorrhages are at high-risk of recurrent bleeding, with a mortality of 33%, and thus should have secondary therapy to prevent further variceal bleeding5. The main means of secondary prophylaxis are:

- Pharmacological,
- Endoscopic treatment, or;
- A combination of pharmacological and endoscopic treatment, or;
- The use of shunts.

The results of randomized, controlled trials comparing variceal ligation with β-blockers showed

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that combination treatment gives the lowest rebleeding rates, but without differences in survival6. The combination therapy of EVL and nonselective β-blockers for the prevention of recurrent variceal haemorrhage is now the preferred therapy.[7]

Aims and Objectives

This study was conducted at J.N. Medical College, AMU, Aligarh from the year 2011 to 2013 with the following aims and objectives:

1. To study the effect of endoscopic variceal ligation (EVL) alone versus endoscopic variceal ligation (EVL) plus non selective beta blocker (propanolol) in the secondary prophylaxis of variceal haemorrhage.

The primary end points were:

a) The rate of rebleeding in the two groups after the initial control.
b) The recurrence of esophageal varices on follow up endoscopy in the two groups;
c) Mortality rates in the two groups.

MATERIALS AND METHODS

This study was conducted in the Endoscopic unit of the Department of Surgery at Jawaharlal Nehru Medical College and Hospital, AMU, Aligarh from November 2011 to October 2013. A total of 80 haemodynamically stable patient with esophageal varieces were included in this study. The inclusion criteria were

a) Age more than 18 years;
b) Diagnosis of cirrhosis on the basis of clinical, biochemical & USG findings;
c) Esophageal varieces grade III, IV,V on endoscopy;[9]

Patients excluded from the study were

a) Haemodynamically unstable
b) Varices of grade I and grade II.
c) Refused to give consent to participate in the study.

Upper GI endoscopy was performed using Fuginon gastroduodenoscope and the endoscopic findings were digitally recorded. The varices were banded by using six shooter device.

Randomization was done by opening a sealed envelope containing allocation of groups.

Group A – Endoscopic Variceal Ligation alone

Group B - Endoscopic Variceal Ligation plus Propanolol; (40mg/per oral/per day)

In group A EVL was done by six band shooter device. In-group B EVL was done followed by oral propanolol therapy. Propanolol was started as 40 mg given once daily per orally and then dose was adjusted accordingly to reduce resting pulse rate upto 25% or 55 bpm.

At the time of enrolment, the severity of liver disease was classified according to Child-Pugh classification.[8] The size of esophageal varices was classified according to Tytgat classification9.

Endoscopy was performed at 1 week, 1 month and thereafter every 3 months to detect recurrence of esophageal varices. Variceal obliteration was defined as complete disappearance of esophageal varices or when the sizes of esophageal varices were too small to be ligated.

Rebleeding from esophageal varices was defined as the presence of hematemesis and/or melena and the bleeding site was identified to be from esophageal varices by emergency endoscopy.

Recurrence of esophageal varices was defined as reappearance of esophageal varices or enlargement of previous small-size varices that became accessible by EVL. When recurrent esophageal varices or rebleeding from esophageal varices were encountered, repeated sessions of EVL were performed in both groups until the varices were obliterated once again. End points included the following

1. Eradication of varices, defined as nonendoscopic visualization of veins in the lower third of the esophagus.
2. Recurrence of esophageal varices, defined as the observation of new varices after eradication had been achieved.
3. Complications of pharmacological and endoscopic treatments.
4. Treatment failure, defined as the inability to control active bleeding after attempts with the same method, recurrence of bleeding twice in a 3month period, death related to bleeding or complications.
5. Mortality

The statistical analysis was done using a 2x2 contingency table and p value was calculated by Fisher's exact test and their statistical significance was noted.

RESULTS

This study was conducted in the endoscopic unit of department of surgery, J N Medical College, AMU between November 2011 to October 2013. A total of 80 patients with cirrhosis and variceal bleeding met the inclusion criteria. After randomization the patients were placed in two groups A & B. Group A received EVL alone while Group B received EVL plus propanolol. Group A consisted of 35 patients and group B consisted of 45 patients. Both groups were comparable in age, sex, cause of cirrhosis, and severity of liver disease. The number of patients presenting with active bleeding and the size of esophageal varices before institution of EVL were also similar between both groups. Every patient was followed up for at least 1 year or until death. The median follow-up period was 13 months in group A and 11 months in group B. In the present study

group A had 29 male patients (83%) and 6 female patients (17%) whereas in Group B 38 patients were male (84%) and 7 were females (16%). The age range of the patients in this study was from 22-63 years, youngest patient was of 22 years of age while the eldest one was of 63 years. The highest no of patients were in 41-50 years(51%) and least number were in 61-70 years. The chief complaint in both the groups was haematemesis , melena , or both . Cause of cirrhosis was mainly alcohol induced, next being viral hepatitis and the remaining cryptogenic. In Group A 24 patients(69%) had alcohol induced cirrhosis, 11(31%) were cases of postviral cirrhosis and none(0%) had cryptogenic cirrhosis. In Group B 31 patients(69%) were of alcoholic cirrhosis , 12(27%) of post viral cirrhosis and 2(4%) belonged to cryptogenic group. According to Child Pugh classification Group A had 7 patients(20%) in Child A , 18 patients(51%) in Child B and 10 patients(29%) in Child C, while Group B had 8 patients(18%) in Child A , 26 patients(58%) in Child B and 11 patients(24%) in Child C. Grade III varices were present in 19 patients(54%) in Group A, 19 patients(42%) in Group B, Grade IV varices were present in 13 patients(37%) in Group A and 23 patients(51%) in Group B, Grade V varices were present in 3 patients(9%) in Group A and 3 patients(7%) in Group B. Complete variceal obliteration occurred in 22 patients (63%) in Group A and 34 patients(75%) in Group B. The p value came out to be <0.2316. The correlation was found to be insignificant i.e. both the groups met variceal obliteration without having significant benefit of one over the other. Average number of sessions required to achieve complete variceal obliteration in Group A was 2.09 + 0.74 and in Group B was 1.49 + 0.63. The difference was significant ($p < 0.01$) and patients in Group B required less number of sessions to achieve complete obliteration. 13 out of 35 patients(37%) in Group A had repeat bleeding while 8 out of 45 patients(18%) in Group B had rebleeding. The difference in the data in terms of rebleeding in both the groups was clinically insignificant ($p<0.05$). Average no of rebleeding episodes per patients in Group A was 0.37±0.49 and in Group B was 0.18 ± 0.39. Group B had reduction in the frequency of rebleeding episodes and the difference between them was very close to significance ($p<0.05$). Variceal recurrence after obliteration occurred in 17 patients(49%) in Group A and 9 patients(20%) in Group B. the difference between the two was clinically significant and Group B had less recurrence than Group A ($p < 0.08$). Treatment failure occurred in 5 patients (14%) in Group A and 3 patients(7%) in Group B. However there was no significant difference ($p<0.29$) regarding treatment failure in both the groups. Number of deaths in Group A was 3 and Group B was 2. patients died in group A because of rebleeding (3%), hepatic failure(3%) and HCC(3%) respectively while 1 patient in group B died of rebleeding(2%) and other due to hepatic failure(2%). The p was insignificant. Majority of patients in Group A(49%) had thoracic pain as the most frequent complain, others were dysphagia(29%), fatigue(6%), and faintness(3%). In Group B also patients mainly complained of thoracic pain(47%), followed by fatigue(18%), then dysphagia(11%), faintness(4%) and AV block(2%) (p value was insignificant)

	Group A n=35	**GROUP B n=45**
Male	29	38
Female	06	07

Cause of Cirrhosis

Alcoholic	**24**	**31**
Viral Heatitis	11	12
cryptogenic	00	02

Child Pugh Classification

A	07	08
B	18	26
C	10	11

Variceal Grading

Grade III	19	19
Grade IV	13	23
Grade V	03	03

Complete Variceal Obliteration	22	34	P<0.231
Avg No. Of Sessions Reqd. For Obliteration	2.09+0.74	1.49+0.63	p<0.231
Repeat Bleeding Episodes	13	08	p<0.073
Avg No. Of Rebleeding Episodes Per Patient	0.37+0.49	0.18+0.39	p<0.05
Variceal Recurrence	17	09	P<0.08
Treatment Failure	05	03	P<0.29

Cause of Death

Re-Bleeding	01	01
Hepatic failure	01	01
HCC	01	00

Adverse Effects

Faintess	01	02	P<1.000
Fatigue	02	08	P<0.172
Dysphagia	10	05	P<0.081
Esopageal Stenosis	00	00	P<0.000
AV Block	00	01	P<1.000

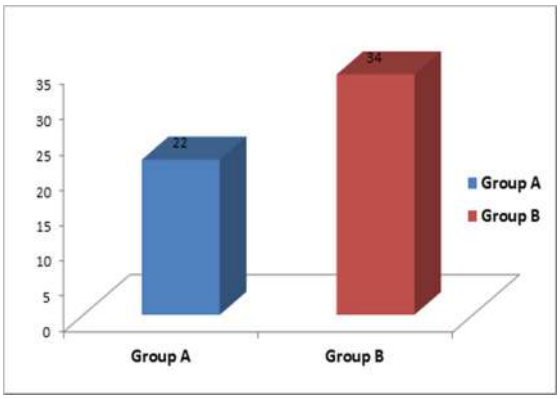


Figure 1: Number of Patients having Complete Variceal Obliteration in Both the Groups.

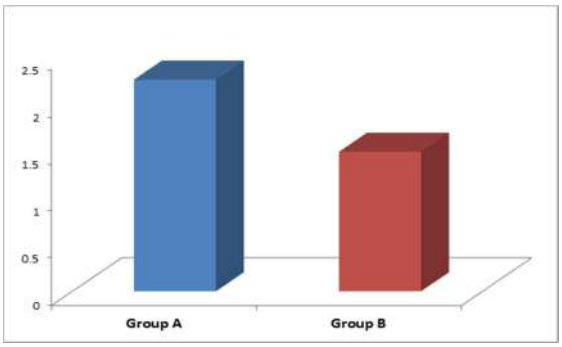


Figure 2: Average no. of sessions required for obliteration

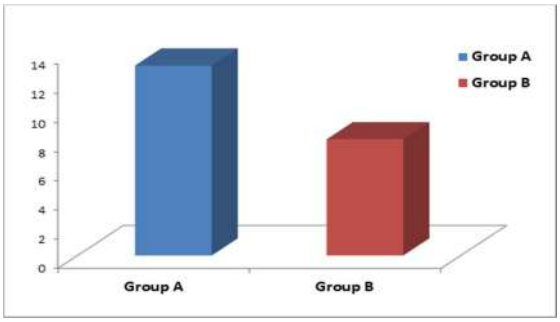


Figure 3: Repeat Bleeding Episodes in Both the Groups

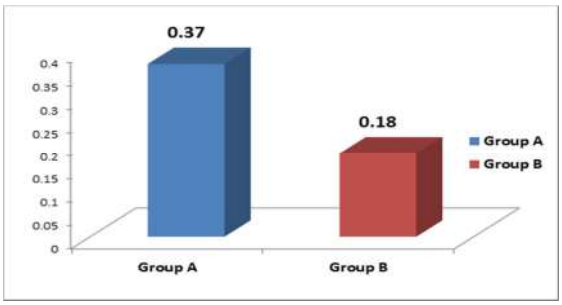


Figure 4: Average No. of Rebleeding Episodes per Patient in both the Groups

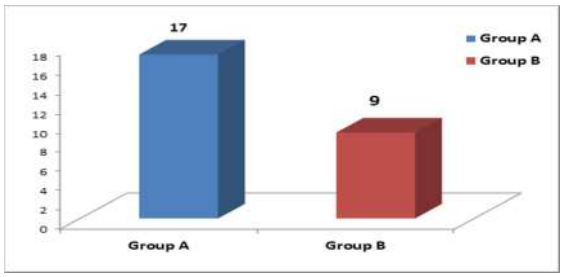


Figure 5: Variceal Recurrence

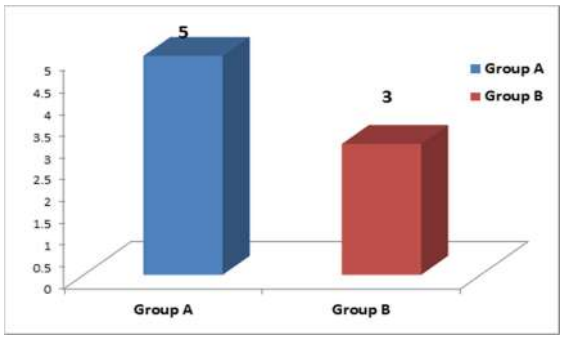
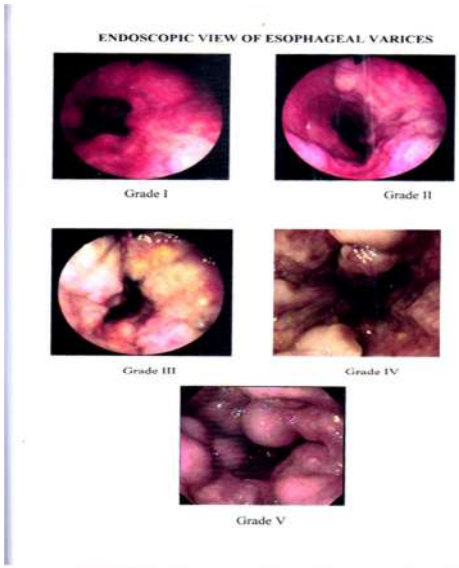
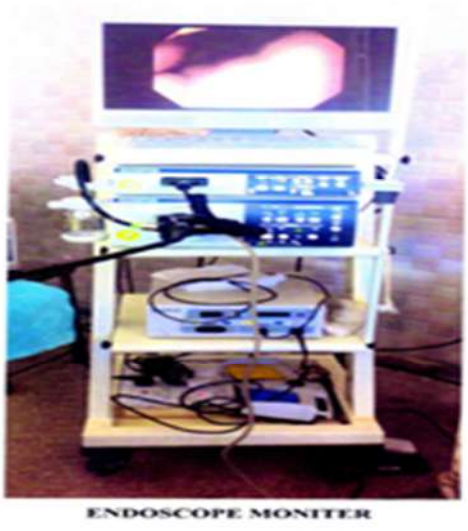


Figure 6: Treatment Failure





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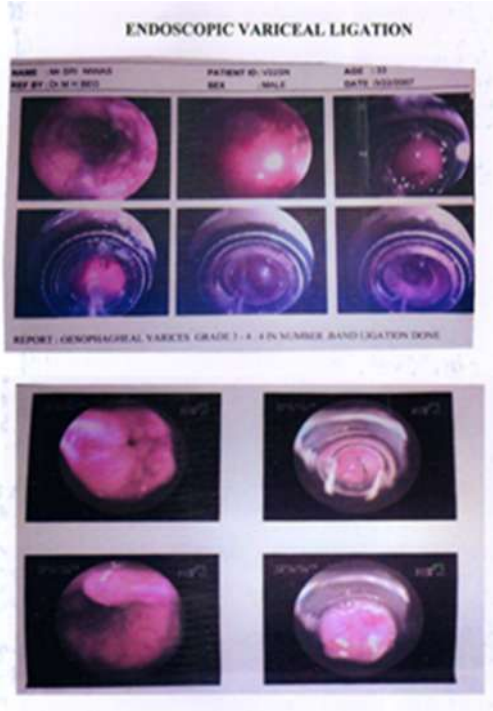

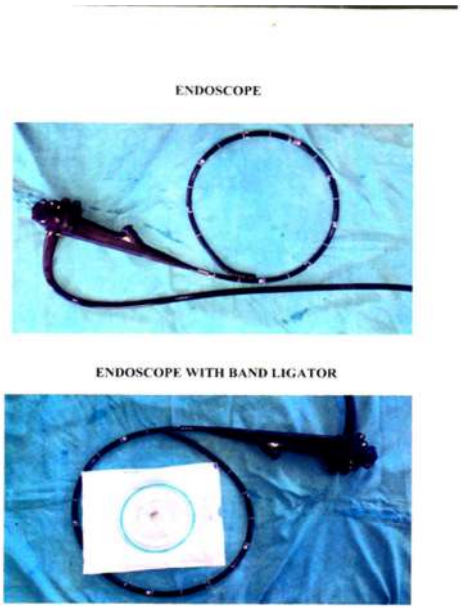

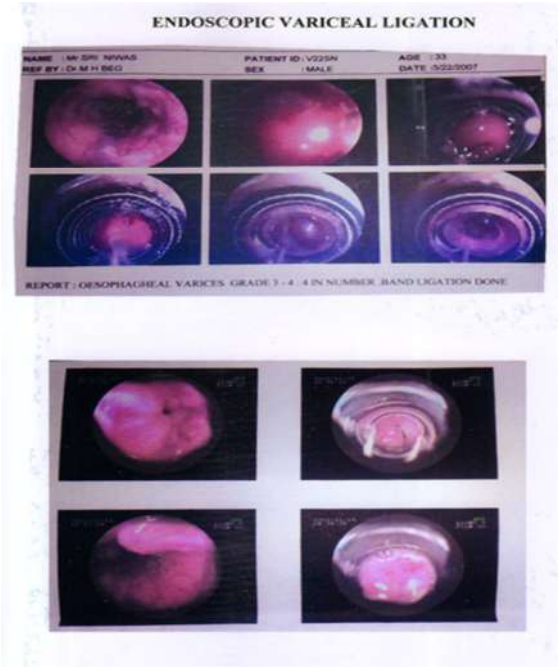

DISCUSSION

Variceal hemorrhage is perhaps the most devastating portal hypertension-related complication in patients with cirrhosis, occurring in up to 30% of such individuals during the course of their illness. Moreover, variceal hemorrhage leads to deterioration in liver function and is a common trigger for other complications of cirrhosis, such as bacterial infections or hepatorenal syndrome. Esophageal varices are present in nearly 30% to 40% of patients with compensated cirrhosis and in 60% of those with decompensated cirrhosis.[1]. Variceal hemorrhages occur only when there is a clinically significant portal hypertension, defined as HVPG > 12 mmHg2.

β-blocker & EVL have proven to be valuable methods for secondary prophylaxis of variceal bleeding .

The total number of patients in the study were 80. They were randomized into two groups. There are various randomized controlled trials in which randomization has been done to study the beneficial effect of combination therapy of EVL and beta blocker as compared to EVL alone in the secondary prophylaxis of esophageal varices.[10-12] In our study the two groups were as follows:

Group A in which EVL was done alone;

Group B in which propanolol was also given along with EVL.

Group A had 83% male patients and 17% female patients, while Group B had 84% male patients and 16% Female patients. The Male-Female ratio in Group was 4.8:1 and in Group B was 5.4:1. The age range of the patients in this study was from 22-63 years, the youngest patient was of 22 years and the eldest one was of 60 years. The mean age in our study was 49.32years. The main cause of cirrhosis in

our study in Group A was alcohol induced (69%), rest of the patients (31%) had cirrhosis due to post viral hepatitis. In Group B 69% of patients had alcohol induced cirrhosis, 27% had post viral hepatitis cirrhosis and 4% had other miscellaneous causes of cirrhosis. In the study by Gin Holo10, 67% patients presented with post viral hepatitis cirrhosis, 31% were case of alcoholic cirrhosis and 2% had other causes of cirrhosis. Severity of cirrhosis was decided by Child Pugh Classification. In our study 51% patients in Group A belonged to Child B, 29% were classified under Child C and 20% in Child A. In Group B 58% were classified in Child B, 24% in Child C and 18% in Child A. In Group A 54% patients had Grade III varices, 37% patients had Grade IV varices and 9% had Grade V varices.

In Group B 42% patients had Grade III varices, 51% patients had Grade IV varices and 7% had Grade V varices. In the present study we found significant reduction ($p<0.001$) in the rebleeding rate in Group B in which combination therapy with EVL and Propanolol was given compared to EVL alone. The reduction in rebleeding in the group of combined treatment was the result of the beneficial effects of the Propanolol which is known to reduce the portal pressure and splanchnic blood flow. Similar findings were reported by Lo et al associating EVL with Beta Blocker and Sucralfate compared with EVL alone.[10]

Our rebleeding rate of EVL alone was 37% which was within the usual range.[10,14,15] There have been 8 randomised controlled trials comparing EVL with EIS.[16,17-23] in 2 of these rebleeding rate in EVL group was low (16% and 18%) but the other studies reported rebleeding rates between 26% and 36%.[16,17-23] There have been 3 randomized controlled trials comparing β blocker plus Isosorbide mononitrate with EVL. Rebleeding rates were between 20% and 54%.[15,17,24] Our result showed a low rebleeding rate in the combined EVL plus Propanolol group (18%) as compared to EVL alone (37%), However the difference was not statistically significant.

An important point is the reappearance of new varices after initial eradication by EVL. In the present study, the association of propanolol was beneficial in slowing down the speed of varicial reappearance and reducing the number of endoscopic sessions required for obliteration of exsisting varices. The difference was statistically significant with p value <0.008 suggesting the beneficial effect of drug which could reduce the risk of late rebleeding. The combination therapy also delays the appearance of new varices after eradication. Our results were consistent with other studies and had similar outcomes which was seen in these studies.[8,10]

Treatment failure occurred in 10% of the patients. 62% of the patients belonged to Group A and 38% patients belonged to Group B, however the difference was not statistically significant.

In our study Group A had 9% mortality. 3% deaths were due to rebleeding, other 3% were due to hepatic failure and the remaining 3% were due to hepatocellular carcinoma. There was 4% death in Group B. 2% deaths were due to rebleeding and the rest 2% because of hepatic failure 6%. The result was statistically not significant. The findings were similar to the study done by De la Pena.[10]

Adverse effects in both the groups were minor and statistically insignificant. The result is compared to other studies.[10]

Nonetheless, the side effects and contraindications of beta blockers limit the area of their use. It is estimated that approximately 15-20% patients who take their medications will have complications.[17,21,25]

In conclusion our randomized controlled study showed that a combination therapy with beta blocker and Endoscopic Variceal Ligation (EVL) has statistically significant benefit ($p<0.001$) over Endoscopic Variceal Ligation (EVL) alone in the secondary prophylaxis of bleeding esophageal varices.

CONCLUSION

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