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ORIGINAL ARTICLE

**Randomized Controlled Trial** 

# Endoscopic polidocanol foam sclerobanding for the treatment of grade II-III internal hemorrhoids: A prospective, multi-center, randomized study

Chun-Ying Qu, Fei-Yu Zhang, Wen Wang, Feng-Yu Gao, Wu-Lian Lin, Hao Zhang, Guang-Yu Chen, Yi Zhang, Ming-Ming Li, Zheng-Hong Li, Mei-Hong Cai, Lei-Ming Xu, Feng Shen

Chun-Ying Qu, Fei-Yu Zhang, Yi Zhang, Ming-Ming Li, Zheng-Hong Li, Mei-Hong Cai, Lei-Ming Xu, Specialty type: Gastroenterology Feng Shen, Department of Gastroenterology & Endoscopy, Xinhua Hospital Affiliated to and hepatology Shanghai Jiao Tong University School of Medicine, Shanghai 200092, China Provenance and peer review: Wen Wang, Wu-Lian Lin, Department of Gastroenterology, The 900th Hospital of the People's Unsolicited article; Externally peer Liberation Army Joint Service Support Force, Fuzhou 350025, Fujian Province, China reviewed. Feng-Yu Gao, Department of Endoscopy, Shandong Provincial Maternal and Child Health Care Peer-review model: Single blind Hospital Affiliated to Qingdao University, Jinan 250014, Shandong Province, China Peer-review report's classification Hao Zhang, Department of Endoscopy, Baoshan People's Hospital of Yunnan Province, Scientific Quality: Grade B, Grade Baoshan 678000, Yunnan Province, China С Novelty: Grade B, Grade C Guang-Yu Chen, Department of Gastroenterology, Xinhua Hospital Affiliated to Shanghai Jiao Creativity or Innovation: Grade A, Tong University School of Medicine, Shanghai 200092, China Grade B Co-first authors: Chun-Ying Qu and Fei-Yu Zhang. Scientific Significance: Grade B, Grade B Co-corresponding authors: Lei-Ming Xu and Feng Shen. P-Reviewer: Kumar R; Seow-Choen Corresponding author: Feng Shen, MD, PhD, Chief Doctor, Department of Gastroenterology & F Endoscopy, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, No. 1665 Kongjiang Road, Shanghai 200092, China. shenfeng01@xinhuamed.com.cn Received: March 11, 2024 Revised: May 28, 2024 Accepted: June 14, 2024 Abstract Published online: July 21, 2024 BACKGROUND Processing time: 122 Days and 5.5 Endoscopic rubber band ligation (ERBL) is a nonsurgical technique for the Hours treatment of symptomatic internal hemorrhoids but is limited by recurrence and post-procedural pain.



#### AIM

To evaluate satisfaction, long-term recurrence, and post-procedural pain in managing internal hemorrhoids using a combination of polidocanol foam sclero-therapy and ERBL.

#### **METHODS**

This was a prospective, multicenter, randomized study. A total of 195 consecutive patients diagnosed with grade II-III internal hemorrhoids were enrolled from four tertiary hospitals and randomly divided into a cap-assisted endoscopic polidocanol foam sclerobanding (EFSB) or an ERBL group. All patients were followed-up for 12 months. Symptom-based severity and post-procedural pain were assessed using a hemorrhoid severity score (HSS) and a visual analog scale (VAS). Continuous variables were reported as medians and interquartile range.

#### RESULTS

One hundred and ninety-five patients were enrolled, with 98 in the EFSB group. HSS was lower in the EFSB group than in the ERBL group at 8 weeks [4.0 (3.0-5.0) *vs* 5.0 (4.0-6.0), *P* = 0.003] and 12-month [2.0 (1.0-3.0) *vs* 3.0 (2.0-3.0), *P* < 0.001] of follow-up. The prolapse recurrence rate was lower in the EFSB group at 12 months (11.2% *vs* 21.6%, *P* = 0.038). Multiple linear regression analysis demonstrated that EFSB treatment [B = -0.915, 95% confidence interval (CI): -1.301 to -0.530, *P* = 0.001] and rubber band number (B = 0.843, 95%CI: 0.595-1.092, *P* < 0.001) were negatively and independently associated with the VAS score 24 hours post-procedure. The median VAS was lower in the EFSB group than in the ERBL [2.0 (1.0-3.0) *vs* 3.0 (2.0-4.0), *P* < 0.001].

#### CONCLUSION

Cap-assisted EFSB provided long-term satisfaction and effective relief from the recurrence of prolapse and pain 24 hours post-procedure.

Key Words: Internal hemorrhoids; Endoscopic therapy; Polidocanol foam; Sclerotherapy; Rubber band ligation; Sclerobanding

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**Core Tip:** Endoscopic rubber band ligation (RBL) is a nonsurgical technique for the management of symptomatic internal hemorrhoids. However, it is constrained by recurrence and post-procedural pain. Endoscopic polidocanol foam sclerobanding (EFSB) is a novel approach known that has been proposed to address these challenges. In this study, we integrated endoscopic polidocanol foam sclerotherapy with RBL in patients presenting with grade II-III internal hemorrhoids and conducted a prospective, multicenter, randomized study to assess the long-term symptomatic and endoscopic efficacy of EFSB. Our findings demonstrated that EFSB offered long-term satisfaction and effective relief from prolapse recurrence and post-procedural pain.

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# INTRODUCTION

Internal hemorrhoids are the most common benign condition of the anorectum. They are characterized by bleeding and prolapse during defecation, resulting in pain. Rubber band ligation (RBL) is a simple, cost-effective, and long-term treatment for symptomatic internal hemorrhoids. Injection sclerotherapy (IS) and RBL are the most commonly employed nonsurgical techniques for hemorrhoids[1]. Considering both efficacy and post-operative complications, Tutino *et al*[2] recommended IS as a first-line treatment option, and RBL for treating persistent symptomatic grade II-III prolapse. More recently, Pata *et al*[3] reported that sclerobanding, which combines RBL with polidocanol foam sclerotherapy using an anoscope, was a safe technique and had a low rate of post-operative complications.

The development of flexible endoscopy allowed use of retroflex endoscopic RBL (ERBL) to provide improved maneuverability, photographic documentation, as well as better performance of hemorrhoidal ligation[4]. However, RBL is associated with a higher long-term recurrence rate than that observed with surgical treatment[5]. The recurrence rate of RBL has been reported to range from 15.5% to 31.1% and varies depending on the hemorrhoid grade, ligation method, follow-up time, and retreatment sessions[5-7]. Post-procedural pain was identified as the most common complication[8, 9].

Polidocanol is a nonionic surfactant that mainly targets endothelial cells, causes vasospasm and inflammation, and is a local anesthetic[10]. Polidocanol induces an inflammatory reaction with sclerosis of the submucosal tissue and consequent contraction of the hemorrhoidal tissue, thus improving bleeding and prolapse. Use of this foam formulation is associated with reduced rates of post-procedural pain and bleeding recurrence when used to manage grade I and II internal hemorrhoids[11]. However, no significant series of retroflex endoscopy sclerobanding have been reported.

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In addition, there is a lack of clinical trials comparing the endoscopic-based improvement of sclerobanding and ERBL for the long-term management of patients with grade II and III internal hemorrhoids. We hypothesized that the submucosal injection of polidocanol foam before RBL would lift the mucosa for easy ligation and increase fibrosis in the submucosal tissue, thus helping to improve long-term efficacy. Therefore, in this study, we evaluated the long-term symptomatic and endoscopic efficacy of endoscopic polidocanol foam sclerobanding (EFSB) for the treatment of grade II and III internal hemorrhoids.

# MATERIALS AND METHODS

This multicenter, single-blind, randomized study was conducted in four Chinese Gastroenterology and Endoscopy centers (Xinhua Hospital, Shanghai; Shangdong Provincial Maternal and Child Health Care Hospital, Shangdong; Baoshan People's Hospital of Yunnan Province, Yunnan; The 900th Hospital of the People's Liberation Army Joint Service Support Force, Fuzhou). The ethics committee of the Xinhua Hospital approved the study (XHEC-C-2020-003-1), and all patients provided written informed consent before enrolling in the study.

#### Inclusion and exclusion criteria

Consecutive adult patients who were 18-60 years of age and diagnosed with grade II or III internal hemorrhoids according to the traditional Goligher classification between May 2020 and March 2021 were prospectively enrolled. The inclusion criteria were obvious symptoms of prolapse with or without bleeding, no previous history of endoscopic treatment, failure of conservative treatment (such as adequate fluid or fiber intake, medication, and lifestyle changes), and a willingness to undergo simultaneous colonoscopy. The exclusion criteria were: (1) Over 60 years of age; (2) Severe cardiopulmonary insufficiency; (3) Diagnosis of malignant tumors; (4) Colon polyps > 1 cm in diameter or at > 3 sites; (5) Diagnosis of inflammatory bowel disease or other perianal diseases (e.g., anal fistulas and fissures); (6) Autoimmune disease; (7) History of internal hemorrhoid surgery; (8) Allergy to polidocanol; and (9) Lost to follow-up.

#### Sample size and randomization

Our primary aim was a superiority comparison of prolapse recurrence at 12 months post-procedure between the EFSB and ERBL groups. In previous studies, the average long-term recurrence rate was approximately 15% [5,6]. However, EFSB is known to reduce the recurrence rate to 10%. First, we performed a power calculation. With a statistical power of 90%, a type I error of 5%, and a superiority margin of 10%, the analysis indicated that we required 166 participants (83 in each group). Assuming a dropout rate of 15%, a final sample of 195 patients was required.

Randomization was performed after the colonoscopy had been completed and indicated that endoscopic treatment of internal hemorrhoids was necessary. Random numbers were generated by a computer with SPSS version 22.0 (IBM Corp., Armonk, NY, United States), written on cards, and placed in envelopes. The participants were randomized to two groups according to the corresponding random numbers to an EFSB group that received 10 mg/mL of polidocanol foam sclerotherapy combined with RBL, and an ERBL group that received endoscopic RBL only.

# Clinic and laboratory variables

We calculated the symptom-based hemorrhoid severity score (HSS)[12] at baseline (T0) to assess its potential effect on the quality of the life of patients. The HSS was used to record five self-assessed symptoms (pain on defecation, itching, bleeding, soiling, and prolapse requiring manual repositioning) according to their frequency (0, never; 1, monthly; 2, weekly; 3, daily) during the previous month, with a total score ranging from 0 to 15. Low scores indicated elevated levels of patient satisfaction [13]. The anthropometric measurements obtained during the initial interview included height, body mass, and body mass index (BMI, kg/m<sup>2</sup>). Fasting venous blood samples were collected to determine preprocedural hemoglobin level, prothrombin time, and alanine aminotransferase (ALT) level 1 d before the procedure.

# Preprocedural preparation

Anticoagulant drugs were stopped 5-7 d before the procedure. A polyethylene glycol solution (with a split dose) was utilized for bowel preparation. A 1% polidocanol foam (20 mg/2 mL, Hameln Pharmaceuticals GmbH, Germany) was prepared as described by Moser et al[14], with a temporary preparation before injection. The endoscopy equipment included an Olympus GIF-H290 gastroscope, a CF H290I colonoscope, a transparent cap (Olympus, Japan), an Interject injection therapy needle catheter (23 g, Boston Scientific, United States), and a Speedband Superview Super 7 Multiple Band Ligator (Boston Scientific, United States).

#### Treatment and endoscopic classification

All patients were required to undergo a complete colonoscopic examination under propofol intravenous anesthesia prior to internal hemorrhoid therapy. Intestinal polyps were removed by cold snare polypectomy before hemorrhoid treatment. We changed to a gastroscope, and the anal canal was opened with a transparent cap, fully inflated, and rinsed with a water jet. Subsequently, the patient was examined by gastroscopy. The evaluation items were assessed in both forward and retroflexed positions and then classified by the degree of range, form, and the presence of red color signs [15]. The range was determined by the circumferential distribution of the internal hemorrhoids and was classified into five grades (0, no hemorrhoids; 1, one-quarter the circumference; 2, half the circumference; 3, three-quarters the circumference; 4, the whole circumference). The form was determined by the diameter of the largest hemorrhoid and was



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classified into three grades (0, no hemorrhoids; 1, < 12 mm in diameter;  $2, \ge 12$  mm or more in diameter). In the EFSB group, polidocanol foam was primarily injected into the submucosa under the pedicle of the hemorrhoids or around the prominent red signs above the dentate line (Figure 1A). The injection was stopped when the mucosa was fully raised, and the amount of foam at each point was < 4 mL (Figure 1B). A transparent cap was used to suppress extensive bleeding while pulling out the needle. A multiple rubber band ligator was attached to the top of the gastroscope in a retroflexed position to remove negative pressure and ligate the upper mucosa of the hemorrhoid. A single band was released in each hemorrhoid while avoiding repeated ligation of the same plane (Figure 1C). The complete procedure is shown in Video, attached. Patients in the ERBL group underwent endoscopic RBL without injection. All patients were treated by gentle manual massage and assisted during their recovery from prolapse to prevent acute thrombosis following the procedure [16]. At each center, all procedures were performed by the same physician.

#### Follow-up and outcomes

Patients were kept under observation in a day ward for 24 hours post-operatively to exclude serious adverse events or complications, and were discharged only after completing the post-procedural pain assessment. All participants were instructed to consume a low-fiber diet for 3 d to ensure a soft stool consistency and were advised to maintain external cleanliness. Participants were followed-up for 12 months and completed questionnaires in the outpatient department, at 24 hours (T1), 1 week (T2), 4 weeks (T3), 8 weeks (T4), and 12 months (T5) after the procedure. Participants in both groups were followed-up as outpatients at 3 months intervals thereafter until 12 months had elapsed or recurrence occurred. Symptom-based HSS questionnaires, post-procedural pain, treatment-induced complications, and recurrence of prolapse and/or bleeding were recorded.

The primary study endpoint was prolapse and/or bleeding recurrence after long-term evaluation. Recurrence was defined as an improved but persistent prolapse with or without bleeding in both grade II and III hemorrhoids. All cases were confirmed by the same endoscopic physician who performed the treatment (Figure 2). Overall satisfaction was assessed at T4 and T5 with the HSS. Safety was evaluated as an additional primary outcome of patient-reported adverse reactions. The secondary endpoint was post-procedural pain and bleeding in terms of short-term and long-term satisfaction, and patient-reported adverse reactions.

#### Statistical analysis

Statistical analysis was performed with SPSS version 22.0 for Windows (IBM Corp. Armonk, NY, United States). Continuous variables were reported as medians and interquartile range (IQR). The Mann-Whitney U test was used to compare between-group differences of continuous variables. Count datas were reported as numbers and proportions. The  $\chi^2$  test was used to compare differences of categorical variables. Correlations of the VAS score and other variables were assessed by Spearman's correlation coefficient ( $\rho$ ). Stepwise multiple linear regression was used for multivariate analysis, and 95% confidence intervals (CIs) were calculated. All statistical tests were two sided. Statistical significance was set at P < 0.05. The statistical methods were reviewed by Guang-Yu Chen of Clinical Research Unit, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine.

# RESULTS

#### Patient characteristics

During the study period, 217 patients with grade II or III internal hemorrhoids with prolapse and/or bleeding underwent endoscopy. A total of 22 patients were excluded, 2 patients with ulcerative colitis (remission), 4 with malignant tumors, 1 with sicca syndrome, 3 over 60 years of age, 7 with colon polyps > 1 cm in diameter or > 3 sites, and 5 who were lost to follow-up (Figure 3). The remaining 195 patients with symptomatic internal hemorrhoids were prospectively enrolled. The majority were men (n = 108, 55.4%) and the median age (IQR) was 46.0 (40.0-50.0) years. Of the 97 patients in the ERBL group, 73.2% (n = 71) were grade II, of the 98 in the EFSB group, 67.3% (n = 66) were grade II. No statistically significant differences of sex, age, BMI, hemoglobin level, prothrombin time, or ALT level in the two groups in terms were observed (Table 1).

#### Endoscopy treatment

Of the total participants (n = 195), 5.0 (4.0-5.0) rubber bands were used for grade III hemorrhoids, which was significantly higher than those used for grade II [3.0 (3.0-3.5), P < 0.001]. The number of rubber bands used in the ERBL and EFSB groups were 3.0 (3.0-4.5) and 3.0 (3.0-4.3), respectively, and the between-group differences were not significant (P =0.821). In the EFSB group, 13.0 (12.0-15.0) mL polidocanol foam was injected at 4.6 (3.8-5.0) sites; no polidocanol was injected in the ERBL group. In the ERBL group, the rubber band fell off during the operation in 3.1% of participants (n =3) because of insufficient suction or premature release. Exhausted rubber bands were identified in 1.0% of the patients (*n* = 1) because of incomplete absorption of intestinal gas following the completion of treatment. All patients underwent colonic endoscopy. A total of 35.9% (*n* = 70) of the patients had intestinal polyps and underwent cold snare polypectomy before ERBL or EFSB (39.2% *vs* 32.7%, *n* = 38 *vs n* = 32, *P* = 0.212).

#### Long-term recurrence and satisfaction

The rate of prolapse recurrence in the EFSB group was 11.2% (n = 11) and was significantly lower than that in the ERBL group (21.6%, n = 21) at T5 (P = 0.038). In general, the HSS decreased with follow-up time in both the ERBL and EFSB



Qu CY et al. Endoscopic sclerobanding for internal hemorrhoids

Table 1 Clinical and laboratory char groups	acteristics of patients in the e	ndoscopic rubber band liç	ation and endoscopic foa	am sclerobanding
Characteristic	Total patients, <i>n</i> = 195	ERBL, <i>n</i> = 97	EFSB, <i>n</i> = 98	P value
Male sex	108 (55.4)	58 (59.8)	50 (51.0)	0.250
Age in years	46.0 (40.0-50.0)	47.0 (40.5-50.0)	45.0 (39.5-50.0)	0.948
Goligher classification				
Grade II	137 (70.3)	71 (73.2)	66 (67.3)	0.231
Grade III	58 (29.7)	26 (26.8)	32 (32.7)	
Haemorrhoid severity score	8.0 (6.0-9.0)	9.0 (7.5-10.0)	8.00 (6.00-9.25)	0.564
Body mass index in kg/m <sup>2</sup>	21.7 (20.0-23.0)	20.7 (19.0-22.1)	21.8 (20.0-23.2)	0.896
Haemoglobin in g/L	130.0 (125.0-138.0)	129.0 (123.0-139.0)	134.5 (125.0-138.0)	0.319
Prothrombin time in sec	12.0 (11.0-12.0)	12.0 (11.0-12.0)	11.0 (10.1-12.8)	0.752
Alanine aminotransferase in U/L	25.0 (16.9-33.0)	25.0 (15.0-33.0)	24.0 (19.0-32.3)	0.316

Continuous variables are medians (interquartile ranges) and compared using the Mann-Whitney U test. Count data are percentages and analysed using the  $\chi^2$  test. EFSB: Endoscopic foam sclerobanding; ERBL: Endoscopic rubber band ligation.



Figure 1 Endoscopic transparent cap-assisted endoscopic foam sclerobanding for the treatment of internal hemorrhoids. A: An obvious red color sign of internal hemorrhoids was observed with the transparent cap (indicated by arrows); B: Submucosal foam polidocanol injection, the white foam, was prominently raised; C: Negative pressure remove and ligation of the hemorrhoids with a retroflexed position. The white ball (arrow) is the ligated mucosa after foam sclerotherapy injection.

groups. The HSS was significantly lower in the EFSB group than in the ERBL group at both T4 [4.0 (3.0-5.0) vs 5.0 (4.0-6.0), P = 0.003], and T5 [2.0 (1.0-3.0) vs 3.0 (2.0-3.0), P < 0.001], see Figure 4A.

#### Post-procedural pain

At T1, the VAS in the EFSB group was 2.0 (1.0-3.0), which was significantly lower than that in the ERBL group [3.0 (2.0-4.0), P < 0.001]. However, the difference was not significant at T2 (Figure 4B). At T1, 65.3% (n = 64) of patients in the EFSB group had non-mild pain and the percentage was significantly higher than that in the ERBL group (40.2%, n = 39, P =0.001). No statistically significant differences were observed at T2 (Table 2).

Next, we focused on T1 and discovered that the VAS values were strongly associated with the EFSB group ( $\rho$  = 0.264, P < 0.001), grade ( $\rho$  = 0.251, P < 0.001), and the number of rubber bands ( $\rho$  = 0.391, P < 0.001). Multiple linear regression analysis revealed that the EFSB group (B = -0.915, 95% CI: -1.301 to -0.530, P = 0.001) and the number of rubber bands (B = 0.843, 95% CI: 0.59-1.092, P < 0.001) were independently associated with VAS. In the ERBL group, one female patient experienced severe persistent pain for more than 4 hours following the procedure. An endoscopic examination revealed that the anal papilla and internal hemorrhoids were bandaged together. Her pain gradually decreased with the use of an anti-inflammatory analgesic suppository.

#### Post-procedural complications

Post-procedural bleeding was another frequent complication, and was recorded in 52.8% (n = 103) of the patients at T2. The rates of no, mild, moderate, and severe bleeding in the ERBL and EFSB groups were 49.5% and 44.9% (*n* = 48 vs *n* = 44), 40.2% and 41.8% (*n* = 39 *vs n* = 41), 8.2% and 9.2% (*n* = 8 *vs n* = 9), and 2.1% and 4.1% (*n* = 2 *vs n* = 4), respectively. No statistically significant differences were observed between the groups (P = 0.815). A 42-year-old male patient with severe



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Table 2 Comparison of post-procedural pain of patients in the endoscopic rubber band ligation and endoscopic foam sclerobanding	
groups	

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Visual analogue scale	Total patients, <i>n</i> = 195	ERBL, <i>n</i> = 97	EFSB, <i>n</i> = 98	P value
T1 <sup>1</sup>				
None-mild, ≤ 2	103 (52.8)	39 (40.2)	64 (65.3)	0.001
Moderate, 3-6	90 (46.2)	56 (57.7)	34 (34.7)	
Severe, ≥ 7	2 (1.0)	2 (2.1)	0 (0)	
T2 <sup>2</sup>				
None-mild, ≤ 2	175 (89.7)	85 (87.6)	90 (91.8)	0.232
Moderate, 3-6	20 (10.3)	12 (12.4)	8 (8.2)	
Severe, ≥ 7	0 (0)	0 (0)	0 (0)	

<sup>1</sup>T1: 24 hours post-procedure.

<sup>2</sup>T2: 1 week post-procedure.

Count data are percentages and analysed using the  $\chi^2$  test.



Figure 2 Treatment and follow-up of a patient with grade III internal hemorrhoids. A: Internal hemorrhoids with prolapse; B and C: Endoscopic foam sclerobanding (EFSB); D: 12 months after EFSB without apparently prolapse; E: Formation of scars (arrow) in retroflexed; F: Formation of scars (arrow) in normal position.

bleeding in the EFSB group was diagnosed with an anal ulcer that resolved with conservative treatment using a hemorrhoid suppository. At T3, the rates of no and mild bleeding in the ERBL and EFSB groups were 55.7% and 59.2% (n = 54 vs n = 58), and 44.3% and 40.8% (n = 43 vs n = 40), respectively (P = 0.363). None of the patients experienced moderate or severe bleeding at T3. A 58-year-old male patient developed urination difficulties that improved after the application of heat without special treatment. No pelvic abscesses, fever, thrombosis, anal fistulas, or fissures were recorded in either group.

# DISCUSSION

To our knowledge, this is the first study to use an endoscope combined with polidocanol foam sclerotherapy and RBL to



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Figure 3 Flowchart of patient inclusion, exclusion and intervention. During the study period, 217 patients with grade II or III internal hemorrhoids were enrolled. A total of 22 patients were excluded, 2 with ulcerative colitis (remission), 4 with malignant tumors, 1 with sicca syndrome, 3 over 60 years of age, 7 with colon polyps > 1 cm in diameter or at > 3 sites, and 5 who were lost to follow-up. The remaining patients were randomly assigned to endoscopic rubber band ligation (n = 97) or endoscopic foam sclerobanding (n = 98). EFSB: Endoscopic polidocanol foam sclerobanding; ERBL: Endoscopic rubber band ligation.



**Figure 4 Box plots.** A: Hemorrhoid severity score in the endoscopic rubber band ligation (ERBL) group and the endoscopic foam sclerobanding (EFSB) group according to follow-up time. Before procedure (T0), at 8 weeks (T4), and at 12 months (T5) post-procedure. Upper and lower whiskers indicate the 75<sup>th</sup> percentile plus 1.5 interquartile range (IQR) and the 25<sup>th</sup> percentile indicates minus 1.5 IQR. Outlier: A value greater than the 75<sup>th</sup> percentile plus 1.5 IQR; B: Pain visual analogue scale score in the ERBL group and the EFSB group on follow-up at 24 hours (T1) and 1 week (T2) post-procedure. Upper and lower whiskers indicate the 75<sup>th</sup> percentile plus 1.5 IQR and the 25<sup>th</sup> percentile minus 1.5 IQR.

treat patients with grade II and III internal hemorrhoids. We demonstrated that the submucosal injection of polidocanol foam before RBL reduced long-term prolapse recurrence and relieved short-term post-procedural pain. Compared to the ERBL group, the EFSB group experienced a lower recurrence rate (11.2% *vs* 21.6%, n = 11 vs n = 21) and a significant reduction in symptomatic HSS [2.0 (1.0-3.0) *vs* 3.0 (2.0-3.0)] at the end of follow-up. Multiple linear regression analysis confirmed that EFSB treatment was independently and negatively associated with the VAS at 24 hours post-procedure. After 1 week, pain was relieved in both groups. This multi-center study found that EFSB was associated with a high level of satisfaction, low recurrence at 12 months follow-up, and effective relief of pain at 24 hours post-procedure.

Currently, nonoperative management of internal hemorrhoids is considered a valid alternative to surgical therapy[7]. One theory suggests that internal hemorrhoids are caused by abnormal expansion and distortion of blood vessels and destructive changes in the anal cushion that supports connective tissue [17]. The primary principle of RBL is to remove abnormal anal cushion tissue, promote fibrosis, and attach the anal cushion to the mucosa, thereby alleviating the main

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symptoms of prolapse. Compared to traditional proctoscopy, RBL use of a flexible endoscope is considered to provide better maneuverability, better vision, more rubber band release, and a lower bleeding recurrence rate[18]. However, use of RBL or ERBL to treat internal hemorrhoids with severe prolapse is associated with a high recurrence rate. A systematic review by Dekker *et al*[5] reported a recurrence rate of 31.1% (n = 50) with RBL treatment and was higher than that observed after hemorrhoidectomy. Compared to hemorrhoidal artery ligation, the recurrence rate of grade II and III internal hemorrhoids 1 year after RBL treatment was 49%[19]. To date, various evaluation criteria such as hemorrhoid grades, session times, and different follow-up periods have been used to determine the recurrence rate, and the results have been variable [7]. The primary goal of treating grade II and III internal hemorrhoids with EBL is to alleviate prolapse. Thus, the primary aim of our study was to investigate the recurrence of prolapse but not bleeding. This multicenter study, which had a 12-month follow-up period, indicated that sclerotherapy decreased the recurrence of prolapse by promoting submucosal fibrosis. The submucosal injection of foam helps lift the mucosa for easy ligation and prevents aspiration of the muscularis propria, thereby reducing post-operative pain caused by visceral innervation.

The treatment of internal hemorrhoids is now believed to involve the improvement of symptoms instead of cushion removal. Therefore, in the present study, we used the HSS to assess overall satisfaction, and symptom-based question-naires are now required to guide the management of internal hemorrhoidal disease[20]. In this study, we observed that post-procedural pain was frequently experienced following treatment with RBL or ERBL. Approximately, 25% to 50% of the patients experienced post-procedural pain, especially in the first 48 hours following the procedure[21]. Komporozos *et al*[7] reported that multiple banding, a young age, male sex, and external hemorrhoids were all risk factors for increased pain. In this study, post-procedural pain mainly occurred after 24 hours and was independently associated with the number of rubber bands. The findings agree with those reported by Komporozos *et al*[7]. Thus, a clear need exists to improve the post-procedural pain caused by band ligation. The infiltration of local anesthesia, the administration of analgesia, warm salt baths, and the removal of the elastic bands, have all been used to reduce pain[7,9]. In this study, the submucosal injection of a foam sclerosing agent effectively improved acute perianal pain caused by the rubber band. We hypothesize that complete separation of the mucosa and muscularis propria after submucosal injection can avoid incorrect ligation or excessive tension of the muscular layer and results in relieving splanchnic-nerve pain.

Polidocanol is a detergent-type sclerosant that is widely used for the management of varicose veins[22]. Polidocanol is also a local anesthetic and the foam formulation leads to a homogeneous distribution of drug microbubbles[10]. Previous studies confirmed that 30 mg/mL (3%) of polidocanol foam is a safe, cost-effective, and repeatable conservative treatment for grade I, II, and III hemorrhoids[10,14]. Additionally, polidocanol foam leads to marked vasospasm, damage of the hemorrhoidal endothelium, an inflammatory reaction within 2 min, and induces a fibrotic reaction 30 min after administration. Anoscope-assisted sclerobanding (*i.e.* combined RBL with polidocanol foam sclerotherapy) has recently been deemed a safe technique with a low rate of minor post-operative complications[3]. Our findings were similar, but we used 10 mg/mL (1%) polidocanol and performed one treatment procedure to avoid potential side effects and maintain participant safety.

Post-operative bleeding is a common complication of this procedure. In this study, we discovered that the multi-site injection of a foam sclerosing agent in the EFSB group increased the incidence of post-operative bleeding that may have been related to mucosal injury with oozing at the needle insertion site. Most patients experienced mild-to-no bleeding without special medical therapy. In a previous study, Caetano *et al*[23] reported that a micronized purified flavonoid fraction, an oral drug used to treat capillary fragility, reduced the amount of bleeding during the first month. A recent study reported that clopidogrel bisulfate did not increase bleeding complications in patients undergoing RBL[24]. However, considering the risk of massive bleeding caused by antiplatelet or anticoagulant drugs, these patients were instructed to discontinue these drugs 5–7 d before the procedure.

Rare complications of RBL including perianal abscesses, vascular-vagal symptoms, priapism, dysuria, anal fistula, and longitudinal mucosal ulcers have been reported[25-27]. The complications of RBL with negative-pressure suction are believed to be less likely than those of forceps-assisted band ligation, which often results in unclear vision while performing the procedure and is more likely to damage the mucosa[28]. In this study, 1 patient had dysuria and another had a mucosal ulcer, confirming that EFSB was safe, with minimal adverse events. We believe that transparent cap assistance and rectal rinsing with a water jet provides clear vision and avoids injection-induced infections.

Our study had some limitations to consider. First, patients with severe disease may require additional treatment sessions to improve their symptoms and success rate. However, EFSB was performed for the first time, and only one session was conducted to avoid unexpected side effects. Second, the study followed patients for only 12 months. Therefore, long-term follow-up studies should be conducted. Third, recurrence is known to be associated with other factors that require further exploration. Finally, no established criteria are available for the endoscopic diagnosis of internal hemorrhoids. Inserting a scope could reduce the prolapsing cushions to their normal position, thus leading to misdiagnosis[29].

#### CONCLUSION

Prospective analysis of grade II and III internal hemorrhoids revealed that the use of the EFSB technique effectively reduced the 12-m prolapse recurrence rate and relieved 24-h post-procedure pain. However, whether repeated treatment is effective and safe remains unclear. Therefore, further long-term follow-up and treatment sessions should be conducted to further reduce the recurrence of prolapse.

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# FOOTNOTES

Author contributions: Qu CY and Zhang FY contributed equally to this work as co-first authors; Xu LM and Shen F contributed equally to this work as co-corresponding authors; Qu CY and Zhang FY drafted the manuscript; Xu LM and Shen F designed the study and supervised its implementation; Chen GY analyzed the data; Qu CY, Wang W, Gao FY, Lin WL, Zhang H, Zhang Y, Li MM, Xu LM, and Shen F completed the endoscopic manipulations; Zhang FY, Li ZH and Cai MH participated in the experiments; and all authors made critical revisions and approved the final version to be published. The reasons for designating Xu LM and Shen F as co-corresponding authors are that Xu LM is responsible for multicenter coordination and quality control; Shen F is responsible for multi-center coordination and design of the project.

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