Comparison between Combination of Band ligation and Propranolol with Propranolol alone in Secondary Prophylaxis of Variceal bleed

Muhammad Hanif, Amir Hussain, Muhammad Aamer, Muhammad Adrees, Salman Shakoor

ABSTRACT

Introduction: Variceal bleeding is the one of the most important complication of cirrhosis of liver and also the common cause of death in cirrhotics. Cirrhotics with varices have 60% chance of re-bleeding within two years of the index bleed and each re-bleeding episode is associated with a 20% to 35% mortality risk. Endoscopic band ligation and pharmacotherapy are recommended therapeutic modalities for the prevention of secondary variceal re-bleeding. **Objective:** To compare the efficacy of combination of band ligation and propranolol with propranolol alone in secondary prevention of re-bleed in cirrhotics. **Study design:** Randomized control trial. **Study duration and settings:** The study was completed in Medical Unit-II Allied Hospital, Faisalabad for six months from 1st March 2015 to 31st August 2015. **Methods:** A total number of 60 cirrhotic patients with variceal bleed were randomized into two groups, each group containing 30 patients. Group A, receiving a combination of band ligation and propranolol and Group B, receiving propranolol alone. Any evidence of variceal bleed was observed during the research period confirmed by endoscopy. **Results:** 60 patients were included in the study with a mean age 56.97 ± 5.886. In Group A, 38 (63.3%) were male, 22 (36.7%) were female (table-5). In Group B, 13 (43.3%) were male and 17 (56.7%) were female (table-5). In Group A, bleeding occurred in 3 patients (10%). In Group B, bleeding occurred in 12 patients (40%). P-value was .007. **Conclusion:** Combination therapy of EBL+propranolol was superior in providing secondary prophylaxis than propranolol alone.

Keywords: Secondary prophylaxis, endoscopic band ligation, propranolol, variceal bleed.

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INTRODUCTION

Cirrhosis of liver is among the leading causes of death all over the world. Complications occurring in cirrhosis of liver are encephalopathy, spontaneous bacterial peritonitis, variceal bleed, hepatopulmonary & hepatorenal syndrome. Cirrhotics may develop any one of these complications with the passage of time. [1] there are different scoring systems which are being validated in variceal bleeding.[2]

Varices occur in 50% of cirrhotics patients at the rate of 10% per year.[3] Patients who have survived 1st episode of variceal bleed have 60% chances of re-bleeding within two years of that index bleed. Early re-bleeding occurs mostly in first month after band ligation and the associated mortality with each re-bleed is 30% to 50%.[4] EBL and pharmacotherapy are recommended therapeutic modalities for the secondary prevention of variceal re-bleeding.[5,6]

Endoscopic therapy comprises of sclerotherapy and band ligation. Recently, band ligation has replaced sclerotherapy as endoscopic therapy of choice because it is safer, more effective and associated with lower morbidity.[1,6] Pharmacological treatment includes non-selective β-blockers like propranolol & carvidilol. Non-selective β-blockers decrease portal pressure by decreasing cardiac output via β_1 receptor blockage and cause splanchnic vasoconstriction and decrease portal pressure.[6,7]

According to recent data, combination of band ligation and Beta Blocker reduces the risk of re-bleed more than beta blocker alone.[8] Meta-analysis of randomized controlled trials also suggested that combination of band ligation and β-blocker is superior to either band ligation or β-blocker alone.[9]

The recent joint guidelines of the American Association for the study of liver diseases and the American College of Gastroenterology on the management of gastroesophageal varices in cirrhosis indicate that the combination therapy of banding and β-blocker is best for preventing re-bleeding.[6]

In our local setting this combination is not being widely practiced, only band ligation or propranolol is given for secondary prophylaxis of variceal bleed. This study will reinforce the superiority of combination of EBL & propranolol over β-blocker alone.

Objective

To compare the efficacy of combination of band ligation and propranolol with propranolol alone in secondary prophylaxis of variceal re-bleed in cirrhotics.

Hypothesis

Combination of band ligation & propranolol is more effective than propranolol alone in secondary prophylaxis of variceal bleed.

METHODOLOGY

Study design: Randomized control trial.

Sampling Method: Non-probability consecutive sampling.

Study settings and duration: Medical Unit-II Allied Hospital Faisalabad, from 1st March 2015 to 31st August 2015.

Inclusion Criteria:

- All proven cases of de-compensated liver cirrhosis due to any cause confirmed by clinical examination (ascities, hepatic encephalopathy, dilated superficial abdominal veins, pedal edema), laboratory investigations (liver function tests with raised bilirubin, prolonged prothrombin time, S. Albumin less than 3.5g/dl) and ultrasound abdomen (shrunken liver, coarse echotexture, spleenomegaly).
- Age above 18 years.
- Having previous history of variceal bleeding confirmed by endoscopy.

Exclusion Criteria:

- Causes of upper GIT bleed other than variceal bleed. Like gastritis, bleeding ulcer, Mallory wiess tear, bleeding diathesis diagnosed by endoscopy and complete blood counts.
- 1st episode variceal bleed

Data Collection Procedure

After approval from ethical review committee, data was collected after informed consent to the patients. Patients fulfilling the inclusion criteria were taken from the Allied Hospital OPD, Indoor and Emergency and excluding the patients by applying exclusion criteria. They were randomly divided into two groups by using computer generated random number table. The endoscopic procedure was done.

Group A: Patients received endoscopic band ligation with Saeed's six shooter and propranolol.

Group B: Patients received propranolol alone. The dose of propranolol was adjusted such that in order to achieve 25% reduction in basal heart rate of the patients in both groups.

Any history of variceal bleed was asked in the form of malena or hematemesis from the patients.

Patients were followed up in both groups in next six months by taking their contact numbers and through routine follow up OPD visit. Follow up endoscopy was done if any variceal bleed occurred. Reduction in recurrent variceal bleeding was recorded in specially designed proforma at the end of six months duration.

RESULTS

A total number of 60 patients were included in this study. 38 (63.3%) were male and 22 (36.7%) were female (table-1). Minimum age included in this study was 40 years maximum age was 66 years with a mean age of 56.97 and standard deviation of 5.886 (table-3).

In Group A, 3 patients out of 30 had bleeding with a percentage of 10.0%. In Group B, 12 patients were having bleed with a percentage of 40%.

The results obtained were statistically significant. P-value was found to be .007.

Table 1: Gender frequency in the study

	Frequency	Percent
Male	38	63.3
Female	22	36.7
Total	60	100.0

Table 2: Percentages of gender in both groups in study

	Groups		Total
	Group A	Group B	
Male	25 83.3%	13 43.3%	38
Female	5 16.7%	17 56.7%	22
Total	30	30	60

Table 3: Descriptive statistics of age in patients

	N	Minimum	Maximum	Mean	Std. Deviation
Age	60	40	66	56.97	5.886

Table 4: Descriptive Statistics of ages in two groups

Groups (Age)	n	Minimum	Maximum	Mean	Std. Deviation
Group A	30	40	66	56.30	5.808
Group B	30	40	66	57.63	5.986

Table 5: Bleeding in two groups

		Groups		Total
		Group A	Group B	
Bleeding	Yes	3 10.0%	12 40.0%	15 25.0%
	No	27 90.0%	18 60.0%	45 75.0%
Total		30	30	60

Chi-Square value = 7.200
P-Value = .007

DISCUSSION

Various therapies are recommended in the prevention of variceal re-bleeding both for primary as well as for secondary variceal bleeding like pharmacotherapy, EBL, endoscopic sclerotherapy and TIPS. Most commonly prescribed are EBL and pharmacotherapy, as sclerotherapy and TIPS are associated with higher risk of complications. Pharmacotherapy includes non-selective β-blockers and nitrates. Nitrates are usually prescribed in the patients intolerant to β-blockers or having contraindications to the β-blockers. EBL is used as a single therapy for prophylaxis as well as in combination with the pharmacotherapy.[1,4,5]

The study conducted at Mayo hospital Lahore conducted by Sarwar S, et al on the secondary prophylaxis of variceal bleed included 60 patients of variceal bleed due to cirrhosis. The study period was six months. All the patients were divided into four groups i.e. propranolol alone 14 patients, EBL at two week intervals 13 patients, EBL at four week interval 15 patients, till obliteration of varices and combination of EBL and propranolol 18 patients. Re-bleeding was seen in 5 (8.6%) patients at three months out of which 3 were from propranolol group, 1 from each EBL group. At six months bleeding was observed in 7 (12.7%) patients, 4 from propranolol group and 1 from EBL at 2 week and 2 from EBL at four week interval, no bleeding occurred in the combination group even at three and six months interval. Re-bleeding was 50% in propranolol group with 50% reduction in re-bleeding, whereas it was 15% in EBL at 2 week with 85% reduction and 13% in EBL at 4 week with 87% reduction and no bleed observed in combination group with 100% reduction in re-bleeding.[1]

In my study, comparison was made between propranolol alone with combination of EBL and propranolol, 60 patients were divided into two groups each containing 30 patients, as compared to Sarwar's study where the group were small as 60 patients were divided in four groups and seven patients were lost during follow up. 10% re-bleeding was seen in my study in group of combination of EBL and propranolol and 90% reduction was seen. On the other hand 40% re-bleeding was seen in propranolol group with 60% reduction in re-bleeding. So my results are statistically significant as it was done on larger group.

In a meta-analysis study by Funakoshi N et al. 17 trials were included. Fourteen trials comparing sclerotherapy with combination of sclerotherapy and β-blockers. Among these 925 patients, 887 were analyzed: 435 were treated by sclerotherapy alone and 452 by sclerotherapy plus β-blocker. 38 were dropped as not fulfilling criteria. Three articles comparing banding ligation with combined banding ligation and β-blocker therapy were included, with a total of 256 patients. Among these 256 patients, 252 were analyzed, 4 dropped because of not fulfilling the criteria. One hundred and twenty-five were treated with EBL alone and 128 with EBL plus β-blockers. Follow-up period was from 2 to 39 months (mean16.6) for sclerotherapy group where as it was from <3 months to 16 months (mean 10.3). [10]

Re-bleeding was observed in 162 patients in the sclerotherapy group (39.2%) whereas 110 patients (25.4%) had re-bleed in the sclerotherapy plus β-blocker group. Four sclerotherapy trials found re-bleeding rates to be significantly lower in the sclerotherapy plus β-blocker group. In band ligation studies, 49 patients bleed in the band ligation only groups (39.5%), Whereas 22 patients bleed in the band ligation plus β-blocker group (17.2%).[10]

As compared to my study this was made on the EBL and sclerotherapy with and without β-blockers. However, the results obtained showed that combination of β-blockers and EBL is superior in preventing VB. In my study re-bleeding was 10%, 3 out of 30 patients bleed as compared with this of 17.2%, 22 out of 128 patients. P-value was found statistically significant, as in mine. Main difference was the comparison between EBL / sclerotherapy and combination of EBL / sclerotherapy and propranolol and not with the propranolol.

In systematic review study by Chenung J et al, twelve trials were included, 6 were between EBL and pharmacotherapy, 4 trials were between EBL + pharmacotherapy and EBL, 2 trials were between EBL + pharmacotherapy and pharmacotherapy. Pharmacotherapy used in all trials was β-blockers ± Isosorbide mononitrates. Outcome measures were re-bleeding and mortality. In EBL vs pharmacotherapy 698 patients were included with 25 patients lost in a follow-up. Mortality was almost same in this group 25% and 21%, similarly no significant difference was seen in terms of re-

bleeding from varices i.e. 39% and 40%. In EBL + pharmacotherapy vs EBL, 404 patients were included. Insignificant difference was observed in terms of mortality 13% and 15% while significant difference was noticed in reduction of re-bleeding 10% and 25%. In EBL + pharmacotherapy vs pharmacotherapy, 279 patients were included. No significant difference was seen in terms of mortality i.e. (20%) and (22%), while significant reduction in re-bleeding (22%) and (38%) was seen.[5]

As compared with my study re-bleeding incidence was decreased. Hence favoring my study that combination therapy was superior to pharmacotherapy. Outcome variables were more in this than mine, only difference was addition of Isosorbide mononitrates in pharmacotherapy group.

In Ravipati M, et al meta-analysis study, twenty six clinical trials with a total of 2159 patients, it was found that pharmacotherapy + endoscopic intervention was more effective than pharmacotherapy or endoscopic intervention alone in secondary prevention of VB. Outcome variables were mortality, mortality from VB, all-cause re-bleeding and re-bleeding from varices. Endoscopic intervention includes sclerotherapy and EBL and pharmacotherapy includes propranolol in most of trials, nadolol and sucralfate.

A total of 1252 patients from 12 studies were evaluated for the pharmacotherapy vs endoscopic intervention in cirrhotics. The risk of VB was found to be lower with endoscopic interventions in six studies with statistically significant in four of them and three studies showed decreased risk of VB. Fourteen randomized controlled trials including 1069 patients compared the effectiveness of combination pharmacotherapy and endoscopic interventions with endoscopic alone. Relative and cumulative risk of re-bleeding from varices was significantly lowered in combination therapy.[7]

This study favors my study indirectly as pharmacotherapy is as effective as endoscopic therapy in reducing the risk of VB, while combination therapy of pharmacotherapy and endoscopic intervention is more effective than endoscopic intervention alone, hence combination therapy would be better than pharmacotherapy as well. In this study outcome variables were more than mine and endoscopic intervention includes sclerotherapy as well, as we have discussed previously and in review as well that EBL is more effective than sclerotherapy regarding its technique and with less complications as well.

In another multi-center trial by Ouakaa-kchaou A, et al on variceal band ligation role in preventing VB, Six hundred and three patients were included in the study, secondary prophylaxis was given to 554 patients and primary prophylaxis to 49 patients. Total duration of period was 32 months. Propranolol was prescribed in association with EBL in 454 patients as a secondary prophylaxis of VB. VB occurred less commonly in patients on β-blockers (15%) and in (18%) patients without β-blockers that was not statistically significant.

Results obtained in this study statically do not favor my study because of many reasons as propranolol was not given to every patients on secondary prophylaxis of VB. Follow-up period was long. However, this study concludes that improvement in VB is seen in combination therapy but, more evaluation is still needed.[11]

In Gonzalez R, et al meta-analysis study on combination of endoscopy and drug therapy to prevent VB in cirrhotics, eighteen trials were evaluated comparing combination of endoscopic treatment and pharmacotherapy with endoscopic treatment alone. Combination therapy was more effective than endoscopic therapy at preventing re-bleeding in 7 trials and did not differ from endoscopic therapy in the other 11. Re-bleeding was less frequent in combination group (25%) and in (37%) with endoscopic therapy alone.[6]

In another study conducted by Bonilha DQ, et al, It was found that esophageal band ligation alone and esophageal band ligation plus beta blocker were effective in primary prophylaxis. However in variceal re-bleed, combination of esophageal band ligation and beta blocker was superior to beta blocker alone.[12]

This study favors my results that combination therapy of EBL and pharmacotherapy was more effective than pharmacotherapy group alone.

CONCLUSION

Variceal re-bleeding is one of the most occurring complication of DCLD and important cause of death as well. Various therapeutic modalities are available for prophylaxis of variceal re-bleed. EBL and pharmacotherapy are the commonly used treatment options. At the end of my research I concluded that propranolol and EBL are the good options for secondary prophylaxis of VB, but their use as a combination in secondary prophylaxis would be better than the propranolol alone. As both have different mechanisms of actions in preventing re-bleeding.

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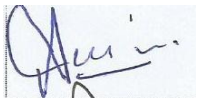
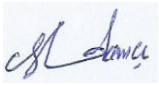
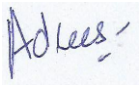
Prof. Dr. Amir Hussain Professor of Medicine FMU / Allied Hospital, Faisalabad	Supervised the Study	
Dr. Muhammad Aamer Assistant Professor, Medicine FMU / Allied Hospital, Faisalabad	References	
Dr. Muhammad Adrees Assistant Professor, Medicine FMU / Allied Hospital, Faisalabad	Statistical analysis	
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