

# COMPARISON OF ENDOSCOPIC BAND LIGATION ALONE VERSUS PROPRANALOL PLUS ENDOSCOPIC BAND LIGATION FOR CONTROL OF REBLEEDING OESOPHAGEAL VARICES IN PATIENTS WITH PORTAL HYPERTENSION

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## ABSTRACT

**Objective:** To compare oesophageal varices band ligation alone versus the combination of beta blocker (Propranolol) plus band ligation.

**Materials and Methods:** A randomized control trial was carried out in 150 patients who presented with upper GI bleeding as a complication of cirrhosis of liver. After hemodynamic stabilization in the hospital with pharmacological options and/or band ligation procedures through endoscopy, the patients were randomly distributed in two separate groups at discharge from hospital. Group A had endoscopic band ligation every 4 weeks till obliteration of varices and group B were assigned in a group with both beta blocker and band ligation every 4 weeks. Patients were followed monthly for re-bleeding and other complications for six months.

**Results:** Ascites was observed in 103 (68.66%) patients and 11.3% had hepatic encephalopathy. High grade oesophageal varices was observed in 111 (74%), 26 (17.3%) patients had moderate grade varices, while 13 (8.6%) also had fundal varices. Band ligation was done in all the patients. Patients were randomly distributed in Group A and group B having included 76 and 74 patients respectively through the random table. Seven (4.6 %) patients were lost to follow up. Re-bleeding occurred in 19 (12.66%) after 6 months. A total of 35 (23.3 %) died after 6 months but only one death was attributed to re-bleeding. Re-bleeding occurred in 19 (25%) patients in Group A and none in Group B ( $p = 0.00$ ). Eleven (14.5%) patients in Group A and 8 patients in group B (10.8%) expired due to complications other than re-bleeding. A significant difference was observed in rebleeding pattern of two groups where more re-bleeding was noted in group A as compared to group B ( $p = 0.02$ ).

**Conclusion:** Endoscopic band ligation plus pharmacological treatment (Propranolol) significantly reduces re-bleeding in patients with oesophageal variceal bleed as compared to band ligation alone.

**Keywords:** Oesophageal Varices, Endoscopic band ligation, Propranolol

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## INTRODUCTION

Globally, cirrhosis of liver is one of the major causes of morbidity<sup>1</sup> with associated complications including ascites, encephalopathy and variceal bleed-

ing. Patients are prone to one of these complications in majority of cases.<sup>2</sup>

Oesophageal varices (EV) are present in 40% of compensated and 60% in decompensated cirrhotic patients at the time of diagnosis.<sup>3</sup> The reported incidence of new varices in cirrhotic patients is more than 5% per year. It has been observed in a multi-center study that hepatic vein pressure gradient (HVPG) above 10 mmHg, doubles the risk of developing EV.<sup>4</sup>

It is of utmost importance to formulate a strategy to prevent the high risk of re-bleeding and high mortality associated with cirrhosis. Endoscopic sclerotherapy of Varices is considered an effective remedy to control rebleed. This is done with the use of materials including ethanol and succinyl tetra-decoylsulphonate (STD) but it is associated with bleeding, pain and strictures development. Oesophageal Variceal Band ligation (EVBL) has largely replaced sclerotherapy

by proving its simplicity and effectiveness.<sup>5-7</sup> Propranolol (beta blocker) is one of the recommended pharmacological preparation to be used for effective control of portal hypertension<sup>9</sup> which reduces the chances of variceal bleeding.<sup>8</sup>

The effective use of band ligation versus band ligation along with chemoprophylaxis is still debatable.<sup>9</sup> Literature search of scientific studies showed varied evidence in favour of endoscopic therapy alone<sup>10</sup> versus endoscopic therapy with pharmacological treatment.<sup>11</sup> Many studies showed conflicting results when a combination of both therapies was used.<sup>12-14</sup> this study aimed to compare the efficacy of endoscopic ligation alone versus endoscopic ligation with propranolol prophylaxis in the prevention of rebleeding in patients presenting with oesophageal varices.<sup>10</sup>

## MATERIALS AND METHODS

A randomized control trial was conducted in 150 patients, admitted in the Gastroenterology division of the department of Medicine, Akhtar Saeed Trust hospital, Lahore. The sample size was calculated keeping margin of error less than 5% with a confidence interval 95% and an estimated re-bleeding rate of 30% from Raosoft.com/samplesize.html. The inclusion criteria consisted of patients who presented with hematemesis, melena, haematochezia, or blood admixture on nasogastric aspiration, secondary to

cirrhosis of liver. After getting Institution Research Board (IRB) clearance and informed consent of participants, patients were assessed and initial assessment was recorded on a standardized proforma. The variables included in tools of collection were related to sociodemographic profile, presenting signs and symptoms of disease and initial investigations. All patients included, received standard treatment with plasma volume replacement as needed, vasoactive drug octreotide 50µg bolus followed by 25-50µg/hr. infusion and antibiotics. Endoscopic therapy using Olympus GIF II 140 diagnostic endoscope was carried out in each patient. Oesophageal varices band ligation using Saeed' six shooters was performed. Patients were followed for bleeding control, after stabilization of haemoglobin and clearance of melena during the hospital stay.

At time of discharge, patients with successful control of bleeding were randomly distributed into two groups using the random table.

1. Group A patients underwent endoscopic therapy 4 weekly till obliteration of varices
2. Group B patients had repeated endoscopic therapy 4 weekly till obliteration of varices along with propranolol 20 mg BID.

Patients were followed monthly, for 6 months for a new episode of re-bleeding. Patients in both the groups with re-bleeding were offered standard hospital care as indicated.

Post procedure follow up was recorded on the same proforma and complications were also recorded during both procedures. The data collected was analyzed using Statistical Package for Social Sciences (SPSS version 13.0) for statistical analysis. Quantitative variables were presented in terms of their mean with standard deviation values and statistical difference was assessed through a student's t test. The qualitative variables were analyzed through chi square test. Out come in terms of re-bleeding or no re-bleeding in two groups of patients was compared using ANOVA (Analysis of variance). A p value below 0.05 was considered for significant interaction.

## RESULTS

Out of 150 patients included, 120 (80%) patients were of age > 40yrs while 30 patients (20%) were under 40 years. The male to female ratio was 2:1. Liver cirrhosis was diagnosed after admission in 16

(10.6%) patients while remaining 134 (89.33%) were already diagnosed cases of cirrhosis. Hematemesis along with melena was presenting complaint in 112 (74.66 %)

patients, while 27 (18 %) presented with hematemesis and 10 (6.9%), had melena only at the time of admission. The use of NSAIDs was found in 12 (8%) patients.

Laboratory workup revealed that 134 (89.33 %) patients were Hepatitis C positive while HBsAg was detected only in 5 (3.33 %) patients, 4 (2.66 %) patients were positive for both hepatitis B and C while 7 (4.66 %) were negative for both hepatitis B and C.

Patients were classified according to child Pugh Turcotte score. According to this score patients are classified in three categories depending upon levels of bilirubin in micro moles/L, Serum albumin in g/L, PT INR values, presence of Ascites and presence of hepatic encephalopathy. Depending upon the scores and category, one-year survival is calculated. 98 (65.3%) patients were in child class A, 41 (27.33%) in child class B while 11 (7.3%) patients had child class C. All patients after stabilization underwent upper G.I. endoscopy and had high-grade varices in 112 (74.6%). Stigmata of recent bleed on varices were present in 109 (72.6 %) patients. Fundal varices were present in 16 (10.66%) patients, of whom 7 (43.75 %) were of Gastroesophageal Varices (GOV 1), while 9 (56.25 %) were Gastroesophageal Varices (GOV 2). Portal hypertensive gastropathy was mild to moderate in 81 (54 %) patients while severe gastropathy was noted in 59 (39.33 %) patients and in 10 (6.66 %) patients there was no portal hypertensive gastropathy. All patients underwent oesophageal varices band ligation.

Once stabilized, patients were randomly allocated in two groups. Seventy-six (50.6 %) patients were in group A who were managed with only endoscopic band ligation, while 74 (49.33 %) patients were in other group B managed with band ligation first and added tablet propranolol, (20 mg BD) with band ligation as secondary prophylaxis. Male/female ratio was 2:1(100/50). Hepatitis C was detected as the cause of cirrhosis in 140 (93.3%), while Hepatitis B was detected only in 10 (6.66 %) patients. Forty (26.66 %) patients presented first time with upper GI bleeding. A total of 103 (68.66 %) patients accounted for ascites and 7 (11.3%) patients were diagnosed

with hepatic encephalopathy. High grade esophageal varices on endoscopy were present in 111 (74%) and 26 (17.3%) patients had moderate grade varices, while 13 (8.6%) also had fundal Varices. (Table 1)

Group A, all patients were admitted through the emergency, resuscitated and managed with all measures including octreotide and band ligation. Received 4 weekly sessions of endoscopic band ligation and a total of 76 (50.66 %) patients were enrolled. Below 40 years were 11 (14.47%) while above 40 years were 65 (85.53 %) patients. Anti. HCV positive were 70, four patients were HBs Ag positive and 2 patients were both Anti. HCV and HBs Ag positive. In 7 patients fundal varices was present. Nineteen patients (25%) had re-bleed in 6 months follow up. Eleven patients expired due to complications other than re-bleeding.

Group B, all were admitted through emergency, resuscitated and managed with all measures including octreotide, beta blockers and endoscopic band ligation every 4 weeks along with propranolol as measure of secondary prophylaxis and it included 74 (49.33 %) patients. Below 40 years were 16(21.2%) while above 40 years were 58 (78.37 %) patients. Seventy patients were Anti. HCV positive and 3 patients were HBs Ag positive. One patient was both Anti. HCV and HBs Ag positive. 6 patients also had fundal varix (GOV1). No patient had re-bleeding in six months follow up. Eight patients expired due to complications other than re-bleeding.

Both two groups compared for multiple clinical and laboratory variables and no difference was noted in terms of stage of liver disease.

Overall, 1 month follow up of 150 (100%) patients, 5 (3.3%) had re-bleeding while 10 (6.66%) patients expired with complication of cirrhosis other than variceal bleeding. Patients were followed monthly for 6 months. During this time period, 7 (4.6 %) patients were lost to follow up. During this follow up time, 13 (8.6%) patients presented with re-bleed at 3 months' time and 19 (12.66%) presented with same complaint after 6 months interval. Mortality rate was recorded upto 18.6% (28) after three months and 23.3 % (35) died after six months. Of the note, only one patient in total deaths was died due to re-bleeding problem. (Table 2)

**Table 1: Comparison of blood profile in two groups of patients. The value in parenthesis present standard deviation. \* sign presents the significant interaction of the variables.**

Variables	Group A (76)	Group B (74)	p value
Hemoglobin g/dl	8.75± (1.74)	8.6± (1.6)	0.789
Platelet count x 109/L	.75± (.31)	.66± (.27)	0.437
Prothrombin time (sec)	7.58± (11.48)	9.59± (13.5)	0.309
INR	2.11± (0.91)	2.13± (1.3)	0.924
Bilirubin mg/dl	1.34± (0.73)	1.38± (0.93)	0.745
Male/ Female	55/21	54/20	0.609
Encephalopathy patients	4	3	0.65
Systolic BP < 90mm	7	8	0.26
Patients with jaundice	16	11	0.466
Patients with ascites	52	51	0.028**
Serum albumin g/dl	3.21± (0.43)	3.41± (0.37)	0.002**
Serum creatinine mg/dl	1.29± (1.5)	1.12± (0.39)	0.325
Child Class A/B/C	51/23/7	47/18/5	0.32

**Table 2: Comparison of two groups of patients for rebleeding and mortality**

Outcome of interest	Group A	Group B	p-value
Re-bleeding after 3 months	8	5	0.02
Re-bleeding after 6 months	13	6	0.000
Deaths after 3 months	14	14	0.571
Deaths after 6 months	18	17	0.541

## DISCUSSION

The results of this study showed that the combination of endoscopic treatment with propranolol versus endoscopic treatment alone is more effective in reducing the episodes of rebleeding. For oesophageal varices, secondary to hepatic cirrhosis, band ligation is the preferred endoscopic treatment.<sup>15,16</sup> Fewer episodes of recurrent bleeding and lower mortality rates are observed with this procedure.<sup>17-19</sup>

Initially, sclerotherapy was used to be done for the prevention of variceal re-bleeding but it resulted in high blood loss during procedure and later on with stricture formation. This procedure has largely been replaced with repeated sessions of EVBL at 3-6 weeks interval which has a lower incidence of complications and re-bleeding.<sup>20</sup>

Tomassini. et.al conducted a study to assess the effectiveness of beta-blockers for the prevention of re-bleeding with oesophageal varices secondary to cirrhosis of liver. These patients were followed for

the period of one year for recurrence of bleeding episode. Significant the difference was observed in the occurrence of rebleeding in patients using propranolol as compared to those who were on placebo (p=0.05).<sup>21</sup>

In a similar study conducted by Engin. et al. endoscopic band ligation was performed every three weeks on twenty-one selected patients. This procedure was performed until complete obliteration of the varices or downgraded to level 1. It was observed that obliteration of varices took place in 11.57±6.8 weeks. Recurrence of varices was observed in a mean period of 34 months which is reflecting a high rate. Re-bleeding was also reported in 19.04% of the patients.<sup>22</sup>

Another randomized control trial to assess the efficacy of EVBL alone vs EVBL plus pharmacologic therapy was conducted on 120 patients. After a follow-up of 23 months, results showed that 75% of the patients had variceal obliteration in the com-

combination group as compared to endoscopic banding alone. Episodes of rebleeding were observed in 38% of the patients with the combination therapy group and 51% of the pharmacological therapy group with ( $p=0.21$ ).<sup>23</sup> Results of a meta-analysis revealed that, no significant difference was observed in episodes of re-bleeding when two groups of band ligation and pharmacological therapy alone were observed ( $RR=1.00$ , 95% CI 0.73-1.37). There was no significant difference observed in adverse events with both procedures.<sup>24,25</sup>

According to the guideline of the American Association for the study of liver disease (AASLD), a combination of nonselective  $\beta$ -blockers plus oesophageal varices band ligation (EVBL) is the recommended option for secondary prophylaxis of variceal haemorrhage. It is further recommended to adjust the dose of  $\beta$  blocker along with EVBL require repetition with a minimal interval of one to two weeks to achieve effective obliteration.<sup>26</sup>

In this study, the group analysis was strongly in favour of combined treatment as far as prevention of rebleeding is concerned ( $p < 0.0001$ ). It is a proven fact that propranolol has a beneficial effect in prevention of variceal rebleeding as it reduces portal hypertension.<sup>27,28</sup> Role of beta blockers has proven to reduce complications of cirrhosis as well. The conditions including ascites, progressive renal failure in case of hepatorenal syndrome (HRS), gastropathy due to portal hypertension, unprompted bacteriological peritonitis have shown high incidence with persistent use of beta blockers in many scientific studies.<sup>29,30</sup>

One of the limitations of this study was that a high proportion of the patients had advanced liver disease. With prolonged duration of study, higher Child-Pugh score at follow-up was observed. The incidence of side effect was similar in both treatment groups which were mentioned by other studies as well.<sup>22,26,28</sup>

Therefore, it was concluded that band ligation with combination of propranolol is more effective than band ligation alone in secondary prophylaxis of variceal bleeding, with a significant decrease in re-bleeding rates.

## CONCLUSIONS

Results of the current study clearly demonstrated

that endoscopic band ligation with combination of propranolol was a better option to control re-bleeding in patients presenting variceal bleeding comparing with band ligation alone.

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