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ORIGINAL ARTICLE

Sclerotherapy with 3% polidocanol foam to treat second-degree haemorrhoidal disease: Three-year follow-up of a multicentre, single arm, IDEAL phase 2b trial

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Abstract

Background: Sclerotherapy with 3% polidocanol foam is becoming increasingly popular for the treatment of symptomatic I–II or III degree haemorrhoidal disease (HD). However, there are no studies that have reported a follow-up of more than 1 year. The purpose of this study was to analyse the long-term outcomes of sclerotherapy with 3% polidocanol foam in the treatment of II–degree HD.

Methods: This was an open label, single-arm, phase 2b trial conducted in 10 tertiary referral centres for HD. A total of 183 patients with II–degree HD, aged between 18 and 75 years with symptomatic HD according to the Goligher classification and unresponsive

Vito D'Andrea and Pierluigi Lobascio contributed equally.

Clinical Trial Registration: ClinicalTrials.gov, NCT03791775.

to medical treatment, were included in the study and underwent sclerotherapy with 3% polidocanol foam. The efficacy was evaluated in terms of bleeding score, haemorrhoidal disease symptom score (HDSS) and short health scale for HD (SHS–HD) score. Successful treatment was defined as the complete absence of bleeding episodes after 7 days (T1) according to the bleeding score.

Results: The overall success rate ranged from 95.6% (175/183) at 1 year to 90.2% (165/183) after the final 3 year follow-up. The recurrence rate, based on the primary outcome, ranged from 12% (15/125) to 28% (35/125). The greatest increase in recurrence (15) was recorded between 12 and 18 months of follow-up, then another five between 18 and 24 months. Both the HDSS and the SHS score remained statistically significant ($p < 0.001$) from a median preoperative value of 11 (10–13) and 18 (15–20) to 0 (0–2) and 4 (0–4), respectively. Symptom-free (HDSS = 0) patients, excluding patients converted to surgery, increased from 55.5% (101/182) at 1 year to 65.1% at 3 years (110/169). There were no intraoperative complications in redo-sclerotherapy nor additional adverse events (AEs) compared to the first 12 months.

Conclusions: Sclerotherapy with 3% polidocanol foam is gradually establishing itself in the treatment of bleeding HD due to its repeatability, safety, convenience in terms of direct and indirect costs with the absence of discomfort for the patient as well as AEs rather than an excellent overall success rate.

KEYWORDS
bleeding haemorrhoids, follow-up, haemorrhoidal disease, polidocanol foam, sclerofoam trial, sclerotherapy

INTRODUCTION

The treatment of haemorrhoidal disease (HD) is becoming more and more tailored and symptom-based [1]. A recent online survey including 81 members of the European Society of Coloproctology (ESCP) has further highlighted the limitations of the Goligher classification especially for the decision-making process of II and III-degree HD [2]. These results were consistent with another survey in which a total of 329 gastrointestinal surgeons, residents and fellows from Netherlands were asked to rate the Goligher HD degree of 25 photographs and whose findings were a fair agreement between respondents concerning the II and III degree HD (k statistic 0.206 and 0.37) [3].

This new belief in the patient's symptom and quality of life has led to greater use of office-based procedures with a step-up approach from the least invasive to the most invasive treatment.

Sclerotherapy with 3% polidocanol foam is becoming increasingly popular for the treatment of symptomatic I–II or III degree HD, who failed conservative treatment [4,5], particularly in those patients with bleeding HD, or in those who could not undergo surgical treatment due to the presence of comorbidities or bleeding disorders [6].

Several studies have demonstrated its safety and efficacy in the last 10 years [6-12]. Among the main advantages that favoured its acceptance, especially during the COVID-19 pandemic where the availability of operating rooms had been reduced and elective procedures stopped or suspended [13], were the low cost, repeatability, almost total absence of complications as well as of procedural pain and discomfort for the patient even at the cost of a recurrence rate still not well defined.

However, to date, there are no studies that have reported a follow-up of more than 1 year.

The purpose of this study was to assess the long-term effectiveness of sclerotherapy with 3% polidocanol foam (Aethoxysklerol 3%, Chemische Fabrik Kreussler & Co. GmbH).

What does this paper add to the literature?

This is the first trial evaluating the long-term efficacy and safety of 3% polidocanol foam for the treatment of symptomatic II degree haemorrhoidal disease. The absence of adverse events or major complications, even after repeating the procedure, and the high-success rate at 3 years represent the clinical rationale for the use of foam sclerotherapy.

PATIENTS AND METHODS

This multicentre, open label, single-arm, IDEAL phase 2b [14] trial involved 10 tertiary referral centres for HD belonging to the Italian Society of Colorectal Surgery (Società Italiana di Chirurgia Colorettale, SICCR). It represents the three-year follow-up of the SCLEROFOAM trial [7].

Demographics, type, and severity of symptoms of HD, HD-related quality of life, continence level and procedural details were prospectively collected. A constant monthly data check was performed with the participating centres for the entire duration of the study. The study protocol was approved by the ethics committees and was registered at ClinicalTrials.gov with the identifier NCT03791775. The study was conducted in accordance with the Declaration of Helsinki (1996) and International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines. Written informed consent was obtained from all the patients included in the study.

Here, we report data up to 3 years after the first sclerosing agent injection. Full details of the study design, the patient eligibility criteria, and the outcomes of the study after 1 year of follow-up have been already published [7]. Apart from enrollment (baseline, T0), patients underwent eight follow-up visits at 1 week (T1), 4 weeks (T2), 3 months (T3), 6 months (T4), 12 months (T5), 18 months (T6), 24 months (T6) and final follow-up visit at 36 months (T8). Patients converted to surgery at different timepoints were all excluded from clinical follow-up.

Study design

The degree of HD was assessed by proctological examination including digital rectal examination and anoscopy. Except at T1, where only an external clinical evaluation was performed, the other follow-ups, from T2 to T8, included a complete proctological evaluation.

Bleeding was assessed using the Giamundo Score (0 = absence of bleeding, 1 = <1 episode per month, 2 = 1 episode per week, 3 = 1–3 episodes per week and 4 = 4 or more episodes per week) preoperatively and at all follow-up visits [15].

The haemorrhoidal disease symptom score (HDSS), considering pain, itching, bleeding, soiling and prolapse, based on a 5 point-scale (0 = never, 1 = less than once a month, 2 = less than once a week, 3 = 1–6 days per week, 4 = every day or always), and the short health scale for HD (SHS-HD) score, based on a 7-point Likert scale for each question (1 = minimum score, 7 = maximum score), were used, to evaluate symptoms severity and HD-related quality of life preoperatively, at T3 and from T5 to T8, respectively [16].

Anal continence was assessed by the Vaizey incontinence score (minimum score = 0, perfect continence/maximum score = 24, totally incontinent) at T0, T2, T5 and T8 [17].

The procedural pain, the amount and type of painkillers and the resumption of normal activities were evaluated in our previous study, but we considered inappropriate to include them in the 3-year outcome assessment due to insufficient numbers involved.

For the same reason we preferred to avoid the evaluation of symptoms from the patient's clinical diary.

Successful treatment was already defined as the complete absence of bleeding episodes at T1 according to the Giamundo bleeding score [15].

Recurrences were defined as the new onset of bleeding after T1 in the successfully treated patients, namely, from a bleeding score of 0 to at least 2 at any time point between T2 and T8.

Eligibility criteria

Patients aged between 18 and 75 years with symptomatic HD according to the Goligher classification and unresponsive to medical treatment were included in the study.

Patients were excluded if they had a history of cardiac disease, coagulopathy, and anticoagulant therapies, colorectal or anal neoplasia, IBD, or other proctological diseases (anal fistulas and fissures; thrombosed internal or external HD); or if they had previous anal surgical procedures, previous sclerotherapy or rubber band ligation in the last 12 months; or if they had positive pregnancy test and breastfeeding, HBV, HCV or HIV infection, proctitis, known allergy to polidocanol, or pelvic radiotherapy were excluded. The inability or unwillingness to attend the follow-up visit were also considered an exclusion criterion.

Procedure (treatment plan)

The procedure was performed on an outpatient basis as previously described and the details of the pre-, intra- and postoperative management as well as of the preparation and pathophysiology of action of the foam have already been published [7,9,18]. The patient was discharged approximately 20 min after the procedure following a clinical safety check. Stool softeners and flebotonics were administered postoperatively.

Outcomes

Complete resolution of bleeding at T1 was the primary outcome.

Predefined secondary outcomes were as follows: success rate in terms of partial or complete resolution of the symptoms at 12 months; the average number of sessions necessary to obtain the complete resolution of the bleeding; the rate of complications and adverse events (AEs). Patients' quality of life and the average time required to resume normal daily activities, including work, were evaluated as well.

Safety

Safety was recorded by reporting AEs, serious adverse events (SAEs), and toxicity after each polidocanol foam injection. Toxicity

was defined according to the WHO toxicity scale [19]. The AEs were classified as none, remote, possible, probable, or not assessable based on the relation with the foam.

Statistical analysis

The results are reported as counts and percentages for categorical variables and as the mean ± SD (range) for continuous normally distributed variables and the median (interquartile range [IQR]) for ordinal categorical variables and for continuous non-normally distributed variables. The chi-square test was used for crosstabulations and independent samples *t*-test to evaluate differences between means. The time to recurrence was evaluated as the time elapsed from treatment success to the relapse of bleeding (at least 2 for the Giamundo bleeding score). Kaplan–Meier curves were used to evaluate freedom from recurrence. The changes in the HDSS, the SHS score and the Vaizey score over time were analysed with the Friedman test because these scores were not normally distributed. The results associated with a *p*-value <0.05 were considered statistically significant. Statistical data analysis was performed using IBM SPSS Statistics 20 and MedCalc 12.5.

RESULTS

A total of 183 patients with II-degree HD underwent sclerotherapy with 3% polidocanol foam in the selected referral centres from January and June 2019. The baseline demographics as well as the clinicopathological characteristics of the patients have already been described in detail [6] and are reported in Table 1.

The overall success rate ranged from 95.6% (175/183) at 1 year to 90.2% (165/183) after the final 3 year follow-up (Tables 2 and 3). During the study period, 87% (143) patients underwent one sclerotherapy session and 12% (20) and 1% (2), respectively, underwent two and three sessions. Most of the redo-sclerotherapy was performed at T6 (12). Eight out of 12 of those patients have become successes while the other four underwent surgery.

The remaining three patients who recurred at T6 had preferred to wait for the next follow-up and underwent surgery at T7. Two out of five patients who recurred at T7 underwent a successful second sclerotherapy session. The other three recurred patients underwent surgery together with one patient who stopped bleeding but had a worsening of the prolapse at T7 (Figure 1).

TABLE 1 Patient characteristics

Male (*N*, %)	111/183 (60.7%)
Mean age (years)	51.3 ± 13.5 (18–75)
Weight (kg)	72.8 ± 11.87 (48–101)
Height (cm)	171.82 ± 8.97 (152–190)
Body mass index (kg/m^2)	24.57 ± 2.9 (18.67–33.95)

Four out of the 169 patients who were considered at T8 still had a bleeding score of 1 according to the Giamundo bleeding score (Table 3).

There were no intraoperative complications in redo-sclerotherapy nor additional AEs or SAEs compared to the first 12 months (Table 2).

The number of patients converted to surgery rose from 1.6% (3/183) to 7.7% (14/183), of which 10 underwent dearterialization and mucopexy and four excisional haemorrhoidectomy. In particular, four patients were excluded from follow-up at T7, and seven at T8. Only one of these had undergone a second unsuccessful sclerotherapy session.

The recurrence rate, based on the primary outcome, varied from 12% (15/125) to 28% (35/125). The greatest increase in recurrence (15) was recorded between 12 and 18 months of follow-up, then another five between 18 and 24 months (Figure 2A,B).

Both the HDSS and the SHS score remained statistically significant ($p < 0.001$) from a median preoperative value of 11 (10–13) and 18 (15–20) to 0 (0–2) and 4 (0–4), respectively (Table 4).

The median treatment effect was 10 for the HDSS and 15 for the SHS. Symptom-free (HDSS = 0) patients, excluding patients converted to surgery, increased from 55.5% (101/182) at T5 to 65.1% at T8 (110/169; Figures 3 and 4; Table 4). The Vaizey incontinence score did not change compared to T5 (0 [0–0]).

Concerning the variables reported in the patient's clinical diary at T0, there was no statistically significant correlation with conversion to surgery and recurrence except for type and frequency of painkillers.

In fact, 23/35 (65.7%; $p = 0.005$) were taking painkillers with a frequency of 1–3 per day for less than 2 days. Moreover, a weak trend occurred with respect to the type of painkillers with 19/35 (54.3%; $p = 0.056$) of the recurrences that used minor analgesics (type 1). There was no correlation between the same variables and the final success rate.

Sex was associated with recurrence ($p = 0.024$; Table 5).

Interestingly, the number of recurrences in males was more than double that of females with respect to the primary outcome (26/71 [36.6%] vs. 9/54 [16.7%]; Figure 2A,B). There was no recurrence in female patients after 18 months while there were five further

TABLE 2 Procedural results

Mean operation time (min)	7.4 ± 2.5 (3–15)
Success rate after 1 week (T1)	125/183 (68.3%)
Success rate (T5)	175/183 (95.6%)
Success rate (T8)	165/183 (90.2%)
Recurrence (T5)	15/125 (12%)
Recurrence (T8)	35/125 (28%)
Number of required sclerotherapy sessions for overall treatment success at T8 (*N*°)	
1	143 (87%)
2	20 (12%)
3	(1%)
Adverse events	3 external thrombosis (1.6%)

TABLE 3 Cumulative persistence of bleeding according to Giamundo et al. [8]

	T0 (*N* = 183)	T1 (*N* = 183)	T2 (*N* = 183)	T3 (*N* = 183)	T4 (*N* = 183)	T5 (*N* = 182)	T6 (*N* = 180)	T7 (*N* = 176)	T8 (*N* = 169)
Bleeding (any frequency)	183 (100%)	58 (31.7%)	71 (38.8%)	46 (25.1%)	19 (10.4%)	7 (3.8%)	24 (13.3%)	22 (12.5%)	4 (2.4%)

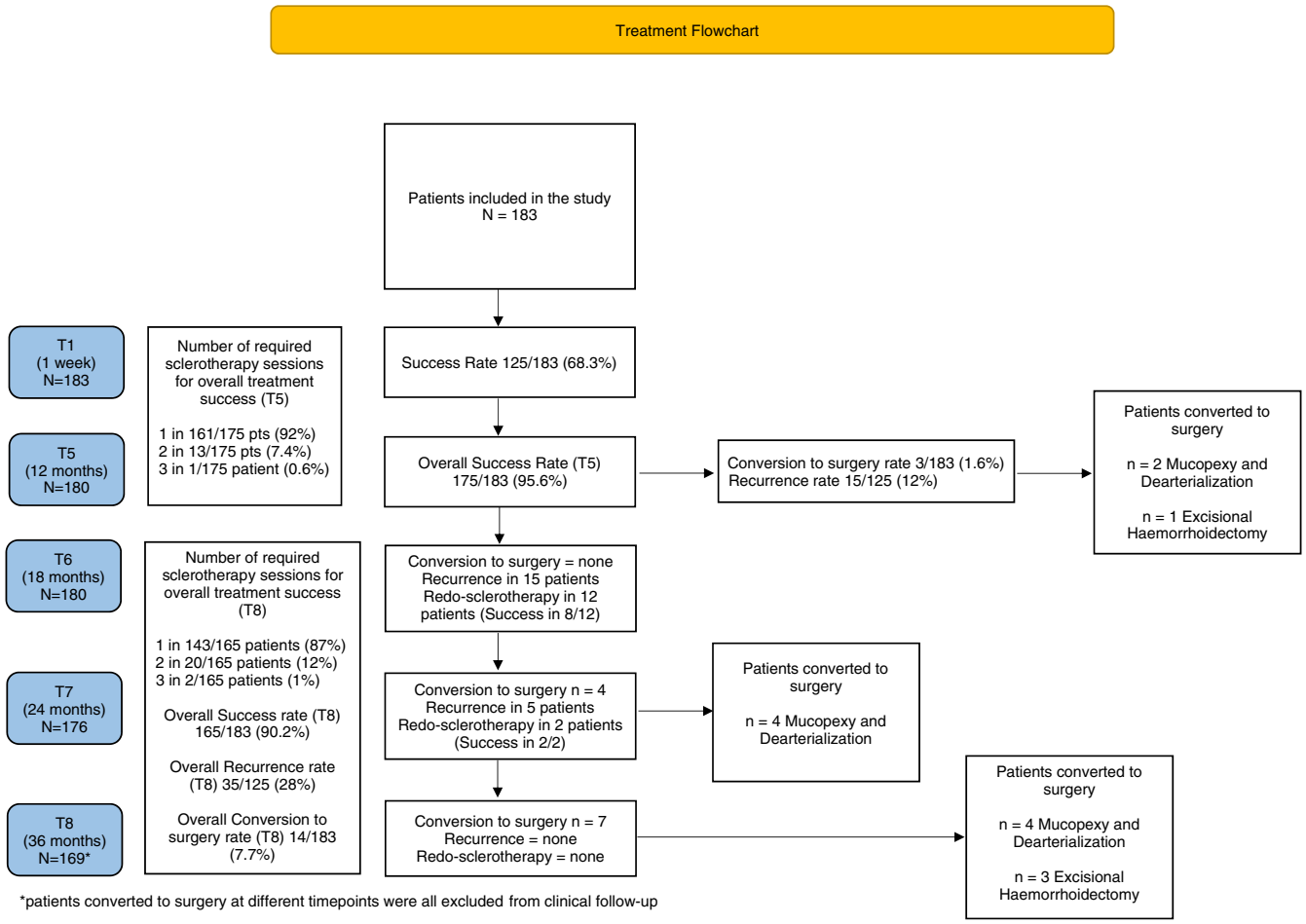


FIGURE 1 Treatment flowchart

recurrences in male patients (Table 6). Moreover, 12 out of the 14 patients converted to surgery (85.7%) were male ($p = 0.087$).

In this context, there has been a correlation trend between weight and conversion to surgery, recurrences, and overall success rate (Table 5.). This was probably due to the greater representation of male patients in the respective categories. There was no other correlation with the clinical-demographic variables.

DISCUSSION

Sclerotherapy with 3% polidocanol foam is certainly one of the emerging approaches in the treatment of HD [20]. So far, the immediacy of action of the foam which promotes a consistent vasospasm with endothelial damage, inflammatory reaction and a localized sclerosis and fibrosis following the injection has been recognized. For this reason, our primary outcome was the complete resolution of bleeding 7 days after the procedure. Moreover, the obliteration of the vascular bed may lead to the shrinkage of the piles resulting in HD downstaging and downsizing as demonstrated by Lobascio et al. [9] and Salguiero et al. [8] who have reported a complete success also in patients with III-degree HD.

To our knowledge, this is the first trial showing sclerotherapy results 3 years after the procedure.

In the present study we have demonstrated not only the speed of action but also the stability and safety over time of 3% polidocanol foam. In fact, not only did the overall success rate remain consistent during the entire follow-up period (90.2%) but also the patients' freedom from symptoms increased from 55.5% (101/182) to 65.1% (110/169; Figure 1).

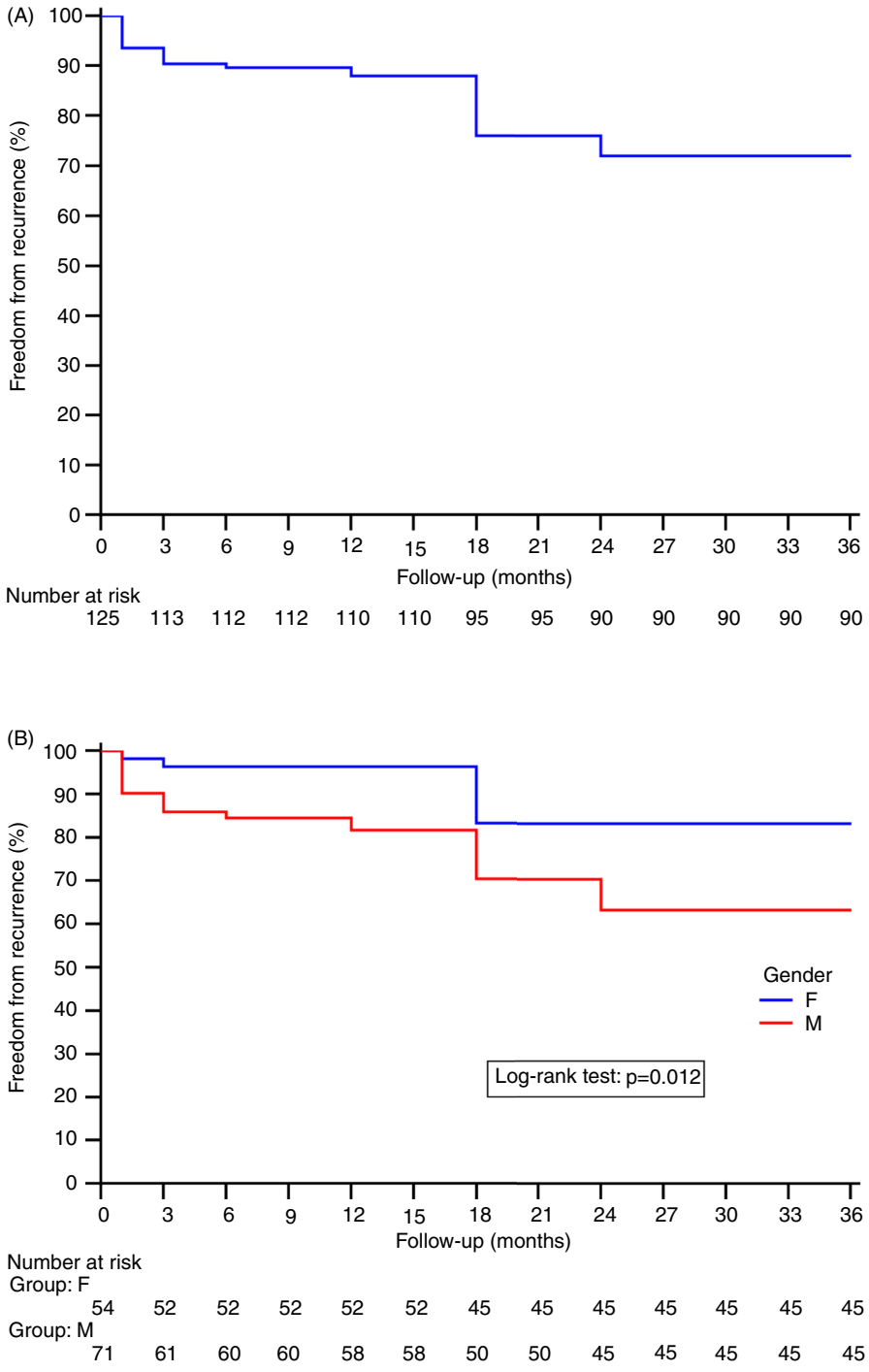


FIGURE 2 Kaplan–Meier curve concerning freedom from recurrence based on the primary outcome. (a) overall patients; (b) gender-based subdivision of freedom from recurrence

TABLE 4 Haemorrhoidal disease symptom score and short health scale for HD

	T0	T3	T5	T6	T7	T8	Treatment effect (preoperative-3 years)	*p*-value
HDSS[a]	11 (10–13)	0 (0–3)	0 (0–2)	0 (0–3)	0 (0–2)	0 (0–2)	10 (9–12)	<0.001
SHS[a]	18 (15–20)	0 (0–6)	0 (0–5)	4 (0–4)	4 (0–4)	4 (0–4)	15 (12–18)	<0.001

[a]Median and IQR + Friedman test.

Although several studies have recently been published, there is no standardization regarding the quantity and type of foam to be used [20].

Our foam has been prepared by using the EasyFoamKit syringe system mixing 1.6 ml of 3% liquid polidocanol and 7.4 ml sterile air and the injection was performed using a 20G needle. In fact, while

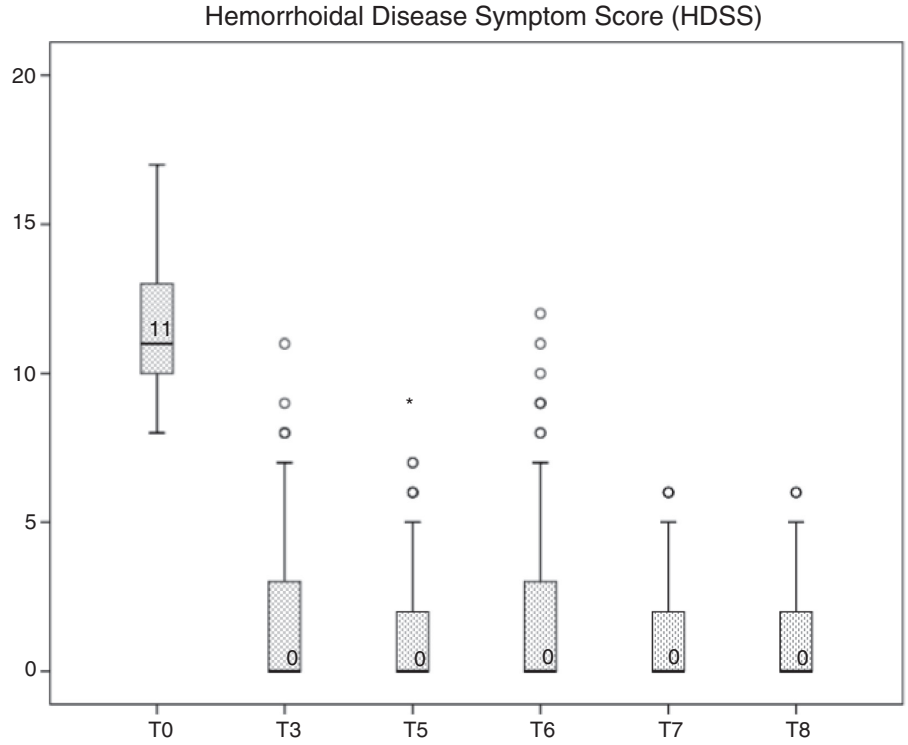
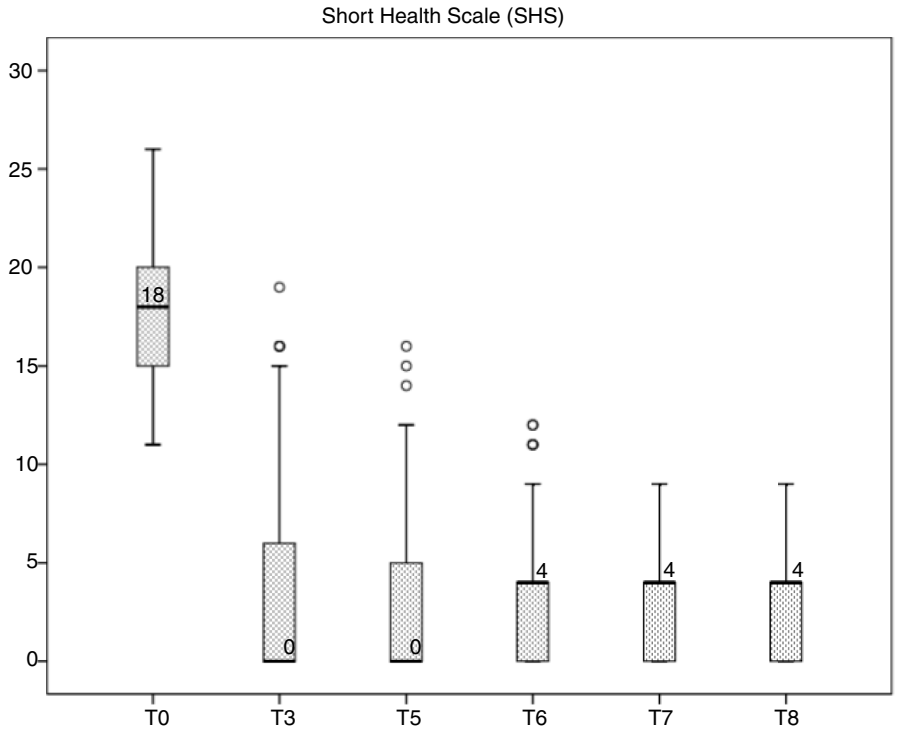


FIGURE 3 Boxplots of haemorrhoidal disease symptom score (HDSS) from T0 to T8

FIGURE 4 Boxplots of short health scale (SHS) score from T0 to T8



some studies have reported a similar technique to that used in this study [9-11], Salgueiro and colleagues [6,8] have published two recent studies where the foam was obtained by mixing 4 ml of liquid polidocanol 3% with 16 ml of air using Tessari's method. The maximum dose per session was 20 ml contrary to what was suggested in our previous experience in which we recommend not to exceed 8–10 ml in total (2–3 cc per pile). Interestingly, despite this, their success rate is consistent with ours (93.4% and 93.3%).

While the surgical technique notes including the tangential direction of the needle, especially at 11 o'clock in male patients in

TABLE 5 Correlation between conversion to surgery, recurrence and final success rates and clinical-demographic variables

	Conversion to surgery	Recurrence rate	Final success rate
Gender	0.087	0.024	0.190
Age	0.239	0.997	0.259
Weight	0.054	0.063	0.052
Height	0.199	0.243	0.181
BMI	0.127	0.130	0.079
Bleeding T0	0.708	0.628	0.402
HDSS T0	0.241	0.469	0.586
SHS T0	0.941	0.702	0.957

TABLE 6 Time to recurrence in both sexes

	Gender	
Time to recurrence	Female	Male
T2	1	7
T3	1	3
T4	0	1
T5	0	2
T6	7	8
T7	0	5
T8	0	0
Overall	9	26

order to avoid urinary complications, and the injection above the dentate line to reduce both postoperative pain and ensure maximum effectiveness of the foam have become the gold standard, the foam consistency still remains the main topic of discussion on which we can work to improve and stabilize the results of sclerotherapy.

The ideal foam should have physicochemical characteristics that guarantee a homogeneous size of the bubbles avoiding diffusion and allowing a local action.

Furthermore, a concept that should be developed is that of standardization of foam that is independent of human error, as Tessari's method can certainly induce.

Recently, we published the preliminary results, with 3 months of follow-up and 78% success rate, of the first 50 patients undergoing sclerotherapy with the foam produced using an automated device that allowed us to maintain a liquid / gas ratio between 1: 5 and 1: 7 without the need to re-emulsify the foam before each injection [12]. It will be necessary to treat large numbers with prolonged follow-up but it seems that this is the way to go.

The use of 3% polidocanol foam allowed a consistent reduction of local and systemic complications in comparison with previous sclerosing agents used in the past [21]. In fact, apart from one episode of acute prostatitis, described by Moser et al. [10], and some of external thrombosis [7,9], there were no major complications or adverse events [6-12].

The recurrence rate in male (26/35 patients; $p = 0.024$) was consistent with the one-year follow-up (13/15 patients; $p = 0.027$).

Moreover, recurrences are not only higher in male patients but occur both more quickly and in the long term, compared to female patients that have no recurrence after 18 months (Figure 2A,B).

In our first study on sclerotherapy in patients with II–III degree HD we correlated tenesmus ($p = 0.029$) to recurrences hypothesizing excessive defaecation stimuli caused by foam as the cause. In the present study, the greater representation of male patients (110/183; 60.7%) and the increased physiological muscle representation may be the rationale [22].

The rubber band ligation is still the most commonly used office-based procedure [23], not only for the simplicity of execution and for the repeatability, but also because of the lack of substantial innovations and modifications in the choice of reusable devices.

Iyer et al. [24] reported a case series of 805 patients, with I–IV degree HD and a median follow-up of 1.204 days, undergoing 2.114 ligations over the course of 25 years with a cumulative success rate of 70.5% (494/701), excluding patients lost to follow-up, after more than four bandings with no difference when the degree of HD was considered. According to the authors, repetition of banding was associated with an increased risk of failure and a predisposition in favour of excisional surgery.

Aside from comparative articles regarding liquid agents [25], only Salgueiro et al. [8] compared polidocanol foam sclerotherapy and rubber band ligation in 120 patients with I–III degree HD randomly assigned to receive one technique or the other.

The authors demonstrated a superiority of sclerotherapy due to the presence of fewer recurrences (41.2% vs. 16.1%; $p = 0.004$), fewer complications (30.0% vs. 10.0%; $p = 0.01$), fewer sessions to achieve success (1.6 ± 0.76 vs. 1.3 ± 0.60; $p = 0.02$), as well as a higher overall success rate (88.3% vs. 66.7%; $p = 0.009$). Time to recurrence was significantly in favour of sclerotherapy (10.74 months vs. 11.78; $p = 0.002$). However, future trials will be necessary to confirm this trend. Interestingly, when RBL was compared to the haemorrhoidal artery ligation in the biggest trial published so far, the recurrence rate was higher (49% vs. 30%) [26] but the procedure was less painful.

The main limitation of the study continues to be the lack of a control group. Moreover, we did not consider some variables, that is, procedural pain, the amount and type of painkillers, the resumption of normal activities and the patient's clinical diary, that would not have had the same objective value as the scores considered. In addition, patients were selected with no comorbidities or factors that could alter the results. Interestingly, contrary to the latter concept, sclerotherapy is becoming an arrow in the bow of every proctologist even in unfit for surgery patients regardless of the degree of HD [27]. Future studies in this direction will be able to clarify this point.

CONCLUSION

Sclerotherapy with 3% polidocanol foam is gradually establishing itself in the treatment of bleeding HD due to its repeatability, safety,

convenience in terms of direct and indirect costs with the absence of discomfort for the patient as well as AEs rather than an excellent overall success rate.

AUTHOR CONTRIBUTIONS

Conceptualization: Gaetano Gallo. *Data Curation:* Gaetano Gallo, and Eugenio Novelli. *Methodology:* Gaetano Gallo and Eugenio Novelli. *Formal analysis:* Eugenio Novelli. *Project Administration:* Gaetano Gallo and Eugenio Novelli. *Writing –original draft preparation:* Gaetano Gallo. *Writing –review and editing:* All authors. *Supervision:* Renato Pietroletti, Mario Trompetto, Roberto Perinotti, Vito D'Andrea, and Pierluigi Lobascio. *Critical Revision and Final Approval of the manuscript:* All authors.

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FUNDING INFORMATION

None.

CONFLICT OF INTEREST

All authors declare no personal conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

ETHICS STATEMENT

This study was approved by all ethics committees at all study centres and written informed consent was obtained from all patients. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

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