Observational Study

Defining the advantages and exposing the limitations of endoscopic variceal ligation in controlling acute bleeding and achieving complete variceal eradication

Jake Krige, Eduard Jonas, Urda Kotze, Christo Kloppers, Karan Gandhi, Hisham Allam, Marc Bernon, Sean Burmeister, Mashiko Setshedi

ORCID number: Jake Krige 0000-0002-7057-9156; Eduard Jonas 0000-0003-0123-256X; Urda Kotze 0000-0003-1405-474X; Christo Kloppers 0000-0003-2438-6879; Karan Gandhi 0000-0003-3543-1428; Hisham Allam 0000-0001-5344-3532; Marc Bernon 0000-0002-7967-8548; Sean Burmeister 0000-0003-0888-7606; Mashiko Setshedi 0000-0002-7979-2981.

Author contributions: Krige J, Jonas E and Kotze U devised the study concept and design; Krige J, Kotze U were involved in acquisition of data; Krige J, Jonas E, Kotze U, Kloppers C, Gandhi K, Allam H, Bernon M and Burmeister S analyzed and interpreted the data; Krige J, Jonas E and Kotze U drafted the manuscript; Krige J, Jonas E, Kotze U, Kloppers C, Gandhi K, Allam H, Bernon M and Burmeister S and Setshedi M critically revised the manuscript for important intellectual content; Krige J, Kotze U and Setshedi M carried out the statistical analysis; Krige J and Jonas E provided final approval of the article.

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Abstract

BACKGROUND

Bleeding esophageal varices (BEV) is a potentially life-threatening complication in patients with portal hypertension with mortality rates as high as 25% within six weeks of the index variceal bleed. After control of the initial bleeding episode patients should enter a long-term surveillance program with endoscopic intervention combined with non-selective β-blockers to prevent further bleeding and eradicate EV.

AIM

To assess the efficacy of endoscopic variceal ligation (EVL) in controlling acute variceal bleeding, preventing variceal recurrence and rebleeding and achieving complete eradication of esophageal varices (EV) in patients who present with BEV.

METHODS

A prospectively documented single-center database was used to retrospectively identify all patients with BEV who were treated with EVL between 2000 and 2018. Control of acute bleeding, variceal recurrence, rebleeding, eradication and survival were analyzed using Baveno assessment criteria.

RESULTS

One hundred and forty patients (100 men, 40 women; mean age 50 years; range, 21–84 years; Child-Pugh grade A = 32; B = 48; C = 60) underwent 160 emergency
Cape Town Health Sciences Faculty.

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and 298 elective EVL interventions during a total of 928 endoscopy sessions. One hundred and fourteen (81%) of the 140 patients had variceal bleeding that was effectively controlled during the index banding procedure and never bled again from EV, while 26 (19%) patients had complicated and refractory variceal bleeding. EVL controlled the acute sentinel variceal bleed during the first endoscopic intervention in 134 of 140 patients (95.7%). Six patients required balloon tamponade for control and 4 other patients rebled in hospital. Overall 5-d endoscopic failure to control variceal bleeding was 7.1% (n = 10) and four patients required a salvage transjugular intrahepatic portosystemic shunt. Index admission mortality was 14.2% (n = 20). EV were completely eradicated in 50 of 111 patients (45%) who survived > 3 mo of whom 31 recurred and 3 rebled. Sixteen (13.3%) of 120 surviving patients subsequently had 21 EV rebleeding episodes and 10 patients bled from other sources after discharge from hospital. Overall rebleeding from all sources after 2 years was 21.7% (n = 26). Sixty-nine (49.3%) of the 140 patients died, mainly due to liver failure (n = 46) during follow-up. Cumulative survival for the 140 patients was 71.4% at 1 year, 65% at 3 years, 60% at 5 years and 52.1% at 10 years.

CONCLUSION
EVL was highly effective in controlling the sentinel variceal bleed with an overall 5-day failure to control bleeding of 7.1%. Although repeated EVL achieved complete variceal eradication in less than half of patients with BEV, of whom 62% recurred, there was a significant reduction in subsequent rebleeding.

Key Words: Endoscopy; Variceal ligation; Variceal bleeding; Secondary prophylaxis; Esophageal varices; Variceal recurrence

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Core Tip: Control of acute bleeding is crucial in patients with portal hypertension and actively bleeding esophageal varices (BEV). The present study demonstrated that endoscopic variceal ligation (EVL) was highly effective in controlling acute variceal bleeding during the first endoscopic intervention in 95.7% of 140 patients with an overall 5-d failure to control bleeding of 7.1%. Although repeated EVL achieved complete variceal eradication in less than half of patients with BEV, of which 62% recurred, there was a significant reduction in subsequent rebleeding. EVL was effective and safe with a low complication rate in treating BEV.

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INTRODUCTION
Bleeding esophageal varices (BEV) is a potentially life-threatening complication in patients with portal hypertension with mortality rates as high as 25% within six weeks of the index variceal bleed[1]. Although endoscopic intervention provides the optimal emergency method to control actively BEV, the risks of bleeding complications remain substantial and as many as 23% of patients have treatment failure within 5-d due to either uncontrolled or early rebleeding[2]. Approximately 60% of survivors rebleed within two years after the initial bleeding episode with a mortality rate of 30%-[3]. Secondary prophylaxis of variceal bleeding is thus crucial and there is a general consensus, supported by the American Association for the Study of Liver Diseases (AASLD), the American Society for Gastrointestinal Endoscopy (ASGE) and the British Society of Gastroenterology (BSG) guidelines that following an initial bleeding episode patients should enter a long-term surveillance program with endoscopic intervention.
combined with non-selective β-blockers to pre-empt further bleeding and eradicate EVL[1-5].

Endoscopic variceal ligation (EVL) has replaced injection sclerotherapy (IST) as the endoscopic interventional procedure of choice for BEV, supported by randomized controlled trial data that show more rapid eradication of varices with lower rates of recurrent bleeding and fewer endoscopic-related complications[6]. However, few studies have specifically evaluated detailed outcomes in relation to the inherent technical constraints of ligating device design which may influence the effectiveness of EVL in controlling acute variceal bleeding and in particular, achieving complete eradication of varices, a problem conceptually more relevant to endoscopic banding than sclerotherapy. This prospective study, based on a protocol-driven standardized EVL technique from a high-volume academic endoscopy referral center, assessed the efficacy of EVL in controlling acute variceal bleeding, preventing early rebleeding and achieving complete and durable variceal eradication to prevent late recurrent bleeding in a cohort of patients who presented with an index variceal bleeding event.

MATERIALS AND METHODS

Patients and methods
Consecutive adult patients with endoscopically proven BEV admitted to a specialist surgical gastroenterology unit with a particular interest in portal hypertension in Groote Schuur Hospital, Cape Town between January 2000 and December 2018 were assessed. Patients who had received sclerotherapy or had endoscopic treatment initiated elsewhere were excluded. The outcome of all endoscopic treatments, both emergency and subsequent elective therapy, was analyzed to assess the efficacy of EVL in acute variceal bleeding control and achieving complete and lasting variceal eradication. The study was a monocentric retrospective analysis following STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statements of all patients. After approval from the institutional Human Research and Ethics Committee, the unit database was searched and filtered for adult patients with endoscopically proven BEV who received EVL as the endoscopic method of treatment.

Data extraction
All data were entered prospectively into a bespoke computer programme by a dedicated research and data manager. Data collected included demographic and clinical information, cause of portal hypertension, Child–Pugh score, hematologic and liver function tests, liver biopsy, imaging results, endoscopy information, including variceal size, number of bands placed at each session, the interval between and the number of banding sessions. Outcome data included the efficacy of EVL in controlling the acute index bleed, preventing early rebleeding, achieving complete variceal eradication, minimizing late recurrent bleeding and overall survival. Data were analyzed on January 30, 2020.

Study endpoints
The primary endpoints of the study were (1) effective endoscopic control of the index variceal bleeding event; and (2) success in achieving complete variceal eradication as defined in the analysis criteria. Secondary endpoints included (1) early rebleeding; (2) variceal recurrence and rebleeding; and (3) overall survival.

Acute bleeding management and technique of variceal ligation
Details of the acute bleeding management protocol in our unit have been published previously[7-9]. As soon as the patient was stable, diagnostic endoscopy and EVL were performed[10]. Endoscopic banding devices used during the study period included the Saeed Multi-band Ligator (Cook Endoscopy, Winston-Salem, NC, USA), and the Speedband Superview Super 7 Multiple Band Ligator (Boston Scientific Corp., Natick, MA, USA)[11]. Full details of the variceal ligation technique used have been published previously[12-14]. During endoscopy for the sentinel bleed and subsequent bleeds, a band was applied first to the bleeding varix and then proximally in a helical fashion for approximately 10 cm to the remaining varices. In patients in whom bleeding could not be controlled a Sengstaken-Blakemore or Minnesota balloon tube was inserted for immediate tamponade and further endoscopic procedures were performed within 24 h. When endoscopic measures failed transjugular intrahepatic portosystemic shunt (TIPS) was used as rescue treatment.
Patients underwent regular EVL until complete variceal eradication, defined as the absence of varices, was achieved. In a subcategory of patients who had residual varices which were too small or insufficiently pliable to be suctioned into the banding device to allow secure and safe band deployment, complete eradication was not pursued. After the initial EVL session during the index admission to hospital, subsequent variceal ligation procedures were undertaken at two-week intervals as an outpatient until the varices were eradicated or unsuitable for continued ligation. Surveillance endoscopy was performed at 3 and 6 monthly intervals and then annually to identify recurrence or persistent varices and repeat EVL performed whenever technically feasible. All patients were given non-selective β-blockers (NSBB) during follow-up unless specifically contra-indicated.

Rebleeding

Baveno criteria were used to define 5-d and 6 wk failure to control bleeding\(^5\). Additional variceal ligation was undertaken if bleeding was due to residual or recurrent varices. Other sources of bleeding, such as gastric varices, portal hypertensive gastropathy, peptic ulcers or erosive gastritis were included in the definition of rebleeding and treated on their merits.

Statistical analysis

The Student \(t\)-test and \(\chi^2\) test were used when appropriate and the Kaplan–Meier method was used to estimate the cumulative incidence of re-bleeding and actuarial survival. Multivariate analysis was used to assess risk factors for rebleeding. A \(P\) value < 0.05 was considered significant. SAS System Package version 9.2.1 software (SAS Systems International, Cary, NC, USA) was used for statistical analysis. Data were censored at the time of the last clinic or endoscopy visit, TIPS placement or death. Ethical and institutional review board approval (HREC 120/2019) was obtained before study initiation and data analysis.

RESULTS

The 140 patients (100 men, 40 women, median age: 50 years; range: 21-84 years) included 32 Child-Pugh grade A, 48 grade B and 60 grade C patients when assessed on first admission to hospital (Table 1). The underlying diagnoses were alcoholic cirrhosis \(n = 75\) (53.6%), hepatitis B infection \(n = 13\) (9.9%), cryptogenic cirrhosis \(n = 13\) (9.9%), hepatitis and alcohol \(n = 9\) (6.4%), non-alcoholic fatty liver disease \(n = 8\) (5.7%), schistosomiasis \(n = 7\) (5%), and portal vein thrombosis \(n = 5\) (3.6%). The remaining ten patients had autoimmune hepatitis \((n = 3)\), hepatitis C \((n = 2)\), and one each of granulomatous hepatitis, myelofibrosis, Budd-Chiari syndrome, chronic active hepatitis and primary sclerosing cholangitis. The 140 patients received 160 emergency and 298 elective EVL procedures during a total of 928 endoscopy sessions.

Control of bleeding during the index endoscopic procedure

Acute bleeding was successfully controlled by EVL in 134 of 140 patients (95.7%) during the index endoscopic procedure (Figure 1). A balloon tube was used in six patients in whom acute bleeding could not be controlled by EVL, and a further four patients rebled within 5-d, resulting in a cumulative 5-d failure to control bleeding of 7.1% \((n = 10)\); Child-Pugh grade A \(n = 0\), grade B \(n = 1\), grade C \(n = 9\). These ten patients required 11 additional endoscopic banding sessions and four patients with recalcitrant variceal bleeding required a salvage TIPS.

Index admission mortality

The index in-hospital admission mortality was 14.2% \((n = 20)\) with a median survival of 8 d (range 1-44). Ten patients died of multi-organ failure (MOF) including two of the four patients who had a salvage TIPS. A further seven patients died of progressive liver failure, another as a result of advanced hepatocellular carcinoma and two elderly patients with vasculopathy died of a myocardial infarction. The index admission mortality for the 32 Child-Pugh grade A patients was 0, for the 48 Child-Pugh grade B patients was 2.1% and for the 60 Child-Pugh grade C patients was 31.7% (19 of 60 patients).

Rebleeding after index admission

Overall, 26 (21.7%) of the 120 surviving patients had 31 recurrent bleeding episodes
Table 1 Number of banding procedures and time to eradication of varices

| Child-Pugh grade | Number of patients | Survival > 90 d | Number eradicated | Number of banding procedures median (range) | Months to eradicate median (range) | Number of patients | Survival > 90 d | Number eradicated | Number of banding procedures median (range) | Months to eradicate median (range) | Number of patients | Survival > 90 d | Number eradicated | Number of banding procedures median (range) | Months to eradicate median (range) | Number of patients | Survival > 90 d | Number eradicated | Number of banding procedures median (range) | Months to eradicate median (range) | Number of patients | Survival > 90 d | Number eradicated | Number of banding procedures median (range) | Months to eradicate median (range) |
|------------------|--------------------|-----------------|------------------|---------------------------------------------|----------------------------------|------------------------|-----------------|------------------|---------------------------------------------|----------------------------------|------------------------|-----------------|------------------|---------------------------------------------|----------------------------------|------------------------|-----------------|------------------|---------------------------------------------|----------------------------------|------------------------|-----------------|------------------|---------------------------------------------|----------------------------------|------------------------|
| A                | n = 32             | 32              | 15               | 3 (1-13)                                    | 15 (1-55)                        | 9                      |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |
| B                | n = 48             | 44              | 18               | 2 (1-12)                                    | 4 (1-29)                         | 12                     |                 |                  |                             |                                  |                        | 16                     |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |
| C                | n = 60             | 35              | 17               | 2 (1-5)                                     | 3 (1-47)                         | 10                     |                 |                  |                             |                                  |                        |                        |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |
| **Total**        | **n = 140**        | **111**         | **50**           | **2 (1-13)**                                | **5 (1-55)**                    | **13**                  |                 |                  |                             |                                  |                        |                        |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |                  |                             |                                  |                        |                 |

Eradication of varices

Eradication was achieved in 50 of 111 patients (45%) who survived longer than 3 mo, after a median of 2 banding procedures (range 1-13), during a median of 6 mo, (range 0.5-55 mo) (Table 1). EV remained eradicated in 19 (Child-Pugh grade A n = 6, grade B n = 6, grade C n = 7) patients with a median follow-up from eradication of 25 mo (range 4-112 mo) (Figure 1). Seven of the 19 patients died after a median survival of 44 mo (range 4-112 mo).

Recurrent bleeding after variceal eradication

Three of the 31 patients with recurrent EV after eradication presented with variceal rebleeding at 3, 4 and 25 mo, respectively, and were successfully treated with EVL.

Varices not eradicated

The 61 patients whose EV were not eradicated had a total of 224 banding procedures (median 5 banding procedures, range 1-11) during a mean of 25 mo (Figure 1). Twenty three of the 61 patients died (18 due to progressive liver failure, 3 with MOF aggravated by recurrent BEV and 2 due to hepatorenal failure) at a median of 23 mo (range 3-103 mo). The remaining 38 patients were followed up for a median of 6 mo (range 0.5-99 mo). In 41 patients who had at least 4 banding sessions, EV reduced in size to either grade 1 (n = 25) or grade 2 (n = 16) none of whom rebled despite no further EVL. This group in whom EVL was not technically possible was regarded as having “functional eradication” as results were comparable to those with complete eradication.

Esophageal complications

Esophageal stricture at the banding site was noted in 16 patients during a follow-up endoscopy, none of whom required esophageal dilatation for relief of symptoms and resolved after passage of the endoscope.

Survival analysis

During a median follow-up period of 42 mo (range 9-220 mo), 69 (49.3%) of the 140 patients died (mean: 6.7 mo, range 0.03-141.7 mo). Liver failure (n = 46) was the most common cause of death followed by MOF in 14 patients. The cumulative overall survival of all 140 patients by life table analysis was 71.4% at 1 year, 65% at 3 years, 60% at 5 years and 52.1% at 10 years. Overall survival according to Child-Pugh grading is presented in Table 3. No significant specific risk factors for rebleeding were evident on multivariate analysis (Table 4).
### Table 2 Rebleeding after index admission in 120 surviving patients

| Overall bleeding from all sources | Bleeding from esophageal varices |
|----------------------------------|---------------------------------|
| Patients                         | Bleeding events                  |
| < 6 mo                           | 16 (13.3%)                       |
| 6-12 mo                          | 21 (17.5%)                       |
| 1-2 yr                           | 25 (20.8%)                       |
| > 2 yr                           | 26 (21.7%)                       |
| Overall                          | 26 (21.7%)                       |
| Patients                         | 22                               |
| Bleeding events                  |                                  |
| < 6 mo                           | 10 (8.3%)                        |
| 6-12 mo                          | 15 (12.5%)                       |
| 1-2 yr                           | 15 (12.5%)                       |
| > 2 yr                           | 16 (13.3%)                       |
| Overall                          | 16 (13.3%)                       |

### Table 3 Cumulative survival by Child-Pugh grade, n (%)

| Child-Pugh Grade | Number of patients | 1-yr survival | 3-yr survival | 5-yr survival | 10-yr survival |
|------------------|--------------------|---------------|---------------|---------------|----------------|
| A                | n = 32             | 30 (93.7)     | 29 (90.6)     | 29 (90.6)     | 25 (78.1)      |
| B                | n = 48             | 40 (83.3)     | 36 (75)       | 34 (70.8)     | 31 (64.5)      |
| C                | n = 60             | 30 (50)       | 26 (43.3)     | 21 (35)       | 17 (28.3)      |

### Table 4 Specific risk factors for rebleeding on multivariate analysis

| Total, n = 140 | No rebleeding, n = 104 | Rebleeding, n = 36 | P value |
|----------------|------------------------|--------------------|---------|
| Age            |                        |                    | 0.149   |
| 20-39 yr       | 36                     | 30                 | 6       |
| 40-59 yr       | 74                     | 50                 | 24      |
| > 60 yr        | 30                     | 24                 | 6       |
| Gender         |                        |                    | 0.112   |
| Male           | 100                    | 78                 | 22      |
| Female         | 40                     | 26                 | 14      |
| Child-Pugh grade |                    |                    | 0.965   |
| A              | 32                     | 24                 | 8       |
| B              | 48                     | 35                 | 13      |
| C              | 60                     | 45                 | 15      |
| Cause of varices |                    |                    | 0.343   |
| Alcoholic      | 84                     | 60                 | 24      |
| Non-Alcoholic  | 56                     | 44                 | 12      |

### DISCUSSION

In this prospective study the efficacy of EVL was evaluated in a large cohort of consecutive portal hypertensive patients treated at a specialist endoscopy referral center using specific and validated endpoints including control of the initial bleeding event and subsequent variceal eradication, rebleeding and recurrence. Acute control of active variceal bleeding was highly successful and hemostasis was achieved in 95.7% of patients with minimal banding morbidity. However, varices were completely eradicated in only 45% of patients who survived more than 3 mo. Furthermore, varices recurred in 62% of patients previously eradicated and 9.7% of these had further variceal bleeding. Overall, 81% of patients in this study had bleeding that was effectively controlled during the index banding procedure and, after repeat banding, never bled again from esophageal varices. However, the remaining 19% of the cohort had refractory and complicated variceal bleeding and required either balloon tamponade during the index endoscopy (4%) or rebleed during the initial...
hospitalization (3%) or rebled subsequently (12%) over the next 24 mo from residual or recurrent esophageal varices. As EVL is now universally regarded as the endoscopic method of choice for treating EV\cite{6} the data in this study are relevant and pertinent to current endoscopic variceal management and emphasize several important and unresolved issues related to the role of EVL in achieving hemostasis in actively bleeding varices and variceal eradication to prevent rebleeding\cite{1-4}.

Experts agree that EVL requires a high level of manipulative skill and mature
The incidence of variceal rebleeding after EVL in RCTs ranges from 0% to 36% (Table 4). In a meta-analysis of 14 RCTs, the overall rebleeding rate for EVL patients was 21.7% compared to an earlier analysis of RCTs which showed a median rebleeding rate of 32%. However, the calculations and denominators in many papers are not clearly defined and lack adherence to uniform standard definitions of rebleeding including time periods, whether overall or confined to variceal bleeding, or uncontrolled, or during the first admission or during long-term follow-up. In addition, there is non-uniformity among different trials in the definition of recurrent bleeding which may include esophageal, gastric and ectopic varices and non-variceal sources (portal hypertensive gastropathy, treatment-induced or peptic ulcer). In our study, we defined these criteria and analyzed the three specific and crucial time periods. The most common source of recurrent bleeding in our patient cohort during the early phase after initiation of endoscopic therapy and before variceal eradication was from patent residual varices which occurred in two-thirds of bleeding episodes, while one-third rebled from other sources.

Current AASLD/ACG guidelines emphasize total eradication of all varices as the desired endpoint of EVL. Similarly, the reported incidence of variceal eradication varies widely, ranging from a high of 95% to a low of 55% in RCTs (Table 5). A plausible explanation is that inconsistent definitions were used and in some reports the definition of variceal eradication included varices too small to be ligated. The wide variation in eradication rates may also be related to different treatment protocols such as different treatment intervals, number of bands applied per session and selective banding of EV in some centers which band only grade 3–4 varices. In our study, we indicated that EVL achieved variceal eradication rates between 79% and 100%. While there is some evidence to suggest that the methodology and technique of EVL might affect the number of sessions necessary to achieve obliteration, this alone does not explain the substantial differences found between patients. Furthermore, the reproducibility, method and accuracy with which residual variceal size is recorded is dependent on the degree of insufflation used during endoscopy as prolonged or over-inflation during endoscopy tends to flatten varices which then appear misleadingly small.

A major drawback of EVL is the higher propensity to variceal recurrence when compared to IST in RCTs (Table 5). Although new varices formed following initial eradication in 31 of 50 (62%) patients in our study, this was associated with rebleeding in only 3 (9.7%) patients. Variceal recurrence in other studies ranged between 8% and 48% after banding. More recent studies have shown recurrence rates of 12% to 36% (mean 25%) using EVL and NSBB. Interpretation of these results is
Table 5 Updated summary of published randomized controlled trials of endoscopic variceal ligation vs injection sclerotherapy

| Ref.                  | Year | Number of patients | Number in each group | Control of bleeding | Varices eradicated | Eradication sessions | Rebleeding | Major complications | Variceal recurrence | Survival |
|-----------------------|------|--------------------|----------------------|---------------------|-------------------|----------------------|-------------|---------------------|---------------------|----------|
|                       |      |                    | EVL                  | IST                 | EVL               | IST                  | EVL         | IST                 | EVL               | EVL      |
| Stiegmann et al[21]   | 1992 | 129                | 64                   | 65                  | 86%               | 77%                  | 55%         | 56%                 | 4                  | 5        |
| Laine et al[22]       | 1993 | 77                 | 38                   | 39                  | 89%               | 89%                  | 59%         | 69%                 | 4.1               | 6.2      |
| Gimson et al[23]      | 1993 | 103                | 54                   | 49                  | 91%               | 92%                  | 82%         | 71%                 | 3.4               | 4.9      |
| Lo et al[26]          | 1995 | 120                | 61                   | 59                  | 94%               | 80%                  | 74%         | 63%                 | 3.8               | 6.5      |
| Hou et al[25]         | 1995 | 134                | 67                   | 67                  | 100%              | 88%                  | 87%         | 79%                 | 3.5               | 4.6      |
| Sarin et al[26]       | 1997 | 95                 | 47                   | 48                  | 86%               | 80%                  | 94%         | 94%                 | 4.1               | 5.2      |
| Baroncini et al[37]   | 1997 | 111                | 57                   | 54                  | -                 | 93%                  | 93%         | 3.5                 | 4.0               | 16%      |
| Avgierinos et al[38]  | 1997 | 77                 | 37                   | 40                  | -                 | 95%                  | 98%         | 3.7                 | 5.8               | 27%      |
| Lo et al[39]          | 1997 | 71                 | 37                   | 34                  | 97%               | 76%                  | -           | -                   | -                 | 17%      |
| Siqueira et al[40]    | 1998 | 40                 | 20                   | 20                  | -                 | 90%                  | 100%        | 3.1                 | 3.7               | 0%       |
| De la Pena et al[5]   | 1999 | 88                 | 42                   | 46                  | -                 | 79%                  | 71%         | 5.3                 | 6.6               | 31%      |
| Masci et al[21]       | 1999 | 100                | 50                   | 50                  | -                 | 88%                  | 82%         | 3.4                 | 5.3               | 12%      |
| Fakhry et al[42]      | 2000 | 84                 | 43                   | 41                  | 94%               | 94%                  | -           | -                   | 2.8               | 4.8      |
| Zargar et al[43]      | 2005 | 73                 | 37                   | 36                  | 100%              | 85%                  | 95%         | 92%                 | 3.7               | 7.7      |
| Villanueva et al[5]   | 2006 | 179                | 90                   | 89                  | 96%               | 85%                  | -           | -                   | -                 | 7%       |
| Luz et al[44]         | 2011 | 100                | 50                   | 50                  | 92%               | 96%                  | -           | -                   | -                 | 22%      |
| Ali et al[45]         | 2017 | 124                | 60                   | 64                  | 100%              | 100%                 | 87%         | 80%                 | -                 | 23%      |

EVL: Endoscopic variceal ligation; IST: Injection sclerotherapy. Bold color highlighted comparisons are significant, \( P < 0.05 \).

Complicated by the differences in length of follow up, definitions of variceal recurrence, different medications and dosage used and the etiology of portal hypertension. Accumulated evidence suggests that patent para-esophageal and peri-esophageal variceal feeder vessels predispose to variceal recurrence. Data from RCTs show lower recurrence rates after IST, probably because sclerotherapy induces fibrosis and eradication of perforating veins in contrast to band ligation, which does not affect collateral vessels in the deeper esophageal wall layers[18,42].

The current study has several limitations. Firstly, as the study was conducted in a single center academic tertiary referral hospital with experienced on-call endoscopists
and staff available around the clock, patient selection and treatment bias may occur as similar advanced interventions may not be available or replicated in smaller hospitals. Secondly, half the patients in the study were Child-Pugh grade C with hepatic decompensation associated with the highest mortality and our results cannot be generalized to all other patient populations. The use of an inclusive “all-cause” definition for rebleeding was applied to minimize bias found in previous definitions which often excluded non-variceal causes of re-bleeding.

The strengths of this study are derived from the implementation of a modern protocol-driven and standardized EVL technique in a specialist endoscopy center. In order to provide the highest possible level of uniformity and to minimize differences in the zero-time entry, only patients who received their initial and subsequent treatment in our unit were included. The study design minimized possible biases that may arise from patient selection, referral practices and local variations in treatment strategies. The use of rebleeding and death as the main outcomes provided robust, consistent and objective end-points in the study. Unlike other studies which included non-consecutive patients, incomplete reporting of inclusion and exclusion criteria and have incomplete follow-up or inclusion of patients at differing disease stages without separate analyses, our study design avoided these pitfalls by excluding non-measurable biases.

CONCLUSION

In conclusion, this study confirms that EVL provides the optimal endoscopic method both for control of acute bleeding and for the long-term treatment of varices despite the higher tendency for recurrence. Consistent with previous reports, EVL in this study was safe with low procedure-related complication rates. While complete visual eradication of varices is more frequently achievable with IST and has consistently been used as the desired endpoint for endoscopic variceal intervention, this goal is not always attainable in EVL. As alluded to above, the inherent attributes of EVL and IST are dissimilar and complete eradication may not be achievable in all patients undergoing EVL. Overall four-fifths of patients in this study had EV that were easily managed and responded to β-blockers and EVL with no further bleeding after the initial index intervention. However, the remaining one-fifth of patients were complicated and had bleeding that was difficult to control in the short and long-term despite being on combination therapy. We have identified a subgroup of patients with small (Grade 1 and 2) varices where size and mucosal scarring preclude further safe banding. Importantly, we have shown that these patients have “stable varices” with no rebleeding or progression which resulted in “functional eradication” despite the presence of residual small visible varices. The results of this study should stimulate further research to optimize robust and objective endpoints for reporting of EVL which are likely to differ from the historical outcomes reported in previous RCTs. The elusive Holy Grail of endoscopic variceal banding remains the attainment of long-term bleed-free survival.

ARTICLE HIGHLIGHTS

Research background
Bleeding esophageal varices (BEV) is a potentially life-threatening complication in patients with portal hypertension with mortality rates as high as 25% within six weeks of the index variceal bleed. Although endoscopic intervention provides the optimal emergency method to control actively BEV, the risks of bleeding complications remain substantial and as many as 23% of patients have treatment failure within 5-d due to either uncontrolled or early rebleeding. Approximately 60% of survivors rebleed within two years after the initial bleeding episode with a mortality rate of 30%. Secondary prophylaxis to prevent further variceal bleeding is thus crucial.

Research motivation
Endoscopic varical ligation (EVL) has replaced injection sclerotherapy (IST) as the endoscopic interventional procedure of choice for BEV, supported by randomized controlled trial data that show more rapid eradication of varices with lower rates of recurrent bleeding and fewer endoscopic-related complications. However, few studies have specifically evaluated detailed outcomes in relation to the inherent technical
constraints of ligating device design which may influence the effectiveness of EVL in controlling acute variceal bleeding and in particular, achieving complete eradication of varices, a problem conceptually more relevant to endoscopic banding than sclerotherapy.

**Research objectives**
This analysis, based on a protocol-driven standardized EVL technique from a high-volume academic endoscopy referral center, used STROBE guidelines to assess the efficacy of EVL in controlling acute variceal bleeding, preventing early rebleeding and achieving complete and durable variceal eradication to prevent late recurrent bleeding in a cohort of patients who presented with an index variceal bleeding event.

**Research methods**
Consecutive adult patients with endoscopically proven BEV between January 2000 and December 2018 were assessed. The outcome of all endoscopic treatments, both emergency and subsequent elective therapy, was analyzed to assess the efficacy of EVL in acute variceal bleeding control and achieving complete and lasting variceal eradication. Data collected included demographic and clinical information, cause of portal hypertension, Child-Pugh score, hematology and liver function tests, liver biopsy, imaging results, endoscopy information, including variceal size, number of bands placed at each session, the interval between and the number of banding sessions. Outcome data included the efficacy of EVL in controlling the acute index bleed, preventing early rebleeding, achieving complete variceal eradication, minimizing late recurrent bleeding and overall survival. The primary endpoints of the study were (1) effective endoscopic control of the index variceal bleeding event and (2) success in achieving complete variceal eradication as defined in the analysis criteria. Secondary endpoints included (1) early rebleeding; (2) variceal recurrence and rebleeding and (3) overall survival.

**Research results**
Acute control of active variceal bleeding in the 140 patients was highly successful and hemostasis was achieved in 95.7% of patients with minimal banding morbidity. However, varices were completely eradicated in only 45% of patients who survived more than 3 months. Furthermore, varices recurred in 62% of patients previously eradicated and 9.7% of these had further variceal bleeding. Overall, 81% of patients in this study had bleeding that was effectively controlled during the index banding procedure and, after repeat banding, never bled again from esophageal varices. However, the remaining 19% of the cohort had refractory and complicated variceal bleeding and required either balloon tamponade during the index endoscopy (4%) or rebled during the initial hospitalization (3%) or rebled subsequently (12%) over the next 24 months from residual or recurrent esophageal varices.

**Research conclusions**
In conclusion, this study confirms that EVL provides the optimal endoscopic method both for control of acute bleeding and for the long-term treatment of varices despite the higher tendency for recurrence. Consistent with previous reports EVL in this study was safe with low procedure-related complication rates. While complete visual eradication of varices is more frequently achievable with IST and has consistently been used as the desired endpoint for endoscopic variceal intervention, this goal is not always attainable in EVL.

**Research perspectives**
In this study we have identified a subgroup of patients with small varices where size and mucosal scarring preclude further safe banding. Importantly we have shown that these patients have “stable varices” with no rebleeding or progression which resulted in “functional eradication” despite the presence of residual small visible varices. The results of this study should stimulate further research to optimize robust and objective endpoints for reporting of EVL which are likely to differ from the historical outcomes reported in previous randomized controlled trials. The elusive Holy Grail of endoscopic variceal banding remains the attainment of long-term bleed-free survival.
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