

# A Prospective Study of Esophageal Variceal Recurrence and Rebleed Rates after Primary Eradication

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## Abstract

**Introduction:** Variceal bleeding is a life-threatening complication of portal hypertension with a high probability of recurrence. Treatment to prevent first bleeding or rebleeding is mandatory.

**Aim:** The aim of this study is to evaluate prospectively the overall long-term clinical outcome in terms of recurrence of varices and rebleed rates after eradication of varices following endoscopic sclerotherapy (EST) in consecutively treated cirrhotic patients with bleeding esophageal varices.

**Materials and Methods:** Consecutive patients presenting with bleeding esophageal varices for the first time and registered in the liver clinic of the institution were included in the study. Those patients with an earlier variceal bleed and on EST schedule, initiated elsewhere, were excluded from the study. Child C patients who failed to recover and presented with variceal bleed were also excluded.

**Results:** A total of 133 consecutive patients were treated for esophageal variceal bleeding, there were 86 men and 47 women (mean age: 45.51 + 11.8 years; age range, 20-77 years). A total of 611 EST sessions were performed with a mean of 4.6 injections. 43 (32.3%) of the 133 patients continued to have recurrent bleed in between the EST sessions and eradication of varices. 16 (12%) patients died within 3 months of registration, 8 from massive GI bleed, 4 from hepatic encephalopathy, 2 from hepatorenal syndrome, and 2 from spontaneous bacterial peritonitis. They had overall 28 EST sessions with a mean of 1.8 injections.

**Conclusion:** Ultimately, the use of sequential combined endoscopic techniques with variceal banding initially when varices are large followed by sclerotherapy when varices are small may enhance the endoscopic management of esophageal varices in terms of reducing complications, facilitating earlier eradications, and preventing recurrence.

**Key words:** Cirrhosis, Esophageal varices, Variceal bleeding

## INTRODUCTION

Bleeding from esophageal varices is the leading cause of death in patients with portal hypertension, with a mortality of up to 50% for the initial bleed and 30% for subsequent bleeds.<sup>1,2</sup> Endoscopic variceal sclerotherapy

(EST) has been widely used in the emergency treatment of patients with actively bleeding esophageal varices. Even though the initial bleed may effectively be controlled by sclerotherapy, the risk of subsequent rebleeding is substantial.<sup>3,4</sup>

There is a general consensus that patients surviving a bleed episode should be treated to prevent rebleeding. Considerable evidence has supported the use of repeated sclerotherapy to obliterate esophageal varices to prevent further variceal bleeding. While undergoing sclerotherapy before eradication, patients may continue to have variceal bleeds. Repeated injection also increases the cumulative risk of developing complications in patients.<sup>5</sup>

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Endoscopic variceal ligation (EVL) is widely used and may provide safer and quicker eradication of varices. However, no long-term data for recurrent bleeding after variceal eradication by ligation exists, and there is a concern that rebleeds may be higher after ligation than after sclerotherapy.<sup>6</sup> The cost and affordability by the patient have resulted in selective use of EVL when compared to EST which cheaper and readily available in all centers in the Indian subcontinent. Furthermore, a recent study from our institution has highlighted the natural history of esophageal varices in an era of sclerotherapy. The rebleed rate was 29.4%.

Despite the previous widespread use of EST, accurate data on long-term recurrence and rebleeding after variceal eradication and the need and optimal frequency of endoscopic surveillance are scant.

### Aim

The aim of this study was to evaluate prospectively the overall long-term clinical outcome in terms of recurrence of varices and rebleed rates after eradication of varices following EST in consecutively treated cirrhotic patients with bleeding esophageal varices.

## MATERIALS AND METHODS

Consecutive patients presenting with bleeding esophageal varices for the first time and registered in the liver clinic of the institution were included in the study. Those patients with an earlier variceal bleed and on EST schedule, initiated elsewhere, were excluded from the study. Child C patients who failed to recover and presented with variceal bleed were also excluded.

Patient details at the time of registration were recorded in a pre-structured pro forma. Details included address, cell number, age, gender, etiology of portal hypertension, and Child-Pugh Score. The latter was applied to grade the severity of cirrhosis. This was based on serum bilirubin, serum protein, ascites, prothrombin time, and encephalopathy (Table 1).

Based on the scoring system, cirrhosis was classified as Child A when the total score was 5 and 6, Child B when the total scores 7-9, and Child C when the total score was 10-15.

Bleed details included the date of index bleed, subsequent bleed until eradication, details of EST such as grades of varices, features of imminent bleed, nature and volume of sclerosant used, and number of sessions required to obliterate the varices. The protocol for variceal injection followed by the department was as follows: 14-18 ml of

**Table 1: Child-Pugh score**

Variables	Child A	Child B	Child C
Serum bilirubin	<2 mg %	2-3 mg %	>3 mg %
Serum albumin	>3.5 g %	2.8-3.5 g %	<2.8 g %
Ascites	Nil	Mild	Moderate/severe
Prothrombin time	<14 s	15-1 s	>18 s
Encephalopathy	Nil	Mild/moderate	Moderate/severe

1% sodium tetradecylsulfate was used to inject the varices in the first sitting. All patients were admitted for a day and were on prophylactic parenteral ciprofloxacin 200 mg 1 h before the EST session. EVL was not available at all times, and hence, only those cases on regular EST were included for the study.

The varices were injected both intra- and para-variceal close to the gastroesophageal junction using 23-gauge needle. For larger varices, Grades III and IV para-variceal were followed by intravariceal injection. The second and subsequent injections were done at three weekly intervals until eradication of varices. The end point was sclerosed varices. The number of sessions and complications if any during or after the procedure were noted. The injection was deferred in those patients who had odynophagia, chest pain, and esophageal ulcers or had fever or focus of infection. Those patients who had a bleed in between the recommended sessions had an EST at that point of time. Patients with large fundal varices were excluded from the study. Revascularization with or without shunt is the recommended protocol of management for these patients in our institutions.

All patients were on secondary prophylaxis with propranolol 40 mg twice a day or until the pulse rate decreased by 25% of the baseline rate.

Follow-up protocol of eradicated varices included rescope for variceal recurrence at 3-month intervals. Eradication of varices was defined as the absence of varices on subsequent endoscopy examination during follow-up visits.

The grades of varices, signs of imminent bleed such as red wale sign, cherry red spots, and hematocystis spots were noted. Details of bleed after eradication, i.e., defined as rebleed were noted, and sclerotherapy was done as per the protocol. The end point of the study was the first bleed after eradication. Further, EST was done for residual or recurrent varices.

## RESULTS

A total of 133 consecutive patients were treated for esophageal variceal bleeding. There were 86 men and

47 women (mean age:  $45.51 \pm 11.8$  years; age range, 20-77 years). A total of 611 EST sessions were performed with a mean of 4.6 injections.

43 (32.3%) of the 133 patients continued to have recurrent bleed in between the EST sessions and eradication of varices. 16 (12%) patients died within 3 months of registration, 8 from massive GI bleed, 4 from hepatic encephalopathy, 2 from hepatorenal syndrome, and 2 from spontaneous bacterial peritonitis. They had overall 28 EST sessions with a mean of 1.8 injections.

Of the 39 (29.3%) patients who did not complete the study, 26 (19.5%) were lost to follow-up. They had 89 EST sessions with a mean of 3.4 injections. In 13 patients, oesophageal varices persisted at the end of 6 months despite repeated EST sessions (mean: 9.4 injections). Six patients died during the interim period due to hepatic encephalopathy (4 patients) and hepatorenal syndrome (2 patients). Three patients required elective surgery (revascularization). Four patients declined regular long-term follow-up and further injection therapy.

The 133 patients received a total of 611 emergency and elective injection treatments during the study period. A minor complication of sclerotherapy consists of transient fever and chest pain.

Esophageal mucosal ulceration at the injection site was found on 128 (20.9%) occasions in 62 patients. Subsequent sclerotherapy was delayed in patients who had mucosal ulceration in greater than one quadrant of the esophageal circumference.

A contained injection leak occurred on 2 occasions in 2 patients and was treated with intravenous antibiotics and nasogastric tube feeding.

Esophageal stricture at the injection site occurred in 4 patients after sclerotherapy. One patient required esophageal dilation, with complete relief of symptoms after dilation (Table 2).

78 (58.6%) patients had eradication of the varices and were available for follow-up of 1 year (Table 3).

Majority of the patients had alcohol-related cirrhosis (42.3%), followed by HBV-related cirrhosis (19.2%). In 22 patients, the cause remained unknown (28.2%).

There were 48 men and 30 women. The mean age for men was  $41.2 \pm 11.8$  years and for women was  $48.1 \pm 11.76$  years. Minimum period of follow-up of obliterated esophageal varices was for 12 months, and the longest follow-up was

**Table 2: Complications in 133 patients**

Type of complication	Complications per sclerotherapy (%)
Esophageal ulceration	128 (20.9)
Injection site leak	2 (0.3)
Stricture	4 (0.7)

**Table 3: Causes of cirrhosis in 78 cases**

Cause	Total number of patients (%)
Alcoholic cirrhosis	33 (42.3)
HBV-related cirrhosis	15 (19.2)
HCV-related cirrhosis	3 (3.8)
NAFLD	1 (1.3)
Wilson's disease	4 (5.1)
Cryptogenic cirrhosis	22 (28.2)

for 22 months. Eradication of varices was possible after a median of 4.77 injections.

### Recurrence of Varices, Bleed Rates, and Bleed-related Mortality

In follow-up of 32 cases, 17 had eradication of varices after the mean of 4.8 sessions. 9 patients (52.9%) had recurrence of varices on follow-up of 21.5 months. The grades of varices were I, II, and III in 3 (33.3%), 5 (55.5%), and 1 (11.1%), respectively. Four patients (44.4%) bled during the follow-up period. One of the two deaths was due to variceal bleed.

In follow-up of 35 cases, 23 cases had eradicated the varices after a mean of 5 EST sessions. These patients could be followed up 18 months. Of the 11 (47.8%) who had recurrence of varices, 5 (45.5%) had Grade I varices, 5 (45.5%) had Grade II varices, and one (9.1%) had Grade II varices. Three patients (27.3%) had a variceal bleed. There were no bleed-related deaths. After eradication, bleed occurred in 3 (27.3%) patients.

In follow-up of 29 cases registered, 16 had varices eradication after a mean of 4.5 injection. Follow-up for 15.8 months after eradication showed recurrence of varices in 8 (50%), 2 of whom, i.e. 25% had Grades I and III and 4 (50%) had Grade II varices. Two patients had variceal bleed after eradication.

Of the 37 cases registered in the fourth quarter, 22 cases had varices eradication within 4 months of registration after a mean of 4.8 variceal injections. On follow-up at 12 months after eradication, 13 (35.1%) had recurrence of varices, among whom 5 (38.4%) had Grade I varices, 6 (46.1%) had Grade II varices, and 2 (15.4%) had Grade III varices. Bleed after eradication occurred in 5 (38.4%) patients; one of the two deaths was due to variceal bleed.

On summarizing, of the 41 variceal recurrences, majority, i.e., 32 (78%) patients had recurrence of varices within 6 months of follow-up and the rest subsequently. Furthermore, majority of rebleed occurred within 3 months, i.e., in 11 patients (78.6%) and the rest later.

There were 27 (65.9%) non-bleeders. The grades of varices were I, II, and III in 7 (26%), 15 (55%), and 5 (19%), respectively. 10 (27%) patients died, 5 from hepatic encephalopathy, 3 from hepatorenal syndrome, and 2 from spontaneous bacterial peritonitis. One (63%) patients were alive at the end of the study.

### **Non-recurrence of Varices, Bleed Rates, and Bleed-related Mortality**

In 37 of the 8 (47.3%), the varices remained eradicated until the end of follow-up. 12 (32.4%) patients died, 6 from hepatic encephalopathy, 4 from hepatorenal syndrome, and 2 from spontaneous bacterial peritonitis.

## **DISCUSSION**

Bleeding from esophageal varices is the leading cause of death in patients with portal hypertension, with a mortality of up to 50% for the initial bleed and 30% for subsequent bleeds. The greatest risk is during the first 72 h, and more than 50% of all early rebleed episodes occur within the first 10 days after cessation of active hemorrhage.

The most common source of recurrent bleeding before variceal eradication is from residual patent varices. This was 32.3% in the present series, a figure similar to that reported by Krige *et al.*<sup>7</sup> emergency endoscopy is essential since in 85.9% of patients with recurrent bleeding, the source is invariably the varices. These can be optimally treated by sequential EVL or sclerotherapy.

Overall, the esophageal varices remained eradicated in 37 (47.3%) patients after a follow-up period of 1 year. Although new varices formed following initial obliteration in 41 (52.6%) of the 78 patients, this was associated with varices-related rebleed in 14 patients (34.1%), a figure similar to that reported by Krige *et al.*<sup>7</sup> (37.5%). Of the 41 variceal recurrences, majority, i.e., 32 (78%) patients had recurrence of varices within 6 months of follow-up and the rest subsequently. Furthermore, majority of rebleed occurred within 3 months, i.e., in 11 patients (78.6%) and the rest later.

The present study evaluated the complications occurring in 133 patients undergoing emergency and elective sclerotherapy. Complications were mostly minor and occurred in half of patients similar to Krige *et al.* their figure

of 20.9% corresponds to the 20-23% reported in earlier series by Westaby *et al.*<sup>8</sup> this is in contrast to the 39.4% reported by Krige *et al.*, who performed EST sessions at weekly intervals.

Asymptomatic esophageal ulceration at the injection site was the most common complication and was detected at follow-up endoscopy. Ulcers are generally considered an inevitable temporary consequence of the sclerosant, occurring after frequent or large volume injections.

In most of the patients, in this study, mucosal ulceration healed without sequelae. Our present policy is to use lower volumes of sclerosant as varices decrease in size in an attempt to reduce the extent of ulceration.

EVL has now replaced injection sclerotherapy in the elective treatment of esophageal varices. Data from randomized controlled trials show more rapid eradication of varices with lower rates of recurrent bleeding and fewer complications such as strictures and perforation.<sup>9</sup> However, a recent survey by the American College of Gastroenterology International GI Bleeding Registry shows that sclerotherapy is still used as frequently as bleeding for endoscopic intervention during index bleeding and more frequently than banding for control of variceal rebleeding. Likely, reasons include convenience, cost, and widespread availability. It is noteworthy that several recent randomized controlled trials comparing band ligation with sclerotherapy have reported a higher recurrence rate of varices in patients undergoing band ligation.<sup>10</sup>

Our current management policy is to have regular endoscopic therapy to achieve early variceal eradication, appreciating those factors such as esophageal ulceration, and poor patient compliance may interfere with the endoscopic therapy program. After eradication of the varices, patients have surveillance endoscopy at 3-month intervals, and if recurrent varices are identified, a comprehensive endoscopic treatment schedule is instituted again.<sup>11,12</sup>

## **CONCLUSION**

Over the past two decades, several treatment modalities have been improved and introduced to practice with a decreased rebleeding risk and mortality. Combination of EVL plus drug therapy is indicated because of the high risk of recurrence, despite that the side effects are more common than in a single agent therapy (recommended for primary prophylaxis). Ultimately, the use of sequential combined endoscopic techniques with variceal banding initially when varices are large followed by sclerotherapy

when varices are small may enhance the endoscopic management of esophageal varices in terms of reducing complications, facilitating earlier eradications and preventing recurrence. The choice of treatment should be based on local resources and expertise, patient preference and characteristics, side effects, and contraindications.

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