

# Optimum Therapy for Secondary Prophylaxis of Variceal Bleeding Patient: Endoscopic, Pharmacological or Combination, A Randomized Study

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**Aims and Objective:** To compare pharmacological therapy alone, endoscopic band ligation every 2 weeks, band ligation every 4 weeks and combination of drugs and band ligation 2 weekly for prevention of rebleeding in patients being admitted with haematemesis and malena due to esophageal varices.

**Patients and Methods:** All patients being admitted with upper GI bleeding due to cirrhosis of liver were included in study after being stabilized with in hospital treatment and endoscopic band ligation. Patients were randomized in four groups, i.e. propranolol alone, endoscopic band ligation every 2 week till obliteration of varices, band ligation every 4 weeks and combination of beta blocker and band ligation every 2 weeks for secondary prophylaxis of GI bleed. Patients were followed monthly there after for rebleeding or other complications for six months.

**Results:** Total of 62 patients were included with male/female ratio 2.64/1 (45/17). Hepatitis C was the etiology of cirrhosis in 55 (88.7%) of them. Ascites was present in 25 (40.4%) patients while 7 (11.3%) had hepatic encephalopathy. On endoscopy high grade esophageal varices were noted in 51 (82.3%) of them and 13 (21%) also had fundal varices. Band ligation was done in all patients. Patients were randomized in four groups and numbers in groups were 14/13/15/18 respectively. After 6 months follow up 7 patients were lost to follow up. Rebleeding was noted in 5 (8.6%) patients at 3 months, and in 7 (12.7%) after 6 months. Total of 11 (18.6%) patients died after 3 months while 13 (23.6%) were not alive after 6 months but only one due to rebleeding. Significantly more rebleeding was noted in group 1, on propranolol only while no difference in other 3 groups was noted.

**Conclusion:** Endoscopic band ligation has shown better results for control of rebleeding in patients with variceal bleeding as compared to pharmacological treatment alone.

**Key Words:** Band ligation, Cirrhosis, Esophageal varices, Secondary prophylaxis.

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## Introduction

Cirrhosis of liver is among the leading causes of death all over the world. Complications which can be confronted in these patients include ascites, Porto systemic encephalopathy or variceal bleeding. In majority of cases patients succumb to one of these complications.<sup>1</sup>

Variceal bleeding is a life threatening complication in cirrhosis. Once bleeding from esophageal varices stop spontaneously or after medical and endoscopic intervention, there is 70% chance of rebleeding in next 6 months.<sup>2</sup> It is precisely why mortality attributed to varices related complications is around 20 – 25%.<sup>3</sup>

In view of high risk for rebleeding and high mortality associated with it, it is imperative to formulate a strategy to prevent rebleeding. Endoscopic sclerotherapy of varices with materials like ethanol, succinyl tetradeceoyal sulphonate (STD) has been shown to be effective in controlling rebleeding. But it is associated with multiple complications like post-procedure pain, rebleeding during endoscopy and strictures.<sup>4</sup> Sclerotherapy has mostly been replaced by band ligation of varices which is simple, complication free and effective way of managing these varices.<sup>5</sup>

Pharmacological options in this regard include beta

blockers like propranolol, carvedilol and nadolol. These drugs have shown good control of portal pressure with reduction in chances of variceal bleeding.<sup>6</sup>

Which of these options will work best for patients of variceal bleeding and is there any benefit of combination of these treatment modalities is the question which is still debatable. There are trials in favor of endoscopic therapy but other studies have shown better results with pharmacological treatment. Combination of both has also shown conflicting results in number of studies. Thereby it is imperative to conduct a randomized well designed study to identify the best suited option for secondary prophylaxis of patients with esophageal varices.

## Patients and Methods

We provisionally included patients being admitted in Department of Medicine Mayo Hospital Lahore with either haematemesis or malena or both. Patient had initial management in Accident and Emergency with double I/V lines, volume expanders in the form of blood or fresh frozen plasma, I/V antibiotics, I/V omeprazole and octreotide and close monitoring for maintenance of hemodynamic status.

Once stabilized, patients were shifted to endoscopy room. Patients who were found to have esophageal varices as source of bleed i.e. active spurting or oozing of blood from varices, presence of red wheel marks over varices or absence of any other potential source of bleeding on endoscopy were included in study. All of these patients underwent endoscopic therapy for varices in the form of esophageal varices band ligation with Saeed's six shooter®.

Patients were admitted at Medical floor after endoscopy. They were monitored for settling of malena, haematocrit, postural drop and development of rebleed or other complications of cirrhosis. Diagnosis of cirrhosis of liver was confirmed with investigations including complete blood count, liver function tests, viral serology for hepatitis B and C, ultrasound abdomen to look for liver size, texture, portal vein diameter, spleen size and presence or absence of ascites.

Once stable and recovered, patients were randomized in four groups for follow up management of esophageal varices at time of discharge. Group 1 was to receive propranolol tablet starting with 30mg/ day. Dose was to be increased on follow up till the maximum tolerated dose with upper limit of 160 mg/day. Desired reduction in portal pressure was to be confirmed by 25% reduction in baseline pulse rate of patient.

Group 2 was to undergo follow up band ligation on endoscopy every 2 weeks till complete obliteration of varices. Group 3 was treated with band ligation for secondary prophylaxis every 4 weeks till complete eradication of esophageal varices. Group 4 had band ligation on endoscopy 2 weekly along with propranolol tablet with a starting dose of 30 mg/day and increasing up to maximum tolerated dose to achieve 25% reduction in pulse rate.

Patients were followed initially after fortnight and monthly thereafter. On each follow up visit, patients were questioned regarding recurrence of haematemesis or malena, development of ascites or encephalopathy. Compliance with drugs was ensured. Endoscopic findings on follow up sessions were also recorded. All patients were to be followed for 6 months after being discharged from hospital. Those having rebleeding in the form of either haematemesis or malena after at least one follow up session of endoscopy or 1 month follow up time and confirmed to have variceal rebleed on endoscopy were considered as failure of treatment. Completion of 6 months follow up or rebleeding were primary end points of study. Data of all patients was recorded on pre-designed Performa.

### Statistical Analysis

Data was entered in PASW 18 (IBM®. SPSS®. Statistics). Numerical variables were described as mean  $\pm$  standard deviation (SD) while categorical variables as percentage. Unpaired two tail student t test and analysis of variance (ANOVA) was used to compare numerical variables among four groups of patients while chi square for categorical and qualitative variables.

### Results

Total of 62 patients were included in final analysis. Male/female ratio was 2.64/1 (45/17). Forty seven (75.8%) patients were above 40 years of age while 15 (24.2%) were less than 40 years old. Hepatitis C was responsible for cirrhosis in 55 (88.7%) patients while 2 (3.2%) had both hepatitis B and C and 5 (8.1%) patients were negative for both B and C. Cirrhosis was diagnosed less than one year before being admitted for upper GI bleeding in 51 (82.3%) patients.

Ascites was present at time of admission in 25 (40.4%) patients while 7 (11.3%) patients had porto-systemic encephalopathy. Tachycardia (pulse  $>$  100/min) was noted in 42 (67.7%) patients while hypotension (systolic BP  $<$  90 mm of Hg) was present in 24 (38.7%) of them. Jaundice was seen in 15 (24.2%) patients and 47 (75.8%) of them had splenomegaly on abdominal ultrasonography.

On endoscopy high grade esophageal varices were noted in 51 (82.3%) patients while 11 (17.7%) had low grade varices. Fundal varices were noted in 13 (21%) patients and 45 (72.6%) patients were found to have moderate to severe portal hypertensive gastropathy. All patients had band ligation.

After randomization, 14 (22.6%) patients were in group 1, 15 (24.2%) in group 2, 15 (24.2%) in group 3 and 18 (29%) patients were in group 4. Demographic characteristics, haematological and biochemical variables in patients of all four groups were comparable as shown in table 1.

Patients were followed thereafter for 6 months. Outcome was analyzed at 3 and 6 months of follow up. Patients lost to follow up were 4 after 3 months while 7 patients failed to complete 6 months follow up. At 3 months rebleeding was seen in 5 (8.6%) patients while total of 7 (12.7%) patients had re-bleeding after 6 months follow up. Total of 11 (18.6%) patient were dead at 3 months while 13 (23.6%) patients expired before completion of 6 months follow up however only one patient's death, of group 1 on propranolol only, was due to rebleeding.

When we compared all four groups for rebleeding, significantly more incidence of rebleeding was noted in group 1, group of patients on Propranolol only. (Table II). Relatively more patients died in group 2 but difference was not significant.

### Discussion

Decision regarding best treatment option for avoiding rebleeding in patients of cirrhosis of liver will enable us to improve patient care and will reduce economic burden on health service. Our study has revealed that patients who received follow up sessions of band ligation either alone or with beta blocker had better outcome as compared to those on propranolol alone.

Patch D et al in a well designed study identified that combination therapy of endoscopic intervention and beta blocker is superior as compared to propranolol alone.<sup>7</sup> Similar benefit of endoscopic therapy was noted by Gournay J et al.<sup>8</sup> In another study by Kumar A et al, re-bleeding

**Table 1:** Comparison of four groups of patients.

Variables	Group 1	Group 2	Group 3	Group 4	P value
Hemoglobin g/dl	9.03 ± (1.81)	8.36 ± (2.2)	7.9 ± (2.2)	7.04 ± (1.9)	NS
TLC/mm <sup>3</sup>	5.9 ± (3.02)	7.8 ± (3.6)	7.2 ± (3.2)	6.1 ± (2.3)	NS
Platelet count x 10 <sup>9</sup> /L	.75 ± (.31)	.66 ± (.27)	1.24 ± (.79)	.81 ± (.39)	0.05
Prothrombin time (sec)	19.5 ± (23)	16.5 ± (16.9)	9.8 ± (14.1)	12.0 ± (17.9)	0.03
INR	2.43 ± (1.08)	2.71 ± (1.84)	2.08 ± (1.6)	2.61 ± (2.08)	NS
Bilirubin mg/dl	1.48 ± (0.81)	1.35 ± (0.93)	1.24 ± (0.67)	1.78 ± (1.73)	NS
Patients of > 40 yrs age	13	9	14	11	0.03
Male/ Female	11/3	12/3	9/6	13/5	0.6
Patients with HCV	14	13	14	14	0.34
Encephalopathy patients	2	2	1	2	0.65
Systolic BP < 90mm	7	8	4	5	0.26
Patients with jaundice	4	3	4	4	0.94
Patients with ascites	6	4	7	8	0.40
Serum albumin g/dl	3.4 ± (0.42)	3.5 ± (0.44)	3.3 ± (0.43)	3.6 ± (0.42)	NS
Serum creatinine mg/dl	1.36 ± (0.49)	1.2 ± (0.57)	1.32 ± (0.66)	1.12 ± (0.56)	NS
Serum sodium (mEq/dl)	133 ± (3.1)	135.7 ± (4.9)	135.0 ± (4.9)	135.6 ± (5.7)	NS
Child Class A/B/C	5/5/3	6/7/7	6/7/2	8/8/2	0.98

Group 1: Propranolol alone

Group 2: Endoscopic band ligation every 2 weeks

Group 3: Endoscopic band ligation every 4 weeks

Group 4: Endoscopic band ligation every 2 weeks and propranolol

rate was 27% in combination group while it was 31% in those treated with band ligation alone in follow up and difference was not significant. Study concluded that addition of drugs does not affect outcome.<sup>9</sup> In a review article by Garcia-Pagan JC et al combination of pharmacological therapy and endoscopic treatment was regarded as best option to avoid rebleeding.<sup>10</sup> In a survey conducted on 122 Gastroenterologist and published in Canadian Journal of Gastroenterology, 70.9% of them were using combination of beta blockers and endoscopic band ligation.<sup>11</sup> There are studies which have attempted to combine sclerotherapy and band ligation for prevention of re-bleeding but no additional benefit was identified and this approach was associated with higher rate of complications.<sup>12</sup>

A Meta analysis regarding secondary prophylaxis was published in Annals of Internal Medicine in 2008. Analysis of 18 well designed studies comprising of 1125 patients revealed 19% re-bleeding rate with combination of drugs and band ligation while it was 28% with endoscopic therapy

**Table 2:** Comparison of 4 groups of patients for rebleeding and mortality.

	Group 1	Group 2	Group 3	Group 4	P value
Re-bleeding after 3 months	3	1	1	0	0.02
Re-bleeding after 6 months	4	1	2	0	0.01
Deaths after 3 months	2	5	2	2	0.20
Deaths after 6 months	3	5	3	2	0.56

alone.<sup>13</sup> This difference in outcome was statistically not found to be significant in this Meta analysis.

Endoscopic band ligation of varices has consistently shown better results as compared to pharmacological therapy alone. Combination of endoscopic therapy and beta blockers has not shown statistically superior results as compared to band ligation alone in our study. Considering the grave prognosis of rebleeding in cirrhotic patients, it would still be appropriate to manage patients with combination of drug and endoscopic treatment. Difference in interval between follow up sessions of band ligation, i.e. 2 weeks vs. 4 weeks has no effect in outcome in terms of rebleeding. It seems most cost effective to treat patients with combination of pro-

pranolol and endoscopic band ligation 2 weekly to avoid re-bleeding.

### References

1. Garcia-Tsao G. Current management of the complications of cirrhosis and portal hypertension: variceal hemorrhage, ascites, and spontaneous bacterial peritonitis. *Gastroenterology* 2001; 120: 726-48.
2. Khurram M, Saima J, Hamama-tul-Bushra K, Goraya F, Hasan Z. Endoscopic evaluation of 2484 patients with upper GI hemorrhage. *J Rawal Med Coll* 2003; 7: 89-91.
3. Lake JR, Howdle PD. Gastrointestinal hemorrhage and portal hypertension. In: O'Grady, Lake JR, Howdle PD, (edi). *Comprehensive hepatology*. 1st ed. London: Mosby, 2000. p. 1-13.
4. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. *Hepatology* 1995; 22: 332-54.
5. Villanueva C, Minana J, Ortiz J, Gallego A, Soriano G, Torras X, et al. Endoscopic ligation compared with combined treatment with nadolol and isosorbide mononitrate to prevent recurrent variceal bleeding. *N Engl J Med* 2001; 345: 647-55.
6. Gournay J, Masliah C, Martin T, Perrin D, Galmiche JP. Isosorbide mononitrate and propranolol compared with propranolol alone for the prevention of variceal rebleeding. *Hepatology* 2000; 31: 1239-45.
7. Patch D, Sabin CA, Goulis J, Gerunda G, Greenslade L, Merkel C, et al. A randomized-controlled trial of medical therapy versus endoscopic ligation for the prevention of variceal rebleeding in patients with cirrhosis. *Gastroenterology* 2002; 123: 1013-9.
8. Gournay J, Masliah C, Martin T, Perrin D, Galmiche JP. Isosorbide mononitrate and propranolol compared with propranolol alone for the prevention of variceal rebleeding. *Hepatology* 2000; 31: 1239-45.
9. Kumar A, Jha SK, Sharma P, Dubey S, Tyagi P, Sharma BC et al. Addition of propranolol and isosorbide mononitrate to endoscopic variceal ligation does not reduce variceal rebleeding incidence. *Gastroenterology* 2009; 137 (3): 892-901.
10. Garcia-Pagan JC, De Gottardi A, Bosch J. Review article: the modern management of portal hypertension-primary and secondary prophylaxis of variceal bleeding in cirrhotic patients. *Aliment Pharmacol Therapy* 2008; 28 (2): 178-86.
11. Cheung J, Wong W, Zandieh I, Leung Y, Lee SS, Ramji A et al. Acute management and secondary prophylaxis of esophageal variceal bleeding: a western Canadian survey. *Can J Gastroenterol* 2006; 20 (8): 531-4.
12. Singh P, Pooran N, Indaram A, Bank S. Combined ligation and sclerotherapy versus ligation alone for secondary prophylaxis of esophageal variceal bleeding: a Meta analysis. *Am J Gastroenterol*; 2002: 97 (3): 623-9.
13. Gonzalez R, Zamora J, Gomez-Camarero J, Molinero LM, Ban R and Albillos A. Meta analysis: Combination Endoscopic and drug therapy to prevent variceal rebleeding in cirrhosis. *Ann Intern Med* 2008; 149: 109-22.