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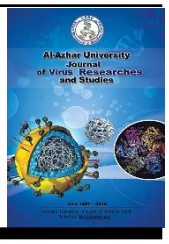

# Impact of Ulcer Healing Medications on Outcome after Esophageal Variceal Ligation in Patients with Liver Cirrhosis

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## Abstract

Endoscopic variceal band ligation (EVL) has been used successfully for the prophylaxis and therapy of variceal bleeding. Empirical treatment of post-band ulcers with medications used for treatment of peptic ulcers with or without prophylactic antibiotics is sometimes used with conflicting data regarding their beneficial effect ulcers' healing. Aim of the work is to study the impact of use of ulcer healing medications on healing and early UGIB from post EVL ulcers. 250 patients with liver cirrhosis and esophageal varices underwent EVL. Patients were randomly subdivided into five equal subgroups. Four types of regimens containing ulcer healing medications and antibiotics were used: Group 1: included patients treated by Pantoprazole 40 mg/day for 14 days, Group 2: included patients treated by Pantoprazole 40 mg/day for 14 days plus Rebamipide 100 mg three times daily for 14 days, Group 3: included patients treated by Pantoprazole 40 mg/day for 14 days plus Ciprofloxacin 750 mg/day for 7days, Group 4: included patients treated by Pantoprazole 40 mg/ day for 14 days plus Ciprofloxacin 750 mg/ day for 7days and Rebamipide 100 mg three times daily for 14 days and Group 5: included patients who did not receive any ulcer healing medications after EVL. Patients were re- evaluated by EGD after 4 weeks to assess healing of post band ulcers. Early UGIB (hematemesis, and/or melena) occurring within 4 weeks after EVL was recorded. 184 patients showed healing of post EVL ulcers while 66 patients had bad healing signs. Also, 196 patients developed UGIB after EVL while 54 patients passed the follow up period with no UGIB. None of the ulcer healing medications' regimens had significant impact on healing of post EVL ulcers nor development of UGIB. The use of ulcer healing medications to aid healing of post EVL ulcers is still questionable.

**Keywords:** Liver Cirrhosis, Esophageal Varices, Endoscopic variceal ligation, post-band ulcers.

## 1. Introduction

Esophageal varices are one of the most serious complications of portal hypertension detected in about 50% of patients with liver cirrhosis. Approximately, 5–15% of these patients with liver cirrhosis develop newly formed

varices or worsening of varices each year [1]. Endoscopic variceal band ligation (EVL) has been used successfully for the prophylaxis and therapy against variceal bleeding, and it significantly reduced the incidence of first and recurrent variceal hemorrhages [2]. The ligated tissue falls off within few days after the application of the bands over the varices. Following the sloughing of varices, shallow esophageal ulcers are formed at ligated sites of esophageal varices [3]. Endoscopic variceal ligation is now considered to be more effective and have fewer side effects than sclerotherapy [4]. Proton-pump inhibitors (PPIs) are the most effective medication used for the treatment of peptic ulcers. However, studies have shown that PPI monotherapy does not heal ulcers sufficiently specially induced ulcers like the endoscopic submucosal dissection induced ulcers [5].

Increased understanding of the mucosal defense system prompted the development of mucoprotective agents for clinical use. Rebamipide, a novel mucosal-protective and ulcer-healing drug, is now widely prescribed in East Asia. Studies have indicated that Rebamipide is effective in the treatment of gastric ulcers and decreasing its recurrence [6].

Combining PPIs and Rebamipide may have beneficial effect on healing of ulcers. PPIs decrease gastric acid production, whereas Rebamipide stimulates the production of prostaglandins, epidermal growth factor, and nitric oxide, and decreases the level of oxygen-free radicals [7]. Also, bacterial infections are common in patients with liver cirrhosis and variceal bleeding, with increased risk of death in these patients [8]. In one study, early rebleeding was present in 43.5% of patients with bacterial infection compared to 9.8% in those without infection [9]. Treatment of EVL ulcers has been mostly empirical with drugs used for treatment of peptic ulcer diseases. [10]. However, there are only few studies that investigated whether proton pump Inhibitors (PPIs) can lower the risk of bleeding after EVL. It is very difficult to demonstrate the efficacy of PPIs, because variceal bleeding is more closely associated with an increase in portal pressure and poor hepatic function [11].

## 2. Patients and Methods

This This study was conducted on 250 patients with liver cirrhosis and esophageal varices who underwent esophageal variceal ligation. Patients were recruited from Endoscopy Unit of Hepatology and Gastroentrology Department, National Liver Institute, Menofia University, Egypt, in the period between February 2019 and January 2020.

Patients with secondary liver malignancies, those with peptic gastric or duodenal ulcers seen during endoscopy, those with recent active upper gastrointestinal tract bleeding and those with liver cirrhosis due to other etiologies than HCV were excluded from this study.

For each patient, full medical history was taken with detailed clinical examination. Base-line assessment of patients' laboratory data was collected including Liver function tests [Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), serum bilirubin (total and direct), serum albumin, international normalized ratio (INR) and serum alpha fetoprotein (AFP)], Complete Blood count (CBC) including hemoglobin levels (Hb), hematocrit (HCT), white blood cells count (WBCs) and platelets (PLTs) counts and kidney function tests (blood urea and serum creatinine). Imaging evaluation was done for all patients using abdominal ultrasonography (U/S).

Esophagogastroduodenoscopy (EGD) was done for all patients and endoscopic band ligation for esophageal varices was done using multi-shooter ligator of rubber bands. Included patients of the study were randomly subdivided into five equal subgroups (with 50 patients in each group) by simple randomization method. Five types of regimens of ulcer healing

medications and antibiotics were used with aim to treat ulcers formed after band ligation:

**Group 1**: included patients treated by Pantoprazole 40 mg per day for 14 days, **Group 2:** included patients treated by Pantoprazole 40 mg per day for 14 days plus Rebamipide 100 mg three times daily for 14 days, **Group 3:** included patients treated by Pantoprazole 40 mg per day for 14 days plus Ciprofloxacin 750 mg per day for 7days, **Group 4:** included patients treated by Pantoprazole 40 mg per day for 14 days plus Ciprofloxacin 750 mg per day for 7days and Rebamipide 100 mg three times daily for 14 days and **Group 5:** included patients who did not receive any Ulcer Healing Regimens after esophageal variceal ligation.

Patients were followed up and reevaluated one week after esophageal band ligation by detailed history stressing on symptoms of upper gastrointestinal bleeding (UGIB) (Hematemesis, and/or melena), Chest pain, dysphagia, vomiting and compliance of patients in using ulcer healing medications. Gastrointestinal bleeding (hematemesis, and/or melena) occurring within 4 weeks after EVL was always checked. Patients who developed UGIB after EVL were admitted to the hospital of National liver institute and after initial resuscitation, they underwent second endoscopic examination by EGD.

After 4 weeks of the initial EVL, patients who didn't develop early UGIB were re-evaluated by EGD to assess regression of the number and grade of varices, number and size of ulcers and other endoscopic finding.

Patient's data were collected, tabulated and subjected to statistical analysis to study factors affecting both healing of post-band ulcers and UGIB after EVL including the impact of use of ulcer healing aiding medications.

## 3. Results

The enrolled patients in this study were 190 males (76%) and 60 females (24 %). Among these patients, 18 patients (7.2%) had hepatocellular carcinoma (HCC). According to staging of liver cirrhosis for studied patients, 188 patients were of class A (75.2%), 50 of class B (20%) and 12 of class C (4.8%) of Child-Pugh score with mean value of MELD score13.068 ± 3.702. Initial assessment of patients' demographics, their base-line laboratory and ultrasound findings are illustrated in tables 1 and 2.

**Table (1):** Shows demographics and base-line laboratory and ultrasound data of all enrolled patients on initial assessment.

| Variable | Range | Mean ± SD |
|---|---|---|
| **Age** | 43- 79 | 59.340 ±8.490 |
| **HBA1c** | 6.2-12.8 | 8.850 ± 1.493 |
| **Spleen diameter** | 11.7-22.7 | 17.761 ± 2.262 |
| **PV Diameter** | 1.2-2.2 | 1.703 ± 0.173 |
| **Child-Pugh score** | 4-11 | 6.092 ± 1.319 |
| **MELD score** | 8-23 | 13.068 ± 3.702 |
| **Albumin** | 1.6 -4.8 | 3.370 ± 0.595 |
| **Bilirubin** | 0.6 – 2.7 | 1.266 ± 0.446 |
| **INR** | 1.06 -1.75 | 1.401 ± 0.166 |
| **ALT** | 12 -134 | 43.012 ± 18.303 |
| **AST** | 12 – 117 | 45.828 ± 17.867 |
| **Hemoglobin** | 8.2 – 16.3 | 11.088 ± 1.270 |
| **WBCs** | 4– 11.3 | 6.594 ± 1.788 |
| **Platelets count** | 90 – 154 | 85.712 ± 21.309 |
| **Creatinine** | 0.6 – 2.6 | 1.171 ± 0.365 |
| **BUN** | 10.2 – 38.1 | 15.13 ± 3.740 |

Enrolled patients were followed up for 4 weeks after the initial session of endoscopic EVL. During this period, 54 patients (21.6%) had an attack of upper gastrointestinal bleeding (UGIB) in the form of hematemesis and/or melena while 196 patients (78.4%) passed this period without any evidence of gastrointestinal bleeding. Patients who developed early UGIB were admitted to the hospital of National liver institute and after initial resuscitation, they underwent urgent second endoscopic sessions. The 196 patients who didn't develop UGIB were re-valuated at the end of follow up period by a second endoscopic examination. On the second endoscopic examination of all studied patients (including those who had UGIB during the follow up period), 184 patients (73.6%) showed good healing of post EVL ulcers, while 66 patients (26.4%) still had necrosis or inflammation at the sites of variceal ligation indicating inadequate ulcers' healing.

**Table (2):** Correlation between patients' demographics, base-line U/S and endoscopic parameters and healing of post EVL ulcers.

| variable | | Healing of post EVL ulcers | | | | | | Chi-Square | |
|---|---|---|---|---|---|---|---|---|---|
| | | No (n= 66) | | Yes (n=184) | | Total (n=250) | | | |
| | | N | % | N | % | N | % | $X^2$ | P-value |
| **Gender** | **Female** | 50 | 27.17 | 10 | 15.15 | 60 | 24.00 | 3.849 | 0.050* |
| | **Male** | 134 | 72.83 | 56 | 84.85 | 190 | 76.00 | | |
| **Liver disease** | **No HCC** | 182 | 98.91 | 50 | 75.76 | 232 | 92.80 | 38.98 | <0.001* |
| | **HCC** | 2 | 1.09 | 16 | 24.24 | 18 | 7.20 | | |
| **Child-Pugh score** | **CTP A** | 165 | 89.67 | 23 | 34.85 | 188 | 75.20 | 82.10 | <0.001* |
| | **CTP B** | 18 | 9.78 | 32 | 48.48 | 50 | 20.00 | | |
| | **CTP C** | 1 | 0.54 | 11 | 16.67 | 12 | 4.80 | | |
| **Ascites** | **No** | 166 | 90.22 | 23 | 34.85 | 189 | 75.60 | 82.55 | <0.001* |
| | **Yes** | 18 | 12.76 | 43 | 66.67 | 61 | 24.4 | | |
| **DM** | **No** | 98 | 53.26 | 11 | 16.67 | 109 | 43.60 | 26.45 | <0.001* |
| | **Yes** | 86 | 46.74 | 55 | 83.33 | 141 | 56.40 | | |
| **O.V Number** | **One** | 2 | 1.09 | 0 | 0.00 | 2 | 0.80 | 20.99 | <0.001* |
| | **Two** | 95 | 51.63 | 19 | 28.79 | 114 | 45.60 | | |
| | **Three** | 67 | 36.41 | 25 | 37.88 | 92 | 36.80 | | |
| | **Four** | 17 | 9.24 | 18 | 27.27 | 35 | 14.00 | | |
| | **Five** | 3 | 1.63 | 4 | 6.06 | 7 | 2.80 | | |
| **O.V Size** | **Small** | 22 | 11.96 | 4 | 6.06 | 26 | 10.40 | 4.31 | 0.115 |
| | **Medium** | 39 | 21.20 | 9 | 13.64 | 48 | 19.20 | | |
| | **Large** | 123 | 66.85 | 53 | 80.30 | 176 | 70.40 | | |
| **IGV** | **No** | 89 | 48.37 | 5 | 7.58 | 94 | 37.60 | 34.45 | <0.001* |
| | **Yes** | 95 | 51.63 | 61 | 92.42 | 156 | 62.40 | | |

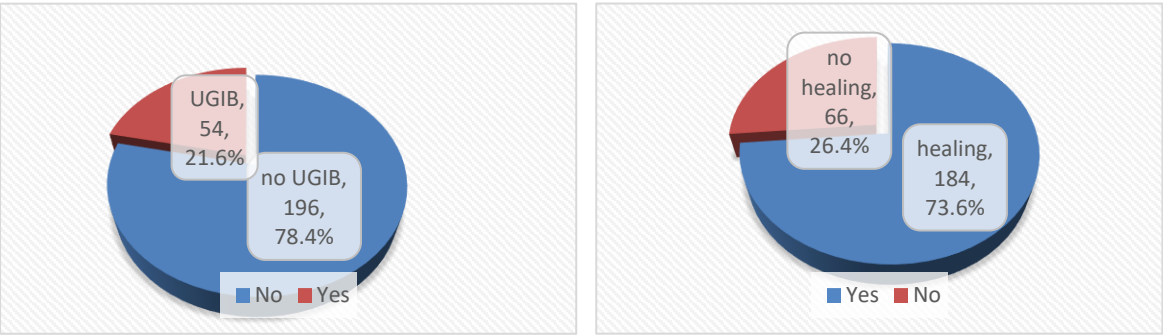


**Figure (1):** Distribution of studied patients according to healing of the post EVL ulcers and development of early UGIB after EVL.

On trying to study factors that affected patients' outcome after EVL (as regard both healing or early upper gastrointestinal bleeding from post EVL ulcers), we had 2 steps of statistical analysis for patients' data at base- line assessment and after 4 weeks of follow up. As regard factors affected healing of post EVL ulcers, different parameters including patients' demographics, base-line laboratory, U/S and endoscopic findings were correlated with detecting healing signs on the second endoscopic examination. This is illustrated at Table 1 & 3.

**Table (3):** Correlation between patients' demographics, base-line U/S and endoscopic parameters and healing of post EVL ulcers.

| variable | | Healing of post EVL ulcers | | | | | | t -test | |
|---|---|---|---|---|---|---|---|---|---|
| | | Yes (n=184) | | | No (n= 66) | | | t | P-value |
| **Age** | **Range** | 43-75 | | | 45- 79 | | | -6.614 | <0.001* |
| | **Mean ±SD** | 57.38 ± 7.86 | | | 64.82 ±7.82 | | | | |
| **MELD** | **Range** | 8 - 21 | | | 9 - 23 | | | -11.241 | <0.001* |
| | **Mean ±SD** | 11.78 ± 3.07 | | | 16.65 ± 2.86 | | | | |
| **Albumin** | **Range** | 2.4 | - | 4.8 | 1.6 | - | 4.3 | 10.887 | <0.001* |
| | **Mean ±SD** | 3.572 | ± | 0.492 | 2.806 | ± | 0.486 | | |
| **Bilirubin** | **Range** | 0.6 | - | 2.7 | 0.7 | - | 2.6 | -9.411 | <0.001* |
| | **Mean ±SD** | 1.129 | ± | 0.355 | 1.647 | ± | 0.455 | | |
| **INR** | **Range** | 1.11 | - | 1.67 | 1.06 | - | 1.75 | -8.845 | <0.001* |
| | **Mean ±SD** | 1.353 | ± | 0.148 | 1.537 | ± | 0.137 | | |
| **ALT** | **Range** | 17 | - | 87 | 12 | - | 134 | -6.024 | <0.001* |
| | **Mean ±SD** | 39.103 | ± | 13.603 | 53.909 | ± | 24.465 | | |
| **AST** | **Range** | 12 | - | 85 | 19 | - | 117 | -6.547 | <0.001* |
| | **Mean ±SD** | 41.728 | ± | 14.190 | 57.258 | ± | 21.813 | | |
| **Hb** | **Range** | 8.5 | - | 16.3 | 8.2 | - | 13.6 | 6.471 | <0.001* |
| | **Mean ±SD** | 11.377 | ± | 1.200 | 10.284 | ± | 1.109 | | |
| **WBCs** | **Range** | 0.4 | - | 11.2 | 3.1 | - | 11.3 | -0.641 | 0.522 |
| | **Mean ±SD** | 6.551 | ± | 1.617 | 6.715 | ± | 2.204 | | |
| **platelets** | **Range** | 0.9 | - | 154 | 6.4 | - | 149 | 4.332 | <0.001* |
| | **Mean ±SD** | 89.091 | ± | 20.821 | 76.294 | ± | 19.917 | | |
| **creatinine** | **Range** | 0.6 | - | 1.9 | 0.6 | - | 2.6 | -8.885 | <0.001* |
| | **Mean ±SD** | 1.064 | ± | 0.327 | 1.470 | ± | 0.292 | | |
| **BUN** | **Range** | 10.2 | - | 25.4 | 11.4 | - | 38.1 | -7.282 | <0.001* |
| | **Mean ±SD** | 14.191 | ± | 3.143 | 17.745 | ± | 4.043 | | |

As regard factors associated with UGIB after EVL, different factors including patients' demographics, base-line laboratory, U/S and initial and second endoscopic examination findings were correlated occurrence of UGIB after EVL. This is illustrated at Tables 4 & 5.

**Table (4):** Correlation between patients' demographics, base-line U/S and endoscopic parameters and early UGIB after EVL.

| variable | | UGIB after EVL | | | | | | Chi-Square | |
|---|---|---|---|---|---|---|---|---|---|
| | | No (n=196) | | Yes (n=54) | | Total (n=250) | | | |
| | | N | % | N | % | N | % | X2 | P-value |
| **Gender** | **Female** | 55 | 28.06 | 5 | 9.26 | 60 | 24 | 8.205 | 0.004* |
| | **Male** | 141 | 71.94 | 49 | 90.74 | 190 | 76 | | |
| **Liver disease** | **No HCC** | 193 | 98.47 | 39 | 72.22 | 232 | 92.8 | 43.651 | <0.001* |
| | **HCC** | 3 | 1.53 | 15 | 27.78 | 18 | 7.2 | | |
| **Child-Pugh score** | **CTP A** | 170 | 86.73 | 18 | 33.33 | 188 | 75.2 | 70.346 | <0.001* |
| | **CTP B** | 24 | 12.24 | 26 | 48.15 | 50 | 20 | | |
| | **CTP C** | 2 | 1.02 | 10 | 18.52 | 12 | 4.8 | | |
| **Ascites** | **No** | 171 | 87.24 | 18 | 33.33 | 189 | 75.6 | 70.174 | <0.001* |
| | **Yes** | 25 | 12.76 | 36 | 66.67 | 61 | 24.4 | | |
| **DM** | **No** | 99 | 50.51 | 10 | 18.52 | 109 | 43.60 | 17.621 | <0.001* |
| | **Yes** | 97 | 49.49 | 44 | 81.48 | 141 | 56.40 | | |
| **O.V Number** | **One** | 2 | 1.02 | 0 | 0.00 | 2 | 0.8 | 22.402 | <0.001* |
| | **Two** | 101 | 51.53 | 13 | 24.07 | 114 | 45.6 | | |
| | **Three** | 70 | 35.71 | 22 | 40.74 | 92 | 36.8 | | |
| | **Four** | 20 | 10.20 | 15 | 27.78 | 35 | 14 | | |
| | **Five** | 3 | 1.53 | 4 | 7.41 | 7 | 2.8 | | |
| **O.V Size** | **Small** | 24 | 12.24 | 2 | 3.70 | 26 | 10.4 | 7.456 | 0.024* |
| | **Medium** | 42 | 21.43 | 6 | 11.11 | 48 | 19.2 | | |
| | **Large** | 130 | 66.33 | 46 | 85.19 | 176 | 70.4 | | |
| **IGV** | **No** | 91 | 46.43 | 3 | 5.56 | 94 | 37.60 | 30.145 | <0.001* |
| | **Yes** | 105 | 53.57 | 51 | 94.44 | 156 | 62.40 | | |
| **Healing signs on second EGD** | **Yes** | 182 | 92.86 | 2 | 3.70 | 184 | 73.60 | 173.183 | <0.001* |
| | **No** | 14 | 7.14 | 52 | 96.30 | 66 | 26.40 | | |

**Table (5):** Correlation between age & base-line laboratory parameters and early UGIB after EVL.

| Variable | | | | UGIB after EVL | | | | t-test | |
|---|---|---|---|---|---|---|---|---|---|
| | | No (n=196) | | | | Yes (n=54) | | t | p-value |
| Age | Range | 43 | - | 75 | 45 | - | 79 | -5.634 | <0.001* |
| | Mean ±SD | 57.842 | ± | 8.022 | 64.778 | ± | 7.964 | | |
| MELD score | Range | 8 | - | 21 | 9 | - | 23 | -10.321 | <0.001* |
| | Mean ±SD | 12.005 | ± | 3.155 | 16.926 | ± | 2.900 | | |
| Albumin | Range | 2.2 | - | 4.8 | 1.6 | - | 4.3 | 9.304 | <0.001* |
| | Mean ±SD | 3.528 | ± | 0.519 | 2.794 | ± | 0.490 | | |
| Bilirubin | Range | 0.6 | - | 2.7 | 0.7 | - | 2.6 | -8.103 | <0.001* |
| | Mean ±SD | 1.159 | ± | 0.386 | 1.654 | ± | 0.438 | | |
| INR | Range | 1.11 | - | 1.72 | 1.06 | - | 1.75 | -8.091 | <0.001* |
| | Mean ±SD | 1.361 | ± | 0.152 | 1.546 | ± | 0.134 | | |
| ALT | Range | 17 | - | 124 | 12 | - | 134 | -4.434 | <0.001* |
| | Mean ±SD | 40.413 | ± | 15.415 | 52.444 | ± | 24.167 | | |
| AST | Range | 12 | - | 117 | 19 | - | 115 | -5.433 | <0.001* |
| | Mean ±SD | 42.776 | ± | 15.466 | 56.907 | ± | 21.452 | | |
| Hb | Range | 8.5 | - | 16.3 | 8.2 | - | 14.2 | 6.224 | <0.001* |
| | Mean ±SD | 11.333 | ± | 1.199 | 10.201 | ± | 1.125 | | |
| WBCs | Range | 0.4 | - | 11.2 | 3.1 | - | 11.3 | -0.879 | 0.380 |
| | Mean ±SD | 6.542 | ± | 1.668 | 6.783 | ± | 2.176 | | |
| Platelets | Range | 0.9 | - | 154 | 61 | - | 149 | 3.716 | <0.001* |
| | Mean ±SD | 88.276 | ± | 21.558 | 76.407 | ± | 17.634 | | |
| Creatinine | Range | 0.6 | - | 1.9 | 0.9 | - | 2.6 | -8.485 | <0.001* |
| | Mean ±SD | 1.080 | ± | 0.332 | 1.500 | ± | 0.284 | | |
| BUN | Range | 10.2 | - | 25.4 | 12.2 | - | 38.1 | -6.515 | <0.001* |
| | Mean ±SD | 14.381 | ± | 3.253 | 17.848 | ± | 4.145 | | |

The impact of use of medications that may aid ulcer healing on healing of post EVL ulcers or occurrence of UGIB after EVL was studied. No statistically significant correlations were detected between use of different regimens of these medications and healing of post EVL ulcers or development of UGIB after EVL, Tables 6 & 7.

**Table (6):** Correlation between type of medications used after EVL and healing of post band ulcers

| Healing | Type of medications used | | | | | | | | | | Chi-Square | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Group I | | Group II | | Group III | | Group IV | | Group V | | | |
| | N | % | N | % | N | % | N | % | N | % | $X^2$ | P-value |
| Yes | 34 | 68.00 | 40 | 80.00 | 40 | 80.00 | 35 | 70.00 | 35 | 70.00 | 3.582 | 0.466 |
| No | 16 | 32.00 | 10 | 20.00 | 10 | 20.00 | 15 | 30.00 | 15 | 30.00 | | |
| Total | 50 | 100.00 | 50 | 100.00 | 50 | 100.00 | 50 | 100.00 | 50 | 100.00 | | |

**Table (7):** Correlation between types of medications used after EVL and occurrence of early UGIB after EVL

| UGIB | Type of medications used | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Group I | | Group II | | Group III | | Group IV | | Group V | | | |
| | N | % | N | % | N | % | N | % | N | % | $X^2$ | P-value |
| No | 37 | 74.00 | 40 | 80.00 | 43 | 86.00 | 41 | 82.00 | 35 | 70.00 | 4.819 | 0.306 |
| Yes | 13 | 26.00 | 10 | 20.00 | 7 | 14.00 | 9 | 18.00 | 15 | 30.00 | | |
| Total | 50 | 100.00 | 50 | 100.00 | 50 | 100.00 | 50 | 100.00 | 50 | 100.00 | | |

## 4. Discussion

ESP Post-ligation ulcers are usually serious consequences of EVL. They heal by time as follows; by the end of the third day, about one half of the varices have overlying ulcers, after one-week, ligated varices are replaced by superficial ulcers of the same size; more than one half of them heals within two weeks, and all of them will completely heal by the end of the third week [12]. These ulcers carry a potential risk of upper gastrointestinal bleeding (especially very deep ulcers). In view of their rapid spontaneous healing, it is unclear whether the presence of post-EVL ulceration requires specific therapy to accelerate the healing process or not [10].

This study was conducted on 250 patients presented to the endoscopy unit of the National liver institute hospital, Menofia University, Egypt at the period of February 2019 to January 2020. On trying to understand factors that affected healing of post EVL ulcers or development of UGIB after EVL, base-line assessment patients' variables before EVL and re-assessment after 4 weeks of EVL were done.

Age of studied patients was statistically significant as regard development of UGIB after EVL. Age distribution in this study showed that patients with bleeding were slightly older than those who did not bleed. Xu et al., reported similar results [13]. Conflicting results were found as regard age by Grothaus J. et al., who reported that patients who bled were slightly younger than those who did not bleed [14].

Male gender in our study was a significant risk factor for UGIB after EVL and healing of post EVL ulcers. This contradicts other studies by Grothaus et al and Xu et al who reported that gender was not significantly different between both groups [13 & 14].

In this study, there was strong association between severity of liver disease, measured by Child-Pugh score, and UGIB after EVL. This was consistent with previously

reported findings by Berreta et al, Grothaus et al & Xu et al [13, 14 & 15].

Sinclair et al and Shendy et al studies showed that poor liver condition (CTP-class C, high MELD score) was identified as a predictive factor of bleeding in cirrhotic patients. Reduced coagulation ability increased vascular fragility and a large extension of submucosal esophageal varices (induced by portal hypertension) might explain the importance of bleeding from post–banding ulcer without effective local thrombosis [16 & 17].

On the other hand, Elhawari, reported that no significant relation between CTP classes or MELD score and occurrence of post EVL ulcer bleeding in Egyptian patients. This may be related to past endemicity of bilharziasis in Egypt which causes more vascular decompensation than cellular decompensation, so it is represented by more increase in portal hypertension than decrease in synthetic functions which affect Child and MELD score [18].

This study revealed that DM significantly correlated with UGIB after EVL in patients with Child-Pugh Class A, with 81.48 % diabetic patients and 18.52% non-diabetics with (p-value <0.001).

Moreau et al, stated that diabetes mellitus co-existing with cirrhosis was one of the factors involved in the development of variceal bleeding as well as re-bleeding [19]. Khafaga et al and Assem et al, also reported that diabetes mellitus was associated with higher re-bleeding rates [20 & 21].

Assem et al reported that there was no significant difference regarding mean HbA1c about variceal re-bleeding. Possible explanation is that the patients in the present study had poor glycemic control and repeated attacks of GEVB in which there was high levels of blood sugar and higher HBA1c [21].

As regard other factors associated with ulcer healing, presence of HCC had negative impact on healing of post EVL ulcers. Only 2 patients with HCC of 16 (24.2%) had signs of ulcer healing on second endoscopic examination This agreed with Giannini et al, who found that HCC patients with esophageal or gastric varices had poorer liver functional reserves, more active hepatic necro-inflammation, and even advanced fibrosis [22].

This is also illustrated by Lo G.H. et al who found that the presence of hepatocellular carcinoma (HCC), frequently influences either early re-bleeding or mortality in these patients [23].

Treatment of post-band ulcers has been mostly empirical with drugs used for peptic ulcer diseases with very few data existing regarding their beneficial effect.

Shaheen et al, found that pantoprazole reduces the size of post-banding ulcers after variceal band-ligation in a randomized controlled trial. The double-blind RCT by Shaheen et al was quoted in guidelines to support PPI use post-EVL [10].

Elsayed et al, in a randomized controlled trial (for assessing of PPI after EVL) conducted on 46 patients, showed no statistically significant difference in post banding ulcer's size between both groups (placebo &pantoprazole) [24].

In our study, we observed that there was no statistically significant difference as regard healing of post- band ulcers between groups used different ulcer healing medications.

Elsayed also demonstrated that the number of patients who developed post banding ulcers (68.4%) in those used pantoprazole after EVL [24].

Shaheen et al and El Sayed demonstrated that no significant difference in the number of post banding ulcers in the pantoprazole group and the placebo group [10 & 24].

## 5. Conclusion

Variceal band ligation is an effective maneuver for both prophylaxis and therapy of UGIB from esophageal varices, but development of post EVL ulcers may carry potential risk of UGIB. Aiding post EVL ulcers healing by ulcer healing medications still having conflicting results in different research. In this study, there was no significant impact of using different ulcer healing medications on healing or bleeding of post EVL ulcers

## References


1. Garcia Tsao G, Abraldes JG, Berzigotti A et al. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology. 2017; 65:310-335.

2. Bosch, J., Groszmann, R. J., & Shah, V. H. Evolution in the understanding of the pathophysiological basis of portal hypertension: how changes in paradigm are leading to successful new treatments. Journal of hepatology. 2015; 62:121-130.

3. Kang SH, Yim HJ and Kim SY. Proton Pump Inhibitor Therapy Is Associated with Reduction of Early Bleeding Risk After Prophylactic Endoscopic Variceal Band Ligation: A Retrospective Cohort Study. Medicine. 2016, 95.

4. Ibrahim, M., Mostafa, I., & Devière, J. New developments in managing variceal bleeding. Gastroenterology. 2018; 154:1964-1969.

5. Hiroaki Nema, Mototsugu Kato. Comparative study of therapeutic effects of PPI and H2RA on ulcers during continuous aspirin therapy. World J Gastroenterol 2010 November 14; 16(42): 5342-5346.

6. Satoh, K., Yoshino, J., & Akamatsu, T. Evidence-based clinical practice guidelines for peptic ulcer disease 2015. Journal of gastroenterology .2016, 177-194.

7. Kangwan, N., Park, J. M., Kim, E. H., et al. Quality of healing of gastric ulcers: natural products beyond acid suppression. World Journal of Gastrointestinal Pathophysiology. 2014, 40.

8. Fernández, J., Prado, V., Trebicka, J.et al. Multidrug-resistant bacterial infections in patients with decompensated cirrhosis and with acute-on-chronic liver failure in Europe. Journal of hepatology.2019, 398-411.

9. Siau, K., Chapman, W., Sharma, N., et al. Management of acute upper gastrointestinal bleeding: an update for the general physician. Journal of the Royal College of Physicians of Edinburgh .2017, 219.

10. Soliman, G. M. M., Amer, Y., & Mostafa, S. Comparative study between the efficacy of rebamipide, sucralfate and pantoprazole in treatment of post banding variceal ulcers. Al-Azhar Assiut Medical Journal. 2015; 13: 28-35.

11. Kistler, C. A., Martin, A., Kaplan et al. Complications of Upper Endoscopy and Their Management. In Upper Endoscopy for GI Fellows. 2017, 105-123.

12. Vanbiervliet G., Giudicelli-Bornard S., Piche T., et al. Predictive factors of bleeding related to post banding ulcer following endoscopic variceal ligation in cirrhotic patients: a case control study. Alimentary pharmacology & therapeutics .2010, 225-232.

13. Shaheen NJ, Stuart E, Schmitz SM, et al. Pantoprazole reduces the size of post banding ulcers after variceal band ligation: a randomized,

controlled trial. Hepatology. 2005.588–594.

14. Wedemeyer, R. S., & Blume, H. Pharmacokinetic drug interaction profiles of proton pump inhibitors: an update. Drug safety. 2014, 201-211.

15. Samuel, R., Bilal, M., Tayyem, O, et al. Evaluation and management of non-variceal upper gastrointestinal bleeding. Disease-a-Month. 2018, 333-343.

16. Xu L., Ji F., Xu Q.W., et al. Risk factors for predicting early variceal rebleeding after endoscopic variceal ligation. World journal of gastroenterology: WJG. 2011, 3347-3353.

17. Grothaus J, Petrasch F, Zeynalova S et al. Risk Factors for Bleeding Complications after Endoscopic Variceal Ligation Therapy. Z Gastroenterol. 2010, 1200–1206.

18. Berreta J, Kociak D, Corti R et al. Predictors of intrahospitalary mortality in the upper gastrointestinal variceal bleeding due to chronic liver disease treated endoscopically. Acta Gastroenterol Latinoam; 2008, 43-50.

19. Sinclair M, Vaughan R, Angus BW, et al. Risk factors for band induced ulcer bleeding after prophylactic and therapeutic endoscopic variceal band ligation. Eur. J. Gastroenterol. Hepatol. 2015, 928–932.

20. Shendy SM, Elnaggar MK, Salem HM, et al. Incidence and risk factors contributing for early variceal rebleeding after esophageal variceal ligation Sch. J. App. Med. Sci. 2015; 3(3G): 1553-9.

21. Elhawari SA, Moustafa EA, Zaher T, Frequency and Risk Factors of Post Banding Ulcer Bleeding Following Endoscopic Variceal Ligation in Patients with Liver Cirrhosis. Afro-Egyptian Journal of Infectious and Endemic Diseases. 2019, 252-259.

22. Moreau R., Chagneau C., Heller J., Et Al.: Hemodynamic, metabolic and hormonal responses to oral glibenclamide in patients with cirrhosis receiving glucose. Scand J. Gastroenterol. 2001, 303-308.

23. Khafaga S., Khalil K., Abdou M., Et Al.: Acute variceal bleeding in patients with liver cirrhosis with and without diabetes. Liver Res. Open J. 2015, 14-20.

24. Assem M., Al Sayed M., Metwally K., Et Al.: Comorbidity of diabetes mellitus and bleeding esophageal varices. Internal Medicine/Medicine Int. 2016, 1-9.

25. Giannini E. G... Prevalence and prognostic significance of the presence of esophageal varices in patients with hepatocellular carcinoma. Clin Gastroenterol Hepatol .2006, 1378–1384.