# 94064_Auto_Edited.docx

WORD COUNT 5944
TIME SUBMITTED 12-JUN-2024 12:18PM
PAPER ID 109585794

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

Qu CY *et al*. Endoscopic sclerobanding for internal hemorrhoids


**Abstract**

BACKGROUND

Endoscopic rubber band ligation (ERBL) is a non-surgical technique for the 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 polidocanol foam sclerotherapy and ERBL combination.

METHODS

This was a prospective, multi-center, and 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 visual analog scale (VAS). Continuous variables are presented as medians and interquartile ranges.

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-week [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), $P < 0.001$] follow-ups. 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 VAS 24 hours post-procedure. The median VAS in the EFSB group was lower [2.0 (1.0-3.0) *vs* 3.0 (2.0-4.0), $P$ < 0.001].

CONCLUSION

Cap-assisted EFSB provides 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

Qu CY, Zhang FY, Wang W, Gao FY, Lin WL, Zhang H, Chen GY, Zhang Y, Li MM, Li ZH, Cai MH, Xu LM, Shen F. Endoscopic Polidocanol foam sclerobanding for the treatment of grade II-III internal hemorrhoids: A prospective, multi-center, randomized study. *World J Gastroenterol* 2024; In press

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

## INTRODUCTION

Internal hemorrhoids are the most common benign condition of the anorectum. Moreover, internal hemorrhoids 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 non-surgical techniques for hemorrhoids[1]. Considering both efficacy and post-operative complications, Tutino *et al*[2] recommended IS as a first-line treatment option, whereas RBL was recommended for persistent symptomatic grade II-III prolapse. More recently, Pata *et al*[3] reported that sclerobanding, which combines RBL with polidocanol foam sclerotherapy under an anoscope, is a safe technique with a low rate of post-operative complications.

With the development of flexible endoscopy, the use of retroflex endoscopic RBL (ERBL) will provide improved maneuverability, photographic documentation, as well as better performance of haemorrhoidal ligation[4]. However, RBL is associated with a higher long-term recurrence rate than that observed with surgical treatment[5]. The recurrence rate for 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 re-treatment sessions[5-7]. Post-procedural pain was identified as the most common complication[8,9].

Polidocanol is a non-ionic surfactant that mainly targets endothelial cells, causes vasospasm and inflammation, and exerts a local anesthetic effect[10]. In addition, polidocanol induces an inflammatory reaction with sclerosis of the submucosal tissue and consequent suspension of the hemorrhoidal tissue, thus improving bleeding and prolapse. This foam formulation resulted in 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 had been reported.

In addition, a notable lack exists of clinical trials comparing the endoscopic-based improvement of sclerobanding and ERBL in 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 the present 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 multi-center, single blind and 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 this study (XHEC-C-2020-003-1), and all of the enrolled patients provided written informed consent before the start of the study.

### *Inclusion and exclusion criteria*

Consecutive adult patients (18-60 years old) diagnosed with grade II or III internal hemorrhoids (according to the traditional Goligher's classification) from May, 2020 to March, 2021 were prospectively enrolled. The inclusion criteria were obvious symptoms of prolapse with or without bleeding, no previous history of endoscopic treatment, the failure of conservative treatment (such as adequate fluid or fibre intake, medication, and lifestyle changes), and a willingness to undergo simultaneous colonoscopy.

The exclusion criteria of the study population included: (1) Over 60 years of age; (2) With severe cardiopulmonary insufficiency; (3) Diagnosed malignant tumour; (4) Colon polyps > 1 cm in diameter or > 3 sites; (5) Diagnosis of inflammatory bowel disease and other perianal diseases (anal fistulas and fissures); (6) With autoimmune diseases; (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. According to previous studies, the average long-term recurrence rate is 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 demonstrated 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 only performed after the colonoscopy had been completed, and having decided that endoscopy treatment of internal hemorrhoids was necessary. Random numbers were generated by a computer with SPSS version 22.0 software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.), written on cards, and placed into envelopes. The participants were randomized into two groups according to the corresponding random numbers and blinded to the treatment methods. Using this system, patients were randomly divided into an EFSB group, which received 10 mg/mL of polidocanol foam sclerotherapy combined with RBL, and an ERBL group, which received endoscopic RBL alone.

### *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 at 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; calculated by dividing body mass by the square of height). Fasting venous blood samples were also collected to determine pre-procedural hemoglobin levels, prothrombin time, and alanine aminotransferase (ALT) levels one day before the procedure.

***Pre-procedural preparation***

Anticoagulant drugs were stopped 5 to 7 days 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 ga, Boston Scientific, United States), and a Speedband Superview Super 7™ Multiple Band Ligator (Boston Scientific, United States).

***Treatment methods and endoscopic classification***

All patients were required to undergo a complete colonic examination using a colonoscope under propofol intravenous anesthesia prior to internal hemorrhoid therapy. Intestinal polyps were removed using the cold snare polypectomy method before hemorrhoid treatment. Next, we changed to a gastroscope, the anal canal was opened with a transparent cap, fully inflated, and rinsed with a water jet. Subsequently, the patient was examined using gastroscopy. The evaluation items were assessed in both forward and retroflexed positions and then classified according to 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, all of the circumference). The form was determined by the diameter of the largest hemorrhoid and was classified into three grades (0, no hemorrhoids; 1, less than 12 mm in diameter; 2, 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 press a considerable 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 hemorrhoids. A single band was released in each pile while avoiding repeated ligation of the same plane (Figure 1C). The complete procedure presented in the attached Video 1. Patients in the ERBL group underwent endoscopic RBL without injection. All patients were treated with 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 only discharged after completing the post-procedural pain assessment. All participants were instructed to consume a low-fiber diet for 3 days to ensure a soft consistency of stools and were advised to maintain external cleanliness. Participants were followed up for 12 months and completed questionnaires at set time points in the outpatients departments, 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-month intervals thereafter, until 12 months had elapsed or recurrence occurred. Symptomatic-based HSS questionnaires, post-procedural pain, treatment-induced complications, and recurrence of prolapse and/or bleeding were recorded.

The primary endpoint of this study was the evaluation of long-term prolapse and/or bleeding recurrence. 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 to assess post-procedural pain and bleeding in terms of short-term and long-term satisfaction, and patient-reported adverse reactions.

### *Statistical analysis*

Statistical analyses were performed using SPSS version 22.0 for Windows (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Continuous variables are presented as medians and interquartile ranges (IQRs). The Mann-Whitney *U* test was used to compare continuous variables between the two groups. Count data are expressed as numbers and proportions. The $\chi^2$ was used to compare categorical variables. Correlations between visual analog scale (VAS) and other variables were assessed by Spearman's correlation coefficient ($\rho$). Multiple linear regression (the stepwise method) 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 of this study were reviewed by Guang-Yu Chen from 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. In total, 22 patients were excluded: two patients with ulcerative colitis (remission), four with malignant tumours, one with sicca syndrome, three over the age of 60 years, seven with colon polyps > 1 cm in diameter or > three sites, and five who were lost to follow-up (Figure 3). Therefore, 195 patients with symptomatic internal hemorrhoids were enrolled in this prospective study. The majority were male ($n$ = 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 were observed between the two groups in terms of sex, age, BMI, hemoglobin level, prothrombin time, or ALT levels (Table 1).

***Endoscopy treatment***

Among the total participants ($n$ = 195), 5.0 (4.0-5.0) rubber bands were used for grade III hemorrhoids; this 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; no statistically significant differences were observed between the two groups ($P$ = 0.821). In the EFSB group, 13.0 (12.0-15.0) mL of 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); this was due to insufficient suction or premature release. In addition, exhausted rubber bands were identified in 1.0% of the patients ($n$ = 1); this was related to the incomplete inhalation 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 groups. The HSS was significantly lower in the EFSB group than that in the ERBL group [4.0 (3.0-5.0) *vs* 5.0 (4.0-6.0), $P$ = 0.003] at T4, as well as at 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); this was significantly lower than that in the ERBL group [3.0 (2.0-4.0), $P < 0.001$]. However, no statistically significant difference was observed between the two groups at T2 (Figure 4B). At T1, 65.3% ($n = 64$) of patients in the EFSB group had non-mild pain; this 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 focussed 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 further 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: 0.595 to 1.092; $P < 0.001$) were independently associated with VAS.

In the ERBL group, one female experienced severe persistent pain for over 4 hours following her procedure. An endoscopic examination of this patient 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 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 bleeding in the EFSB group was diagnosed with an anal ulcer that was relieved using a conservative 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 developed urination difficulties that improved after applying 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 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 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 further 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 identified that EFSB was associated with high levels of satisfaction, low recurrence at 12-month follow-up, and effective relief of pain 24 hours post-procedure.

Currently, the non-operative management of internal hemorrhoids is considered a valid alternative to surgical therapy[7]. According to one theory, internal hemorrhoids are caused by the abnormal expansion and distortion of blood vessels and destructive changes in the anal cushions supporting the connective tissue[17]. The main principle underlying RBL is to remove abnormal anal cushion tissue, induce fibrosis, and fix the anal cushion to the mucosa, thereby relieving the main symptoms of prolapse. Compared to traditional proctoscopy, RBL using a flexible endoscope is considered to provide easier maneuvrability, better vision, more rubber band release, and a lower bleeding recurrence rate[18]. However, the application of RBL or ERBL treatments for internal hemorrhoids with severe prolapse is associated with a high recurrence rate. Dekker *et al*[5] conducted a systematic review and reported a recurrence rate of 31.1% ($n$ = 50) with RBL treatment; this was higher than that observed after hemorrhoidectomy.

In contrast to hemorrhoidal artery ligation, the recurrence rate of RBL treatment for grade II and III internal hemorrhoids was 49% after 1 year[19]. To date, the evaluation of recurrence rate based on different criteria, hemorrhoid grades, session times, or different follow-up periods, has yielded variable results[7]. The main purpose of EBL treatment for grade II and III internal hemorrhoids is to relieve prolapse. Thus, the primary aim of our study was to investigate the recurrence of prolapse but not bleeding. This multi-center study included a follow-up period of 12 months and suggested that sclerotherapy could reduce the recurrence of prolapse by enhancing 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. Further symptom-based questionnaires are now required to guide the management of internal hemorrhoidal diseases[20].

In the present study, we observed that post-procedural pain was frequently experienced following treatment with RBL or ERBL. Approximately, 25% to 50% of patients experience post-procedural pain, especially within the first 48 hours following the procedure[21]. Komporozos *et al*[7] established that multiple banding, a young age, male sex, and external hemorrhoids were all risk factors for increased pain. In the present study, post-procedural pain mainly occurred after 24 hours and was independently associated with the number of rubber bands; these findings concurred 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 the present study, the submucosal injection of a foam sclerosing agent effectively improved the acute perianal pain caused by the rubber band. We hypothesize that the complete separation of the mucosa and muscularis

propria after submucosal injection can avoid incorrect ligation or excessive pulling of the muscular layer and relieve splanchnic nerve pain.

Polidocanol is a detergent-type sclerosant that is widely used for the management of varicose veins[22]. Furthermore, polidocanol also exerts a local anesthetic effect, while 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 to the hemorrhoidal endothelium and a subsequent inflammatory reaction after only 2 minutes and induces a fibrotic reaction 30 minutes after administration. Over recent years, anoscope-assisted Sclerobanding (combined RBL with polidocanol foam sclerotherapy) has been deemed a safe technique with a low rate of minor post-operative complications[3]. Our findings were similar; however, we selected 10 mg/mL (1%) of polidocanol and conducted a single session of treatment to avoid potential side effects and maintain participant safety.

Post-operative bleeding is a common complication of this procedure. In the present study, we discovered that the multi-site injection of a foam sclerosing agent in the EFSB group increased the incidence of post-operative bleeding; this 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 intensity 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 to 7 days before the procedure.

Rare complications of RBL have also been reported, including perianal abscesses, vascular-vagal symptoms, priapism, dysuria, anal fistula, and longitudinal mucosal ulcers[25-27]. The complications of RBL with negative-pressure suction are believed to be

less likelyl than those of forceps-assisted band ligation, which often results in unclear vision and is more likely to damage the mucosa[28]. In the present study, one patient had dysuria and another had a mucosal ulcer, thus confirming that EFSB was safe with minimal adverse events. We believe that transparent cap assistance and rectal rinsing by the water jet function can provide clear vision and avoid injection-induced infections.

Our study had some limitations that need to be considered. First, patients with severe disease may require additional treatment sessions to improve their symptoms and success rates. However, EFSB was performed for the first time, and only one session was conducted to avoid unexpected side effects. Second, this 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

Our prospective analysis of grade II and III internal hemorrhoids revealed that the use of the EFSB technique effectively reduced the 12-month prolapse recurrence rate and relieved 24 hours post-procedural pain. However, whether repeated treatments are effective and safe remains unclear. Therefore, further long-term follow-ups and treatment sessions should now be conducted to further reduce the recurrence of prolapse.

## ACKNOWLEDGEMENTS

The authors thank the patients for their consent to share the whole treatment and follow-up procedures. All authors agree to be accountable for the content of the work.

## REFERENCES

1 **Sandler RS**, Peery AF. Rethinking What We Know About Hemorrhoids. *Clin Gastroenterol Hepatol* 2019; **17**: 8-15 [PMID: 29601902 DOI: 10.1016/j.cgh.2018.03.020]

2 **Tutino R**, Massani M, Jospin Kamdem Mambou L, Venturelli P, Della Valle I, Melfa G, Micheli M, Russo G, Scerrino G, Bonventre S, Cocorullo G. A Stepwise Proposal for Low-Grade Hemorrhoidal Disease: Injection Sclerotherapy as a First-Line Treatment and Rubber Band Ligation for Persistent Relapses. *Front Surg* 2021; **8**: 782800 [PMID: 35083270 DOI: 10.3389/fsurg.2021.782800]

3 **Pata F**, Bracchitta LM, D'Ambrosio G, Bracchitta S. Sclerobanding (Combined Rubber Band Ligation with 3% Polidocanol Foam Sclerotherapy) for the Treatment of Second- and Third-Degree Hemorrhoidal Disease: Feasibility and Short-Term Outcomes. *J Clin Med* 2021; **11** [PMID: 35011962 DOI: 10.3390/jcm11010218]

4 **Su MY**, Chiu CT. Endoscopic hemorrhoid ligation is simple, safe, and effective. *Am J Gastroenterol* 2010; **105**: 1448-1449 [PMID: 20523321 DOI: 10.1038/ajg.2010.135]

5 **Dekker L**, Han-Geurts IJM, Rørvik HD, van Dieren S, Bemelman WA. Rubber band ligation versus haemorrhoidectomy for the treatment of grade II-III haemorrhoids: a systematic review and meta-analysis of randomised controlled trials. *Tech Coloproctol* 2021; **25**: 663-674 [PMID: 33683503 DOI: 10.1007/s10151-021-02430-x]

6 **Wehrmann T**, Riphaus A, Feinstein J, Stergiou N. Hemorrhoidal elastic band ligation with flexible videoendoscopes: a prospective, randomized comparison with the conventional technique that uses rigid proctoscopes. *Gastrointest Endosc* 2004; **60**: 191-195 [PMID: 15278043 DOI: 10.1016/s0016-5107(04)01551-2]

7 **Komporozos V**, Ziozia V, Komporozou A, Stravodimos G, Kolinioti A, Papazoglou A. Rubber band ligation of symptomatic hemorrhoids: an old solution to an everyday problem. *Int J Colorectal Dis* 2021; **36**: 1723-1729 [PMID: 33751210 DOI: 10.1007/s00384-021-03900-2]

8 **Forlini A**, Manzelli A, Quaresima S, Forlini M. Long-term result after rubber band ligation for haemorrhoids. *Int J Colorectal Dis* 2009; **24**: 1007-1010 [PMID: 19387663 DOI: 10.1007/s00384-009-0698-y]

9 **Behrenbruch C**, Kong J, Chen F. Local anaesthesia for haemorrhoidal rubber band ligation reduces immediate post-operative recovery time and use of opioid analgesia. *ANZ J Surg* 2020; **90**: 576-579 [PMID: 31970873 DOI: 10.1111/ans.15694]

10 **Lobascio P**, Laforgia R, Novelli E, Perrone F, Di Salvo M, Pezzolla A, Trompetto M, Gallo G. Short-Term Results of Sclerotherapy with 3% Polidocanol Foam for Symptomatic Second- and Third-Degree Hemorrhoidal Disease. *J Invest Surg* 2021; **34**: 1059-1065 [PMID: 32290709 DOI: 10.1080/08941939.2020.1745964]

11 **Mishra S**, Sahoo AK, Elamurugan TP, Jagdish S. Polidocanol versus phenol in oil injection sclerotherapy in treatment of internal hemorrhoids: A randomized controlled trial. *Turk J Gastroenterol* 2020; **31**: 378-383 [PMID: 32519957 DOI: 10.5152/tjg.2020.19276]

12 **Lee MJ**, Morgan J, Watson AJM, Jones GL, Brown SR. A validated severity score for haemorrhoids as an essential prerequisite for future haemorrhoid trials. *Tech Coloproctol* 2019; **23**: 33-41 [PMID: 30725242 DOI: 10.1007/s10151-019-01936-9]

13 **Nyström PO**, Qvist N, Raahave D, Lindsey I, Mortensen N; Stapled or Open Pile Procedure (STOPP) trial study group. Randomized clinical trial of symptom control after stapled anopexy or diathermy excision for haemorrhoid prolapse. *Br J Surg* 2010; **97**: 167-176 [PMID: 20035531 DOI: 10.1002/bjs.6804]

14 **Moser KH**, Mosch C, Walgenbach M, Bussen DG, Kirsch J, Joos AK, Gliem P, Sauerland S. Efficacy and safety of sclerotherapy with polidocanol foam in comparison with fluid sclerosant in the treatment of first-grade haemorrhoidal disease: a randomised, controlled, single-blind, multicentre trial. *Int J Colorectal Dis* 2013; **28**: 1439-1447 [PMID: 23775099 DOI: 10.1007/s00384-013-1729-2]

15 **Fukuda A**, Kajiyama T, Kishimoto H, Arakawa H, Someda H, Sakai M, Seno H, Chiba T. Colonoscopic classification of internal hemorrhoids: usefulness in endoscopic band ligation. *J Gastroenterol Hepatol* 2005; **20**: 46-50 [PMID: 15610445 DOI: 10.1111/j.1440-1746.2004.03536.x]

16 **Tomiki Y**, Ono S, Aoki J, Takahashi R, Sakamoto K. Endoscopic sclerotherapy with aluminum potassium sulfate and tannic acid for internal hemorrhoids. *Endoscopy* 2014; **46** Suppl 1 UCTN: E114 [PMID: 24676816 DOI: 10.1055/s-0034-1364884]

17 **Ma W**, Guo J, Yang F, Dietrich CF, Sun S. Progress in Endoscopic Treatment of Hemorrhoids. *J Transl Int Med* 2020; **8**: 237-244 [PMID: 33511050 DOI: 10.2478/jtim-2020-0036]

18 **Jutabha R**, Jensen DM, Chavalitdhamrong D. Randomized prospective study of endoscopic rubber band ligation compared with bipolar coagulation for chronically bleeding internal hemorrhoids. *Am J Gastroenterol* 2009; **104**: 2057-2064 [PMID: 19513028 DOI: 10.1038/ajg.2009.292]

19 **Brown SR**, Tiernan JP, Watson AJM, Biggs K, Shephard N, Wailoo AJ, Bradburn M, Alshreef A, Hind D; HubBLe Study team. Haemorrhoidal artery ligation versus rubber band ligation for the management of symptomatic second-degree and third-degree haemorrhoids (HubBLe): a multicentre, open-label, randomised controlled trial. *Lancet* 2016; **388**: 356-364 [PMID: 27236344 DOI: 10.1016/S0140-6736(16)30584-0]

20 **Sha HL**, Roslani AC, Poh KS. Evaluating the ability of the Sodergren score to guide the management of internal haemorrhoidal disease. *Colorectal Dis* 2020; **22**: 1379-1387 [PMID: 32337794 DOI: 10.1111/codi.15091]

21 **Sajid MS**, Bhatti MI, Caswell J, Sains P, Baig MK. Local anaesthetic infiltration for the rubber band ligation of early symptomatic haemorrhoids: a systematic review and meta-analysis. *Updates Surg* 2015; **67**: 3-9 [PMID: 25724281 DOI: 10.1007/s13304-015-0286-3]

22 **Star P**, Connor DE, Parsi K. Novel developments in foam sclerotherapy: Focus on Varithena® (polidocanol endovenous microfoam) in the management of varicose veins. *Phlebology* 2018; **33**: 150-162 [PMID: 28166694 DOI: 10.1177/0268355516687864]

23 **Caetano AC**, Cunha C, Arroja B, Costa D, Rolanda C. Role of a Micronized Purified Flavonoid Fraction as an Adjuvant Treatment to Rubber Band Ligation for the Treatment of Patients With Hemorrhoidal Disease: A Longitudinal Cohort Study. *Ann Coloproctol* 2019; **35**: 306-312 [PMID: 31937070 DOI: 10.3393/ac.2018.09.18]

24 **Hite N**, Klinger AL, Miller P, Beck DE, Whitlow CB, Hicks TC, Green HM, Margolin DA. Clopidogrel bisulfate (Plavix) does not increase bleeding complications in patients

undergoing rubber band ligation for symptomatic hemorrhoids. *J Surg Res* 2018; **229**: 230-233 [PMID: 29936995 DOI: 10.1016/j.jss.2018.04.004]

25 **Albuquerque A**. Rubber band ligation of hemorrhoids: A guide for complications. *World J Gastrointest Surg* 2016; **8**: 614-620 [PMID: 27721924 DOI: 10.4240/wjgs.v8.i9.614]

26 **Yoshikawa K**, Kawashima R, Hirose Y, Shibata K, Akasu T, Hagiwara N, Yokota T, Imai N, Iwaku A, Kobayashi G, Kobayashi H, Kinoshita A, Fushiya N, Kijima H, Koike K, Saruta M. Liver injury after aluminum potassium sulfate and tannic acid treatment of hemorrhoids. *World J Gastroenterol* 2017; **23**: 5034-5040 [PMID: 28785156 DOI: 10.3748/wjg.v23.i27.5034]

27 **Aram FO**. Rubber Band Ligation for Hemorrhoids: an Office Experience. *Indian J Surg* 2016; **78**: 271-274 [PMID: 27574343 DOI: 10.1007/s12262-015-1353-1]

28 **Ramzisham AR**, Sagap I, Nadeson S, Ali IM, Hasni MJ. Prospective randomized clinical trial on suction elastic band ligator versus forceps ligator in the treatment of haemorrhoids. *Asian J Surg* 2005; **28**: 241-245 [PMID: 16234072 DOI: 10.1016/s1015-9584(09)60353-5]

29 **Cosman BC**. Piles of Money: "Hemorrhoids" Are a Billion-Dollar Industry. *Am J Gastroenterol* 2019; **114**: 716-717 [PMID: 30998519 DOI: 10.14309/ajg.0000000000000234]

**Figure 1 Endoscopic transparent cap-assisted endoscopic foam sclerobanding for the treatment of internal hemorrhoids.** A: The obvious red color sign of internal hemorrhoids was observed with 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.

**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: The formation of scars (black arrow) in retroflexed; F: The formation of scars (black arrow) in normal position.

**Figure 3 Flowchart of inclusion, exclusion and intervention of enrolled patients.** During the study period, 217 patients with grade II or III internal hemorrhoids were enrolled. In total, 22 patients were excluded: Two patients with ulcerative colitis (remission), four with malignant tumour, one with sicca syndrome, three over the age of 60 years, seven had colon polyps > 1 cm in diameter or > 3 sites, and five lost in follow-up were excluded. Remaining patients were randomly assigned to endoscopic rubber band ligation group ($n$ = 97) and endoscopic foam sclerobanding group ($n$ = 98). ERBL: Endoscopic rubber band ligation; EFSB: Endoscopic polidocanol foam sclerobanding.

**Figure 4 Box plots.** A: Box plots of the hemorrhoid severity score in the endoscopic rubber band ligation (ERBL) group and the endoscopic foam sclerobanding (EFSB)

group according to follow-up time at before procedure (T0), 8 weeks (T4), and 12 months (T5) post-procedure. The upper and lower whiskers indicate the 75$^{th}$ percentile plus 1.5 interquartile range (IQR) and the 25$^{th}$ percentile minus 1.5 IQR, respectively. Outlier: A value greater than the 75$^{th}$ percentile plus 1.5 IQR; B: Box plots of the pain visual analogue scale in the ERBL group and the EFSB group according to follow-up time at 24 hours (T1), 1 week (T2) post-procedure. The upper and lower whiskers indicate the 75$^{th}$ percentile plus 1.5 IQR and the 25$^{th}$ percentile minus 1.5 IQR, respectively. ERBL: Endoscopic rubber band ligation; EFSB: Endoscopic polidocanol foam sclerobanding.

**Table 1 Clinical and laboratory characteristics of patients in endoscopic rubber band ligation and endoscopic foam sclerobanding group, *n* (%)**

| Characteristics | Total patients (*n* = 195) | ERBL (*n* = 97) | EFSB (*n* = 98) | *P* value |
|---|---|---|---|---|
| Male sex | 108 (55.4) | 58 (59.8) | 50 (51.0) | 0.250 |
| Age (years) | 46.0 (40.0-50.0) | 47.0 (40.5-50.0) | 45.0 (39.5-50.0) | 0.948 |
| Goligher's 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 ($kg/m^2$) | 21.7 (20.0-23.0) | 20.7 (19.0-22.1) | 21.8 (20.0-23.2) | 0.896 |
| Haemoglobin (g/L) | 130.0 (125.0-138.0) | 129.0 (123.0-139.0) | 134.5 (125.0-138.0) | 0.319 |
| Prothrombin time (second) | 12.0 (11.0-12.0) | 12.0 (11.0-12.0) | 11.0 (10.1-12.8) | 0.752 |
| Alanine aminotransferase (U/L) | 25.0 (16.9-33.0) | 25.0 (15.0-33.0) | 24.0 (19.0-32.3) | 0.316 |

All continuous variables are presented as medians (interquartile ranges) and compared using the Mann-Whitney *U* test. The count data were expressed as percentages and analysed using the $\chi^2$ test. ERBL: Endoscopic rubber band ligation; EFSB: Endoscopic foam sclerobanding.

**Table 2 Comparison of post-procedural pain of patients in endoscopic rubber band ligation and endoscopic foam sclerobanding group, *n* (%)[1]**

| Visual analogue scale | Total patients (*n* = 195) | ERBL (*n* = 97) | EFSB (*n* = 98) | *P* value |
|---|---|---|---|---|
| T1[2] | | | | |
| 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[3] | | | | |
| 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) | |

1

2

3

The count data are expressed as percentages and analysed using the $\chi^2$ test. T1 and T2: Postprocedural at 24 hours (T1) and 1 week (T2).

# 94064_Auto_Edited.docx

ORIGINALITY REPORT

11%
SIMILARITY INDEX

PRIMARY SOURCES

| | | |
|---|---|---|
| 1 | AKIHISA FUKUDA. "Colonoscopic classification of internal hemorrhoids: Usefulness in endoscopic band ligation", Journal of Gastroenterology and Hepatology, 1/2005<br>Crossref | 91 words — 2% |
| 2 | www.mdpi.com<br>Internet | 60 words — 1% |
| 3 | discovery.researcher.life<br>Internet | 36 words — 1% |
| 4 | www.science.gov<br>Internet | 34 words — 1% |
| 5 | www.frontiersin.org<br>Internet | 33 words — 1% |
| 6 | mobt3ath.com<br>Internet | 28 words — 1% |
| 7 | www.ncbi.nlm.nih.gov<br>Internet | 25 words — 1% |
| 8 | www.wjgnet.com<br>Internet | 24 words — 1% |
| 9 | www.researchsquare.com<br>Internet | 22 words — < 1% |

| | | |
|---|---|---|
| 10 | sciendo.com<br>Internet | 21 words — < 1% |
| 11 | journals.lww.com<br>Internet | 20 words — < 1% |
| 12 | pubmed.ncbi.nlm.nih.gov<br>Internet | 20 words — < 1% |
| 13 | d.docksci.com<br>Internet | 19 words — < 1% |
| 14 | Pierluigi Lobascio, Rita Laforgia, Eugenio Novelli, Fabrizio Perrone et al. "Short-Term Results of Sclerotherapy with 3% Polidocanol Foam for Symptomatic Second- and Third-Degree Hemorrhoidal Disease", Journal of Investigative Surgery, 2020<br>Crossref | 18 words — < 1% |
| 15 | pure.eur.nl<br>Internet | 17 words — < 1% |
| 16 | www.referencecitationanalysis.com<br>Internet | 15 words — < 1% |

| | | | |
|---|---|---|---|
| EXCLUDE QUOTES | ON | EXCLUDE SOURCES | < 15 WORDS |
| EXCLUDE BIBLIOGRAPHY | ON | EXCLUDE MATCHES | < 10 WORDS |