International Journal of Advances in Medicine
Yadav AKS et al. Int J Adv Med. 2017 Aug;4(4):1053-1058
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: http://dx.doi.org/10.18203/2349-3933.ijam20173230

Original Research Article

Comparison of endoscopic variceal ligation and beta-blocker (carvedilol) plus nitrate for the primary prevention of variceal bleeding

Anilesh Kumar Singh Yadav[1], Priyadarshi B. P.[1]*, Gupta A. C.[1], Mahendra Singh[2], Ashok Kumar Verma[3], Vishal Gupta[1]

[1]Department of Medicine, GSVM Medical College, Kanpur Nagar, Uttar Pradesh, India
[2]Department of Pathology, GSVM Medical College, Kanpur Nagar, Uttar Pradesh, India
[3]Department of Radiology, GSVM Medical College, Kanpur Nagar, Uttar Pradesh, India

Received: 24 May 2017
Accepted: 23 June 2017

***Correspondence:**
Dr. Priyadarshi B. P.,
E-mail: njmsonline@gmail.com

ABSTRACT

Background: Esophageal variceal bleed is a major problem in patients with cirrhosis. Endoscopic sclerotherapy and variceal ligation are effective in stopping bleeding in up to 90% of patients. Beta-blocker (Carvedilol) + Isosorbide Mononitrate are promising alternative to other nonselective beta blocker or endoscopic band ligation for the prevention of first variceal bleeding of medium to large varices, which needs to be further explored.
Methods: The present study was an observational study in 200 patients at LLR and Associated Hospitals PG Department of Medicine GSVM Medical College, Kanpur. After randomization 120 patients underwent for Endoscopic Variceal ligation and 80 patients were put on beta-blocker (Carvedilol) + Isosorbide Mononitrate therapy for the primary prevention of variceal bleeding.
Results: Most common cause of portal hypertension was liver cirrhosis (in carvedilol plus isosorbide mononitrate group 70%, and it was 85%. in EVL group. Bleeding in patients of carvedilol plus isosorbide mononitrate was significantly lower (23.75%) than patients of EVL (60%) group. Reduction in bleeding was statistically highly significant (p value < 0.05). Mortality among patients receiving combination therapy with carvedilol plus isosorbide mononitrate was (12.5%) comparison to EVL (21.66%). Reduction in mortality was statistically not significant. (p value >0.05). Adverse effects were significantly lower among patients receiving combination therapy with carvedilol plus isosorbide mononitrate (38.75%) than patients of EVL (86.66%) group.
Conclusions: Both EVL and beta-blockers may be considered first-line treatment to prevent first variceal bleeding, whereas beta-blockers (carvedilol) plus isosorbide mononitrate may be the best choice for the prevention of re-bleeding.

Keywords: Beta-blocker (Carvedilol) + Isosorbide Mononitrate, Cirrhosis of liver, Endoscopic variceal ligation, Esophageal varices, Portal hypertension

INTRODUCTION

Portal hypertension in liver cirrhosis results from the anatomical changes and the development of contractile element in the liver vascular bed secondary to progressive hepatic fibrosis and formation of regenerative nodules.[1-2] The prevalence of esophageal varices in patients with compensated liver disease is approximately 30%, whereas their prevalence in decompensated patients is higher at 60%. The incidence of new esophageal varices ranges from 5% to 10% per year in published series.[3-5] The risk of death from a bleeding episode has declined

considerably over the last 20 years, mostly as a result of new effective treatments. However, the reported mortality rate, ranging from 12% to 44%, is still appreciable.[6-7]

Primary prevention of variceal hemorrhage remains an important and much-debated topic in the management of esophageal varices.[8]

EVL was recommended in the UK guidelines as the treatment of choice for acute oesophageal varies bleed, whereas some experts still favor using vasoactive drugs as first-line therapy.[9]

Beta blockers also prevent rebleeding and are used in secondary prophylaxis, eventually in combination with EVL.[10] Carvedilol has greater portal hypotensive effect than propranolol in patients with cirrhosis.[11] Carvedilol is a promising alternative to propranolol, waiting to gain popularity in the treatment of portal hypertension.[12]

Nitrates (isosorbide dinitrate and, most commonly, isosorbide mononitrate [ISMN]) have also been shown to reduce portal pressure by selective venodilation in the splanchnic circulation, via promoting reflex splanchnic vasoconstriction as a response to reduced mean arterial and cardiac filling pressures, and also by reducing intrahepatic resistance.[13,14]

Combined β-adrenergic blocker and 5-isosorbide mononitrate (BB + ISMN) was more effective than BBs alone in the prevention of esophageal variceal rebleeding.[15,16] It is still unknown whether drug therapy is superior to EBL for preventing variceal rebleeding. Several randomized controlled trials have shown different results.[17-20]

METHODS

The study was conducted in the KPS. P.G. Institute of Medicine, L.L.R. and Associated Hospitals, GSVM Medical College, Kanpur, from December 2014-November 2016. Those who attended emergency/outdoor and indoor clinic in the Department of Medicine of LLR. Hospital, GSVM, Medical College, Kanpur.

The patients aged of 16-75 years old either sex was enrolled. Those who were satisfied with inclusion criteria are selected as candidates for primary prevention of variceal bleed according to standard guidelines (AASLD, ACG, AGA, ASGE, WGO).[21]

The aim of the study was role of endoscopic variceal ligation and beta blocker (Carvidilol) plus nitrate for the primary prevention of variceal bleeding and comparison between them.

Detailed history of each patients was taken in details under following headings; age at onset of symptoms, time since diagnosis of portal hypertension, any precipitating factors, previous treatment (medical and/or surgical) and current medications if any.

Inclusion Criteria

- Patients with cirrhosis of liver without any past history of upper (or) lower gastro-intestinal bleed were included in the study. Diagnosis of cirrhosis based on a combination of history, clinical findings, impaired liver function tests, deranged coagulation profile and abdominal ultrasound
- Patients with clinical, analytical, ultrasonographic and pathological data compatible with cirrhosis and portal hypertension with esophageal varices without previous variceal bleeding
- Patients with endoscopic evidence of medium and large varices and patient with small varices with red wale signs, haematocystic spots, diffuse erythema, bluish colour, cherry red spots, or white - nipple spots.

Exclusion Criteria

- Pregnancy or lactation
- Advanced liver disease as indicated by (Child Pugh Score > 11)[22]
- Multinodular hepatocellular carcinoma or single hepatocellular carcinoma > 5 cm
- Previous porto-systemic shunts
- Concomitant gastrointestinal bleeding from sources / causes other than gastro-esophageal varices e.g. peptic ulcer, coagulation disorders etc.
- History of severe cardiovascular disease including acute myocardial infarction, atrio-ventricular block, heart failure, chronic peripheral ischemia, severe bradycardia, Sick sinus syndrome, shock or mean arterial pressure <55mmHg
- Patients of COPD / bronchial asthma
- Patients of renal failure (Serum creatinine > 2mg/dl)
- Diabetes mellitus
- Hypertension (BP≥140/90mmHg)
- Severe cardio-respiratory illness, sepsis or other debilitating illness.
- A known hypersensitivity to drug
- Chronic renal failure
- Age < 16 years >75 years.

Total number of 200 patients were randomly assigned into two treatment groups of EVL, and beta-blocker (carvedilol) plus Isosorbide mononitrate group with use of opaque, sealed envelopes that contained a treatment assignment derived from computer generated random numbers.

In the banded group/arm ligation was performed with the use of commercial devices - a multiband ligating device. Each varix was ligated at least once. Up to six bands per session were placed within the lower esophagus. Following randomization patients underwent EVL every

two weeks until eradication. EVL was performed as soon as possible following randomization, excluding the day of randomization.

In the beta-blocker (Carvedilol) plus isosorbide mononitrate group beta-blocker (Carvedilol) was given orally at an initial dose of 3.125 mg twice daily, increasing 6.25 mg till there was a 25% reduction of the basal heart rate or heart rate of 55 per minute was reached or a BP of 90/60 mmHg was attained. Along with beta-blocker (carvedilol), oral isosorbide mononitrate was started immediately thereafter. Over the course of one week, the dose was progressively increased from 20 mg once a day at bedtime to 40 mg twice a day, unless side effects such as headache or hypotension (systolic blood pressure of less than 85 mm Hg) appeared, in which case we gave the maximal dose tolerated.

The initial follow-up was scheduled at 1-week intervals till the doses of the drugs in respective treatment groups were stabilized. There after the follow-up were scheduled at every 6 weeks and then at 3 monthly intervals till a follow-up period of 1 year. Full biochemical and hematological profile was obtained every three months, Doppler ultrasonography and UGI endoscopy was performed every 6 months and full clinical examination was performed every 3 months. Compliance to treatment was assessed through direct questioning and collateral history from relatives. Where appropriate, continued alcohol consumption was assessed by direct questioning. Patients who were lost to follow up were censored. After recruitment patients were followed up till they reached primary end point (bleeding, complications, death) or till a period of 1 year.

Data was collected in a pretested and predesigned working proforma both at randomization and at follow up.

The primary end point for patients under primary prevention was the first variceal bleed, defined as hematemesis and/or melaena with endoscopic evidence of variceal bleeding or stigmata of recent hemorrhage and at least a 2 g/dL reduction in hemoglobin within 24 hours of admission. Patients who attained the primary end point were excluded from study.

Baseline parametric data were expressed as the mean ± standard deviation, and any differences in the groups were analyzed using an unpaired Student t test with Welch's correction. Differences in parametric data over time were analyzed using the paired sample t test. Nonparametric data were analyzed using the Fisher's exact test. A p value < 0.05 was taken as statistically significant.

RESULTS

A total of 200 patients were randomized to take part in the study. The patients who underwent Endoscopic Variceal Ligation were 120 and 80 patients were put on beta-blocker (carvedilol) plus Isosorbide Mononitrate combination therapy for the primary prevention of variceal bleeding.

Maximum numbers of patients belong to age group 46-60 years and minimum age group were 16-30 years in both groups.

The number of male participants in the Endoscopic variceal ligation (EVL) group and beta-blocker (Carvedilol) + Isosorbide mononitrate group were 92 and 60 respectively. Similarly, the number of female participants in EVL and beta-blocker (carvedilol) + Isosorbide mononitrate group were 28 and 20 respectively.

Table 1: Etiological distribution.

Etiology	Treatment given		Total
	EVL (120)	Beta-blocker (carvedilol) + Isosorbide mononitratate (80)	
EHPVO	10 (8.3%)	3 (3.75%)	13 (6.50%)
PVT	8 (6.66%)	7 (8.75%)	15 (7.50%)
Cirrhosis	102 (85%)	70 (87.5%)	172 (86.00)
Total	120	80	200

Out of 200 patients, cause of portal hypertension was Cirrhosis in 172 (86.00%) patients, portal vein thrombosis in 15 (7.50%) patients and extra hepatic portal vein obstruction in 13 (6.50%) patients the distribution among treatment groups.

173 patients of cirrhosis were included in the study out of which 63 (36.41 %) were of Child Pugh-Class A, 110 (63.58%) of class B. The distribution of these patients in the two treatment groups.

The difference was found significant (x^2 cal 25.436, P value <0.05). The treatment plan with beta-blocker (carvedilol) plus Isosorbide Mononitrate was better than EVL.

Table 2: Demographic and clinical profile.

Variables	EVL (120)	Beta-blocker (carvedilol) + Isosorbide mononitrate (80)
Sex ratio	Male: 92 Female: 28	Male: 58 Female: 22
Haematocrit (%)	34.91±5.41	23.22±3.14
S. Albumin (mg%)	3.07±1.02	1.88±0.48
S. Bilirubin (mg%)	1.84±1.16	0.93±0.64
Prothrombin time	17.6±5.11	11.64±3.08

Table 3: Bleeding in the treatment groups during follow up period of one year.

Bleeding	Treatment given		Total (200)
	EVL (120)	Beta-blocker (carvedilol) + Isosorbide mononitrate (80)	
Present	72 (60%)	19 (23.75%)	91 (45.50%)
Absent	48 (40%)	61 (76.25%)	109 (54.50%)

During follow up period of 1 year 26 (21.66%) patients of EVL group expired due to bleeding and other complication and in the beta-blocker (carvedilol) plus Isosorbide mononitrate group 10 (12.5%) patients expired due to bleeding and other complications (hepatic encephalopathy, hepato-renal syndrome, infections). The reduction in mortality was statistically not significant (x^2 cal 2.732 p value >0.05).

Infection occurred in 26 (21.16%) patients of EVL group and 5 (6.25%) patients in combination therapy with beta-blocker (carvedilol) plus isosorbide mononitrate group.

Table 4: Adverse effects in the treatment groups.

Adverse effects	Treatment given		Total
	EVL 120	Beta-blocker (Carvedilol) + Isosorbide mononitrate (80)	200
Present	104 (86.66%	31 (38.75%)	135 (67.50%)
Absent	16 (13.33%)	49 (61.25%)	65 (32.50)

Adverse effects of therapy were present in 104 (86.66%) patients out of 120 patients treated with EVL and 31 (38.75%) out of 80 patients treated with beta-blocker (carvedilol) plus isosorbide mononitrate. The adverse effect was statistically significantly lower among beta-blocker (carvedilol) plus isosorbide mononitrate group. (x^2 cal 100.71 P value <0.05).

DISCUSSION

The mean age of the study population in Endoscopic Variceal ligation was 48.0±0.04 while that in beta-blocker (Carvedilol) plus Isosorbide mononitrate group was 47.38±10.01.

Bleeding in the present study was found in 23.75% patients of Carvedilol plus Isosorbide mononitrate group and 60% patients of EVL Group. Statistically highly significant (P value <0.05).

In comparison with BB + ISMN with EVL in prophylaxis of esophageal variceal bleeding, there was no significant difference in the rate of rebleeding (relative risk (RR), 0.79; 95% CI: 0.62-1.00; P = 0.05 .23

Till date there is no trial for comparison of Endoscopic Variceal Ligation with carvedilol (NSBB) plus isosorbide mononitrate but study by Wang HM et al, for comparison of Endoscopic Variceal Ligation with nadolol (NSBB) plus isosorbide mononitrate found that bleeding in EVL group (10%), nadolol plus isosorbide mononitrate (19%).[24]

Cumulative risk of variceal bleeding was 18% in the nadolol group and 7.5% in the combined beta- blocker (nadolol) plus isosorbide mononitrate treatment group (95% CI for difference 1-25%). The risk of having a first cirrhosis-associated variceal bleed is lowered by about 50% by beta-blockers.[25] Comparing EVL with beta-blockers plus isosorbide mononitrate for secondary prevention, there was no effect on either gastrointestinal bleeding [RR 0.95 (95% CI 0.65 to 1.40)] or variceal bleeding [RR 0.89 (95% CI 0.53 to 1.49)].[26]

Mortality in the present study among Carvedilol plus isosorbide mononitrate (12.5%) was lower than the EVL group (21.66%). In comparison with BB + ISMN with EVL in prophylaxis of esophageal variceal the Bleeding-related mortality was (RR, 0.76; 95% CI: 0.31-1.42; P = 0.40), overall mortality (RR, 0.81; 95% CI: 0.61-1.08; P = 0.15) and complications were (RR, 1.26; 95% CI: 0.93-1.70; P = 0.13).[23]

All used β-blockers plus ISMN. Variceal rebleeding decreased with combined therapy (P <0.01) but rebleeding from oesophageal ulcers increased (P = 0.01). Overall, there was a trend towards lower rebleeding (RR = 0.76, 95% CI = 0.58-1.00) without effect on mortality (RR = 1.24, 95% CI = 0.90-1.70).[27]

The risk for all-cause deaths in the EVL group was significantly higher than in the medical group [RR 1.25 (95% CI 1.01 to 1.55)]; however, the rate of bleeding related deaths was unaffected [RR 1.16 (95% CI 0.68 to 1.97)].[26] In the present study subjects, who had decompensated cirrhosis with Child Pugh Score >12 were excluded to avoid higher mortality in the treatment groups.

In the present study Child Pugh Class, A, (37.57%) and Child Pugh Class B (62.43%).

In the present study, adverse effects among the beta-blocker (carvedilol) plus isosorbide mononitrate (38.75%) was lower than the EVL group (86.66%). Adverse effects were Headache (10), Dizziness (7), Hypotension (6), Nausea and vomiting (2) Fatigue (1) Weakness (1) Flushing (1) and Shortness of breath (1)

CONCLUSION

Endoscopic Variceal Ligation is purely mechanical method of obliterating varices and does not affect underlying pathophysiology (increased portal venous pressure).

Majority of the patients were males 76.66% in EVL group and 75% in beta-blocker (carvedilol) plus isosorbide mononitrate group). Bleeding in combination drug therapy with beta-blocker (carvedilol) plus isosorbide mononitrate was significantly lower (23.75%) than patients of EVL (60%). Reduction in bleeding was statistically highly significant (p value < 0.05). Mortality among patients receiving beta-blocker (carvedilol) was lower (15.31%) and combination therapy with beta-blocker (carvedilol) plus isosorbide mononitrate was (12.5%) than EVL (21.66%) Reduction in mortality was statistically not significant (p value > 0.05).

Combination therapy with beta-blocker (carvedilol) plus isosorbide mononitrate has been found to be better treatment modality compared to endoscopic variceal ligation in primary prevention of variceal bleeding, mortality, infections and adverse effects. This noninvasive modality is promising therapy in primary prevention of variceal bleeding.

The present study was conceived with idea that combination drug therapy with beta-blocker (carvedilol) plus isosorbide mononitrate is better mode of treatment for primary prevention of variceal bleeding than endoscopic variceal band ligation.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

REFERENCES

1. Iwakiri Y, Groszmann RJ. Vascular endothelial dysfunction in cirrhosis. J Hepatol. 2007;46(5):927-34.
2. Groszmann RJ, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. New Eng J Med. 2005;353(21):2254-61.
3. Merli M, Nicolini G, Angeloni S, Rinaldi V, De Santis A, Merkel C, et al. Incidence and natural history of small esophageal varices in cirrhotic patients. J Hepatol. 2003;38:266-72.
4. Pagliaro L, D'Amico G, Tine F, Pasta L. Prevention of upper gastrointestinal bleeding from portal hypertension in cirrhosis: Rationale for medical treatment. Dig Dis. 1992;10(suppl 1):56-64.
5. Christensen E, Fauerholdt L, Schlichting P, Juhl E, Poulsen H, Tygstrup N. Aspects of the natural history of gastrointestinal bleeding in cirrhosis and the effect of prednisone. Gastroenterol. 1981;81:944-52.
6. D'Amico G, De Franchis R. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. Hepatol. 2003;38:599-612.
7. Carbonell N, Pauwels A, Serfaty L, Fourdan O, Lévy VG, Poupon R. Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. Hepatol. 2004;40(3):652-9.
8. Zhang C, Thabut D, Kamath PS, Shah VH. Oesophageal varices in cirrhotic patients: from variceal screening to primary prophylaxis of the first oesophageal variceal bleeding. Liver Int 2011;31:108-119.
9. Jalan R, Hayes PC. UK guidelines on the management of variceal haemorrhage in cirrhotic patients. Gut 2000;46(Suppl):1-15.
10. Gluud LL, Klingenberg S, Nikolova D, Gluud C. Banding ligation versus beta-blockers as primary prophylaxis in esophageal varices: systematic review of randomized trials. Am J Gastroenterol. 2007;102:2842-8.
11. Banares R, Moitinho E, Matilla A, Garcia-Pagan JC, Lampreave JL, Piera C. Randomized comparison of long-term carvedilol and propranolol administration in the treatment of portal hypertension in cirrhosis. Hepatol. 2002;36:1367-73.
12. Tripathi D, Ferguson JW, Kochar N, Leithead JA, Therapondos G, McAvoy NC, et al. Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. Hepatol. 2009;50:825-33.
13. Dawson J, Gertsch P, Mosimann F, West R, Elias E. Endoscopic variceal pressure measurements: response to isosorbide dinitrate. Gut. 1985;26:843-7.
14. Navasa M, Chesta J, Bosch J, Rodes J. Reduction of portal pressure by isosorbide-5-mononitrate in patients with cirrhosis. Effects on splanchnic and systemic hemodynamics and liver function. Gastroenterol. 1989;96:1110-8.
15. Gournay J, Masliah C, Martin T, Perrin D, Galmiche JP. Isosorbide mononitrate and propranolol compared with propranolol alone for the prevention of variceal rebleeding. Hepatol. 2000;31:1239-45.
16. Zhang Q, Yuan R, Wang H. The randomized controlled trial of isosorbide mononitrate plus propranolol compared with propranolol alone for the prevention of variceal rebleeding. Zhonghua yi xue za zhi. 2002;82:1157-9.
17. Villanueva C, Miñana J, Ortiz J, Gallego A, Soriano G, Torras X, Sáinz S, 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.
18. Lo GH, Chen WC, Chen MH, Hsu PI, Lin CK, Tsai WL, et al. Banding ligation versus nadolol and isosorbide mononitrate for the prevention of esophageal variceal rebleeding. Gastroenterol. 2002;123:728-34.
19. 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. Gastroenterol. 2002;123:1013-9.

20. Romero G, Kravetz D, Argonz J, Vulcano C, Suarez A, Fassio E, et al. Comparative study between nadolol and 5-isosorbide mononitrate versus endoscopic band ligation plus sclerotherapy in the prevention of variceal rebleeding in cirrhotic patients: a randomized controlled trial. Aliment Pharmacol Ther. 2006;24:601-11.
21. World Gastroenterology Organisation practice guideline: Esophageal Varices. June 2008.
22. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the esophagus for bleeding esophageal varices. Br J Surg. 1973;60:646-64.
23. Ding SH, Liu J, Wang JP. Efficacy of beta-adrenergic blocker plus 5-isosorbide mononitrate and endoscopic band ligation for prophylaxis of esophageal variceal rebleeding: a meta-analysis. World J Gastroenterol. 2009;15(17):2151-5.
24. Huay-Min Wang, Gin-Ho Lo, Wen-Chi Chen, Wei-Lun Tsai, Hoi-Hung Chan, Lung-Chih Cheng, et al. Comparison of endoscopic variceal ligation and nadolol plus isosorbide-5-mononitrate in the prevention of first variceal bleeding in cirrhotic patients. J Chin Med Asso. 2006;69(10):453-60.
25. Merkel C, Marin R, Enzo E, Donada C, Cavallarin G, Torboli P, et al. Randomised trial of nadolol alone or with isosorbide mononitrate for primary prophylaxis of variceal bleeding in cirrhosis. Lancet. 1996;348(9043):1677-81.
26. Li L1, Yu C, Li Y. Endoscopic band ligation versus pharmacological therapy for variceal bleeding in cirrhosis: a meta-analysis. Liver Int. 2014;34(6):823-33.
27. Puente A1, Hernández-Gea V, Graupera I, Roque M, Colomo A, Poca M, et al. Drugs plus ligation to prevent rebleeding in cirrhosis: an updated systematic review. Liver Int. 2014;34(6):823-33.

Cite this article as: Yadav AKS, Priyadarshi BP, Gupta AC, Singh M, Verma AK, Gupta V. Comparison of endoscopic variceal ligation and beta-blocker (carvedilol) plus nitrate for the primary prevention of variceal bleeding.. Int J Adv Med 2017;4:1053-8.