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Original Article

Endoscopic Band Ligation vs Pharmacological Therapy or Both as Secondary Prophylaxis for Esophageal Variceal Bleeding in Chronic Liver Disease Patients

Muhammad Farooq,[1] Zafar Niaz,[2] Sami Ullah Mumtaz,[2] Ali Asad Khan,[2] Somia Iqtadar,[2] Sajid Abaidullah[2]

[1]District Headquarter Hospital, Multan, [2]King Edward Medical University, Lahore

Abstract

Objective: To compare beta blocker, endoscopic variceal band ligation (EVBL) and combination of both for prevention of re-bleeding of esophageal varices in chronic liver disease (CLD) patients.

Methods: This was a randomized controlled trial done at North Medical ward, Mayo hospital, Lahore for 6 months. After ethical approval, 320 patients of ages 18-80 years with either gender admitted with variceal bleed were included in study. After stabilizing with standard treatment of EVBL & beta blocker, patients were randomly divided in four groups, i.e. group I was put on propranolol, group II had EVBL every 2 weekly, group III had EVBL every 4 weekly and group IV had combination of 2 weekly EVBL with beta blocker. All patients were followed for six months. Quantitative variables in four groups were compared by ANOVA test whereas qualitative variables by chi-square test.

Results: After 6 months follow up re-bleeding was noted in 10 patients after one month (8 in group I, 2 in group II while no patient rebleed in group III and group IV). 61 (19.06%) patients rebleed after 3 months (40/7/14/0). 107 (33.43%) patients rebleed after 6 months (73/16/18/0 respectively). Significantly more re-bleeding occurred in group I patients whereas no rebleed occurred in group IV patients. No significant difference was noted in group II and III. Overall 7 patients lost the follow up.

Conclusion: Combination of beta blocker with EVBL is more effective than EVBL and beta blocker alone in secondary prophylaxis of variceal bleeding in CLD patients.

Key Words: Beta-Blocker, Variceal Bleed, EVBL, CLD, Secondary prophylaxis.

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Corresponding Author: Dr. Sami Ullah Mumtaz **Email:** drsumumtaz@gmail.com

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Introduction

Chronic liver disease is 11th commonest cause of death worldwide.[1] Its common complications are ascites, Porto systemic encephalopathy and upper gastrointestinal bleeding due to esophageal varices. In most patients one of these complications can develop at any stage.[2] At the time of diagnosis, almost 40% and 60% of CLD patients have esophageal varices. The incidence of new varices is <5% per annum. The CLD is grossly divided into compensated and decompensated stages. The ideal management of small varices must include measure of hepatic vein pressure gradient (HVPG). A decrease of ≥ 10% in HVPG by beta blocker therapy decreases the chances of progression to large varices, first variceal bleeding, and liver decompensation.[3] HVPG score >6 mmHg shows portal hypertension and HVPG >10 mmHg means clinically significant portal hypertension.[4] A recent study has shown that patients of CLD without esophageal varices (EV) with HVPG more than 10 mmHg, have double the risk of having EV as compared to those with an HVPG less than 10mmHg.[5]

Endoscopic variceal band ligation (EVBL) is recommended treatment of choice for bleeding esophageal varices, however active variceal bleeding is difficult to manage in the presence of massive bleeding with unclear view. Sclerotherapy is therefore used in such patients.[6] But it causes major complications like pain, strictures and rebleeding. Therefore EVBL is simple

and better way of managing these varices.[7] Apart from endoscopic procedures, there are other agents that are used to reduce portal pressure and rebleed in EV. These include carvedilol, propranolol, nadolol and isosorbid mononitrate.[8]

There is lot of debate on which treatment option or combination is best for the variceal bleeding. In a meta-analysis it was concluded that combination of beta blocker and nitrates does not offer any benefit in re-bleeding, and mortality as compared to EVBL or sclero-therapy.[9] In another recent study, beta blocker reduced variceal bleeding, and hence portal pressure.[10] Therefore we wanted to do a control trial in our population to find out best treatment for secondary prophylaxis of EV in CLD patients.

Methods:

This randomized controlled trial was carried out at North Medical Ward, Mayo hospital, Lahore for 6 months i.e. March to August 2018. After ethical approval 320 diagnosed patients of cirrhosis of ages 18-80 years with either gender presenting with variceal bleed were recruited in this study. All admitted patients with re-bleeding after initial control with endoscopic therapy along with vaso-active drugs, patients unfit for endo-scopy due to co-morbid illness like congestive cardiac failure, oro-pharangeal obstruction or unconsciousness and patients with contraindication for beta blockers like asthma, congestive cardiac failure, peripheral vascular disease and those with diabetes and hypoglycemia were excluded from the study. Sample size was calculated with confidence interval 95% with estimated re-bleed rate of 30% keeping margin of error less than 5% (Raosoft.com/samplesize.html) as described by Ezechi et al.[11] Written informed consent was taken from all patients. Demographic details like name, age, gender, address, symptoms and signs of the gastrointestinal bleeding, liver disease, co-morbids & labs were recorded on a predesigned proforma. After successful control of bleeding with EVBL and vasoactive agents, patients were randomized in four groups using random table. Group I patients received only propranolol starting from 30mg to 160mg/day to reduce pulse rate by 25% of baseline. Baseline pulse at discharge was noted. Patients were advised to record his pulse rate early morning before getting out of bed. These patients were followed fortnightly for 1 month and then monthly. In group II patients had repeated sessions of EVBL every 2 weekly till obliteration of varices. In group III patients underwent EVBL every 4 weekly till obliteration of varices. In group IV patients had weekly EVBL along with propranolol daily dose till obliteration of varices. All four group patients were followed for six months. 6 months bleeding free follow up was the end points of study. Patients in all four groups with rebleeding at any stage of the study were admitted in emergency and offered standard hospital care for variceal bleeding including octreotide, beta blocker, and band ligation.

Data was analyzed by SPSS-21. Quantitative variables were given as mean±SD and qualitative variables by frequency tables and percentages. Quantitative variables were compared by using ANOVA test whereas qualitative variables by chi-square test. P value ≤ 0.05 was taken as significant.

Results:

In our study there were 220 males and 100 females. 256 (80%) patients were > 40 years age and 64 patients (20%) < 40 years. 131 (40.9%) patients had tachycardia (pulse >100/min), 87 (27.2%) presented with systolic blood pressure <90mmHg and postural drop was noted in 194 (60.6%) patients. 286 (89.4%) patients had Anti HCV positive while HBsAg was present in 12(3.8%) patients, 8(2.5%) patients had both hepatitis B and C while 14 (4.4%) were both hepatitis B and C negative. 209 (65.3%) patients were of child class A, 87(27.2%) child class B while 24 (7.5%) had child class C. High grade esophageal varices were present in 238 patients (74.4%), (58 in group I, 55 in group II, 63 in group III and 62 in group IV).Fundal varices were present in 33 (10.4%) patients, of whom 13(39.39%) were of GOV1, while 20(66.6%) were GOV 2 (as one in group I, 6 in group II, 9 in group III and 17 in group IV). 127(39.68%) patients had severe portal hypertensive gastropathy, 173(54.06%) had mild to moderate while 20(6.25%) patients had no portal hypertensive gastropathy.

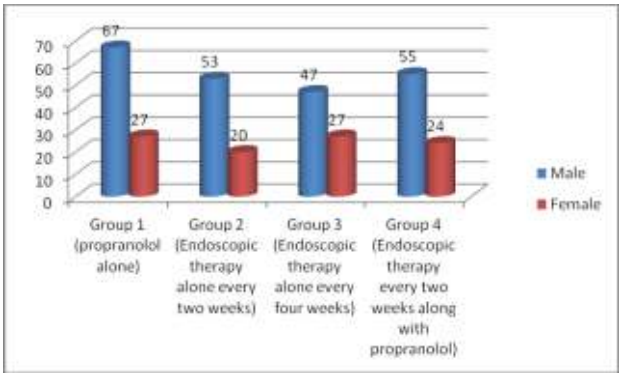

Fig. 1: *Gender Distribution Among The 4 Groups*

In group I, 8 patients had rebleeding at one month, 40 at three month, and 73(77.65%) at six months of follow up. In group II, 2 patients had rebleeding at one month, 7 at three months and 16(21.9%) at 6 months follow up. In group III, no patients had rebleeding at one month, 14 at three months and 18(24.32%) at six months of follow up. In group IV, no patient had rebleeding at one, three and six months of follow up. Five patients

Table 1: *Clinical & Laboratory Parameters of Patients*

Variables	Group I	Group II	Group III	Group IV	P value
Male/Female	67/27	53/20	47/27	53/26	0.609
Jaundice	16	11	10	7	0.466
Ascites	67	41	60	52	0.028
Encephalopathy	2	2	1	2	0.65
Systolic BP < 90mmHg	7	8	4	5	0.26
Hemoglobin g/dl	8.75± (1.74)	8.6 ± (1.6)	8.5 ± (1.98)	7.83 ± (1.71)	0.789
Platelet count x 10^9/L	.75 ± (.31)	.66 ± (.27)	1.24 ± (.79)	.81 ± (.39)	0.437
Prothrombin time (sec)	7.58±(11.48)	9.59 ± (13.5)	6.54± (9.63)	6.84 ± (11.3)	0.309
INR	2.11 ± (0.91)	2.13 ± (1.3)	1.84± (1.13)	2.08 ± (1.31)	0.924
Bilirubin mg/dl	1.34 ± (0.73)	1.38 ± (0.93)	1.15± (0.56)	1.3 ± (0.97)	0.745
Serum albumin g/dl	3.21 ± (0.43)	3.41 ± (0.37)	3.24± (0.32)	3.44 ± (0.37)	0.002
Serum creatinine mg/dl	1.29 ± (1.5)	1.12±(0.39)	1.06± (0.37)	1.04 ± (0.36)	0.325
BUN	22.46±(18.54)	21.99±(8.65)	19.5± (6.63)	19.92 ± (7.8)	0.84

Table 2: *Comparison of 4 Groups of Patients for Follow up Re-bleeding*

Follow up	Group I	Group II	Group III	Group IV	P value
Re-bleeding after 1 month	8	2	0	0*	0.05
Re-bleeding after 3 months	40	7	14	0*	0.02
Re-bleeding after 6 months	73	16	18	0*	0.000

expired due to complications other than rebleeding (3 at one month and 5 each at three and six months follow up).

Overall 1 month follow up of 320 (100%) patients, 10(3.1%) had rebleeding. After 3 months 61(19.1%) patients had rebleeding. After 6 months follow up rebleeding was present in 105 (32.8%) patients.

Discussion

Our study concluded that the combination of EVBL with propranolol is more effective for secondary prophylaxis of esophageal variceal bleed than EVBL or propranolol alone.There are a number of studies that support our results. Sarwar S. et al concluded in their study that EVBL is better treatment option than beta blocker for control of rebleeding due to lesser bleeding, complications & mortality.[12]

Natalie F et.al performed meta analysis of 17 randomized controlled trials to see the role of sclerotherapy and EVBL for control of variceal bleeding. Combination of β-blocker and EVBL significantly reduced rebleeding at 6, 12 and 24 months and overall as compared to EVBL alone (p<0.0001). They recommended combination therapy as the first line therapy for secondary prophylaxis of oesophageal varices.[13]

Gin- H. L et.al, in their study on 120 patients after a median follow up of 23 months found out that with combination therapy of EVBL and Beta Blocker 75% patients achieved variceal obliteration after a mean of 3.8 _ 0.6 sessions of band ligation while only 38% of the had rebleeding. On the other hand 51% patients of the beta blocker therapy had rebleeding (P = 0.21). They concluded that combination of EVBL with beta blocker was more effective than beta blocker alone for the control variceal rebleeding with similar side effects and mortality.[14]

Thiele M.et.al. analyzed 9 randomized control trials consisting of 955 patients. They noted that combination therapy reduced risk of rebleeding but overall no effect on mortality. Hence they concluded that combination of EVBL and beta blocker reduced the risk of rebleeding, but not overall mortality. Rebleeding rate was significantly lower with combination therapy in our patients as compared to medication alone, while no difference was noted in terms of mortality in our study as well.[15]

Cheung J.et.al. analyzed a meta analysis of 12 trials. EVBL reduced rebleeding compared with pharmacological therapy for trials. There were insignificant differences in rebleeding for combination of EVBL with pharmacological therapy to EVBL or pharmacological therapy alone. There was no difference in adverse events as well. They concluded that EVBL and pharmacological therapy alone are comparable for secondary control of rebleeding after EVBL which is similar to our study results.[16]

Kumar A et.al. studied that EVBL alone is sufficient

to prevent variceal rebleeding in cirrhotic and non-cirrhotic patients with variceal bleeding. Addition of Pharmacological agent to EVBL does not reduce the incidence of variceal rebleeding but increases severe side effects.[17]

According to guideline of AASLD, any cirrhotic patient after an episode of active variceal bleed should receive secondary prophylaxis. Combination of β-blockers and EVBL is the treatment of choice for secondary prophylaxis of variceal bleeding. TIPS should be considered in patients who had recurrent variceal bleeding despite combination therapy.[18]

Our study had certain limitations. It was a single centered study, with a small sample size.In future a large multi-centre study can be conducted for more validated results.

Conclusion

Combination therapy of EVBL and beta blocker is more effective than EVBL or beta blocker alone for secondary prophylaxis of variceal bleeding in CLD patients. There is no significant difference between EVBL done at 2 and 4 weeks for the control of variceal bleeding in cirrhotic patients. Therefore in future combination of EVBL and beta blocker should be used for secondary prophylaxis of variceal bleeding in CLD patients.

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