HAEMORRHOIDAL DISEASE: OLD SOLUTIONS AND FUTURE PERSPECTIVES

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HAEMORRHOIDAL DISEASE: OLD SOLUTIONS AND FUTURE PERSPECTIVES

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Table of Contents

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EDITORIAL
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Editorial: Haemorrhoidal Disease: Old Solutions and Future Perspectives

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Keywords: haemorrhoidal disease, office-based procedures, conservative treatment, haemorrhoids, surgical treatment

Editorial on the Research Topic

Haemorrhoidal Disease: Old Solutions and Future Perspectives

Throughout our history haemorrhoidal disease (HD) has troubled humanity. HD is one of the best-described diseases in medical documentation and records date back to ancient Egyptian and Mesopotamian times (1, 2). A ground for the abundance of antique references on HD could be the high prevalence of this disease, which has not changed over time. About one third of the population is affected by HD (3). Despite the widespread occurrence and an impressive amount of scientific research, the full picture of HD has not yet been grasped. This special issue aims to highlight several dynamically evolving domains in current HD research, ranging from historical viewpoints to technical solutions and patient involvement.

As we can read in the extensive historical overview by Pata et al., the surgical management of HD has altered over the past centuries. With the introduction of anaesthetics and antisepsis in the 19th century, surgery transformed from a butchering art to a modern science, broaching a whole new world of opportunities. Taking away the agony for an awake patient during an operation, most people were initially content with the possibility of performing surgery under general or epidural anaesthesia. However, nowadays, more and more studies show that there is a broad support base for local anaesthesia in HD operations. Colleagues Poskus et al. underline this view, showing local perianal anaesthetic infiltration to be safe and effective for anorectal surgery, with fewer postoperative complications and a reduction of costs. Likewise, Tomasicchio et al. state that a Milligan-Morgan haemorrhoidectomy performed under local anaesthesia and in an outpatient setting is not only successful but has a high patient satisfaction rate as well.

The treatment of HD is based on the severity of prolapse according to the Goligher grading, even if the latter is much debated due to the inappropriate consideration of the patient's symptoms and quality of life (4–6). For low grades, a stepwise approach is advised by Tutino et al., starting with sclerotherapy and – in case of relapse – rubber band ligation (RBL). Indeed, in recent years there has been a rise in the use of the former while rubber band is still the most common office-based procedure (7, 8).

For higher grades of HD, Giordano and Schembari describe a modification of the mucopexy and haemorrhoidal dearterialization by adding an anolift to address the prolapsing component

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in HD. Pietroletti et al. studied the efficacy of a new formulation in rectal cream, containing Zn-L-Carnosine, in relieving acute symptoms of HD. Zinc-L-Carnosine is a cytoprotective compound stimulating mucosal repair in the gastrointestinal tract and shows to be a safe and effective treatment for bleeding or thrombosed haemorrhoids.

Eberspacher et al. focus more on the process after the operation and introduce self-mechanical anal dilatation as a simple trick to minimize postoperative pain and stenosis after haemorrhoidectomy with radiofrequency. The same author presents an in-depth analysis of the wall layers included in the stapled rectal ring of mucosectomies. In this article, Eberspacher et al. demonstrate that a mucosectomy entails a resection of the full rectal wall and that a "full-thickness" resection does not correlate with a higher rate of post-operative complications.

In line with the first treatment step for all grades of haemorrhoids, described in the European international guideline for HD (9), it is of paramount importance to optimize a patient's lifestyle and to indicate risk factors. In the review by De Marco and Tiso, the authors stress the intake of adequate fluids, regular exercise, improving anal hygiene, and avoiding straining at stool.

Additionally, the authors mention the importance of good communication between the doctor and the patient, emphasizing on skilful listening. Understanding the disease-burden of a patient can assist in creating the best treatment approach. The usage of a patient-reported outcome (PROM) can be a valuable tool in this matter. Kuiper et al. evaluate the different PROMs available in the field of HD and endorse the use of such a tool in clinical practice to optimize personalized HD treatment (10, 11).

This special issue of *Frontiers in Surgery* on haemorrhoids addresses several topics including non-surgical solutions, technical operative aspects, and the involvement of patient's experiences with HD. Despite the high incidence of this disabling disease, we know that the level of evidence of treatment remains low. To overcome this issue, a Core Outcome Set (COS) for HD can be utilized in clinical research (12, 13).

By using a COS, which is a minimal set of outcomes, study results can be easier compared to one another. Furthermore, the patient's view should also be taken into account to ensure a patient tailored approach in the management of HD.

We encourage authors in the field of HD to continue their research to stimulate further discussion and understanding of haemorrhoids.

AUTHOR CONTRIBUTIONS

All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Stapled Hemorrhoidopexy: "Mucosectomy or Not Only Mucosectomy, This Is the Problem"

*Chiara Eberspacher[1], Fabio M. Magliocca[2], Stefano Pontone[1], Pietro Mascagni[3,4], Lisa Fralleone[1], Gaetano Gallo[5] and Domenico Mascagni[1]**

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Introduction: Stapled hemorrhoidopexy was originally defined as a rectal mucosectomy. The aims of our retrospective, single-center study were to demonstrate if the excised specimen comprises only the mucosa or more wall rectal layers and if the latter excision should be considered a technical mistake with an increase in complications.

Materials and Methods: We histopathologically analyzed surgical samples from patients who underwent stapled hemorrhoidopexy performed between 2014 and 2019. Patients were divided into three groups, according to the stapler used: Group A (single PPH®), Group B (double PPH®), and Group C (CPH34 HV™). We evaluated the actual wall layers included in the stapled rectal ring. For every specimen, we reconstructed the history of the corresponding patient and the incidence of complications.

Results: Of the 137 histological slides available, 13 were only mucosectomies (9.5%), and 124 presented also the submucosa and muscularis propria (90.5%)—50/58 patients in Group A, 28/28 in Group B, and 46/51 in Group C. No statistically significant difference in the rate of complications was found when stratifying patients according to the thickness of the resection [mucosectomy (M) or "full thickness" (FT)].

Discussion: Stapled hemorrhoidopexy is not a simple mucosectomy but a resection of the rectal wall with almost all its layers. This concept defines the entity of the surgical procedure and excludes a direct correlation with an increased rate of complications.

Keywords: stapled hemorrhoidopexy, rectal mucosectomy, histopathology, complications, full thickness

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INTRODUCTION

Hemorrhoidal disease (HD) is a common proctologic disease, characterized by enlarged, inflamed, thrombosed, or prolapsed hemorrhoids, with symptoms like pain and rectal bleeding. Prevalence of HD changes according to studies and criteria of definition, from 25 to 39% in adult population (1).

The procedure for prolapse and hemorrhoids (PPH) was introduced in 1993 as novel treatment for HD and was originally described as a rectal mucosectomy (2). The procedure gained in popularity thanks to its creator Antonio Longo, who, in his report on this stapled hemorrhoidopexy (SH) (3), described the object of the excision as a rectal internal mucosal prolapse. The first stapler used as a dedicated device for this procedure was PPH; to remove more tissue, in an attempt to

reduce recurrences, two PPH or high volume instruments—CPH34 HV—with a bigger case were used. Today, many articles talk about "mucosectomy" when referring to SH (4). At the same time, many life-threatening complications, such as perforations, vascular lesions, or hematomas, that are connected with these procedures are often ascribed to a presumed uncorrected "more than mucosa" resection (5). The aim of the present study is to evaluate, during SH, despite the different techniques and tips or tricks of the surgeons, if the stapled ring include only the mucosa or it is a "full-thickness" excision and if the latter feature should be considered a technical mistake, increasing the complication rate.

METHODS

This retrospective, observational, single-center study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cohort studies (6). It included samples derived from SH, performed in the Department of Surgical Sciences of our hospital from 2014 to 2019. We enrolled patients, more than 18 years old, who had undergone surgery for hemorrhoidal disease (grade III and IV hemorrhoids or grade II when symptomatic) (7, 8). Exclusion criteria were an association with other anorectal disease (anal fissure, fistula, and perianal diseases), inflammatory bowel disease, chronic therapy with anti-inflammatory drugs, the presence of incontinence, and previous operations for hemorrhoids or prolapse. We also excluded patients who had undergone operations performed by residents to minimize bias due to the lack of experience in the procedure; all surgeons had an experience of at least 50 SH before the lapse of time considered for the study. All patients gave informed consent for surgery and histological examination of the specimen.

Patients were divided into three groups, according to the different stapler devices used, to determine whether a different stapler could change the entity of the resection: Group A underwent operations performed with a single PPH® stapler, Group B with a double PPH®, and Group C with a CPH34 HV™. All operations were performed in lithotomic position under spinal or general anesthesia, and the average hospital stay was 2 days. The rectal ring was obtained, realizing a purse-string suture in all cases. We excluded all the patients treated by SH when we used a "parachute technique," in order to remove more tissue. All stapler rings were fixed in formalin, with no orientation, and arranged on histological slides. The preserved histological slides were re-analyzed by a pathologist (FM) to evaluate the different layers—the presence of only the mucosa (M) or even of the submucosa and muscularis propria (FT). The expert was blinded to the previous description of the specimen.

We traced the patient and their clinical history and any minor complications, including pain evaluated with a Visual Analog Scale (VAS; ranging from 0 to 10, with 10 being full pain and 0 no pain), incontinence evaluated with the Wexner score (WS), time to return to work, and persistent urgency. Data were collected in our prospective PC database. We also evaluated any major complications, including sepsis, bleeding requiring new hospitalization, hematoma, and recurrence in the first year of follow-up. Follow-up consisted of outpatient visits with digital rectal exploration (after 1 week, 1 month, 3 months, and 6 months), with a clinical control consisting of a rectal digital examination and a questionnaire about symptoms. This was followed by a phone call after 1 year, with a further outpatient visit if necessary. The presence of recurrences was also determined by clinical examination.

The definition of the true wall layers of the rectal rings excised during these operations, despite the common use of the term "mucosectomy" in the literature (7), was the main aim of our study. A secondary endpoint was to evaluate if the thickness of the resected specimen was correlated with the incidence of complications and was tested by dividing all the patients into two groups: the M Group (mucosectomy) and the FT Group ("full thickness").

Data were analyzed using SPSS for Windows, version 21 (SPSS Inc., Chicago, IL). Means and standard deviations were used to report continuous data, while numbers and percentages were calculated for all categorical data. Univariate analysis was performed with Student's t-test. $p \leq 0.05$ was considered statistically significant for all analyses.

RESULTS

We identified a total of 304 SH procedures performed in our Department of Surgical Sciences of "Sapienza" University of Rome that met our inclusion criteria. Only 137 had histological slides available for re-examination. Of those, 124 belonged to female patients (90.5%) and 13 to male patients. The mean patient age was 52 years (range: 21–83 years).

Group A (single PPH®) consisted of 58 patients, Group B (double PPH®) 28 patients, and Group C (CPH34 HV™) 51 patients. Of those, we identified a true mucosectomy in eight patients (13.7%) in Group A, none in Group B (0%), and five (9.8%) in Group C (**Table 1**). All the patients in most of the cases (124/137: 90.5%) had a histological slide that included the mucosa, submucosa, and tunica muscularis (**Figure 1**). The anal ring thickness was about 8–10 mm: in 11 cases, a submucosa thicker for an intramural bleeding does not permit to include in the stapler case all the muscularis propria, and only some muscular fibers were found (partial muscularis propria resection) (**Figure 2**).

The patients with pure mucosectomy were almost all male with a rate of 53.8% (7/13). Only 4.8% (6/124) of the female patients had no submucosa and muscular fibers in the specimen.

Stratification of the patients according to the thickness of the resection (the M Group vs. group FT) and considering minor complications revealed no statistically significant differences. We observed 13 patients in Group M and 124 in Group FT: mean VAS after first week was 3.6 (SD 1.68) in Group M vs. 3.7 (SD 1.69) in Group FT ($p = 0.33$), mean WS after 1 month 1.8 (SD

Abbreviations: HD, hemorrhoidal disease; PPH, procedure for prolapse and hemorrhoids; CPH, circular stapler for rectal prolapse and hemorrhoids; SH, stapled hemorrhoidopexy; VAS, Visual Analog Scale; WS, Wexner score; PO, post-operative.

TABLE 1 | Histopathological study of the rectal ring, after SH (137 patients).

	Group A (single PPH)	Group B (double PPH)	Group C (CPH34/CPH36)
Mucosectomy only	8	0	5
Full thickness, with muscularis propria	50	28	46
Total of patients	58	28	51

SH, stapled hemorrhoidopexy; PPH, procedure for prolapse and hemorrhoids.

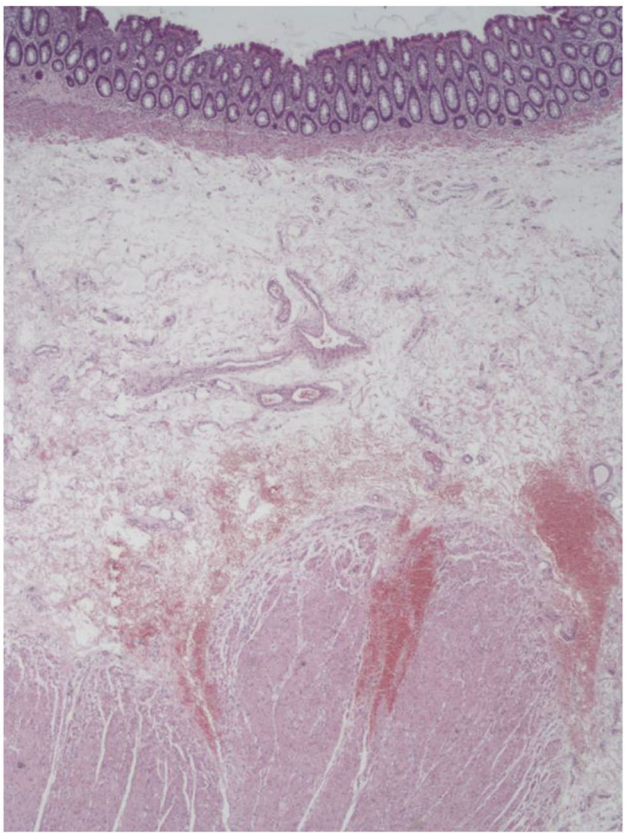

FIGURE 1 | An example of stapled hemorrhoidopexy (SH) specimen: well visible are the mucosa, submucosa, and muscularis propria.

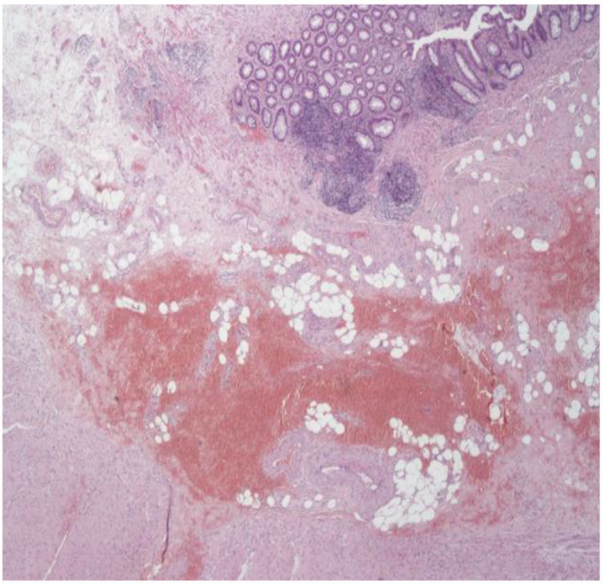

FIGURE 2 | Intramural bleeding in the submucosa of a specimen.

TABLE 2 | Minor and major complications after SH—mucosectomy vs. full thickness.

Complications	M Group (mucosectomy) 13 pts	FT Group (full thickness) 124 pts	*p*
Pain (VAS) Mean (SD)	3.6 (1.68)	3.7 (1.69)	0.33
Incontinence (WS) Mean (SD)	1.8 (1.8)	2.3 (2)	0.22
Return to work (PO days) Mean (SD)	9 (2.6)	9.5 (2.9)	0.26
Major bleeding (pts)	0	1	0.38
Urgency (pts)	0	2	0.32
Recurrences (pts)	1	0	-

SH, stapled hemorrhoidopexy; VAS, Visual Analog Scale; WS, Wexner score.

1.8) in Group M vs. 2.3 (SD 2) in Group FT ($p = 0.22$); the date of return to work was similar [post-operative (PO) day 9 SD 2.6 in Group M vs. 8.6 SD 2.9 in Group FT; $p = 0.26$]. Two patients in the FT Group (one in Group B and one in Group C) reported urgency and a persistent increase in stool frequency, but these complications resolved after 4 and 6 months.

Reports of major complications were very rare: one case in the FT Group (Group A; single PPH) experienced an episode of post-operative bleeding on the fourth PO day and required a new hospitalization with an evaluation under anesthesia and surgical hemostasis. No cases of perirectal hematoma or sepsis occurred. Only in one case did we observe an early recurrence of the hemorrhoidal disease; this was in a male patient in the M Group (Group A) at 8 months (**Table 2**).

DISCUSSION

Treatment of HD by SH is a widespread technique, but since its initial use, it has often been described as a stapled mucosectomy. We conducted a thorough review of the literature using the keywords "mucosectomy" and "hemorrhoids" on PubMed in December 2020 and found six papers among the most recent 40 studies (5, 9–13) that used the term mucosectomy to describe the type of surgery adopted to treat hemorrhoids. We found no prevalence for any particular country or journal: from China to Italy, when a stapler is used to reduce a hemorrhoidal prolapse, the common term used is mucosectomy.

Unfortunately, despite the large number of studies dedicated to the evaluation of follow-up, complications, and costs, there are still no studies that focus on the characteristics of the tissue removed during surgery. Pathology examinations of hemorrhoids and prolapse specimen can, in some cases, reveal

incidental findings (14), but the majority of the reports describe the anal ring generically, as a portion of rectal wall, with no further specification. We decided to do a new examination with the aim of providing a more accurate description of the different rectal wall layers by characterizing actual tissue excised during surgery. In most cases in which the excised tissue allowed a histological re-evaluation, we were faced with a "full-thickness" resection that included, in addition to the mucosa, also the submucosa and the muscularis propria. Only 13/137 specimen (9.5%) were true mucosectomies.

In the majority of cases, an actual mucosectomy was performed only in male patients. This is not surprising considering the characteristics of the mucosal prolapse associated with hemorrhoids, as this prolapse occurs more frequently in women (15) and, in these cases, appear more mobile than in male patients. It is common, in female patients, to include a greater amount of tissue in the stapler case.

If the first endpoint of the study is fundamentally anatomical and to define the entity of the excision, the second endpoint is clinically even more important: it is to evaluate if this type of resection (FT) increases complications. In the past, some studies have reported, for example, an increase in post-operative pain and fecal urgency after stapled hemorrhoidectomy (16), and this has been interpreted as a consequence of incorporation of muscle fibers in the doughnut specimen. Hidalgo et al. (17) reported a perirectal hematoma after a resection that included not only the mucosa but also the submucosa, muscular layer, and perirectal fat tissue. Our observations of common specimens obtained after SH indicate that to remove more than mucosa seems to be the rule (**Figure 1**).

A full thickness resection of a prolapse did not increase complications. Even though dividing the patients into two groups according to the type of resection (the M Group and the FT Group) did not allow a valid statistical comparison because of the different numbers of patients (13 vs. 124), we can still make some suppositions. In the FT Group, the number of complications was not significantly higher than in the M Group, but it was also not higher than in the general reports about complications after SH. Relevant bleeding occurred in only 1/124 patients (0.8%), which was less than that reported in other studies (18). Persistent urgency, without any serious episodes of incontinence, was present in two cases, both in the FT Group (1.6%). The only early recurrence (before 1 year of follow-up) was found in one patient, in the M Group (7.7%).

The small sample size, however, limited the statistical power of the analysis carried out to evaluate the complication rate in relation to the thickness of the removed rings.

In the present study, we histopathologically evaluate the actual wall layers excised during SH, in order to define if the use of the term "mucosectomy" is appropriate. From the beginning of the technique until the present, this has been a "popular" definition. Some surgeons assumed that SH was not only a mucosectomy; others declared that a full thickness excision should be considered a technical mistake, related to post-operative complications (19).

This study demonstrated that this is not only a mucosectomy, but it is actually a true resection of the rectal wall—analysis of the specimens confirmed the presence of muscular fibers in 90% of the cases. Further, this study excluded a correlation between the rate of post-operative complications, mild and severe and a "full thickness" resection. This is almost the rule in SH and not a surgical accident.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CE and DM designed the study, analyzed the data, wrote the manuscript, designed tables, and gave final approvation. FM analyzed the data, realized the pictures, and gave final approvation. SP and GG analyzed the data, corrected the final draft, gave an important contribue to the final draft, revised bibliography, and final approvation. PM and LF collected the data, improved quality of pictures, and gave final approvation. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2021.655257/full#supplementary-material

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Safety and Effectiveness of Tailored Hemorrhoidectomy in Outpatients Setting

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Introduction: Single or double prolapsed pile instead of full muco-hemorrhoidal prolapse is a common finding in patients with symptomatic III or IV degree hemorrhoids. For this selected group of patients, relief of symptoms could be achieved by managing the single/double prolapsed piles instead of performing traditional hemorrhoidectomy. The aim of this single-center study was to evaluate the safety and medium- and long-term effectiveness of an outpatient tailored Milligan-Morgan hemorrhoidectomy (MMH) performed under local anesthesia (LA).

Material and methods: Clinical records of 202 patients submitted to outpatient tailored MMH, under LA and without anal dilation, treated between 2013 and 2020, were retrospectively reviewed using a prospectively maintained database and completed by a telephone interview or outpatient consultation. Postoperative pain score, the need for painkillers, postoperative complications and symptoms recurrence, return to working activities, and patient grading assessment scale were recorded.

Results: Thirty-five (17%) out of 202 patients recruited were lost to the follow-up. One hundred and fifty-two and 15 patients underwent a single and double pile hemorrhoidectomy, respectively. With regard to postoperative outcomes, visual analogue scale (VAS) decreased from a median value of 4 [interquartile range (IQR) 2–6] on the day of surgery to 1 (IQR 0–4) on the 10th postoperative day ($p < 0.001$). Sixty-one patients (37%) needed oral painkillers during the 1st week after surgery. There was no mortality or major postoperative complication. Bleeding requiring hospital readmission was reported in seven (4%) patients, and one patient underwent emergency surgery with no need for blood transfusion. No postoperative urinary retention, anal incontinence, or stricture occurred in the series. During the median follow-up of 39 (IQR 12–60) months, 26 patients (16%) reported symptoms of recurrence but only six underwent traditional MMH. Recovery to normal activity occurred within a median period of 6 days (IQR 3–10) and the Clinical Patient Grading Assessment Scale (CPGAS) at 1 year after surgery was reported to be a "good deal better."

Conclusions: Tailored MMH performed under LA in an ambulatory setting can be considered a safe and effective technique with high compliance and satisfaction of patients.

Keywords: hemorrhoids, ambulatory setting, milligan morgan hemorrhoidectomy, long term outcome, local anaestesia

INTRODUCTION

Hemorrhoidal disease is one of the most common anorectal disorders, with an overall prevalence of 39% (1, 2). Conservative treatments are considered in the early stages, while surgery should be reserved for advanced grades or for the refractory of patients to conservative procedures (3–6). Among surgical procedures, the Milligan-Morgan hemorrhoidectomy (MMH) is still considered the "gold standard" for advanced grades of hemorrhoids (7, 8). However, this operation carries prolonged postoperative pain and convalescence and potential complications such as urinary retention, bleeding, and anal stricture (9). In the last decades, the use of new devices based on ultrasound or radiofrequency, such as Harmonic Scalpel® and Ligasure™ system, has contributed to lower postoperative pain while shortening the recovery time (10–12).

Although, general or epidural anesthesia is the most commonly performed anesthetic techniques, local anesthesia (LA) is considered as a safe alternative with a significant reduction in complications (13–15). Ambulatory anorectal surgery is becoming a routine procedure for several proctologic diseases including fistula, abscess, condyloma, pilonidal disease, and hemorrhoids. The American Society of Colon and Rectal Surgeons suggests that 90% of anorectal diseases might be suitable for ambulatory surgery, with consequent reduction in hospital admissions and hospital charges (16).

However, several patients affected by symptomatic III or IV grade hemorrhoids, with a single or double prolapsed pile, could benefit from a limited excision under LA performed in the ambulatory setting without the need for anal dilation. For this selected group of patients, traditional hemorrhoidectomy could result in an overtreatment even if the recurrence of hemorrhoidal prolapse in other quadrant may occur several years later (17).

This retrospective single-center study aimed is to evaluate the safety and long-term effectiveness of outpatient MMH performed without anal dilation under LA in patients with single or double pile hemorrhoids.

MATERIALS AND METHODS

A retrospective observational study was carried out using a prospectively maintained database of patients who underwent outpatient MMH in a tertiary colorectal unit between September 2013 and January 2020. Follow-up data were collected by a telephone interview or further outpatient consultations. Consecutive patients over 18 years old, with symptomatic grade III-IV hemorrhoids according to the classification of Goligher involving a single or double external piles, that fit for operation under LA (ASA I/II), were enrolled in the study.

Exclusion criteria were the use of anticoagulants or immunosuppressive drugs, pregnancy, severe constipation, concomitant anal condition requiring surgical treatment, previous anal operations for anal fissure or fistula, patients living too far (more than 30 min driving) from the hospital, and allergy to anesthetic drugs.

Postoperative pain at 30 min, 5 and 10 days after surgery was evaluated using a VAS. Postoperative complications, the number of painkillers used, and days to return to normal activity were recorded.

Postoperative clinical outcomes (bleeding and recurrence) and satisfaction of the patient, scored by the Clinical Patient Grading Assessment Scale (CPGAS) (18), were evaluated after a minimum period of 1 year of follow-up.

SURGICAL PROCEDURE

After obtaining written informed consent, all patients were placed in prone or Sims position and received LA by injecting mepivacaine hydrochloride 20 mg/ml, in the submucosa of the prolapsed pile. Harmonic Scalpel® (ETHICON ENDO-SURGERY, LLC, Guaynabo, PR, USA) was used to remove the prolapsed hemorrhoidal piles without anal dilation. The terminal hemorrhoidal artery was just coagulated without ligation. The power of the Harmonic Scalpel® was set at level 3. A resorbable hemostatic swab, made by oxidized regenerated cellulose, was applied into the anal canal at the end of the procedure. Application of hemostatic stitches was considered only in case of incomplete hemostasis.

Patients were revaluated 30 min after the procedure to verify the achieved hemostasis and discharged immediately and reevaluated at 5 and 10 days.

Bulking stool softeners (Psyllogel Nathura® s.p.a., Montecchio Emilia, RE, Italia) were prescribed irrespectively of the bowel habit for 1 month. Painkillers (Ketorolac 10 mg or paracetamol 1,000 mg pills) were taken in case of anal pain. No antibiotic prophylaxis was prescribed. The procedure was performed by resident doctors under the supervision of board-certified colorectal surgeons (**Figure 1**).

STATISTICAL ANALYSIS

All data were expressed as median range and interquartile (IQR), and the statistical analysis to compare the changes in VAS at different times was performed using paired Wilcoxon rank-sum test. A value of $p < 0.05$ was considered statistically significant. Descriptive data were expressed as percentage. Statistical analysis was carried out using RStudio [R version 4.0.3 Copyright (C) 2020 The R Foundation for Statistical Computing].

RESULTS

Two hundred and twelve patients (median age 54.57 IQR 45–65, women 51%) with 1 or 2 symptomatic III or IV degree piles entered in the study. One hundred and sixty-seven patients (women 51%) agreed to participate in the telephone interview or were controlled after a median follow-up of 39.1 (IQR 12–60) months, while the remaining 35 (17%) were lost to the follow-up.

There were 82 men (49%) and 85 women (51%) with a median of 53 years (IQR 45–64) and 55 years (IQR 46–64), respectively. Twenty-five (17%) patients have had previous hemorrhoidal surgical treatments. Eight patients were treated by MM technique, seven by rubber band ligation, seven by

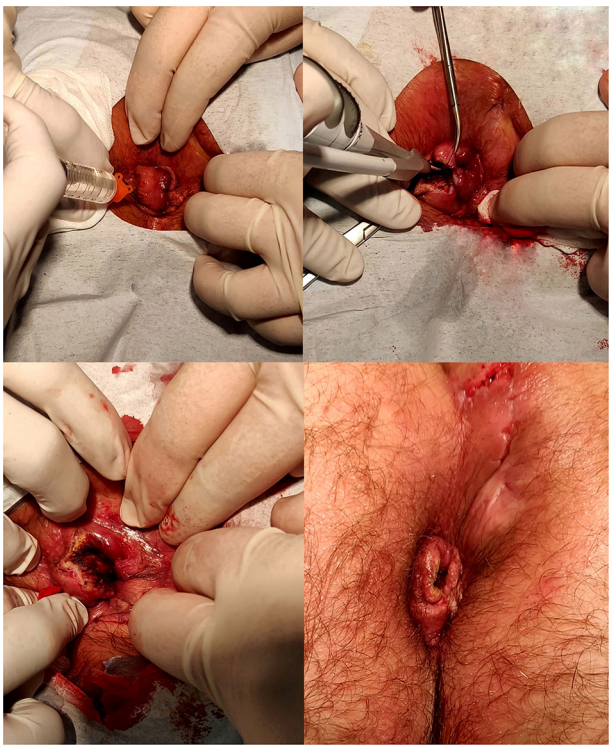

FIGURE 1 | Main steps of the surgical procedure.

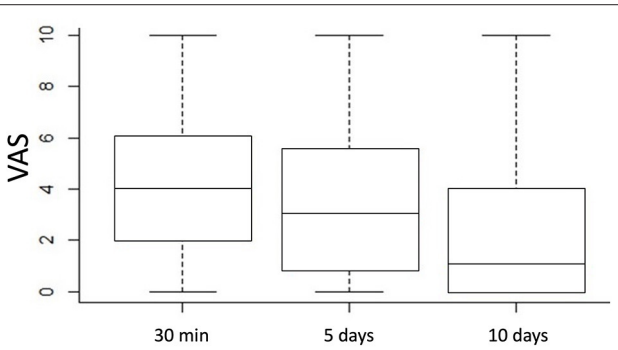

FIGURE 2 | Postoperative pain according to VAS 30 min, 5 and 10 days after surgery.

stapler device, and three patients by trans-anal Doppler-guided hemorrhoid artery ligation.

One hundred and forty-seven patients (87%) were affected by a grade III and 21 patients (13%) by grade IV hemorrhoids. One hundred and fifty-two (91%) patients underwent a single pile removal, while 15 (9%) had the removal of two piles with a median operative time of 10 min.

The 30-min postoperative pain had a median VAS of 4 (IQR 2–6), which decreased to 3 (IQR 1–5.5) ($p = 0.007161$) 5 days later and to 1 (IQR 0–4) ($p < 0.001$) 10 days later (**Figure 2**).

No significant difference in terms of pain was found comparing single and double pile removal (**Table 1**).

TABLE 1 | Evaluation of pain after single and double pile removal.

	VAS 30 min	VAS 5 days	VAS 10 days
Single Pile *n = 151*	4 (IQR 2–6)	3(IQR 1–5)	1(IQR 0–4)
Double Piles *n = 16*	4 (IQR 2–5)	2(IQR 1–4)	2(IQR 0.75–2.25)
p-value	0.87	0.84	0.43

TABLE 2 | Postoperative complications and recurrence rates.

	***n* = 167**
Follow-up (months)	39.1 (12–60)
Post Bleeding	
No	117 (70%)
Yes	50
- Minor	43 (26%)
- Major	7 (4%)
Complications	
No	161 (96%)
Yes	6
- Pain	4 (3%)
- Wound infection	2 (1%)
Recurrence	
No	141 (84%)
Yes	26 (16%)
- Surgery	
No	20 (12%)
Yes	6 (4%)

One hundred and six patients (63%) did not use painkillers during the postoperative period, while 61 (37%) needed paracetamol or ketorolac administration during the first 1st after surgery. Four patients (3%) were reevaluated within 1 month because of persisting anal pain.

No correlation was found between age, previous surgery, sex, and the severity of the pain.

No mortality or major postoperative complications were recorded. Minor bleeding was reported by 43 patients (26%) within the first 10 postoperative days, with spontaneous resolution. Bleeding requiring hospital readmission was reported in seven patients (4%), but only one (0.6%) developed significant anemia (Hb level 7 g/dl) requiring surgery without the need of blood transfusion, while six had conservative treatment and were discharged the day after admission.

Wound infection was reported in two cases (1%). No patient had postoperative urinary retention neither had anal incontinence or stricture.

During the follow-up period, 26 patients (16%) developed some degree of prolapse recurrence, but only 6 (4%) of them underwent a new surgical treatment (traditional MM), while the remaining 20 patients (12%) were treated conservatively (**Table 2**).

Patients were able to recover their normal activity and work after a median period of 6 days (IQR 3–10), and the CPGAS at 1 year after surgery was a "good deal better" with a median value of 5 (IQR 4–6).

DISCUSSIONS

Milligan-Morgan operation is traditionally performed in the operating theater under general or epidural anesthesia. However, in the last few decades, there has been an increasing trend to perform anal surgery in an ambulatory setting under LA with or without intravenous sedation. The American Society of Colon and Rectal Surgeons recommends to consider ambulatory surgery in most patients whenever proctological procedures are contemplated. In fact, this surgical approach has been shown to be safe and effective with reduction in the hospital charges and with high satisfaction of patients (16).

This study demonstrates that a selected group of patients with single or double III/IV grade hemorrhoids can be treated safely in an ambulatory setting by a tailored MM operation using ultrasound devices under LA without the need for anal dilation.

In fact, in this study, postoperative complications occurred in <10 % of the patients. Seven patients (4.2%) reported major bleeding requiring hospital readmission, but only one needed a new surgical treatment, while the remaining six were managed conservatively.

The absence of anal dilatation reduces complications while increasing compliance of patients; in fact, anal dilatation has been shown to potentially cause anal sphincter fragmentation leading to fecal incontinence in some patients (19).

This surgical option can be considered effective in the medium/long-term outcome since a symptomatic recurrence was recorded in only 16% of them after a median of 3 years (IQR 2–5) follow-up, and only 4% needed a standard MM operation.

Several studies report long-term results after MM operation (20–22); however, no study reports the effectiveness of MMH performed under LA without anal dilation in an ambulatory setting in terms of recurrence rate.

Furthermore, the subjective overall evaluation of the results of surgery using the CPGAS indicated that the patients were "a good deal better" after surgery with a return to normal activity and work within 1 week.

Several meta-analyses demonstrated that MMH performed under LA is associated with significantly lower postoperative pain within 24 h after surgery and a lower need for painkiller drugs compared to general or spinal anesthesia (13, 14).

In agreement with the literature, our study reported that these patients complained only a "troublesome pain" (median VAS 4) in the early postoperative time, with a reduction to a median value of 3 on the 5th postoperative day. Furthermore, although, Haveran et al. (23) suggest that the maximum benefit can be realized by the association of LA with propofol/ketamine intravenous sedation, in our series, no intravenous sedation was needed.

Further contribution to minimize the postoperative pain probably results from the use of the Harmonic Scalpel® that has been demonstrated to lower the postoperative pain compared to the diathermy, due to the little spread of the thermal injury, and by avoiding hemostatic suture to the terminal hemorrhoidal artery (24–26).

In our experience, 37% of the patients needed painkillers in the 1st week after surgery and none of them used opioids, while only four of them reported pain at defecation after 1 month. These patients were treated by analgesic and use of bulk stool softeners for further 2–3 weeks.

Despite urinary retention complicates up to 50% of patients undergoing anorectal surgery under spinal anesthesia (27, 28), particularly those undergoing hemorrhoidectomy (29), in our series no cases of urinary retention were recorded. The absence of episodes of urinary retention in this study may be related to the use of LA; in fact, Xia et al. (13), in their meta-analysis, reported a significantly reduced risk of urinary retention after the procedure performed under LA compared to general or spinal anesthesia.

One possible disadvantage of LA is the fear of pain during the anesthetic injection, which can be minimized by the local application of anesthetic ointments before the injection (14).

Postoperative bleeding is another common complication requiring reoperation. The rate of minor bleeding, in our series, was 26%, but all the patients had a spontaneous resolution in the first 10 days. Only 4% of our patients had major bleeding requiring hospitalization; however, only one patient required surgery without the need of blood transfusion. These data match positively with a reported rate of delayed posthemorrhoidectomy bleeding in the literature, which is about 5% (30). The use of the Harmonic Scalpel® contributes to achieving safe hemostasis while minimizing the thermal injury of the surrounding tissues, allowing faster wound healing (10, 23).

The surgical option to treat these patients by a minimal tailored approach got a high grade of patient satisfaction, not only because of the advantages of the ambulatory setting (short duration of the procedure, rapid return home, and minimal off-work period) but also because of the comfortable prone or Sims position without the need for anal dilatation and for absence of intravenous sedation. In fact, the subjective overall evaluation of the results of this surgery using the CPGAS score indicated that the patients were "a good deal better."

The main limitation of this study is its retrospective nature, and the follow-up data have been collected only by a telephone interview although, those complaining of symptom recurrence were controlled as outpatients.

CONCLUSIONS

Tailored ambulatory MMH under LA without anal dilation can be considered a safe and effective technique for patients affected by single or double III/IV grade hemorrhoids with high compliance and satisfaction of patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico Indipendente - Azienda Ospedaliera Universitaria Policlinico di Bari. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

GTo and AP: conception and design of the study, acquisition analysis and interpretation of data, writing the paper, and final approval of the version to be published. GM, GL, RD, GTr, MD, and MR: acquisition analysis and interpretation of the data and final approval of the version to be published. DA: conception and design of the study, interpretation of the results, writing the paper, and final approval of the version to be published. All authors contributed to the article and approved the submitted version.

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MINI REVIEW
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Lifestyle and Risk Factors in Hemorrhoidal Disease

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Constipation, a low fiber diet, a high Body Mass Index, pregnancy, and a sedentary lifestyle are often assumed to increase the risk of hemorrhoidal disease (HD). However, evidence regarding these factors is controversial. This mini-review aims to examine and critically analyze the association between main risk factors and the prevalence of HD, focusing both on the patient's clinical history and on a tailored treatment. Moreover, some practical suggestions about lifestyle and conservative approaches are given to help clinicians in the management of patients with HD and to obtain the best results from therapy.

Keywords: Body Mass Index, constipation, lifestyle, conservative treatment, hemorrhoidal disease

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INTRODUCTION

Hemorrhoidal disease (HD) has been described in depth throughout medical history. The first manuscript dates back to 37 AD in *De Medicina*, a treatise written by the Roman encyclopedist and physician Aulo Cornelio Celso. The seventh book of *De Medicina* deals with proctological disease: fissure, HD, constipation, and condylomas. The author suggests that manual intervention (surgery) should be taken into consideration when medical therapy has proved ineffective. Moreover, he recommends always integrating medical therapy with a healthy diet and lifestyle. Today, according to the most recent guidelines, conservative therapy is still considered "an effective first-line treatment that should be recommended before surgery" (1).

From the first century AD to 2021, much scientific literature has been published concerning proctological diseases, so much so that HD is among the best described diseases in clinical medicine (2). PubMed today shows 10,016 results when searching the term "Hemorrhoids." Most of these publications concern surgery and medical treatments. On the contrary, scientific evidence regarding lifestyle and risk factors in HD are limited.

HD is hypothesized to result from deterioration of the supporting connective tissue, prolapse of hemorrhoidal tissue, distention of the hemorrhoidal arteriovenous anastomoses, or dilation of the veins of the internal hemorrhoidal plexus (3–6). Factors commonly assumed to increase the risk of HD include constipation, a low fiber diet, a high Body Mass Index, pregnancy, and a sedentary lifestyle. All these factors need to be more investigated.

This mini-review has been performed in PubMed to identify and summarize the most recent randomized controlled trials (RCTs), meta-analyses, and retrospective and prospective studies that analyze the above-mentioned risk factors involved in HD. The review further aims to give some practical suggestions addressed to reduce the prevalence of the pathology and to alleviate patients' symptoms in combination with the medical treatment.

RISK FACTORS

HD can present with a variety of symptoms, including anal bleeding, prolapse, itching, and/or perianal skin irritation. All of these physical discomforts can significantly influence the quality of life (QoL) in patients with HD (2). In addition, frequent recurrence and persisting pain and not negligible complication rate even after surgery (7) raise the need to prevent HD through effective management of risk factors.

HIGH BODY MASS INDEX

A study published by Riss et al. investigated the prevalence of HD and associated risk factors in an adult general population. The researcher analyzed the correlation between HD and the Body Mass Index (BMI). Of 976 participants enrolled in this prospective study, 380 patients (38.93%) suffered from HD. Among these, 170 patients (44.74%) complained about symptoms associated with HD, whereas 210 patients (55.26%) reported no symptoms. Researchers have observed that the Body Mass Index (BMI) had a significant effect on the occurrence of HD: an increase in BMI increased the risk of HD by 3.5% (8).

Although the correlation between obesity and HD are not plain elucidated, some pathophysiologic mechanisms such as increased intra-abdominal pressure, venous congestion, and chronic inflammation have been hypothesized to contribute to HD development in the obese patients.

On the contrary, Peery et al. in their investigation of 1,074 patients with HD found no correlation with overweight or frankly obese (4).

Studies concerning the correlation of BMI and HD are controversial. The reason is because BMI value is an anthropometric measurement used for categorizing the population, not for identifying visceral fat and its associated risks such as low-grade inflammation. In this respect Gutin observed that: "the tendency toward standardization of obesity measurement and link between body weight and health is in contrast with BMI's ability to accurately diagnose obesity in individuals or populations" (9). Therefore, BMI will continue to be the primary measure given its ease of use and low cost of collection, but it is not the most suitable parameter for measuring individuals' health.

To improve the management and health of patients with HD, it is recommended to routinely evaluate the waist circumference, a useful parameter for predicting low-grade inflammation and associated risks (intra-abdominal pressure and venous congestion). The waist circumference threshold values indicating increased health risk within each BMI category are reported in **Table 1** (10).

TABLE 1 | Waist circumference thresholds stratified by BMI.

BMI category (kg/m^2)	Waist circumference (cm)	
	Women	Men
Normal weight (18.5–24.9)	≥80	≥90
Overweight (25–29.9)	≥90	≥100
Obese I (30–34.9)	≥105	≥110
Obese II and III (≥35)	≥115	≥125

Waist circumference threshold indicating increased health risk within each BMI category. Data were originally presented in Ross et al. (10).

CONSTIPATION

Constipation, hard and dry stool, can worsen symptoms related to hemorrhoidal prolapse. Peery et al. in their study analyzed 1,074 patients with HD and found that constipation, straining during bowel movements and hard or lumpy stools for at least 25% of the time were all associated with an increased prevalence of HD (4). These data were confirmed by Riss et al., who published a cross-sectional study of 976 participants who had undergone a colonoscopy and found that constipation was associated with an increased risk of HD (8).

Therefore, a balanced diet with adequate fiber and fluid intake to improve of stool consistency should be one of the main purposes in conservative treatment for HD (Level of evidence: 1; Grade of recommendation: B) (1).

Alonso-Coello in his meta-analysis (11) show the results of seven randomized trials (378 patients).

Studies with multiple follow-ups, usually at 6 weeks and then at 3 months, showed consistent results over time:

- The risk of not improving/persisting symptoms decreased by 47% in the fiber group (RR = 0.53, 95% CI 0.38–0.73);
- The risk of bleeding decreased by 50% (RR = 0.50, 95% CI 0.28–0.89);
- One study suggested a decrease in recurrence.

As regards the health benefits (laxative effects) attributable to dietary fibers, it is important to analyze in depth the physical effects of insoluble and soluble fiber in the gut (12):

- Insoluble fiber particles (e.g., wheat bran) stimulate secretion of water and mucous by a mechanically irritating effect on large bowel mucosa;
- Soluble gel-forming fiber (e.g., psyllium) has a high capacity to hold water that resists dehydration in the large bowel.

Patients should be advised to avoid straining at stool and to improve bowel function by increasing the intake of soluble fiber, which can increase the volume and improve the softness of fecal mass. HD symptoms may be eased though a regular defecation with type 3 or 4 stool according to the Bristol Stool Form Scale (11, 13).

McRorie et al., in their review, investigated the presence of meaningful clinical evidence in terms of the beneficial effects of different fiber supplements. Among them psyllium, a non-fermented gel-forming fiber, was demonstrated to provide a dichotomous stool normalizing effect: it softens hard stool in constipation

Abbreviations: QoL, Quality of Life; HD, Hemorrhoidal disease; BMI, Body Mass Index; RR, Relative Risk; CI, Confidence Interval.

and firms up liquid stools in diarrhea, showing to be effective in several clinical studies for constipation treatments (14).

Peery et al. found that fiber intake was associated with a reduced risk of HD. Surprisingly, the association between high fiber intake and reduced risk of HD was held even after adjustment for constipation (4).

Furthermore, recent studies have demonstrated a causal relationship between constipation, dysbiosis, and intestinal peristalsis. Cao et al. in their study suggest that gut dysbiosis could inhibit intestinal motility and contribute to the development and persistence of constipation. The author provides a point of view to demonstrate the pathogenesis of constipation as well as hypothesizing the need for innovative microbiota-mediated therapy for treating chronic constipation (15).

According to the most recent literature, patients suffering from constipation should be treated with a multi-target therapy that acts both on the volume and softness of fecal mass (soluble fiber) and also on gut motility and microbiota (16).

SEDENTARY LIFESTYLE

Data concerning physical activity and HD are controversial: although a sedentary lifestyle is considered a risk factor for developing HD, Perry et al. found an association between a sedentary behavior and a reduced risk, unlike physical activity (4). To better understand this result, it is necessary to analyze the different kinds of sports activity; certain types of exercise can make the problem worse, so it is important to be prudent when choosing how to perform exercise.

The goal of physical activity for people with HD is to promote regular bowel movements, improve circulation, and strengthen muscles in the pelvic area and lower back. On the contrary, a lack of physical activity can contribute to constipation, worsening a current HD, triggering a recurrence, or even causing new problems in those who have never had a hemorrhoid before.

Exercises that are generally considered safe and effective for HD management and prevention include aerobic activities, such as walking and swimming, or controlled-movement exercises to help strengthen the abdominal and rectal tissues, such as yoga.

Patients with HD should avoid exercises that tend to place pressure on sensitive areas, such as cycling, rowing, horseback riding, or some weightlifting exercises that involve the Valsalva maneuver.

Patients should be advised to not give up on exercise, but to pick the right exercise routine. This keeps the system "regular," promotes colon health, and may even prevent constipation and gastrointestinal disorders. Taken together, moderate physical activity (20–60 min, 3–5 days per week) should be recommended to patients because it improves QoL and can help to effectively manage hemorrhoid symptoms (17).

PREGNANCY

Pregnancy and spontaneous vaginal delivery are predisposing factors for the development of HD due to the constipation and the reduction of venous outflow due to increased circulatory blood volume, venous relaxing effect of progesterone, and also to enlarged uterus that increases pressure in the rectal veins.

The prevalence of HD is mostly in the last trimester of pregnancy and in the first month after delivery, with about 25–35% of pregnant women suffering from this disease (1).

In terms of etiology, mechanical and hormonal factors have been proposed to explain the relationship (18). Straining during defecation, impairment of defecation habits during pregnancy, decrease in physical activity, and psycho-social stress may also predispose to constipation and HD. Progesterone tends to lower the strength of venous wall muscle, decrease circular and longitudinal smooth muscle contractility, and slow gastrointestinal transit. This inhibition contributes to constipation, which indirectly predisposes one to the development of HD. Moreover, dietary modifications can be implicated: decreased fluid intake and iron supplementation may cause constipation.

For many women, symptoms resolve spontaneously soon after birth.

Pregnant women should be advised that preventive methods help significantly with symptom management: dietary modification with increased bulk, such as fresh fruit and vegetables and plenty of water, should be applied during pregnancy and in the postpartum period.

Avoidance of constipation is the most important method for prevention of HD during pregnancy.

MANAGEMENT OF RISK FACTORS

When intervention for risk factors is not enough to improve the symptoms of patients with HD, many other options are available, ranging from simple conservative measures to surgical excision of the hemorrhoids. The choice of therapy normally depends on the severity of symptoms and the amount of prolapsing hemorrhoidal tissue.

Conservative treatments comprise modern drugs and traditional medicine, available in a variety of formulations, including pills, suppositories, creams, and wipes. Among these, phlebotonics (flavonoids or synthetic compounds such as calcium dobesilate) are widely used for the control of symptoms (Level of evidence: 1; Grade of recommendation: B) (1); they are able to improve vascular tone, decrease capillary permeability, reduce venous capacity, and facilitate lymphatic drainage, as well as having anti-inflammatory effects (19).

Oral and topical therapies are largely used for the treatment of low-grade hemorrhoids, but unfortunately these treatments have met with criticism. As regards pills and oral delivery, some physiological mechanisms can reduce intestinal absorption of the active ingredients of the drugs. The absorption by the mucous secretions and the cytochrome CYP3A and P450 activity can make the active principles unavailable. Moreover, the peptide nature of the compounds can cause their gastric

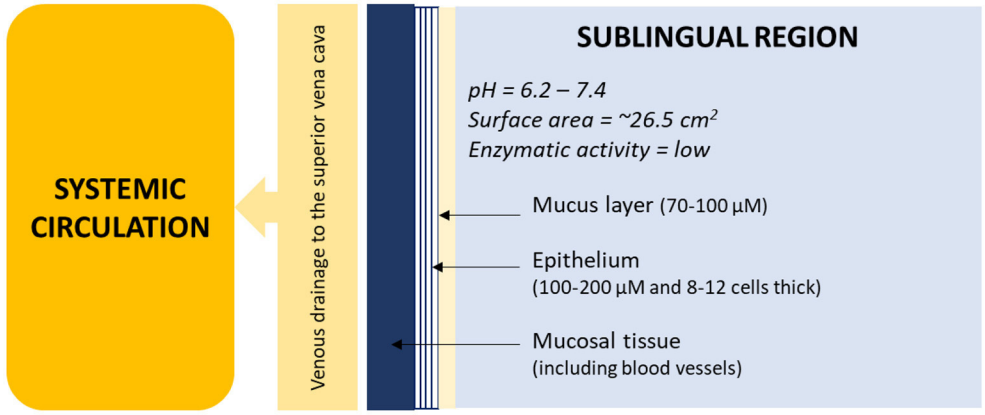

FIGURE 1 | Schematic diagram of the sublingual regions in the oral cavity. Data were originally presented in Hua (22).

hydrolysis, and the saprophytic flora can cause a reduced intestinal absorption of the active ingredients. Consequently, only a small percentage of active compounds is actually absorbed, requiring high doses of treatment to reach the therapeutic level (20). An example could be represented by the flavonoid diosmin: the molecular size impacts on the extent of absorption, and it needs to be micronized to have better clinical efficacy (21).

To further improve the pharmacokinetics of this drug, a solution could be a sublingual formulation. In fact, among the oral administrations, the sublingual route of administration has significant advantages for systemic drug delivery. Drugs can be quickly and directly absorbed into the systemic circulation *via* venous drainage to the superior vena cava. Therefore, sublingual administration is particularly functional for drugs that undergo high hepatic clearance or degradation in the gastrointestinal tract and for patients with swallowing problems (**Figure 1**) (22).

The treatment of HD remains challenging. It involves the degeneration of the supporting tissue of the anal cushions, venous dilation, blood stagnation, the formation of edematous venous plexus, and inflammation. Multiple treatment options are available, but patients rightly demand a tailored and effective approach.

Considering the complexity of the pathophysiology of HD, the treatment option should be oriented to a multi-target treatment capable of acting on all pathological mechanisms simultaneously. Furthermore, a pharmaceutical form with high bioavailability should be preferred.

Among the conservative therapy for HD, topical treatments are used as first-line treatment and as a bridge to surgery. The primary objective of most topical treatment aims to manage the symptoms rather than to cure them. These topical medications can contain different ingredients, such as corticosteroids, antiseptics and anesthetics (23). The main concerns of these topical treatments concern their prolonged application that can induce sensitization reactions, immunosuppression, and vessel reactivity (due to cortisone) (24), irritation, and resistance (due to lidocaine).

An improvement of this kind of treatment can be represented by an anorectal gel based on natural ingredients with film-forming and protective actions. An innovative formulation should have an approach that considers all aspects of HD; it should hydrate and offer immediate comfort by a lubricating activity and, simultaneously, restore the function of the skin barrier and of the tissue repair processes and support the connective tissue stability whose reduction has been associated with the incidence of HD (6).

CONCLUSIONS

The therapeutic treatment of hemorrhoids ranges from dietary and lifestyle modification to radical surgery, depending on the degree and severity of symptoms.

Body weight has been often correlated to an increased risk for HD, but data obtained from clinical studies about the association of high BMI (>25) and HD are controversial. This because HD in the obese is not directly and exclusively associated with one's weight, but to intra-abdominal pressure, venous congestion, and the chronic inflammation (9). Hence, the right indicator for measuring the health status of patients is rather the waist circumference, instead of BMI.

In clinical studies of HD, dietary fiber supplements resulted in an effective treatment in non-prolapsing hemorrhoids, reducing the risk of persisting symptoms and bleeding by ∼50% (25). As fiber supplements are safe and useful, they can represent a first treatment or an integration of other therapeutic modalities of HD. However, fiber supplements could take up to 6 weeks for a significant improvement (26), taking into consideration the need to choose the appropriate fiber and for it to simultaneously act on the intestinal motility and gut microbiota (15).

Beyond the increase in the intake of dietary soluble fiber, lifestyle modification should also be advised to any patient with any degree of hemorrhoids. These changes include adequate fluid intake, regular exercise, improving anal hygiene, avoiding straining at stool, and, when necessary, integrating these with appropriate and tailored treatments.

In order to positively affect the QoL of patients with HD, it is important to analyze the above-mentioned risk factors, remembering that a good analysis starts from good listening.

Several studies have highlighted the importance of good interactions between physicians and patients. The evidence shows that by allowing the patients to discuss their problem without being interrupted for first two minutes, it is possible to optimize the visit time and obtain better results (27, 28).

Skillful listening is essential to make accurate diagnoses, to educate patients on the culture of prevention, and to convey empathy and support. Reporting a quote from Hippocrates, the father of medicine, 2,500 years ago: "It is more important to know what sort of person has a disease than to know what sort of disease a person has".

AUTHOR CONTRIBUTIONS

DT conceived and supervised the review topics. SDM wrote the first draft. All authors contributed to the article and approved the submitted version.

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PERSPECTIVE
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Making Use of Patient-Reported Outcome Measures for Haemorrhoidal Disease in Clinical Practice: A Perspective

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Haemorrhoidal disease (HD) affects millions of people around the world and for most it is a recurring problem. Increasingly, clinicians broaden their focus on the patient's experiences with haemorrhoidal symptoms, including their impact on daily life. The patient's experience can be assessed using a patient-reported outcome measure (PROM). A PROM facilitates a deeper understanding of the disease-burden and allows a clinician to obtain information directly from the patients about their experiences with the ailment. Over the last years, PROMs have shown their additional role to traditional outcomes for several diseases and have earned their place in the daily consultation room. In order to improve and personalize the treatment of HD, we endorse the use of validated PROMs in clinical care.

Keywords: patient-reported outcome measures, core outcome set, haemorrhoidal disease, hemorrhoids, patient perspective

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INTRODUCTION

Haemorrhoidal disease (HD) is the most common proctological disease with prevalence rates of up to 44% within the general population (1). HD has troubled humankind since ancient times and considerably hampers a patient's quality of life (2). Patients report several restrictions or adjustments to be made in daily life: "Because of the massive blood loss, I could not function normally any more. I did not dare to go anywhere, not to a party, not to my son's soccer match" (3). Furthermore, HD may impair a patient's intimate relationship and sexuality: "(…) my sex life, I do think it is difficult, because of the flap coming out of my anus" (3–5).

In the past, traditional clinical outcomes such as "recurrence of disease" have been valued the most in clinical decision making and to denote treatment success. However, the emphasis is gradually shifting to the patients' perspective and patients' experience with symptoms of HD. This is also acknowledged in the recently developed European core outcome set (COS) for HD, by identifying patient-reported symptoms as the primary core outcome for clinical HD studies (6). A COS is a consensus-based agreed minimum set of outcomes that should be measured and reported in all clinical trials of a specific disease (7). A patient-reported outcome measure

(PROM) captures a deeper understanding of the disease-burden by obtaining information directly from the patient about their experiences with the illness without interpretation by the healthcare professional or others (8). PROMs can focus on symptoms, functional outcomes, or broader concepts such as health-related quality of life. They have initially been utilized in health research and are now increasingly being used in daily clinical practice to support treatment decision making and follow-up care (9, 10).

This paper offers a perspective on the importance of PROM use in patients suffering from HD.

THE RISE OF PROMs IN HEALTHCARE

Over the last years the additional value of using PROMs in clinical practice has been demonstrated and their popularity in various healthcare settings is rising (11). The systematic use of PROMs enhances communication and decision-making between doctor and patient, functioning as a ground layer in the process of shared decision-making (SDM) (5). SDM is a method where clinicians and patients decide together on the best treatment option through effective communication (12). In this process, evidence-based knowledge of the clinician and the individual patient's preferences, values and needs are taken into account. An important benefit of this approach is that it promotes value-based health care (VBHC). VBHC is defined as "the creation and operation of a health system that explicitly prioritizes health outcomes which matter to patients relative to the costs of achieving this outcome" (13). Hence, transforming the clinician's question of "What is the matter?" into "What matters to you?" Which is exactly what a PROM aims to capture.

A distinction can be made between generic and disease-specific PROMs. Generic PROMs are not bound to a specific disease and can measure the quality of life or health profile of any patient. Examples are the European Quality of Life—five dimensions (EQ-5D-5L) (14) and the Short Form 36 (SF-36) (15). Disease-specific PROMs evaluate the patient's outcomes related to a particular condition. In the field of gastroenterology alone, there are over 100 disease-specific PROMs available (16). Some successful examples are the PROM for peptic ulcers (PU-PROM) (17) and the Inflammatory Bowel Disease Questionnaire (IBDQ) (18).

CLINICAL DECISION MAKING IN HAEMORRHOIDAL DISEASE

Many therapeutic options have been developed for the treatment of HD. The first management step for HD concerns basic treatment, including laxatives, a high fiber diet and topical treatments. If basic treatment fails, patients are usually referred to the hospital for surgical consultation. Besides outpatient procedures like rubber band ligation and sclerotherapy, surgical options can also be considered, i.e., sutured or stapled haemorrhoidopexy, or traditional excisional surgery (19). The preferred procedure to treat HD mostly depends on the anal pathology of HD, categorized by the Goligher grade. The Goligher grading system categorizes HD into four grades: Grade I are hemorrhoids that do not prolapse; grade II are hemorrhoids that prolapse but reduce spontaneously; grade III are hemorrhoids that prolapse but have to be reduced manually; and grade IV are hemorrhoids that prolapse and cannot be reduced manually (20). Yet, the classification has several limitations. Firstly, a validation study of the Goligher classification has never been performed and thus it is unclear whether this classification is the most appropriate way to categorize HD and guide treatment strategies. Secondly, in the classification, only the symptom "prolapse" is included and is assessed by a clinician. Yet, patients with HD can suffer from other symptoms, i.e., blood loss, soiling, itching and pain (21). The Goligher classification does not consider these associated symptoms of HD (22). As a consequence, the broader impact of the disease on the patient may not be fully understood. While PROMs are ideally suited to assess this broader impact, they are not yet common practice in the treatment pathway for HD. There is indeed great potential in the usage of PROMs, not only to inform a treatment decision, but also to evaluate treatment success and the patient's satisfaction with the treatment (23). It is known that consensus on treatment success can differ substantially between healthcare professionals and patients, given that the doctor observes the disease, yet the patient experiences the symptoms (3, 24).

CURRENT PROMs FOR HAEMORRHOIDAL DISEASE

Over time, several PROMs for HD have been developed. In the recent systematic review of Jin et al., a clear overview of available PROMs for HD is presented (25). Among the five PROMs discussed, the Haemorrhoid and Fissure Quality of Life Questionnaire (HEMO-FISS-QoL) extents its population to patients with fissures (4) and the Proctological Symptom Scale (PSS) aims to address the symptoms of patients with all sorts of proctological ailments (26). Not mentioned in the systematic review but nevertheless a valid and reliable tool to evaluate disease burden of the proctological patient, is the Proctoprom (5). Similar to the PSS, the Proctoprom is a PROM that takes the full range of proctology patients into account instead of focussing on HD. Expanding the population of the PROM can facilitate the swiftness of implementation but may reduce its relevance and validity. Hence, we recommend using a PROM which is specifically developed for use in a HD population.

Jin et al. discusses three of such PROMs for HD in his systematic review. The Sodergren score of Pucher et al. is specifically for HD patients and comprises of three items: intensity of pain, pruritus, and prolapse (27). The score is based on a scoring system developed by Nyström et al. that originally contained five symptoms: pain, pruritus, prolapse, bleeding, and soiling (28). The Sodergren score excluded the latter two symptoms based on a regression analysis and validation of the scoring system in a small sample of HD patients. For these two scores, no consensus-based standards for designing and reporting validation research were used (29). The

Haemorrhoid Severity Score (HSS) of Lee et al. uses the same symptomatology as Nyström and has assessed the psychometric aspect "responsiveness" in two large multi-center, randomized controlled trials (RCT) (30–32). The fifth PROM described in the Jin review is the Haemorrhoidal Disease Symptom Score and Short Health Scale for Haemorrhoidal Disease (HDSS and SHS-HD) developed by Rørvik et al. (33). Validation of the HDSS and SHS-HD was built on consensus-based standards for designing and reporting validation research. This score encompasses all five symptoms as introduced by Nyström barring a modification of the question on prolapse. The scoring system by Nyström assesses how frequently the patient needs to reduce the prolapse, restricting the question to patients with a Goligher grade III. In contrast, the HDSS asks how often the patient experiences a swelling or prolapse in the anus, making the question applicable to Goligher grades II-IV. A short health scale was added to probe the impact of the HD symptoms on daily life, as well as impact on mental and general well-being. A quality of life instrument complements the use of a HD-symptom score since it provides a more generic view on how the symptoms are perceived in a day-to-day setting. The HDSS SHS-HD by Rørvik et al. has shown satisfactory results when methodologically assessed and can be used in the consultation room.

Finally, a PROM for HD has recently been introduced as an important outcome measure for two large clinical trials in The Netherlands (34, 35). The PROM-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS) is the first PROM for HD developed in dialogue with patients suffering from HD (3). It was developed in response to the COS and measures the same HD symptoms as the previously mentioned scoring systems of both Nyström and Rørvik: prolapse, blood loss, pain, soiling and itching. Furthermore, it includes a quality of life question probing the impact of the HD symptoms on performing daily activities. A final question evaluates the patient's satisfaction with treatment related to reducing their symptom burden. A fundamental validation study of the PROM-HISS is currently being performed.

FUTURE DIRECTIONS IN HAEMORRHOIDAL DISEASE PROMs

Symptoms of a disease may be interpreted differently by the patient who experiences them than the clinician who observes them. Especially in a proctological disease like HD, where patients may feel shame or embarrassment, safeguarding an open conversation is crucial. In clinical practice, a HD PROM can support this discussion and indicate the issue or symptom which is most important for the patient. A PROM facilitates the process of SDM and functions as a valuable tool to encourage a patient-centered approach. Consequently, the patient will feel heard and understood, resulting in effective conversations, and providing a more detailed insight into the patients' experiences with HD. Discussion points are not limited to medical subjects, but can also cover the impact of symptoms on daily activities. It is of paramount importance that the patient feels that the conversation is about him and his needs. Exploring the disease burden and treatment expectations of patients with help of a PROM improves patient satisfaction with care (36). Additionally, in our experience as clinicians, the conversation with the patient is facilitated when a PROM has been completed before the consultation since it can quickly identify issues of concern to the patient (37).

We strongly advice the use of a PROM in clinical HD practice, in particular a PROM that has been developed following recommended guidelines and has been validated. Suggestions are the HDSS, and once established valid, the PROM-HISS. These symptom-focused PROMs are ideally complemented with a HD quality of life tool such as the SHS-HD.

Starting to use a PROM in the consultation room will maybe take some time getting used to but in the long run it will increase the quality of patient care. Because a patient who receives a personalized treatment, is a more satisfied patient.

CONCLUSION

The patient's perspective is vital for clinical decision making. Systematic assessment of patient-reported outcomes using PROMs provides a thorough understanding of the symptom burden and experienced health of patients and can inform a tailored clinical HD treatment. We recommend the use of the HDSS and, once validated, the PROM-HISS, preferably combined with an HD quality of life tool suchlike the SHS-HD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

SK wrote the manuscript. MK, HR, GO, and SB provided guidance and a critical review. All authors jointly conceptualized the article and discussed the aspects of the topic to be addressed.

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BRIEF RESEARCH REPORT
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Self-Mechanical Anal Dilatation: A Simple Trick to Minimize Postoperative Pain and Stenosis Following Hemorrhoidectomy With Radiofrequency

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Aim: Hemorrhoidectomy is still the most effective surgical treatment for hemorrhoidal disease, but it is, however, associated with complications such as pain and stenosis. We proposed to break the "vicious circle" of "pain–sphincteric spasm–stenosis–pain" with the postoperative use of self-mechanical anal dilation.

Methods: We retrospectively analyzed patients with hemorrhoidal disease presenting with a minimum of piles of three quadrants, treated with radiofrequency hemorrhoidectomy between January 2018 and December 2019. All the patients that at 3 weeks presented sphincteric spasms with painful defecation, were considered. Thirty-nine patients performed the cycle of self-mechanical anal dilation (Group A). This group was 1:1 matched with homogeneous patients from our historical cohort of patients (Group B). The primary endpoint was the pain evaluation, secondary endpoints: WCS, overall satisfaction of the patient, anal sphincter spasm, scarring, and the incidence of postoperative stenosis.

Results: In Group A mean VAS was 3.25 after 14 days of application and 1.15 at the end of the application. In Group B mean VAS was persistently higher, with a mean VAS of 5 ($p = 0.000002$) and 3.38 ($p = 0.0000000000009$). In Group A we observed an improvement of symptoms at the end, with a good overall satisfaction (Group A 7.4 vs. Group B 5.9; $p = 0.0000007$) and a better mean WCS (Group A WCS 2.8 vs. Group B WCS 4.18; $p = 0.0001$). Stenosis was observed in 3/39 patients of Group B (7.7%).

Conclusions: Self-mechanical anal dilation improves the pain in the late postoperative course, minimizing the risk of anal stenosis.

Keywords: hemorrhoidectomy, postoperative pain, stenosis, dilation, constipation

INTRODUCTION

Hemorrhoidectomy is still the most effective treatment for grade hemorrhoidal disease (1). However, it is associated with a higher rate of postoperative (PO) complications when compared to other procedures, such as hemorrhoids ligation, sclerotherapy, or doppler-assisted artery ligation, usually preferred for not prolapsing diseases. Stapled hemorrhoidectomy, indicated for hemorrhoid prolapse, is also associated with less PO pain and with a lower percentage of anal stenosis, at the cost of other potentially life-threatening complications (2) or recurrence (3). One hateful complication after Milligan Morgan hemorrhoidectomy is the persistent PO pain associated with anal sphincter spasm. This often occurs when three or more piles are excised, even if a radiofrequency device is used (4). Furthermore, pain, inducing involuntary sphincteric anal spasms during defecation, can cause repetitive traumas to the mucosa with a consequent more difficult healing (5). Stenosis of the anal canal, which is another consequence of wide excision, reduces the compliance of all the anorectum, with an alteration in bowel movements, difficulty during defecation, anal bleeding, and an increase in stool frequency, affecting the quality of life of the patient for the worst.

Anal dilators are widely used for anal fissures, despite some recent works contradicting their efficacy (6). We hypothesize that anal dilators could be of use not only for the mechanical break of stenosis but also to teach the patient to relax the sphincter, avoiding the anal spasm, minimizing the daily trauma of defecation, and the associated pain. Thus, in patients suffering from persistent pain and anal spasms following excisional hemorrhoidectomy, we proposed to break the vicious circle of "pain—sphincteric spasm—stenosis—pain" with the use of an anal dilator.

The present study aimed to investigate whether the use of anal dilatators in the postoperative course, could decrease pain, improve the quality of defecation and avoid the risk of stenosis, after a 3 or 4 quadrant radiofrequency hemorrhoidectomy.

METHODS

We retrospectively analyzed all patients with IV grade hemorrhoidal disease, presenting with 3 or 4 quadrants piles treated with excisional radiofrequency hemorrhoidectomy at our specialized Proctologic Surgery Unit, between January 2018 and December 2019. All the patients that, at 3 weeks presented sphincteric spasms with painful defecation, were considered for the study. The first dilation was performed at the third PO week when the risk of severe bleeding was over. The minimum period of follow-up was 1 year.

Patients underwent hemorrhoidectomy by the same surgical team; they were operated in the lithotomy position. A simple enema was given preoperatively. The anus was dilated with an Eisenhammer retractor: all the piles were separated from the skin with an initial incision using a monopolar scalpel. When the correct surgical plan on the internal sphincter was revealed, excisional hemorrhoidectomy was completed with Ligasure™, a radiofrequency device, without any pedicles ligature, stitches, or suture. No internal sphincterotomy was realized in these patients. A Tabotamp® was left in the anal canal and removed the same evening or the day after. All the operations were performed with epidural or general anesthesia (Propofol) plus local anesthesia with Ropivacaine 7.5%.

The patients with associated proctologic pathologies, previous anorectal surgery, diagnosed inflammatory bowel diseases, and chronic assumption of anti-inflammatory therapies were excluded from the study. We obtained specific informed consent from all the patients.

Self-mechanical anal dilatation was indicated only to patients that presented, at the third PO week, a persistent pain, defined as scoring ≥8 on a Visual Analog Score (VAS: 0 min−10 max), a poor quality of defecation, evaluated with Wexner Constipation Score (WCS: 0–30) ≥ 15, and a sphincteric spasm at Rectal Digital Examination (RDE). The edge of eight for VAS to assess chronic pain was decided together with the anesthesiologist and based on a review of the literature.

The dilator has three different sizes (20, 23, and 27 mm in diameter) and has to be soaked in hot water to activate a gel that accumulates and releases heat during dilation, favoring relaxation of the anal sphincter. Before the introduction, the dilatator was lubricated with 2% lidocaine ointment.

All patients were instructed to use the dilator by a member of the surgical team. Self-mechanical anal dilatation had to be performed in Sims' position, introducing the dilatator for at least 3 min a day, preferably before defecation.

It is realized under medical assistance, to verify the complete introduction of the dilator and to increase compliance of the patient toward this potentially embarrassing maneuver. Patients were invited to use the dilator every day, if possible before defecation to minimize its trauma. The scheme indicates the use of a little size dilator, for 1 week, the medium size, for 2 weeks, and the larger size, for the last 2 weeks, for a total application time of 35 days.

Patients were evaluated in the outpatient clinic at 1st PO week (before the beginning of application), 3th PO week (start of application in Group A), 5th PO week (14 days after start of the dilator in Group A), and 8th PO week (end of the application in Group A) by clinical examination, RDE, a VAS pain score, WCS, and overall satisfaction (0–10) at the end of dilator application. Long terms follow-up was performed by phone calls and, in case of doubts, by clinical examination.

All the patients used also stool softeners and analgesic therapy (paracetamol 1 g, maximum 3 for day and, in case of not controlled pain, tramadol hydrochloride 1–2 mg/kg) and were encouraged to practice warm water baths, keeping a daily diary of medication use. They can also apply the same 2% lidocaine ointment, used to lubricate dilator, after defecation.

Self-mechanical anal dilatation patients (Group A) were 1:1 matched by age, gender, and comorbidities, with a historical cohort of patients treated by hemorrhoidectomy, with the same inclusion criteria (a minimum of three piles removed by radiofrequency, score ≥ 8 on a Visual Analog Score at the third

Abbreviations: PO, Postoperative; VAS, Visual Analog Score; WCS, Wexner Constipation Score; RDE, Rectal digital Examination.

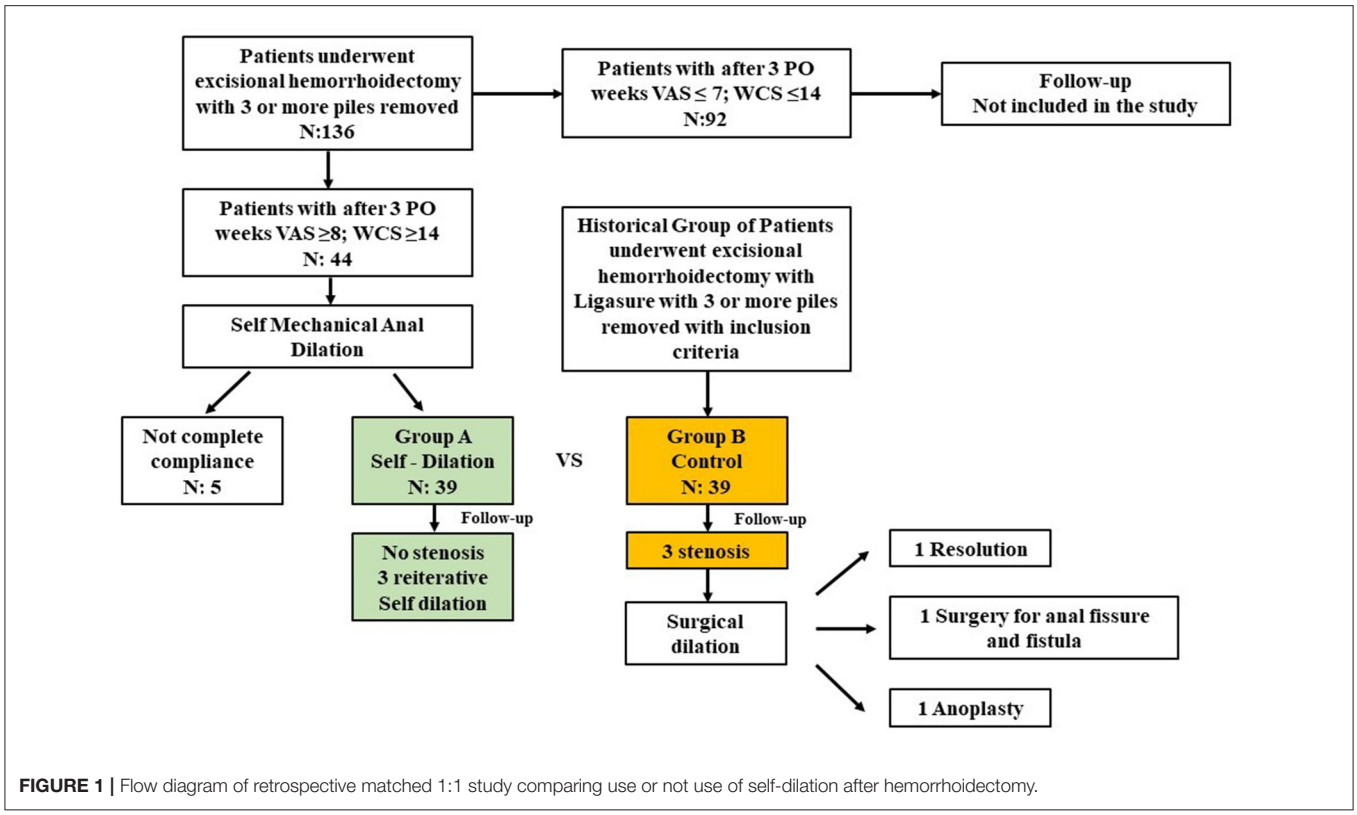

FIGURE 1 | Flow diagram of retrospective matched 1:1 study comparing use or not use of self-dilation after hemorrhoidectomy.

TABLE 1 | Demographic and clinical characteristics at baseline.

	Group A (Dilation) 39 pts	Group B (Control) 39 pts
Age		
Mean (SD)	46.7 (13.9)	44.12 (14)
Range	(21–75)	(22–73)
M	19	14
F	20	25
Number of piles removed		
Mean (SD)	3.31 (0.47)	3.18 (0.39)
VAS (1-10)		
Mean (SD)	8.49 (0.7)	8.15 (0.4)
Range	8–10	8–10
WCS (1-30)		
Mean (SD)	19.6 (3.4)	18.7 (3.05)
Range	15–28	15–27

PO week, a Wexner Constipation Score $\geq$ 15, and a spasm at RDE, not other proctologic diseases) without the use of the anal dilators (Group B).

The primary endpoint of this retrospective case-matched study was the VAS pain score, in particular after 2 weeks of dilation-−5th PO week. Secondary endpoints were WCS, use of analgesic therapy after the operation, overall satisfaction of the patient, anal sphincter spasms and scarring, and the incidence of new pathologies, such as stenosis and fissures, requiring further operations.

Overall satisfaction of the patient was evaluated on a specifically designed Likert scale from 0 (not satisfied) to 10 (extremely satisfied). Anal sphincter spasms and scarring were evaluated by RDE, always by the same doctors (CE, LF), not involved in the previous surgical operation and so blinded, describing paradoxical sphincter contractions, tissue scarring consistency, and anal canal diameter.

We also gave the possibility to resume the use of self-mechanical anal dilation in Group A after the end of application analyzed in the study and collected the data during the long-term follow-up.

Data were analyzed using SPSS for Windows, version 21 (SPSS Inc., Chicago, IL, USA).

Means and SDs were used to report continuous data, while numbers and percentages were calculated for all categorical data. Univariate analysis was performed by Student's *t*-test and ANOVA. A $p \leq 0.05$ was considered statistically significant for all analyses.

RESULTS

From January 2018 to December 2019, 136 patients underwent radiofrequency hemorrhoidectomy with a minimum of three piles removed at our specialized colorectal surgery unit. Of these, 44 patients met all inclusion criteria (**Figure 1**) and were indicated for self-mechanical anal dilatation (Group A). Five were excluded during the study because they were not compliant.

The final Group A was 39 patients. They were matched with 39 control patients (Group B) from our historical cohort, that had the same inclusion criteria. The baseline presentation was comparable, as shown in **Table 1**.

In Group A, the pain decreased very quickly with the use of the dilator, with a mean VAS of 3.25 after 14 days of application (5th PO week) (vs. Group B mean VAS of 5; $p = 0.00002$) and a mean VAS of 1.15 at the end of the application (vs. Group B mean VAS of 3.38 at the 8th PO week; $p = 0.000000000009$). Days of use of analgesic therapy were lower in Group A (mean 12.3 days) than in Group B (mean 17.6 days) ($p = 0.03$).

In Group A, we observed an improvement of the symptoms in a mean period of 14 days after the beginning of the use of the dilator, with a good overall satisfaction vs. lower overall satisfaction in Group B (Group A mean 7.4 vs. Group B mean 5.9; $p = 0.0000007$) and a better quality of defecation (Group A mean WCS 2.87 vs. Group B mean WCS 4.18; $p = 0.0001$).

The digital examination after 8th PO weeks revealed a soft and elastic healing in all the patients of Group A and a persistent reduction of the lumen with fibrosis in 3 (7.7%) patients of Group B ($p = 0.03$) (**Table 2**). There were no complications with the use of a dilator.

During the long-term follow-up (mean 14 PO months) we collected other data: in Group A, in case of constipation or narrow stools, self-dilation was resumed together with stool softener for about 15 days. No patient needed a prolongation of analgesic therapy. There was no evidence of stenosis or chronic pain also at the end of the follow-up.

In Group B, during the long-term follow-up, 14 of 39 patients used analgesic therapy for more than 60 PO days; 10 of 39 patients used fiber/laxative supplements for an average of 6 months; 3 of 39 patients (7.7%) presented severe anal stenosis and underwent, at first, anal dilatation for 2 months: one had a satisfying resolution; two patient presented an anal fissure with fistula that needed a surgical operation after 8 months, with fistulectomy, sphincteroplasty, and anoplasty (7); one patient needed a surgical operation with the removal of the scar and anoplasty for the stenosis.

DISCUSSION

Approximately 10% of all the patients affected by the hemorrhoidal disease were surgically treated (8). Despite the introduction of new procedures (stapled hemorrhoidopexy, trans-anal hemorrhoidal dearterialization), hemorrhoidectomy remains the most common operation performed and the gold standard for recurrence (9). In the case of IV grade, hemorrhoidal disease with three or more piles involving all quadrants, hemorrhoidectomy with radiofrequency allows an easier wide excision with satisfactory hemostasis. This procedure provides the lowest percentages of recurrences but does not eliminate the usual postoperative complications: pain and bleeding. Many attempts are done to minimize PO pain: metronidazole, mesoglycan, or diosmine by mouth and, to reduce the sphincteric spasm, topical use of 2% diltiazem or GTN ointment, botulin toxin injection, and preventive lateral sphincterotomy (10). In a recent trial flavonoid associated with metronidazole seems to reduce pain, and bleeding, after excisional hemorrhoidectomy (11).

After hemorrhoidectomy, another fearsome complication is anal stenosis. It occurs in ∼4% of patients, but this percentage rises (12, 13) when a radical hemorrhoidectomy is performed, with three/four piles removed. With the use of radiofrequency tools or harmonic scalpels, the easiness of surgical procedure can paradoxically produce a wide excision of anoderm and rectal mucosa, without adequate "bridges" (14, 15). This can hesitate in anal stenosis; the average time of onset is ∼4 weeks. When a conservative approach (stool softeners, diet, analgesic therapy, and dilation) failed, the treatment of anal stenosis can be difficult: a second surgical operation with scar excision, sphincterotomy, y-v anoplasty, or, in some cases, flaps (15, 16) can be performed. Despite the good results and minor complications of these procedures, a second hospital admission is needed, with an extension of healing time and of lost working days. Furthermore, there is an evident lack of consensus about what surgical treatment can be most useful and the success rate depends on different coloproctology units, surgical experience, number of cases treated.

According to this study, the use of self-mechanical anal dilation, in an early period after hemorrhoidectomy, is a good clinical practice, especially when a large amount of tissue is removed during the operation. In Group A, we observed the PO pain decreased very quickly with the use of dilator, in the 14 days of application (**Figure 2**), with a constant improvement and the full recovery of patients. The daily dilation seems to increase soft healing, reduces the spasm and the pain, and allows good healing without retracting scars and anal stenosis. The possibility for patients to perform the procedure by themselves reduces the number of visits of the outpatients. The price of the three dilators is <€40, with an economic return given by the decrease in the use of analgesic therapy and stool softeners.

According to the statistical analysis, the most significant results of self-dilation use are the reduction of pain, improvement of defecation quality, in Group A, especially in the early period, and the absence of late clinical stenosis. These three factors are strictly linked with the quality of life after the surgical operation. Patients accepted this solution sometimes with initial doubts and hesitations, overcome by immediate, evident relief of pain right after the first days of use.

Post-hemorrhoidectomy use of anal dilators is a simple procedure that can result in immediate benefit for the patient; further studies are necessary to confirm these initial, promising results.

The limit of this study is that is retrospective and the number of patients is small, but there will be a wide application in the proctologic unit and the possibility to design new prospective studies in the future.

Self-mechanical anal dilation can guarantee a better late operative course, minimizing the risk of consolidated anal stenosis. The most significant data, despite the small number of patients included in this program, are the breakdown of PO pain with the use of the dilator, improvement in the quality of defecation, and the decrease in the number

TABLE 2 | Early results in the two groups after the dilatation.

Early results	Group A (Dilatan) 39 pz	Group B (Control) 39 pz	*P*-value
VAS at day 0			
Mean (SD)	8.49 (0.7)	8.15 (0.4)	
VAS after 14 days			
Mean (SD)	3.25 (1.51)	5 (1.52)	**0.000002**
VAS at the end of application (35 days)			
Mean (SD)	1.15 (0.92)	3.38 (1.31)	**0.000000000009**
Days of use of analgesic therapy from day 0			
Mean (SD)	12.2 (12.1)	17.5 (12.9)	**0.03**
WCS at the end of application			
Mean (SD)	2.87 (1.29)	4.18 (1.49)	**0.0001**
Clinical stenosis at the end of application	0/39	3/39 (7.7%)	**0.03**
Overall satisfaction (8th PO week)			
Mean (SD)	7.4 (1.25)	5.9 (1.09)	**0.0000007**

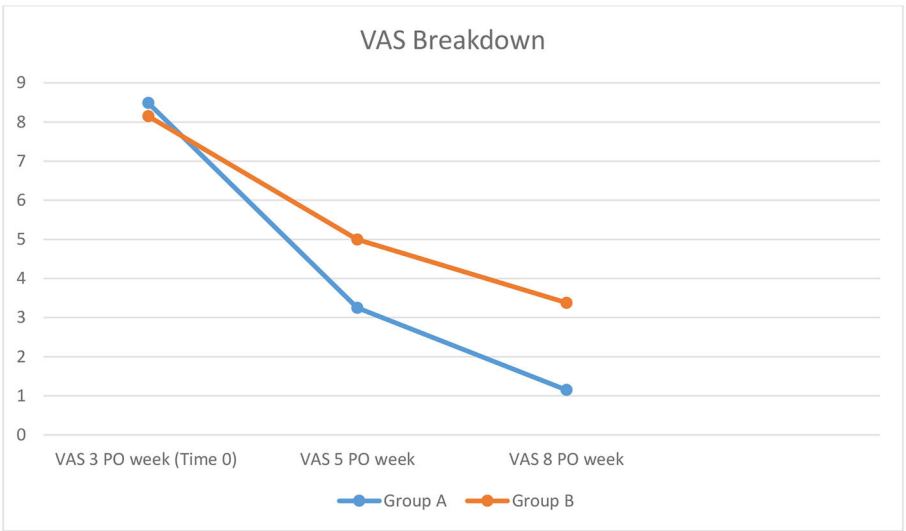

FIGURE 2 | Pain breakdown in the two Groups after the start of dilatation.

of PO stenosis after radical hemorrhoidectomy. Avoiding these complications, with a simple tool that can be used by the patient at home, in total privacy, seems really an encouraging result. We need more prospective studies with a larger number of patients enrolled to evaluate the value of this method to reduce PO pain and the risk of post-hemorrhoidectomy stenosis.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Department of Surgical Sciences Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CE contributed to acquisition, analysis, interpretation of the data, report drafting, and final approval of the version to be published. PM contributed to report drafting, critical revision for important intellectual content, and final approval. KZ contributed to language revision, final draft revision, interpretation of data, and final approval. LF contributed to acquisition and analysis of data and final approval. GN contributed to interpretation of the data, critical revision for important intellectual content, and final approval. DM contributed to design of the work, report critical revision, and final approval of the version to be published. All authors contributed to the article and approved the submitted version.

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frontiers in Surgery

REVIEW
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Evolution of Surgical Management of Hemorrhoidal Disease: An Historical Overview

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Hemorrhoidal disease (HD) is the symptomatic enlargement and/or distal displacement of the normal hemorrhoidal cushions and is one of the most frequent diseases in colorectal surgery. Several surgical or office-based therapies are currently available, with the aim of being a more tailored approach. This article aimed to elucidate the historical evolution of surgical therapy for HD from ancient times, highlighting the crucial steps, controversies, and pioneers in the field. In contrast with the previous literature on the topic that is often updated to the 1990s, with the introduction of stapled hemorrhoidopexy and transanal hemorrhoidal dearterialization, this article describes all new surgical and office-based treatments introduced in the first 20 years of the 2000s.

Keywords: haemorroidal disease, history, surgical therapies, haemorroidectomy, haemorroids, hemorrhoids, hemorrhoidal, surgery

INTRODUCTION

Hemorrhoidal disease (HD) is the symptomatic enlargement and/or distal displacement of the normal anal cushions called hemorrhoids (1) and is the most common anorectal disorder (2, 3). It has been reported that more than 50% of people present at least one episode of symptomatic hemorrhoids during their life (4), and a significant proportion will undergo surgery if unresponsive to conservative treatment. Over the past 100 years, many advances have been made in the surgical approach to HD. New surgical and office-based procedures have been developed to reduce postoperative pain and complications and improve long-term efficacy. The aim of this article is to describe the history of surgical therapy for HD, highlighting the crucial steps and major contributors in this field. In contrast with previous literature that is often updated up to stapled hemorrhoidopexy as the most recently available procedure, all new techniques introduced in clinical practice after the year 2000 are reported.

The introduction of anesthesia and antisepsis in the middle of 19th century created a watershed between a ***pre-modern era***, in which any surgical therapy of HD was a gory experience, often based on empirical rather than theoretical principles, a very poor understanding of human anatomy, and a high risk of mortality and complications, and a ***modern era***, in which several

surgical techniques were finally standardized and developed in safe conditions to achieve a curative effect with low risk of complications.

PRE-MODERN ERA

Old Testament and Egyptian scriptures are the first documents that mentioned anal symptoms suggestive of hemorrhoids and their therapy (5). However, it is impossible to confirm whether the nature of the anal disease and the symptoms described are actually related to hemorrhoids or might have referred to other anorectal diseases such as condylomas or syphilis. "*Before Hippocrates" time 5th Century BC any disease in or around the anus was called hemorrhoids*" (6).

In the Old Testament, God punishes Philistines with "*emerods*" (1 Samuel 5:6), while in Deuteronomy (27:28), Moses warn the Israelites that, in case of breaking the law of God, "*The LORD will smite thee with the botch of Egypt, and with the emerods, and with the scab, and with the itch*." Although the term "emerods" was first reported and popularized by the King James Bible (1611), the actual word used in the Hebrew text was *techorim,* which might have been better translated as *"tumor" or "round shaped tumor-like appendage or protrusion from anus*" (7, 8), making it impossible to unequivocally identify this as hemorrhoids.

Edwin Smith Papyrus (1700 BC) and the Ebers Papyrus (1500 BC) recommend astringent lotions containing honey, myrrh, flour, ibex fat, and sweet beer for anal symptoms that are strongly suggestive of symptomatic hemorrhoids (9, 10). However, no surgical therapy is reported.

Hippocrates (460–375 BC), the father of Medicine, was the first author to propose a surgical therapy for symptomatic hemorrhoids. Hippocrates believed that hemorrhoids resulted from an excess of bile or phlegm in the body and that their bleeding was somewhat beneficial, preventing other diseases such as pleuritis or leprosy. However, in other writings, he seems to contradict himself, proposing surgery for hemorrhoids, the principles of which are still valid today: ligation, excision, or cauterization. In the *Treatise on Hemorrhoids*, he suggests treating hemorrhoids by "*transfixing them with a needle and tying them with very thick and woolen thread*" (11), and in the "On Hemorrhoids" text, he advocates hemorrhoids excision and describes a rectal speculum similar to the Eisenhammer retractor (11). Cauterization is also proposed: "*Having on the preceding day first purged the man with medicine, on the day of the operation apply the cautery*. [. . .] *Having laid him on his back, and placed a pillow below the breech, force out the anus as much as possible with the fingers [. . .] And burn so as to leave none of the hemorrhoids unburnt. [. . .] When the cautery is applied the patient's head and hands should be held so that he may not stir, but he himself should cry out, for this will make the rectum project the more. When you have performed the burning, boil lentils and tares, finely triturated in water, and apply as a cataplasm for 5 or 6 days.*" (12).

Abbreviations: HD, Hemorrhoidal Disease; HAL, hemorrhoidal artery ligation; THD, transanal hemorrhoidal dearterialization; RAR, recto-anal repair; HeLP, Hemorrhoids Laser Procedure.

Roman medicine basically resumed the Egyptian and Greek traditions without any innovative contribution. ***Celsus*** (1st century AD), in the seven books of "*Re Medica*," recommended either the ligation of hemorrhoids by flax followed by the excision of the ligated nodule, or the excision alone followed by a transfixed stitch in case of large hemorrhoidal nodules (13). ***Galen*** (130 −200 AD) suggested a conservative management based on laxatives, leeches, and ointment (10), proposing ligation by a tight thread as the only surgical option.

During the Middle Ages until the 18th century, there have not been great advances in the management of hemorrhoids. The principles and operations described by classic authors were pedantically reported by Arabic and European authors. The high mortality and complications, as well as the frequent practice of operations by charlatans and barber surgeons, discouraged surgery.

Herny de Mondeville (1260–1320), one of the most influential surgeons of his age, warned about operating hemorrhoids (10). ***Lorenz Heister***, in the book *Chirurgie* (1739), described the "*method of the ancient too cruel, and often perniciosus*" (14) and ***Hugues Ravaton***, in the "Pratique moderne de la chirurgie" (1776), judged that the remedies proposed until then "*by the masters of the Art worked out very poorly*" (6).

Don Juan of Austria, the hero of the battle of Lepanto (1571), died in 1578 for uncontrolled bleeding 4 hours after an operation for hemorrhoids (15).

These poor surgical outcomes spread skepticism about the surgery and encouraged "unconventional" attempts. In the Middle Ages, Saint Fiacre (**Figure 1**), already the patron of gardeners, became the patron saint of hemorrhoids, from which the "Illness of St. Fiacre" was used as a polite term to indicate the disease. For centuries, the monastery of St. Fiacre (France) was a place of pilgrimage, in which sufferers of hemorrhoids were used to sit on a stone considered able to cure the disease (16, 17).

The 18th century marked some advancement in the understanding of HD, breaking some dogmas of the Hippocratic tradition. ***Giovanni Battista Morgagni*** (1682–1771) attributed the etiology of hemorrhoids to the upright posture of humans and to a hereditary predisposition, recognizing the absence of a valve in the rectal veins as a contributing factor (18). ***George Ernst Stahl*** (1660–1734), an eminent German Professor of Medicine, defined hemorrhoids as venous reservoirs, whose bleeding was somewhat beneficial as an expression of surplus of blood (19).

It is worth mentioning that the defeat of Napoleon at Waterloo on June 18, 1815 was partially attributed to an episode of presumably thrombosed hemorrhoids that likely affected his performance on the crucial day of the battle (20).

Indeed, the fear of uncontrolled bleeding and lethal sepsis with inability to relieve pain represented significant obstacles to the surgical therapy for hemorrhoids until the mid-19th century, when anesthesia and antisepsis inaugurated scientific surgery.

MODERN ERA

19th Century

Three main surgical trends characterized the 19th century: anal stretching, excision, and sclerotherapy.

FIGURE 1 | Saint Fiacre, patron saint for hemorrhoid suffers, depicted in a sculpture of mid-15th century (from MET, Metropolitan Museum of Art, New York, USA. https://www.metmuseum.org/).

In 1835, ***Frederick Salmon*** founded in London the "*Benevolent Dispensary for the Relief of the Poor Afflicted with Fistula, Piles and other Diseases of the Rectum and Lower Intestines*," which was later moved to a larger premise in London and named "*St Mark's Hospital for Fistula and other Diseases of the Rectum*" (officially opened in 1853) (21). This was the first institution dedicated to the treatment of anorectal disease [1].

Salmon first proposed anal stretching to treat hemorrhoids (22), and then, in the second part of his career, he performed a personal technique for hemorrhoid excision, laying the foundation for open hemorrhoidectomy that was popularized by Milligan and Morgan in the 20th century. Salmon described that internal hemorrhoids were supplied by the superior hemorrhoidal artery, and, as described by Allingham in 1888, he performed a combined technique of excision of the hemorrhoidal nodules by incising perianal skin and ligation of the pedicle above the dental line to reduce pain (23). However, postoperative strictures were common (24).

In 1855, ***Aristide Auguste Stanislas Verneuil*** (1823–1895) suggested that anal dilatation (also called "*rectal bouginage*") was beneficial in the treatment of hemorrhoids, because increased anal tone was considered the cause of HD. The technique gained popularity over the 19th century (25), especially in France and in the United States, originally as a two-finger dilatation technique, which was later replaced by the use of anal dilators, such as the Manx dilators, introduced by Percy Lockhart-Mummery (26, 27). They were easy to introduce, and not slipping out owing to its shape. In 1969, ***Lord*** popularized again the technique (28). According to his theory, the aim was to stretch the fibrotic bands in the internal anal sphincter, causing obstruction and venous engorgement on the basis of the hemorrhoids. This technique was still advocated in the 1980s (29). Currently, this technique has been abandoned, as it may cause injuries to the internal anal sphincter.

In 1882, ***Walter Whitehead*** (1840–1913) proposed a radical approach for the excision of circumferential hemorrhoids (30). He proposed "*the excision of the complete ring of pile-bearing mucous membrane*" by a circular incision at the level of mucocutaneous border (clearly corresponding to the dentate line), without leaving any mucocutaneous bridge, thus removing the entire segment of dilated hemorrhoidal cushions and the overlying mucosa, suturing the proximal end to the skin below.

In 1887, ***Whitehead*** published the first 300 cases that underwent his technique, which was slightly modified compared with the original description, and reported no cases of stenosis or ectropion (31). He highlighted that no skin sacrifices would have occurred. The operation gained wide popularity in the following decades, which gradually decreased in the 20th century due to the high rate of complications reported, such as anal stenosis, incontinence, or persistent soiling due to mucosal ectropion and deformity (also called "Whitehead's anus") (32). In 1924, J. Lockhart-Mummery declared that the death knell of Whitehead operations had been sounded during the London meeting of the American Proctologic Society (33). Nevertheless, Whitehead operation is still performed at some centers for circumferential 4-degree hemorrhoids with acceptable results (34–37). Probably, the poor results of this operation are often the consequence of an incorrect technique, such as excision of the skin or misidentification of the mucocutaneous junction, corresponding to the dentate line, that some surgical texts between the mid-1800s and the first half of the 1900s erroneously identified with the white line of Hilton or the intersphincteric line, 1.3 cm on average distally located (38). "*Mistaking the white line of Hilton for the mucocutaneous junction would mean the difference between good results and mucosal ectropion or a stricture*" (39).

Around the 1860s, the injection of sclerosing agents was introduced in clinical practice, although the technique was already in use by quacks, known as "healers of hemorrhoids," in the United Kingdom and in the USA (6, 9, 10). In 1869, ***James Morgan***, a surgeon in Dublin, first described sclerotherapy using iron sulfate (40). Ten years later, in 1879, ***Andrew Edmunds***, at the Chicago Medical Society meeting, reported 3,000 cases of sclerotherapy for hemorrhoids, mainly by carbolic acid and olive oil, with nine cases of death, 23 cases of major complications such as abscess, dangerous postoperative bleeding, and embolism to the liver, and 25% of severe pain (41). In 1888, ***Swinford Edwards***, from St. Mark, reported the results of 38 patients treated with sclerotherapy with carbolic acid over a 2-year period, with only one case of recurrence (42).

20th Century

The first part of the 20th century was characterized by the affirmation of open hemorrhoidectomy as the gold standard treatment for HD (43). Salmon's operation was slightly modified

[1]Available online at: https://www.stmarkshospitalfoundation.org.uk/about/history/(accessed 09 Jun, 2021).

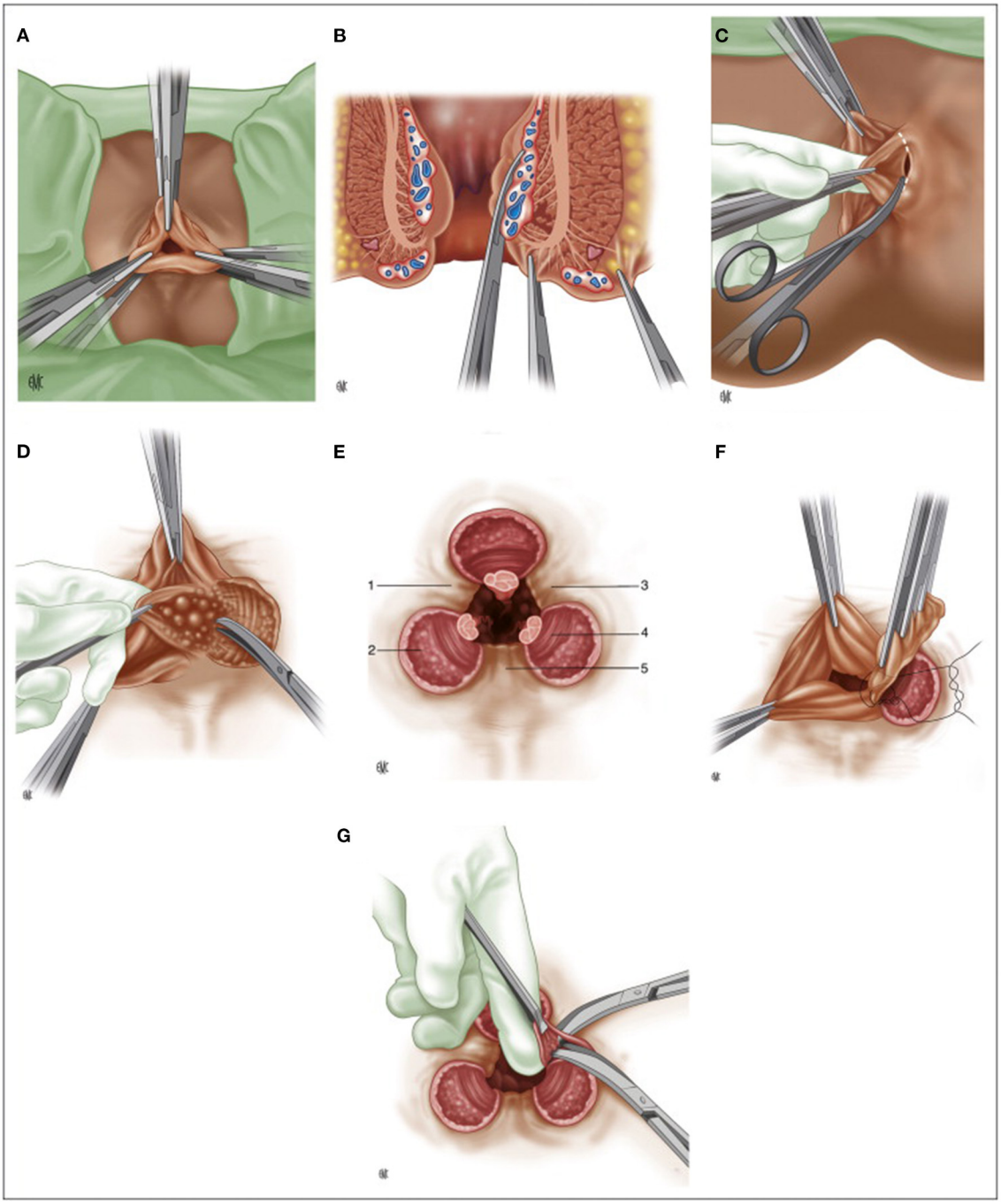

FIGURE 2 | (A) Milligan-Morgan hemorrhoidectomy, position of the three sets of clamps; **(B)** Placement of three clamps on the hemorrhoidal group, frontal view; **(C)** Dissection of the left hemorrhoidal group; **(D)** Exposure of the internal sphincter after division of Parks' ligament; **(E)** Final post-operative appearance. 1: left anterior muco-cutaneous bridge. 2: internal anal sphincter. 3: posterior muco-cutaneous bridge. 4: sub-cutaneous fibers of the external anal sphincter. 5: right anterior muco-cutaneous bridge; **(F)** Suture ligature of the hemorrhoidal pedicle; **(G)** Cleaning up the muco-cutaneous bridges. (Reproduced from Moult HP, Aubert M, De Parades V. Classical treatment of hemorrhoids. *J Visc Surg*. (2015) 152:S3–9. Copyright © 2014 Elsevier Masson SAS. All rights reserved).

by several authors, such as ***Miles*** (1919) or ***Lockhart-Mummery*** (1923), but in 1937, ***Edward Campbell Milligan*** (1886–1972) and ***Clifford Naughton Morgan*** (1901–1986), from St. Mark's hospital, standardized the version, whose principles, for the most part, are still valid nowadays (**Figure 2**): V-shaped incision of the skin, preservation of mucocutaneous bridges to avoid stenosis, meticulous identification of the anatomical canal anatomy and ligation of the hemorrhoidal pedicle, which contains the mucosa,

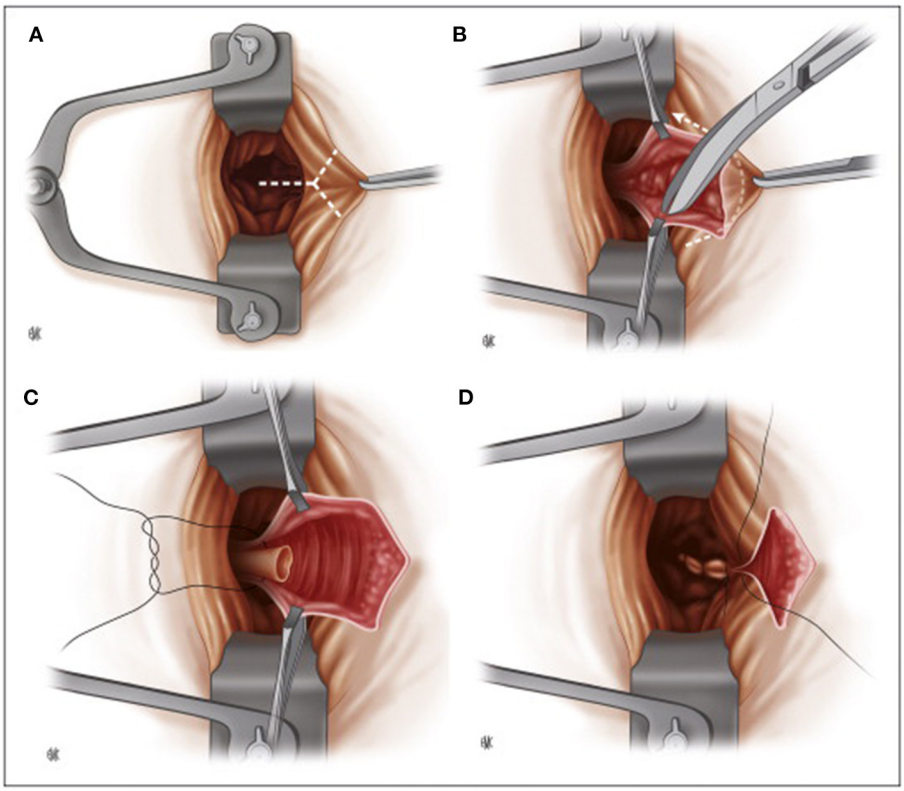

FIGURE 3 | Parks submucosal hemorrhoidectomy. **(A)** Placement of the retractor, intracanular incision. **(B)** Submucosal hemorrhoidectomy. **(C)** Ligation of the pedicle. **(D)** Suture closure of the mucosa of the anal canal (Reproduced from Moult HP, Aubert M, De Parades V. Classical treatment of hemorrhoids. *J Visc Surg*. (2015) 152:S3–9. Copyright © 2014 Elsevier Masson SAS. All rights reserved).

submucosa, the terminal branch of the superior hemorrhoidal artery and vein, and a portion of the anal internal sphincter that in the authors' intentions was necessary to reduce the upward tension and the risk of stenosis (44–46).

In the 1920s, 5% phenol oil became the most used agent in sclerotherapy, although other agents, such as urethane, nitric acid, iodine, alum, or quinine, were reported (47).

In the 1950s, Sir ***Alan Guyatt Parks*** (1920–1982), from St. Mark's hospital, introduced the submucosal hemorrhoidectomy (**Figure 3**), publishing the first article in 1956 (48). He considered the Milligan-Morgan technique suboptimal because of excessive sacrifice of the rectal mucosa (with the risk of stenosis) and due to the pedicle ligation in a sensitive area of the anoderm, resulting in excessive postoperative pain. To overcome these issues, he then proposed a mucosal-sparing technique with high ligation of the hemorrhoidal pedicle in an insensitive area of the rectum (49). However, the idea was not entirely original. In 1774, ***J.C. Petit*** had already proposed the treatment of hemorrhoids by a vertical incision at the hemorrhoidal level, removing the submucosal tissue underneath and ligating the pedicle before re-suturing the flaps created (50).

Parks described an inverted Y-incision 3–5 cm starting from the mucocutaneous junction between the mucosa of the upper canal and the anorectal junction. The hemorrhoidal tissue is completely freed from the mucosa on each side and from the muscle plane below. The pedicle was ligated an inch above the mucocutaneous junction using a transfixed 0 chromic catgut stitch. The mucosal flaps were then sutured, and a small skin area was left open to prevent skin tags and allow drainage. No tube or dressing was placed transanally (45, 48).

Submucosal hemorrhoidectomy is technically challenging and time-consuming, with a risk of significant loss of bleeding and fecal incontinence due to the long-lasting application of the Parks self-retractor (50). Therefore, due to the satisfying results of the Milligan-Morgan operation, the technique never became popular. However, it is still performed, although with some changes, for 4-degree hemorrhoids (48) with gratifying outcomes in two randomized controlled trials comparing the operation to the Milligan-Morgan technique (51, 52).

In 1955, ***James A. Ferguson*** described closed hemorrhoidectomy (**Figure 4**), currently the most popular technique in the USA, with the aim of reducing postoperative pain and bleeding (53). The operation is performed in a similar way as the Milligan-Morgan operation, preserving much mucosa and closing the margins of all wounds by locking stitches, proximally secured with the suture of the pedicle not cut after ligation (45). Some evidence suggests that closed hemorrhoidectomy may have better outcomes, such

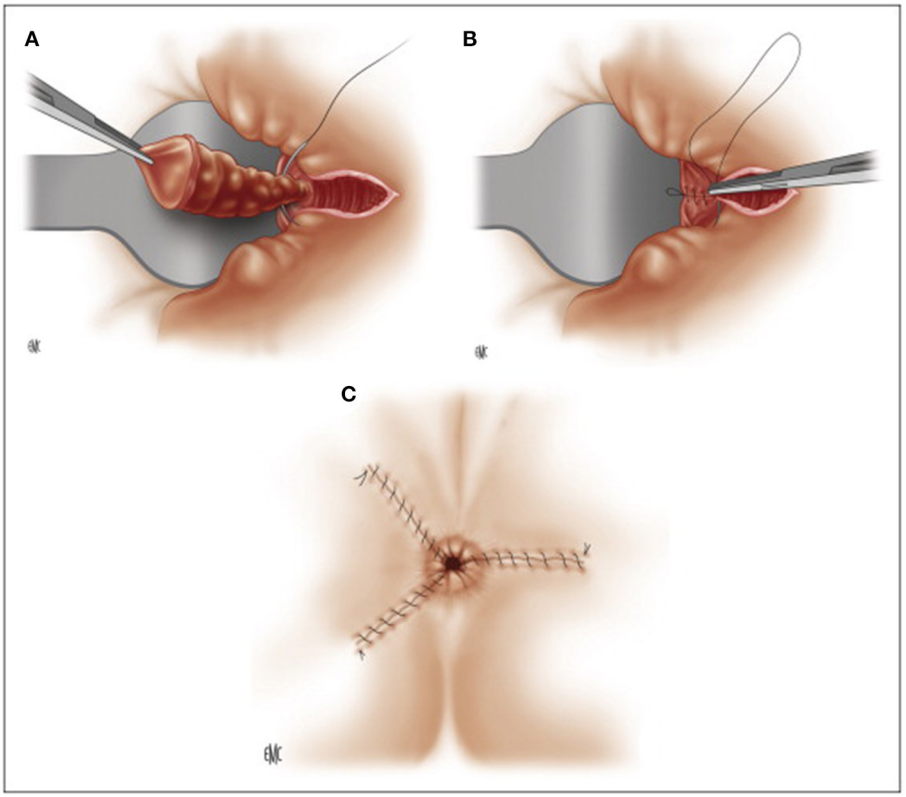

FIGURE 4 | Ferguson hemorrhoidectomy. **(A)** Ligation of the pedicle after dissection. **(B)** Running muco-cutaneous closure. **(C)** Post-operative appearance. (Reproduced from Moult HP, Aubert M, De Parades V. Classical treatment of hemorrhoids. *J Visc Surg*. (2015) 152:S3–9. Copyright © 2014 Elsevier Masson SAS. All rights reserved).

as reduced postoperative pain, lower risk of postoperative bleeding, and faster wound healing than the Milligan-Morgan operation (54–56).

It is worth mentioning that several surgeons often perform these techniques with personal modifications and/or along with anal stretching or anal sphincterotomy, making it difficult to make any comparison, and explaining some great difference in terms of reported complication rates.

In 1963, ***James Barron*** described rubber banding ligation, an office-based procedure for early stage hemorrhoids, reporting only four cases of bleeding among 200 treated patients (57). He was inspired by ***Paul C. Blaisdell***, who described the application of rubber bands for hemorrhoids by an umbilical cord ligator in 1958 (58). Barron introduced the homonym ligator (Baron ligator), describing technical steps that are still valid today.

Other office-based treatments have been introduced in clinical practice such as cryotherapy (1969) (59) and infrared coagulation (1977) (60), although with less fortune than rubber banding ligation and sclerotherapy.

In the 1990s, pioneer centers started to perform day-case hemorrhoidectomy and ***Sharif*** described the diathermy hemorrhoidectomy, in which the pedicle was not ligated but coagulated by diathermy to reduce postoperative pain, which was often attributed to the ligation of the pedicle (61). He presented the short-term outcomes in 72 patients, reporting two cases of postoperative hemorrhage and no anal stenosis at 6-weeks follow-up (61).

The 20th century ended with two new techniques aimed at treating HD by reducing postoperative pain and minimizing unnecessary sacrifice of hemorrhoids, whose functional role in the sensitivity of the anal canal and in the continence was increasingly recognized.

In 1995, ***Morinaga*** described hemorrhoidal artery ligation (HAL) or transanal hemorrhoidal dearterialization (THD) based on Doppler-guided ligation of the terminal branches of the hemorrhoidal arteries by a designated proctoscope associated with a Doppler probe (62). Once identified by Doppler, each terminal arterial branch is ligated using a figure-eight suture. Six ligations are usually necessary. This results in reduced blood supply of the hemorrhoidal plexus, causing atrophy and fibrosis. Currently, this technique is combined with mucopexy or rectoanal repair (RAR), not necessarily using Doppler US, to treat the prolapse and to improve long-term results (**Figure 5**) (63, 64).

In 1998, ***Antonio Longo*** described stapled hemorrhoidectomy, referred to as the *Longo technique* or stapled hemorrhoidopexy (which seems more appropriate) (65). The operation aims to

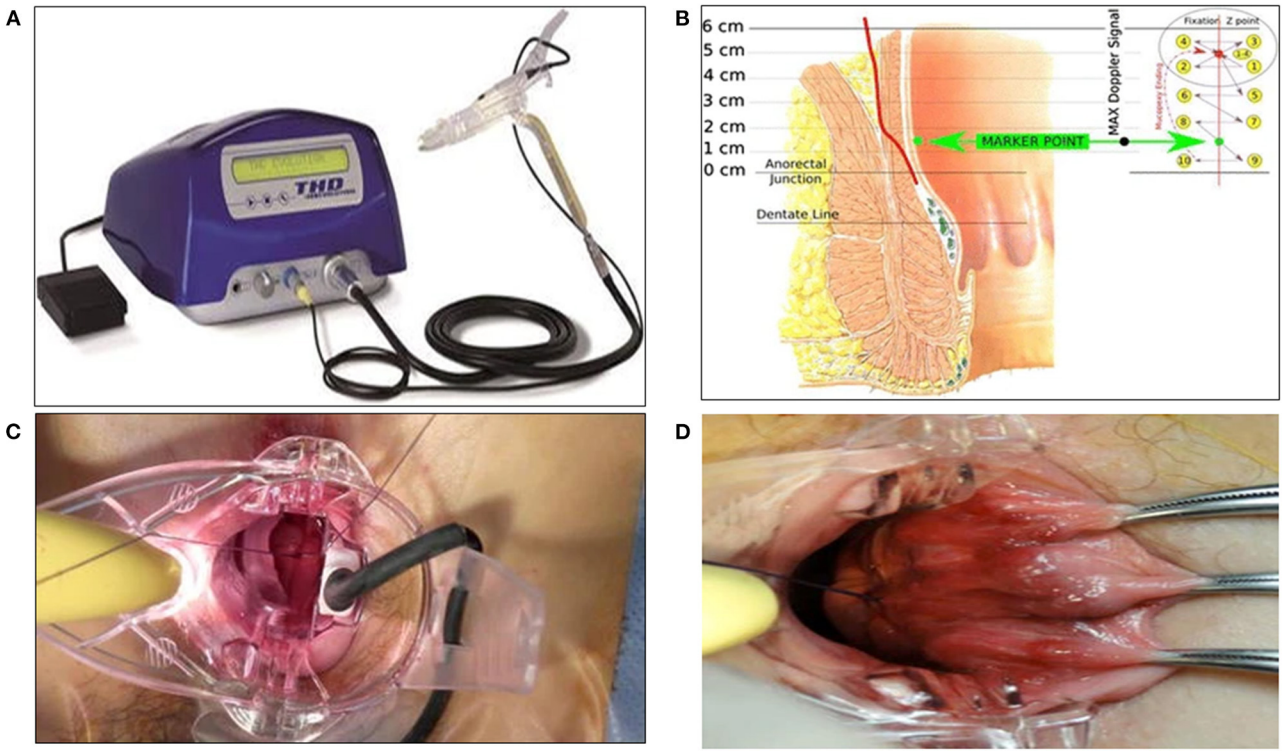

FIGURE 5 | THD Doppler procedure. **(A)** Surgical instruments specifically designed for the THD procedure. **(B)** Schema of the anatomical course of a hemorrhoidal artery and mucopexy fixation point and continuous suture. **(C)** Suture of a hemorrhoidal artery during DDD (Distal Doppler-guided dearterialization). **(D)** Mucopexy suture is secured without including the hemorrhoids. (Reproduced from Ratto C. THD Doppler procedure for hemorrhoids: the surgical technique. *Tech Coloproctol.* (2014) 18:291–298. Creative Commons Attribution 2.0 International License).

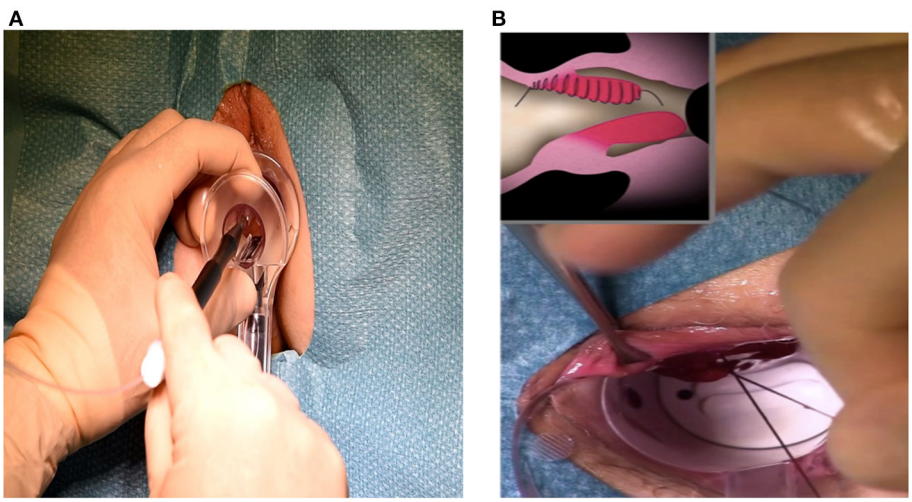

FIGURE 6 | HeLP **(A)** and HeLPexx **(B)** procedures (courtesy of Paolo Giamundo MD, FEBSQ, FRCSE).

resect a circular layer of rectal mucosa above the hemorrhoids using a dedicated stapler (initially PPH 1, then PPH 3), reducing the blood flow to the hemorrhoidal plexus and lifting the hemorrhoids in anatomical position, resolving the prolapse. This technique has gained worldwide popularity as a painless technique with excellent short-term results. To increase the long-term results, new devices, such as high-volume staplers, were introduced in the early 2000s (66). The higher long-term

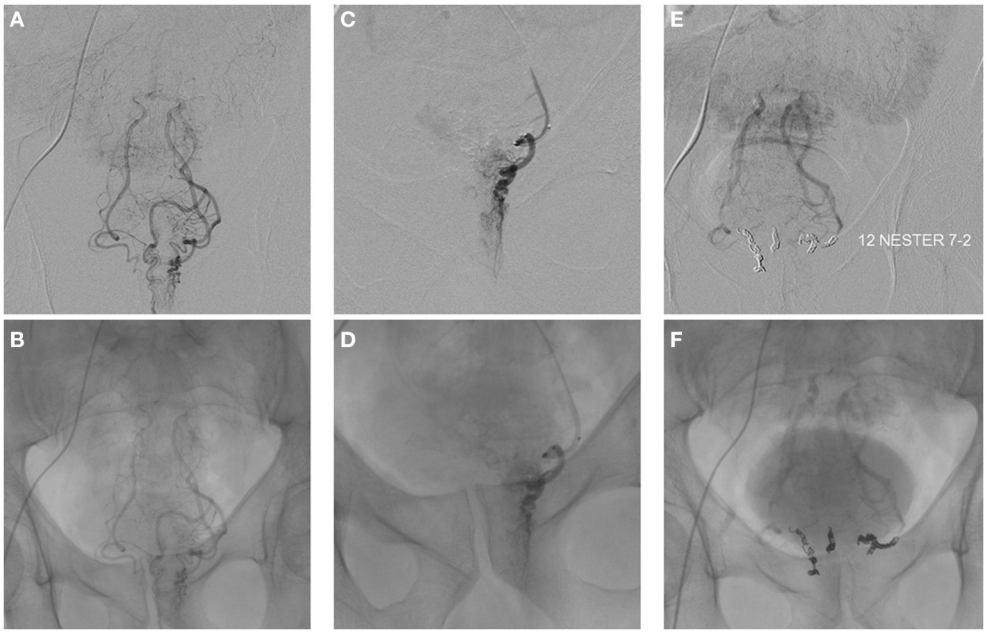

FIGURE 7 | Emborrhoid technique (courtesy of Prof. Vincent Vidal).

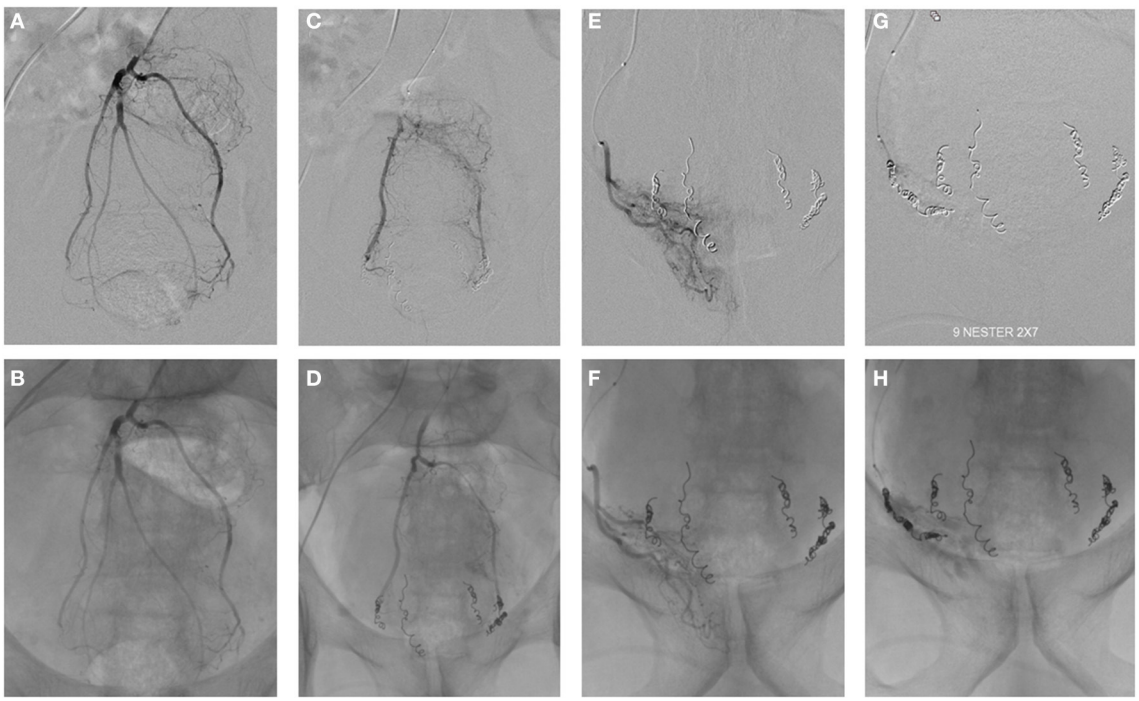

FIGURE 8 | Emborrhoid technique (courtesy of Prof. Vincent Vidal).

recurrences compared to hemorrhoidectomy and the report of serious, albeit rare, complications have reduced the adoption of the technique in many centers (67). Nevertheless, stapled hemorrhoidopexy highlighted two key concepts on which many new surgical techniques for HD are based: avoiding skin excision, as one of the main contributors of postoperative pain, and directing the operation above the dentate line, recognizing the functional role of hemorrhoidal tissue (68).

21st Century

In the first 20 years of the 2000s, the surgical treatments for hemorrhoids have been moving in two directions: on one hand, traditional techniques have been modified according to new devices to increase postoperative outcomes; on the other hand, minimally invasive techniques have been developed to reduce postoperative pain, need for hospital admission, and injuries to the structures of the anal canal. Several authors have described open hemorrhoidectomy performed by high-energy devices, such as ultrasound or radiofrequency, with promising results in some series (69, 70).

According to the "vascular theory," which postulates the blood overflow from the superior hemorrhoidal artery as the main cause of hemorrhoidal disease, and thanks to the positive results of THD, Hemorrhoids Laser Procedure (HeLP) and Emborrhoid were developed as new mini-invasive surgical treatments.

HeLP, first described in 2011 by ***Paolo Giamundo*** (71), involves selective closure of the terminal branches of the superior rectal arteries, which were identified by a 20 MHz Doppler probe, 3 cm proximal to the dentate line using a laser optic fiber (**Figure 6A**). It was initially indicated for 2- or 3-degree hemorrhoids without significant prolapse, although recently, a combination with mucopexy (HeLPexx) has been described (**Figure 6B**), widening the indications for advanced HD (72).

In 2014, Emborrhoid, a radiological interventional technique (**Figures 7**, **8**), was described by ***Vincent Vidal*** based on selective embolization of the terminal branches of the superior rectal artery (73, 74). In analogy with the principles of THD, the terminal branches of the superior rectal arteries are occluded by coils placed by the endovascular route. It is generally indicated in patients not fit for surgery, with major/life-threatening bleeding and unresponsive to conservative therapy (72).

In 2007, sclerotherapy received a new impetus with the introduction of 3% polidocanol foam as a sclerosing agent by ***Moser*** (75). Since then, several studies have shown the superiority of foam in terms of effectiveness and reduced complications compared with oil-based agents, inaugurating a new era for sclerotherapy (76–79). However, these studies mainly focused on the treatment of 1-degree HD, while further studies are needed on 2- and 3-degree HD (79, 80).

In 2021, Sclerobanding, a combined technique of sclerotherapy with 3% polidocanol foam and rubber banding ligation, was described by ***Bracchitta*** et al. (81). The aim of the authors is to further increase the results of both techniques, reducing the risk of delayed bleeding and abscess associated with each technique when applied alone.

All these techniques can be performed as an office-based procedure, under or even without local anesthesia, and they are repeatable in cases of recurrence.

The current mainstream surgical management of HD is represented by using office-based procedures and minimally invasive techniques whenever possible: the wide range of options available allows a tailored approach because "no one size fits all options" (82).

AUTHOR CONTRIBUTIONS

FP, GG, GP, VV, MP, and SD: drafting and writing. GD'A and GS: revision of the text, adding new contributions. All authors read and approved the final version of the manuscript.

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ORIGINAL RESEARCH
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Local Perianal Anesthetic Infiltration Is Safe and Effective for Anorectal Surgery

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Background: General or regional anesthesia is predominantly used for anorectal surgery, however in the recent years more attention was drawn in the use of local anesthesia for anorectal surgery. In this study we present the technique and results of the use of local perianal anesthetic infiltration for minor anorectal operations.

Methods: In this cohort study patients undergoing surgery for hemorrhoids, anal fissures and low anal fistulas were included. Posterior perineal block was induced with a mixture containing 0.125% bupivacaine and 0.5% lidocaine. All patients were followed up at 30 days either by a post-operative visit or a telephone call and all post-operative complications over the post-operative 30-day period were registered.

Results: One thousand and twenty-six consecutive patients were included in our study. For all patients' intraoperative analgesia was achieved after performing perianal anesthetic infiltration and no additional support from the anesthesia team was necessary in any of case. Complications were observed in 14 (1.4%). Urinary retention occurred in 5 (0.5%) cases. Six cases of bleeding occurred after hemorrhoidectomy (0.6%) and 1 (0.1%) after lateral internal sphincterotomy. Perianal abscess developed for two patients (0.2%).

Conclusions: Local anesthesia using posterior perineal block technique is safe and effective for intraoperative analgesia in anorectal surgery, saving a substantial operation cost by avoiding the involvement of an anesthesia team and resulting in minimal incidence of urinary retention and other complications.

Keywords: hemorrhoids, local anesthesia, anorectal surgery, sphincterotomy, hemorrhoidectomy

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INTRODUCTION

Hemorrhoidectomy, anal fistula surgery and lateral sphincterotomy make up a significant part of colorectal surgical practice in adult population. About 13.9 million (4–5%) people suffer from hemorrhoids and other anorectal disease in the USA and ∼10% (1.4 million) of them require surgical intervention (1). Although these commonly performed anorectal operations are short in duration the dense sensory supply of the perineum leads to significant post-operative pain, making adequate anesthesia crucial (2).

General or regional (spinal, caudal) anesthesia is predominantly used for anorectal surgery, however in the recent years several studies explored the use of local anesthesia for anorectal surgery (3–6). In this study we present the technique and results of the use of local perianal anesthetic infiltration for anorectal operations.

MATERIALS AND METHODS

Study Population

Where applicable STROBE guidelines were employed to report this study (7). Patients, undergoing anorectal operations between July 2002 and July 2012, were enrolled in a prospectively collected and maintained database, noting their age, sex, indications for operation, performed operation and any complications within the 30 day after operation. Indications for operation were symptomatic third and fourth degree hemorrhoids (8), anal fissures after failed medical treatment, and low anal fistulas with no suspicion of upward extension and anal polyps. The indications for operation and operative tactics were in line with the current colorectal surgery guidelines (9–11). Exclusion criteria included complicated anal pathologies (incontinence, stenosis, or abscess), other comorbidities (inflammatory bowel diseases, acquired immune deficiency syndrome or tuberculosis), documented allergy to local anesthesia or patient unwillingness to undergo local anesthesia. The study was approved by the bioethics committee and all patients were informed about the technique of the procedure and detailed written consent was obtained beforehand.

Pre-operative Preparation and Local Anesthesia Technique

The anesthesia technique was learned from Lohsiriwat D (personal communication). All patients received lactulose pre-operatively and no bowel preparation was used. No intravenous or oral sedation was used and no anesthesia team was present in the operating room. Electrocardiography, pulse oxymetry and blood pressure monitoring was used in every case. In all cases patients were placed in the prone jackknife position. Posterior perineal block was induced with 42 ml of mixture containing 0.125% bupivacaine and 0.5% lidocaine. Three consecutive injections through one skin puncture site on each side of the anus were performed, with skin puncture points being anteriorly 2–2.5 cm from the dentate line on the skin and 1.5–2 cm from the midline. Each of the three 7 ml injections was pointed at different directions (**Figure 1**). The first was parallel and external to the anal sphincter complex (**Figure 2**). The second was performed at a 45 degrees angle to the skin, aiming at the top midline of the anal canal (**Figure 3**). The third was performed subcutaneously, parallel to the skin surface (**Figure 4**). Skin infiltration was avoided. Injections were performed after aspiration test confirmed that the needle was not in the lumen of the vessel. Same sequence of injections was repeated contralaterally.

Surgical Techniques

Closed hemorrhoidectomy was used for hemorrhoids. Only symptomatic cushions were removed. Internal hemorrhoids in remaining untreated locations were coagulated by bipolar coagulation. Tailored closed lateral internal sphincterotomy was performed for medically untreatable anal fissure. Internal anal sphincter was incised to the level of the dentate line. Only patients, who had low and simple anal fistulas when there was no suspicion of upward extension were treated under posterior perineal block anesthesia. In such cases, fistulotomy with laying open of the fistula track was performed. Anal polyps were simply excised using electrocautery. No wound or anal packing was used.

Post-operative Management and Follow-Up

Patients were discharged on the day of operation if they were able to urinate, if the pain was under control with oral pain medications and if the social circumstances were favorable (support at home, no need to travel far after the operation). All patients were followed up at 30 days either by a post-operative visit or a telephone call and all post-operative complications over the post-operative 30-day period were registered.

Study results are presented as absolute numbers and percentages for categorical variables and as medians with ranges for continuous variables.

RESULTS

One thousand and twenty-six consecutive patients, with the median age of 48 (range 17–89) years, underwent operations for anorectal diseases from July 2002 to July 2016. Of them, 494 (48.1%) were male and 532 (51.9%) female. For all patients' intraoperative analgesia was achieved after performing perianal anesthetic infiltration and no additional support from the anesthesia team was necessary in any of case. Hemorrhoidectomy was performed in 835 (81.4%) cases (**Table 1**). Of them, 100 (12%) patients had simultaneous operations: lateral internal sphincterotomy for concomitant anal fissure in 72 (72.0%), anal polypectomy in 23 (23.0%) and fistulotomy for low fistula in 5 (5.0%) patients.

Closed lateral internal sphincterotomy was performed for chronic anal fissure in 162 (15.8%) patients. Of them, in 25 (15.4%) cases simultaneous procedures were performed: 7 (28.0%) anal polypectomies, 7 (28.0%) fistulotomies for low anal fissures and in 11 (44.0%) cases internal hemorrhoids were coagulated with bipolar coagulation or ligated.

Complications were observed in 14 (1.4%) patients (**Table 2**). Urinary retention occurred in 5 (0.5%) cases, requiring placement of urinary catheter. Six cases of bleeding occurred after hemorrhoidectomy (0.6%) and 1 (0.1%) after lateral internal sphincterotomy. In two cases bleeding occurred within first 2 h after the operation and it was stopped by oversewing of the bleeding spot without any additional anesthesia. Other five patients had to be repeatedly anesthetized with posterior perineal block and underwent a thorough surgical wound hemostasis.

Perianal abscess developed for two patients (0.2%): in one case after hemorrhoidectomy and in the other after a sphincterotomy. Abscesses occurred within 2 weeks after the operation and manifested with fever and increasing perianal pain. In both cases they required surgical drainage and resolved completely.

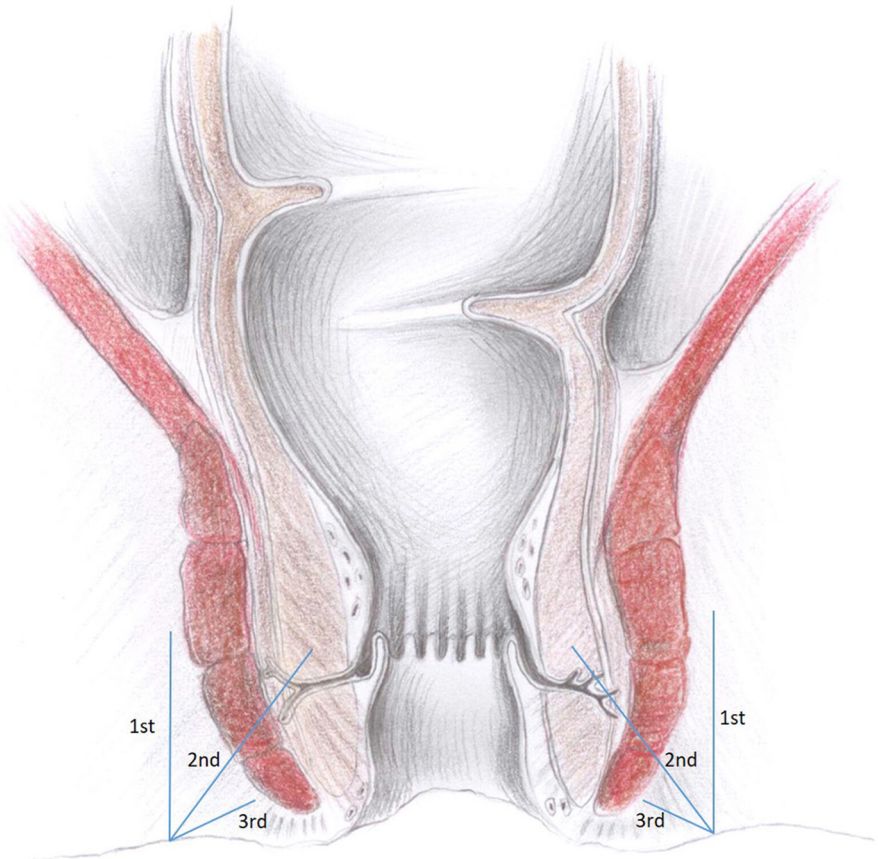

FIGURE 1 | Directions of all anesthetic injections visualized in the frontal plane.

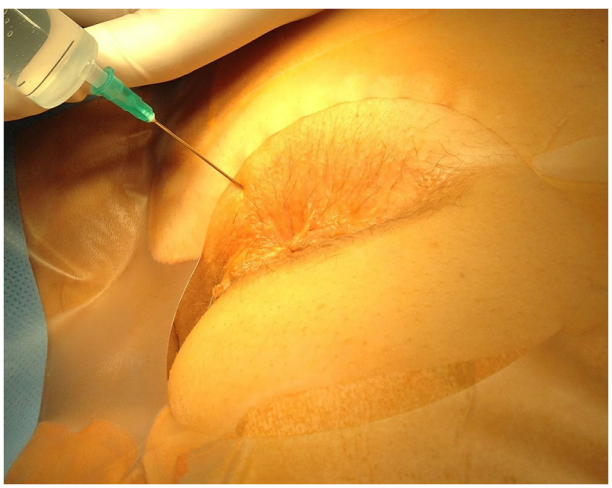

FIGURE 2 | Direction of the first injection.

Seven hundred and fifty-three (73.4%) patients underwent a day-care procedure. The median hospital stay was 1.8 days (1–18 days).

DISCUSSION

Our study suggests that local anesthesia using the posterior perineal block technique ensures safe and effective intra-operative and post-operative analgesia for most commonly performed anorectal operations.

Other studies also confirmed that patients have virtually no complications after posterior perianal block and that this anesthesia technique is easy to perform, can be safely applied by any surgeon, potentially reduce operation costs, is associated with a shorter hospital stay and ensure a faster patients return to full social activities (1, 3, 4, 12–15).

However, this anesthesia technique has some disadvantages. One of them is the inadequate relaxation of the puborectalis muscle (12). Therefore, patients with high perianal fistulas or adenomas higher in the rectum, cannot be operated upon using this anesthesia technique. Also ambulatory anorectal surgery has a limited time for direct post-operative observation of the patient.

The main limitations of the study are the lack of objective pain measuring and no comparison with other anesthesia techniques. Furthermore, this is a descriptive type of study that lacks a thorough statistical analysis, which could help to draw more robust conclusions. However, our study included quite a large

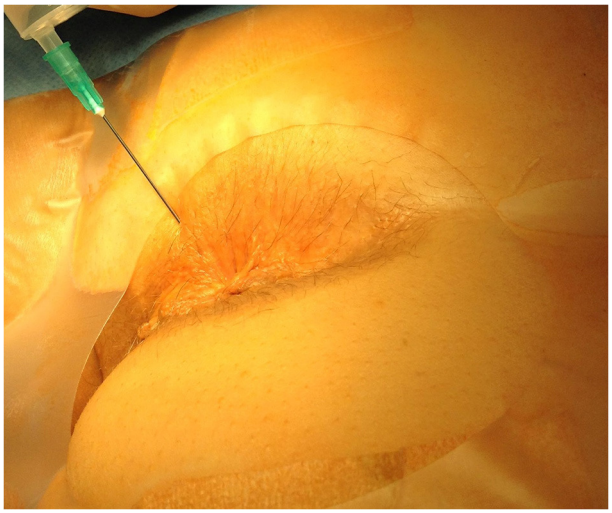

FIGURE 3 | Direction of the second injection.

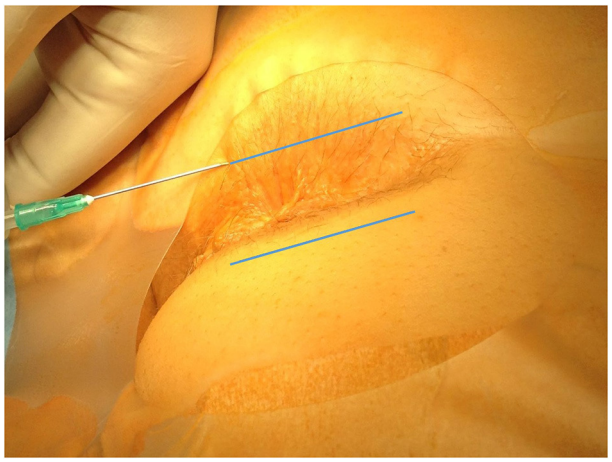

FIGURE 4 | Direction of the third injection (line marks the bearing of the subcutaneous injection).

TABLE 1 | Performed surgical procedures.

Surgical procedure	Number of cases [*n* (%)]
Hemorrhoidectomy	835 (81.4)
Number of cushions removed	
One	318 (31.0)
Two	227 (22.1)
Three	283 (27.6)
Four	7 (0.7)
Grade	
III	452 (54.1)
IV	383 (45.9)
Closed lateral internal anal sphincterotomy	162 (15.8)
Fistulotomy	15 (1,5)
Anal polypectomy	14 (1,4)

TABLE 2 | Post-operative complications.

Complications	Number of cases [*n* (%)]
Hemorrhage	7 (0.7)
Urinary retention	5 (0.5)
Perianal abscess	2 (0.2)

consecutive cohort of unselected patients undergoing different anorectal operations.

During this type of operations patient positioning is important. In most practices lithotomy or jackknife positions are preferred. Lithotomy position is usually preferred by the anesthesiologist, who controls the airways, but it is awkward for the surgeon, as patients' buttocks may obscure vision and manipulation (4). Alternatively, perianal anesthetics infiltration permits the use of a safe jack-knife position, which is convenient in having good exposure of the operative field and direction of injection (3, 4, 16).

According to studies, the most commonly used local anesthetics for such implications are lidocaine, bupivacaine, mepivacaine (3–5, 16). In our study local anesthesia was induced with a mixture of 0.125% bupivacaine and 0.5% lidocaine. Lidocaine is a short-acting local anesthetic which provides an excellent initial pain relief, whereas bupivacaine is a long-acting anesthetic providing several hours of anesthesia post-operatively (17). Some surgeons add adrenaline to the anesthetic, which promotes vasoconstriction and reduces bleeding in the operative field (3). Unfortunately, we were unable to find any studies directly comparing different local anesthetics for anorectal surgery.

We observed quite a low (1.4%) post-operative complication rate in our study. One of the most common complications after anorectal operations is urinary retention (18). It is mostly related to spinal anesthesia, fluid overload and post-operative pain (19, 20). Spinal or caudal anesthesia and pudendal (ischiorectal) nerve blocks may cause urinary retention in up to 36% of patients (1, 12, 21). The reported rate of urinary retention after general anesthesia is around 3% (1, 6). The use of perianal infiltration of local anesthetics allows anorectal surgery to be performed with a very low incidence of urinary retention (3, 21). We report a 0.5% rate of urinary retention in our study, which is very similar to the rates, ranging from 0 to 0.5%, reported by other studies (3–5, 12, 16, 21).

The rate of post-operative bleeding was reported to be up to 3% after general, 12% after regional and from 0.5 to 8% after local anesthesia (1, 3, 16, 21). Few studies have also reported zero bleeding rates after local anesthesia (4, 5, 12). In our study the rate of post-operative bleeding

was 0.7%. We think that the surgical technique with meticulous hemostasis and selection of the patients with normal coagulation parameters are more important in preventing post-operative bleeding, rather than the method of anesthesia.

Since hemorrhoidectomy wounds rarely heal primarily, the true rate of wound infection is unknown, however, the instances of perianal abscess after surgery are reported. Wound infection rate under spinal anesthesia was reported to be up to 4% (21). Local anesthesia studies report almost no cases of wound infection and only two patients (0.2%) in our study developed perianal abscesses (3, 4, 12, 21).

Overall current literature indicates that local anesthesia is safe and even in some cases superior to spinal anesthesia for anorectal surgical procedures.

The reported high patient satisfaction with local anesthesia may be related to the short hospital stay and adequate control of intra-and post-operative pain. The success of the local anesthetics technique is also highly dependent on the skills of the surgeon in providing effective infiltration (3). Specific post-operative recommendations, which include a high residual diet, potent oral analgesics, mild laxative drugs and a warm sitz bath, may help to further increase patient satisfaction after anorectal surgery (14).

CONCLUSION

Local anesthesia using posterior perineal block technique is safe and effective for intraoperative analgesia in anorectal surgery, saving a substantial operation cost by avoiding the involvement of an anesthesia team and resulting in minimal incidence of urinary retention and other complications.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Vilnius Regional Bioethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TP, KS, and NS: conceptualization, methodology, resources, writing-review and editing, and supervision. MJ, KČ, and LJ: software and data curation. TP, MJ, KČ, and LJ: validation. TP, MJ, and NS: formal analysis. TP, MJ, KČ, LJ, KS, and NS: investigation. TP, MJ, and KČ: writing-original draft preparation. TP and MJ: visualization. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2021.730261/full#supplementary-material

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METHODS
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Transanal Hemorrhoidal Dearterialization (THD) Anolift-Prospective Assessment of Safety and Efficacy

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The adjunct of a mucopexy to conventional dearterialization has become a routine part of the transanal hemorrhoidal dearterialization procedure in order to facilitate the management of the prolapsing component and has helped to expand the indications of this technique to more advanced stages of hemorrhoidal disease. A simple technical modification of THD with targeted mucopexy (TM), called Anolift, is described. The aim of the study was to evaluate the safety and effectiveness of this technical variation. The procedure consisted of two parts: one aimed at the dearterialization and the other concentrated on the management of the prolapsing component. Once all the arteries were identified and transfixed an Anolift targeted mucopexy was performed using a continuous barbed suture with a synthetic absorbable monofilament (Polydioxanone) 2/0 Filbloc (Assut Europe) stitch mounted on a 4/8 30 mm needle. Severity of hemorrhoidal symptoms was scored from 0 to 20 using a dedicated questionnaire: the Hemorrhoidal Assessment Severity Score (HASS). From May 2018 to November 2020, 60 patients with hemorrhoidal disease (HD) underwent a THD Anolift procedure. Three patients experienced severe post-operative pain and 10 (23%) suffered with difficulty in evacuation. The median follow-up period was 15.5 months (range 2–32 months). The mean HASS changed from 16.43 pre-operatively to 1.95 post-operatively ($p < 0.0001$). Pre-operative HASS very strongly correlated with the degree of hemorrhoids ($p < 0.001$), while there was no correlation between the pre-operative HASS or the degree of hemorrhoids and the post-operative HASS ($p = 0.163$). There was no significant difference in predicted post-operative HASS according to the pre-operative HD stage. One patient (1.6%) with circumferential IV hemorrhoids had a recurrence and required a further THD. Two patients had excision of skin tags (3%). The Anolift technique is safe and effective for the management of HD even in patients with advanced stages.

Keywords: hemorrhoids, THD, Anolift, HAL, mucopexy, hemorrhoidectomy, dearterialization

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INTRODUCTION

Transanal Hemorrhoidal Dearterialization (THD) has become a well-established procedure for the management of symptomatic hemorrhoids (1, 2). To facilitate the management of the prolapsing component, the adjunct of a mucopexy to conventional dearterialization has become a routine part of the THD procedure and has helped to expand the indications of this technique to more advanced

stages of hemorrhoidal disease (HD) (3, 4). While the dearterialization part of the procedure is well-standardized, different techniques have been described for the mucopexy that can be performed at the same time as the dearterialization (4, 5) or can be targeted and performed separately from the dearterialization (6). In this article we present a simple technical modification of the previously described THD with targeted mucopexy (TM) (6), described as Anolift, to further optimize the management of the prolapsing component. The Anolift procedure is aimed to make the mucopexy part of the procedure easier and quicker to perform, especially when dealing with advanced stages with a very large prolapsing component, and overcome some of the pitfalls of the previous technique. The aim of the study is to evaluate the safety and effectiveness of this technical variation.

METHODS

Study Period

May 2018 to November 2020.

Patients

This is a prospective evaluation of all patients operated on with THD Anolift technique, as modified by the senior author. Patients with symptomatic hemorrhoidal disease of any degree that failed a conservative treatment and required surgical intervention were offered intervention in the form of THD with Anolift. Patients were not consecutive because at the beginning of the series the suture used for the Anolift was not always available, hence some patients could not be treated with this technique. All patients treated with THD Anolift were prospectively entered in a specifically designed database. Prospectively collected data included patients' demographics and relevant history. The degree of severity of hemorrhoidal symptoms was scored for each patient using a specifically designed questionnaire, the Hemorrhoidal Assessment Severity Score (HASS), assessing five different parameters, each scoring from 0 to 4 with 0 corresponding to no symptoms at all and 4 to the presence of the symptom on daily basis or with every defecation[(4)]. A total score of 0 corresponded to the complete absence of hemorrhoidal symptoms while a total score of 20 would correspond to the worst possible degree of symptoms. Patients were asked to score the worse severity of post-operative pain during the first week and on day 7 using a standardized visual analog score 0–10 (0 = no pain, 10 = the worse possible pain). The severity of the pain was defined as mild with a score from 1 to 3, moderate from 4 to 6, and severe from 7 to 10. The overall duration of post-operative pain was also recorded.

Technique

All operations were performed as a day case under general anesthesia or alternatively under spinal anesthesia by a single surgeon (PG). Prior to surgery, a phosphate enema was administered, and a single shot of I.V. antibiotic prophylaxis was performed at induction. The procedure consisted of two parts: one aimed at the dearterialization and the other concentrated on the management of the prolapsing component. The two phases of the operation were separated so that each one of them could be optimized. The procedure was carried out in the lithotomic position using a specifically designed proctoscope (THD slide^{TM}, THD Lab^{TM}, Correggio, Italy), which incorporates a side-sensing Doppler probe and a window for placement of the sutures. The device also has a slide mechanism that, when withdrawn, allows widening of the window. The first part of the procedure consists of the dearterialization phase and was performed as previously described (4). Once all the arteries were identified and transfixed, and therefore the dearterialization phase was completed, attention was given to the areas with the largest prolapse. Once these were identified, a targeted mucopexy was performed. The aim of this part of the procedure was to correct the hemorrhoidal prolapse and any associated mucosal rectal prolapse. For this purpose, the THD slide^{TM} was reinserted, ensuring that the instrument was introduced as deep as possible at the site of the targeted area of the prolapse. From this point, a continuous suture was started using a synthetic absorbable monofilament (Polydioxanone) 2/0 Filbloc (Assut Europe) stitch mounted on a 4/8 30 mm needle (**Figure 1**). This is a unidirectional barbed suture with a self-locking system. The self-locking system consists of a small button of Polydioxanone attached at the end of the suture that also serves as an anchoring point (**Figure 2**). The suture was progressively extended distally toward the dentate line with several passages of the needle taking the mucosa and submucosa at a distance of ∼5 mm. The suture was stopped just proximal to the hemorrhoid and at least 5 mm from the dentate line, taking care not to catch the anal mucosa.

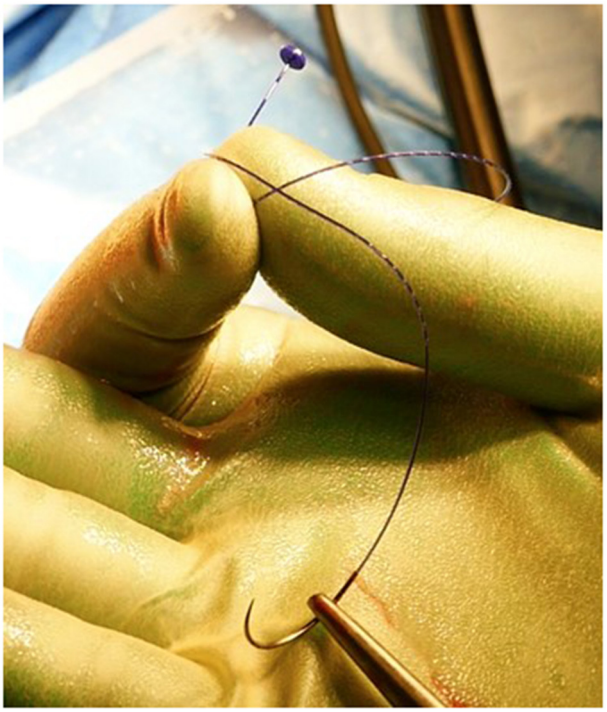

FIGURE 1 | Filbloc suture.

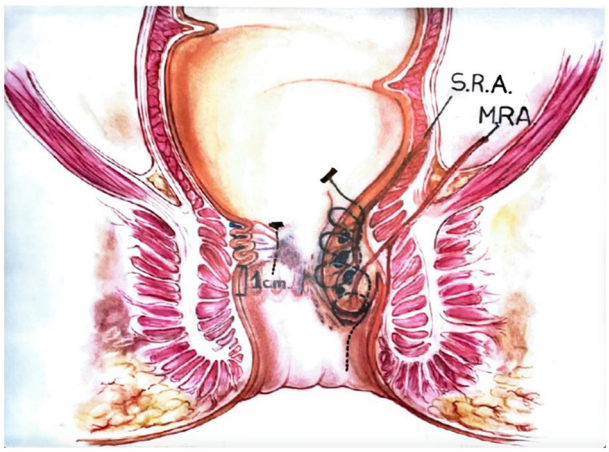

FIGURE 2 | Anolift diagram.

TABLE 1 | Patients' demographics.

Patients	*N*	Range/%
Tot	60	
Sex		
Male	33	55
Female	27	
Age (median)	48	21–89
Previous hemorrhoidal treatments	11	18
Hemorrhoidectomy	4	
THD	4	
Banding	2	
Sclerotherapy	1	
Degree		
II	2	3
III	25	42
IV	33	55

During this process, the slide mechanism of the instrument was progressively widened to allow progression of the suture distally, while keeping the prolapsing mucosa away from the operating field. Once the continuous suture was completed, the sliding part was completely removed, keeping the main body of the instrument fully inserted. Once the desired level for the plication was reached, the Filbloc suture was held with one hand and was put under gentle tension while with the other hand the rectal mucosa caught by the suture was pushed up toward the proximal end of the stitch. By doing so, the rectal wall was plicated with a concertino effect and the hemorrhoid and the anal canal lifted and repositioned proximally. Any external component, if present, was not normally excised.

RESULTS

A total number of 60 patients underwent THD Anolift during the study period (**Table 1**). The mean pre-operative HASS was 16.43 (range 8–20) (**Figure 3**). A six points dearterialization was performed in 55 (91.7%) patients while five arteries were identified and transfixed in the other five. A two quadrants Anolift was performed using the barbed suture in 16 (27%) patients, a three quadrants Anolift was performed in 38 (63%) patients, and a four quadrants Anolift was performed in six (10%) patients (mean of plications 2.9 ± 0.7; range 2–4). Concomitant procedures were performed in five cases (two skin tag removals, two botox injections, one open lay submucosal fistula, one single nodule haemorrhoidectomy). Post-operatively, three patients complained of a severe post-operative pain which settled within 7 days in all cases. Four patients suffered with fecal impaction (6%), and 10 (16%) reported some difficulty in evacuation which all resolved within 5 days. The median follow-up period was 15.5 months (range 2–32 months). The mean HASS changed from 16.43 pre-operatively to 1.95 post-operatively ($p < 0.0001$) (**Figure 3**). Pre-operative HASS very strongly correlated with the degree of hemorrhoids (Kruskal-Wallis, $p < 0.001$), while there was no correlation between the pre-operative HASS or the degree of hemorrhoids and the post-operative HASS (Kruskal-Wallis, $p = 0.163$) (**Figure 4**). Equally, there was no significant difference in predicted post-operative HASS according to the pre-operative HD stage ($p = 0.163$) (**Figure 5**). During the study period, three patients underwent further intervention. One patient (1.6%) with circumferential IV hemorrhoids had a recurrence and required a further THD Anolift to resolve the ongoing symptoms. Two patients had excision of skin tags (3%).

DISCUSSION

A recent consensus statement on management and treatment of HD concluded that THD is a treatment option for II- and III-degree hemorrhoids and in experienced hands possibly also for IV-degree. Indeed, the scope of the mucopexy associated with the THD procedure is to correct the prolapsing component and optimize the outcome of surgery for advanced HD. This is achieved by performing a plication of the mucosa and submucosa of the rectal wall proximal to the prolapsing hemorrhoid that is lifted and repositioned in its natural position within the anal canal. The mucopexy can be performed at the same time as the dematerialization (4, 5) or can be targeted and performed separately from the dearterialization (6). A targeted mucopexy carries the advantages to perform the plication only where the prolapsing component is present using a needle and a suture different from the ones used for the dearterialization and better suited for the purpose. The 5/8 needle used for the dearterialization, while ideal for the transfixation of the artery, poses some limitations to the extent of penetration of the needle restricting the width and depth of tissue caught by the bite, making the management of large prolapsing hemorrhoids and associated mucosal rectal prolapse difficult. The use of different sizes and shapes of needle overcomes this problem. The use of a suture material like PDS also facilitates the sliding of the suture and provides a more durable support to the repair, thus optimizing the management of the prolapsing component. Finally, with the TM technique the mucopexy is only

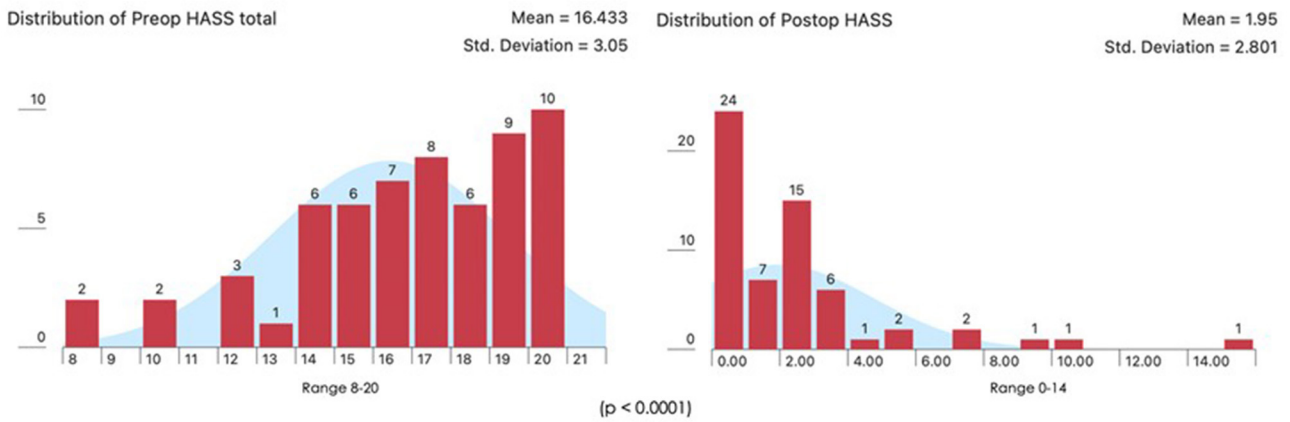

FIGURE 3 | Pre-operative vs. post-operative HASS.

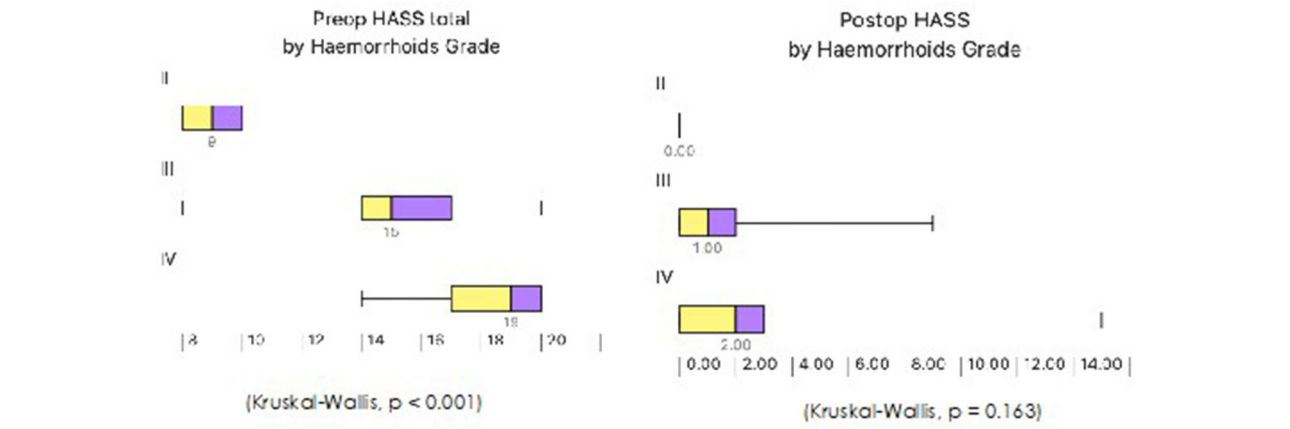

FIGURE 4 | Correlation between hemorrhoids grade and HASS.

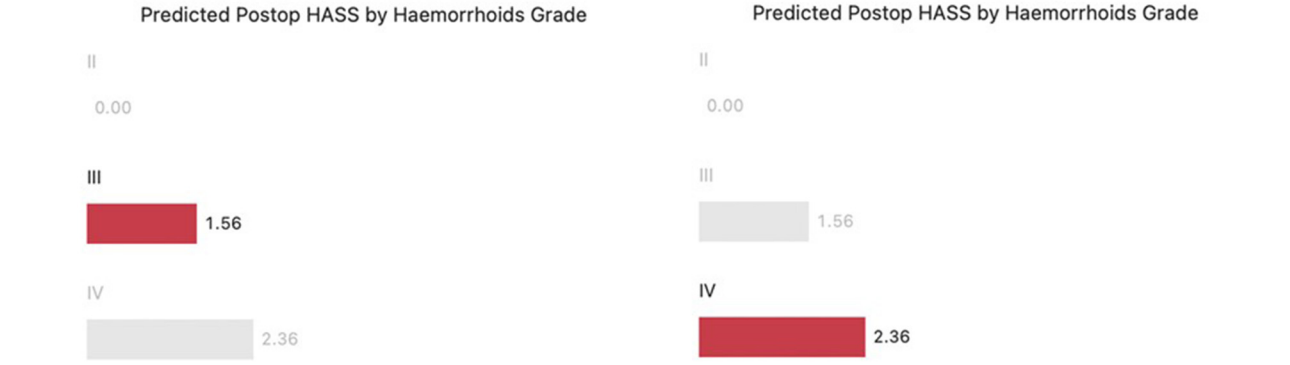

FIGURE 5 | Predicted post-operative HASS by hemorrhoids grade (Kruskal-Wallis, $p = 0.163$).

performed where the prolapsing component is most prominent, thus reducing the number of sutures needed. With this technique the length of the plication can be variable and tailored to the severity of the prolapse. For worse prolapse, the maximum length of the THD Slide™ device should be utilized. Regardless of the type of mucopexy performed, once the suture has been placed

and the rectal mucosa plicated, the two ends of the suture will have to be tied. At the time of tying the knot, the proximal and distal threads of the suture are pulled together, this inevitably leading to a degree of tension at the level of the start and end point of the suture line used for the plication. The tension on the suture line will approximate these two points, causing a C deformity of the rectal wall and creating a degree of pocket effect in the rectal wall. The longer the extent of the plication the more prominent this effect may be. It is unclear whether the presence of these pockets within the rectal lumen have a detrimental effect on post-operative recovery, but it is believed that they may contribute to defecatory disturbance in the early post-operative period. Another potential concern with a conventional mucopexy in patients with a very large prolapsing component is that any excessive tension at the two extremities of the suture line may also lead to a cheese wire effect with the suture cutting through the rectal mucosa and leading to ulceration of the area and possibly counting for those very rare but significant post-operative bleeds occasionally encountered in these patients. To overcome these potential problems and simplify the procedure we have introduced a very simple variation of the previously described technique. The use of a barbed suture allows a sound and effective plication of the rectal wall with a more even distribution of the tension along the suture lines. Avoiding the need to tie the stitch eliminates the risks of creating a pocket in the rectal lumen and the possible cheese wiring effect on the rectal wall. Avoiding the knot for the plication also eliminates the risk of snapping the suture while tying the knot and may reduce operative time. The 30 mm 4/8 needle coupled with the suture fits the size of the THD device well, making it perfectively suited for the purpose, ensuring optimal room for maneuvering within the instrument. In this series of 60 patients treated with THD Anolift technique, more than half had IV-degree HD. The only post-operative events recorded were difficult evacuation in about 20% of patients and very severe post-operative pain in 5% of patients; all symptoms resolved within a week. One patient required further intervention for ongoing hemorrhoid-related symptoms. Two further patients required surgery for symptoms related to external skin tags. Including these two patients, reintervention rate was 5%. This study also demonstrated a very strong correlation between the pre-operative HASS and the degree of hemorrhoids, however, interestingly none of these two parameters correlated to the post-operative HASS, meaning that the severity of the HD did not have a negative impact on the outcome. The main limitations of this study were the fact that this was a single center study with no control group. However, this was an observational study aimed to assess the clinical outcomes of a technique that represents the evolution of a previously described technique for the treatment of hemorrhoids. This modification was introduced to overcome some of the pitfalls of the previous TM technique. Although the concept of the technique is not new and is relatively widely adopted, the way it is performed has been refined. The objective of the study was therefore to standardize the new technique and assess the safety and effectiveness of it, avoiding any potential bias. That was the reason why it was decided to start the assessment from a single center and single surgeon experience with no control group. Furthermore, we previously published a study that included 31 consecutive patients with Grade IV hemorrhoids operated on using the THD TM technique (6). Post-operative pain was reported by 22 (70%) patients on day 1 and 19 (61%) on day 7, while nine (30%) did not experience any pain at all. Overall, severe pain was reported by nine (16%) patients against 5% reported after THD Anolift. At a mean follow-up of 32 months (6–58), two (6.4%) patients required a further intervention for on-going hemorrhoidal symptoms while in the current study one out of 33 patients treated for IV-degree hemorrhoids required further intervention for residual hemorrhoidal symptoms and none in the other 27 patients. Yet, given that this was a non-comparative observational study primarily aimed to assess the safety and effectiveness of the technique, it would be challenging to assert that the Anolift modification carries any definite advantage in term of post-operative pain and recovery, or reduced morbidity and recurrence rate compared to other types of mucopexy, however, based on these preliminary results we believe all those advantages may well be added benefits of the technique.

CONCLUSIONS

The Anolift technique is a simple and practical option that helps to simplify and optimize the management of the prolapsing component during the THD procedure. This option is safe and effective for the management of HD, even in patients with advanced stages. Based on these preliminary data it would be reasonable to call for a larger multicenter study, maybe with a control group, to further assess its role in the management of symptomatic hemorrhoids.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

PG wrote the manuscript. ES organized the database. All the authors contributed to conception and design of the study, performed the statistical analysis, contributed to manuscript revision, read, and approved the submitted version.

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Conflict of Interest: The senior author PG is a trainer in the THD technique.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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A Stepwise Proposal for Low-Grade Hemorrhoidal Disease: Injection Sclerotherapy as a First-Line Treatment and Rubber Band Ligation for Persistent Relapses

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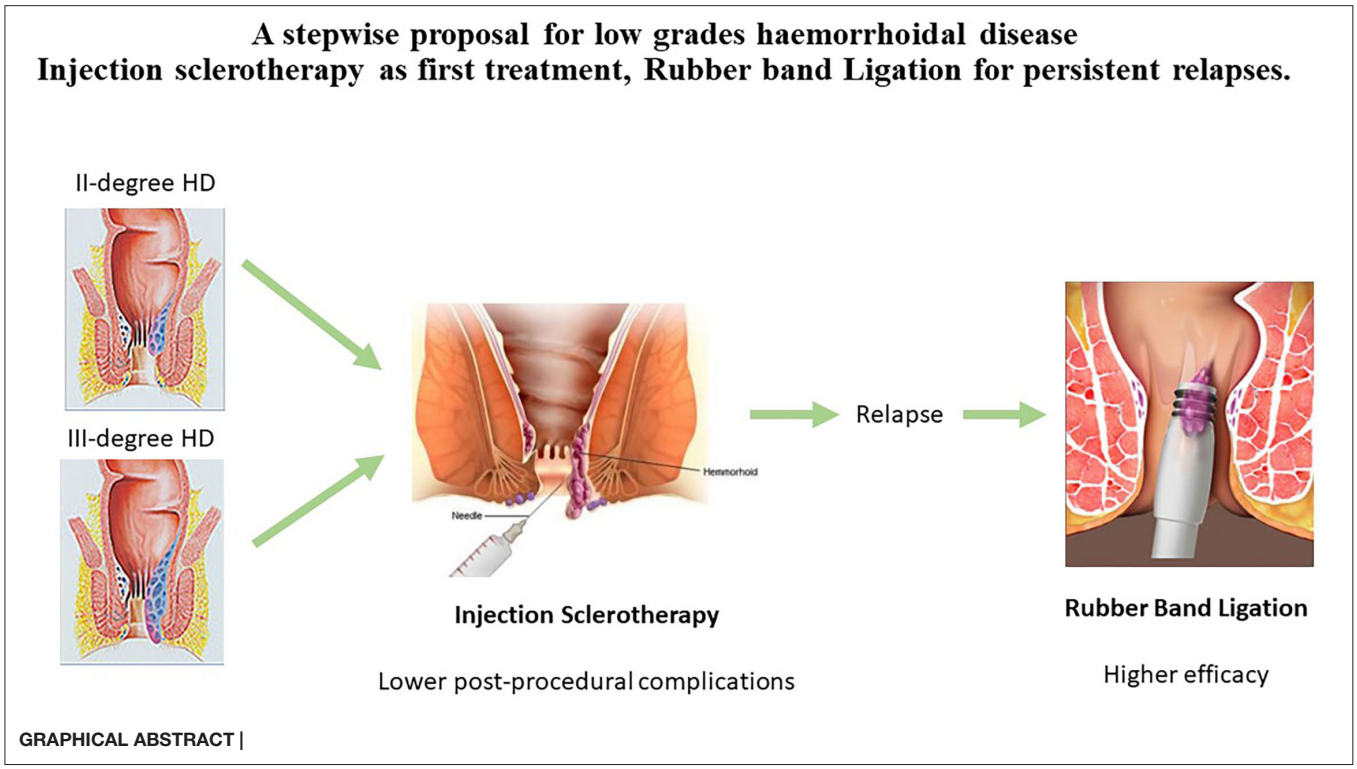
Outpatient treatments are actually the techniques of choice in the management of low-grade hemorrhoidal disease. Among these, rubber band ligation (RBL) and injection sclerotherapy (IS) are the most frequently performed. Both techniques are used, without one having been determined to be superior over the other. We analyzed the studies that compare these two techniques in terms of efficacy and safety in order to offer a proposal for treatment choice. RBL seems to be most efficient in terms of symptom resolution for second-degree hemorrhoidal disease and equal or superior for treatment of third-degree disease. However, IS offers lower rates of severe post-operative pain and minor complications. Since outpatient treatments are offered to patients as painless options that allow a prompt recovery, we propose a stepwise protocol using 3% polidocanol or aluminum potassium sulfate and tannic acid IS as the first treatment option, as it has less complications, followed by RBL in cases of relapse.

Keywords: hemorrhoids, hemorrhoid ligation, hemorrhoid sclerotherapy, review, outpatient treatment, hemorrhoid complications

INTRODUCTION

Patients suffering from hemorrhoidal disease (HD) would can obtain rapid and efficient symptom resolution with low rates of post-operative complications and recurrence (1). In order to provide the correct care for these patients, it is necessary to find a balance between the resolution of symptoms and post-operative morbidity, explaining to the patient that recurrence or incomplete resolution of HD can be treated again. Rubber band ligation (RBL) and injection sclerotherapy (IS) are the most commonly used non-surgical techniques for HD. These are recommended by national and international guidelines (2, 3) for the management of low-grade HD (II–III according to Goligher's classification), (4) while no role for these techniques is recognized in the management of complicated hemorrhoids (5).

The treatments can be offered in an office-based modality and are cost and time-saving techniques that allow the preservation of the working days of patients and avoid the post-operative morbidity associated with hemorrhoidectomy. Unfortunately, these treatments are also not entirely



GRAPHICAL ABSTRACT |

free from complications. Based on previous systematic reviews, post-operative pain in RBL ranges from 8 to 80% and post-operative bleeding is reported in up to 50%. For IS, post-procedural pain is reported in 36–46% of patients, while no post-operative bleeding has been described (6, 7). The COVID-19 pandemic, with its restrictions on hospital admissions of patients, has further strengthened the need for appropriate selection of treatment for HD (8).

Rubber band ligation (RBL) and IS are offered to patients according to the personal choice of their surgeon. Thus, there is likely a need to evaluate the available techniques and develop a consistent method for deciding on their use in accordance with a proper classification (9). The aim of this analysis is to offer a proposal for the use of the office-based treatments, evaluating whether IS and RBL are comparable or if one should be preferred among them. Most of the studies involving IS and RBL are retrospective and few are contemporary. However, some new data are now available from recent randomized controlled trials (RCTs). We performed an up-to-date literature review of studies that compare RBL and IS with the aim of developing a standardized protocol for the management of grade II–III HD. This literature review was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (10).

Eligibility criteria. Studies on patients complaining of bleeding or prolapse due to HD comparing RBL and IS were collected. The hemorrhoidal degree and the presence of bleeding or prolapse were analyzed. The well-defined treatment modality, post-procedural complications, and the symptom resolution rates as outcome measures were checked in the articles, and the follow-up period was considered. The literature search comprised all original papers published from January 2000 to June 2021. No language selection was implemented. The exclusion criteria were lack of information on hemorrhoidal degree, post-operative morbidity, or recurrence.

Information source. Original papers were identified by searching PubMed or MEDLINE database and the Cochrane library database.

Search strategy. The search terms used were: Hemorrhoids, Hemorrhoid ligation, Hemorrhoid sclerotherapy, Review, and Outpatient treatment.

Study Records

Data management. An electronic record using an Excel framework was made, including sample sizes and initial numbers.

Selection process. Articles were searched by two independent reviewers for initial screening and eligibility before inclusion in the review.

Data collection process. Data were extracted using a pilot form and then selected according to the missing or superfluous ones. Disagreements among reviewers were resolved by discussion.

Data items. Number of patients, patient demographic data, hemorrhoidal degree according to Goligher's classification, the occurrence of post-treatment complications, and the recurrence rate at follow-up were recorded.

Outcomes and prioritization. The occurrence of post-operative complications, such as pain and bleeding and the recurrences at follow-up, were the main measured outcomes.

Risk of bias in individual studies. Some reports grouped the hemorrhoidal degrees; this can confound results related to singular degrees. Loss of patients, short periods of follow-up and differences in outcome measures can lead to bias at the outcome level.

TECHNICAL NOTES

RBL

Rubber band ligation (RBL) should be avoided in patients with other anorectal diseases such as fistulas, thrombosed hemorrhoids and fissures, immunodeficient patients, and in those with coagulation disorders. No data on pregnant women are present in the literature (6, 7).

Rubber band ligation (RBL) can be performed by suction or by forceps. Ramzisham compared forceps vs. suction ligations and highlighted how pain during and after the first 24 h was worse with the use of forceps. The forceps procedure was also associated with more intra-procedural bleeding (11). Cazemeier and Wehrmann evaluated the use of endoscopic ligations and concluded that trans-anal ligation with a proctoscope is low-cost and causes little pain in comparison to the endoscopic procedure, and is comparable in terms of recurrences. However, ligation using a flexible endoscope is easier, offers better maneuverability and the possibility of a photographic documentation, and allows the performance of more ligations (12, 13). Notably, data on the proper number of ligations to be inserted are inconclusive (6). The number of sessions required is one in 63–69% of cases and two in 3–30%. The proper interval between two sessions proposed by literature is 4 weeks (6, 14, 15).

IS

Injection sclerotherapy (IS) should be avoided in patients with thrombosed hemorrhoids; cardiac, hepatic, renal, or hematological diseases; pregnant or nursing mothers; and people with asthma, allergic predisposition, hypercoagulability, thrombophilia, anticoagulant therapy, or inflammatory bowel disease (6, 7).

Several agents are used for injection therapy for HD: 5% phenol in almond oil, 50% dextrose in water, 3% polidocanol, and aluminum potassium sulfate and tannic acid. Akindiose et al. compared 5% phenol in almond oil and 50% dextrose in water and found comparable results in terms of 6-month symptom resolution (92.3% vs. 89.7%) in patients with grade I–II and III HD (16). In the comparison of 5% phenol in almond oil with aluminum potassium sulfate and tannic acid, the former obtained poorer results at 1-year follow up. In their study, Yano et al. analyzed third-degree HD and found that 80% of patients treated with 5% phenol in almond oil experience recurrence, while use of aluminum potassium sulfate and tannic acid resulted in a resolution of both bleeding and prolapse in 75% of patients (17).

Mishra et al. evaluated 3% polidocanol vs. 5% phenol in almond oil and found low rates of pain during defecation, permanent pain, and pruritus but also higher satisfaction rates with the use of 3% polidocanol. Permanent pain was described in 2.8% of the patients in the 3% polidocanol group and in 4.8% of the group treated with 5% phenol in almond oil (18).

A special foam formulation of 3% polidocanol has recently been proposed (19). Polidocanol is a non-ionic surfactant that mainly targets endothelial cells, causing vasospasm. According to the authors, the foam formulation leads to homogeneous distribution of drug microbubbles. They demonstrated its efficacy in the management of second and third-degree HD, with reported success rates of 78.8% at 1-year follow-up. On the other hand, 13.6% of patients suffered post-procedural pain lasting up to 5 days. In contrast with other techniques, the authors injected the suspension into the piles and not into the submucosa at the base of each hemorrhoidal pile above the dentate line (20).

Symptom Resolution

Bleeding and prolapse are the principal symptoms suffered by patients with HD. Both IS and RBL are intended to cause local inflammation, which leads to reduced blood flow in the hemorrhoids and fibrosis of the area, retracting the prolapse into the anal canal.

Results of both techniques in terms of symptom resolution are reasonably good and maintained over time. However, patients must be informed of the possible need for second sessions and re-treatment in future.

Kanellos et al. performed an RCT analyzing 161 patients suffering from second-degree HD, comparing RBL and IS with 5% phenol solution in almond oil. Additional sessions for persistent symptoms after 4 weeks were required in 33% of the IS group and 52% of the RBL group ($p = 0.013$). At 6–24 months follow-up, 30% of the patients from the IS group and 17% from the RBL group required further treatments ($p = 0.06$). The results were poorly maintained over time, and at 4-year follow-up, bleeding was present in 81.3% of the IS group and 60.5% of the RBL group ($p = 0.004$), whereas spontaneously or manually reducible prolapse was present in 82.6% of the IS group and 60.4 % of the RBL group ($p = 0.02$). Finally, long term symptom resolution was achieved in only 8% of the IS group and 31% of the RBL group (21).

Jehan et al. performed an RCT comparing RBL and IS in 100 patients with second-degree HD and found symptom resolution in 56% of the patients from the IS group and 88% of the RBL group at 4–6 weeks post-treatment Overall, 32% of the patients in the IS group and 12% of those in the RBL group required a second session. The authors report good results for both techniques at 1-year follow-up, with 100% symptom resolution in the RBL group and 88% in the IS group. Additionally, long-term follow-up showed 100% symptom resolution for RBL vs. 92% in the IS group ($p = 0.041$) (22).

Awad et al. published a prospective comparative study of 120 cirrhotic patients analyzing the efficacy of RBL and two types of IS, ethanolamine oleate 5%, and N-butyl cyanoacrylate, concluding that although RBL was associated with higher satisfaction than IS, there were no statistically significant differences in success rate (23).

Gireboinwad et al. conducted an RCT comparing polidocanol 3% IS, RBL, and hemorrhoidectomy. They collected data from 150 patients with 50 in each treatment group. First and second-degree cases were treated with IS, I–II and III with RBL, and III and IV with hemorrhoidectomy, obtaining 88% improvement or

resolution of symptoms after IS and 88% after RBL. However, the data from this study are biased due to the difference in how the groups selected the treated patients (24).

Nasir et al. conducted an RCT comparing IS with 5% phenol in almond oil and RBL in 116 patients with second-degree HD. They describe only a short-term follow-up of 15 days, reporting that 82.1% of the RBL group and 61.3% of the IS group showed symptom resolution. Overall, 54.8% of patients in the IS group and 3.4% of the RBL group required a second treatment ($p < 0.05$) (25).

Abiodun et al. conducted a prospective comparative study analyzing 60 patients with second and third-degree HD, comparing RBL and IS with 50% dextrose in water. They report that anal prolapse was more frequently partially or completely resolved in the RBL group compared to the IS group ($p = 0.03$), while bleeding resolution was more frequent in the IS group ($p = 0.07$). At 3 months, seven patients (23.3%) in the IS group and four (13.3%) in the RBL group required a further treatment ($p = 0.34$) (26).

Makanjoula et al. performed a prospective comparative study on 74 patients with grade I–III HD, comparing IS with 3% polidocanol and RBL at 3-month follow-up. The authors highlight that the two techniques are equally effective for the treatment of patients with grade I–III HD (27). The data are summarized in **Table 1**.

Post-procedural Complications

The most frequent procedural and post-procedural complications encountered in both techniques are mild to moderate pain, tenesmus, and bleeding. These complications usually do not impair the ability of the patient to return to work the same day. However, low but not negligible rates of severe anal pain have been reported in the literature, alongside some sporadic cases of life-threatening complications (28).

Kanellos et al. reported an up to 69.1% rate of post-operative minor complications in patients treated with RBL, with a rate of 30% in the IS group ($p < 0.001$). It is notable that severe anal pain was suffered by 11.1% of the RBL group vs. 1.3% of the IS group (21).

Gireboinwad et al. conducted an RCT comparing IS, RBL, and hemorrhoidectomy. Mild post-operative anal pain was present in 12% of RBL patients vs. 4% of IS patients, and early complications were seen in 68% of the RBL group vs. 32% of the IS group (24). In the report by Nasir, moderate pain was more common in the RBL group (5.2 vs. 1.7%) ($p > 0.05$), while severe pain was equally reported (1.7%) (25).

Abiodun et al. reported that severe anal pain was more frequent and had a longer time to complete resolution in the RBL group. However, this difference was not statistically significant ($p = 0.35$) (26).

In the study by Makanjoula et al., rates of minor complications were similar in both groups (5.7% in RBL vs. 8.1% in IS; $p = 0.643$). The median pain score was significantly higher in the RBL group compared to the IS group after the first and second sessions ($p < 0.001$) (27). Cirrhotic patients undergoing IS showed higher rates of minor complications and severe anal pain only in the study performed by Awad et al. (23). Data are summarized in **Table 2**.

DISCUSSION

The justification for offering an outpatient treatment for low grade HD is the avoidance of both post-operative complications and the costs of surgical management (i.e., traditional hemorrhoidectomy and its minimally invasive counterpart, arterial ligation).

In terms of efficacy compared to Milligan-Morgan hemorrhoidectomy, non-surgical treatments are equally effective for second-degree HD symptom resolution, but inferior in terms of prolapse resolution for third-degree cases. On the other hand, post-operative pain is present in almost all patients treated by hemorrhoidectomy, with symptoms usually lasting 2 weeks, but in some cases up to 3 months (29).

In comparison to arterial ligation, non-surgical treatments are best for low grades of HD, as stated by the Hubble trial, a UK National Health Service research study that compared hemorrhoidal artery ligation vs. rubber band ligation in terms of cost-effectiveness and serious adverse events (30, 31).

Injection sclerotherapy (IS) and RBL have been considered as two alternative options for the management of low-grade HD, but few data are available to suggest the use of one technique over the other. This is the first review that focuses only on studies that directly compare IS and RBL, offering an evaluation of safety and efficacy.

As summarized in **Table 1**, we observed that RBL has higher rates of bleeding and prolapse resolution, even though several sclerosant solutions are proposed by the different studies with variable efficacy.

In the analysis of the several sclerosants available, polidocanol 3%, and aluminum potassium sulfate and tannic acid seem to be the most effective (16–20).

The evaluation of efficacy for each hemorrhoidal degree is difficult because most previous studies analyze the results of these techniques in patients with grouped second and third-degree HD. The recent studies by Abiodun and Makanjoula analyzed bleeding and prolapse resolution separately. The first study showed a preference for RBL for prolapse resolution and in IS for bleeding resolution, whereas the second showed a comparable efficacy for both techniques (26, 27).

The present study offers new data that differs from those previously reported by reviews, with both techniques being comparable in term of symptom resolution in second-degree HD, while IS resulted in better outcomes in third-degree cases (7).

Unfortunately, outpatient treatments can cause post-procedural complications. A previous review showed that post-operative complications occurred in 1–50% of RBL cases in the literature, pain in 8–80%, and severe pain in 4–20% (6). In line with these results, our analysis also showed that post-procedural complications and anal pain are more frequent in the RBL groups.

TABLE 1 | Data on symptoms' resolution and need for re-treatment offered by RCTs comparing IS vs. RBL.

Authors	Year	Degree	N. of patients	Type of sclerosant	Symptoms' resolution		Re-treatment	
					IS (%)	RBL (%)	IS (%)	RBL (%)
Kanellos	2003	II	161	5% phenol in almond oil	67	48	33	52
Jehan	2012	I–II	100	ND	56	88	32	12
Awad	2012	II–III	120	ethanolamine oleate 5%/N-butyl cyanoacrylate	87	90	20	20
Gireboinwad	2014	I–II (IS)/I–III(RBL)	100	polidocanol 3%	88	88	ND	ND
Nasir	2017	II	116	5% phenol in almond	61	82	54	34
Abiodun	2021	II–III	60	50% dextrose in water	46	76.6	23	13
Makanjoula	2021	I–III	74	3% Polidocanol	$P = 0.391$		ND	ND

TABLE 2 | Minor and severe pain after IS and RBL procedures.

Author, year	Degree	IS	RBL	Minor complications		Severe pain	
				IS	RBL	IS	RBL
Kanellos et al. (21)	II	80	81	30%	69.1%	1.3%	11.1%
Jehan et al. (22)	I-II	50	50	32% (16)	40% (20)	0	0
Awad et al. (23)		60	60	ND	ND	61.6%	20%
Gireboinwad et al. (24)	I-II (IS)/I-III(RBL)	50	50	32%	68%	4%	12%
Nasir et al. (25)	II	58	58	8.6%	10.2%	1.7%	1.7%
Abiodun et al. (26)	II-III	30	30	33.3%	30%	0	13.3%
Makanjoula et al. (27)	I-III	37	37	8.1%	5.7%		>>>

In the overall assessment of IS vs. RBL, no definitive conclusions on the preferable technique can be made, as we have to consider the balance between efficacy and post-operative complications.

Patients must be informed of the potential need for repeated sessions or retreatment, since this is more frequent in patients treated by IS than by RBL, as shown by the results of Abiodun, Nasir, and Jehan (respectively, 23% vs. 13%, 54% vs. 34%, and 32% vs. 12%) (22, 25, 26).

As we must guarantee, to the best of our ability, a prompt recovery of our patients, we propose a stepwise treatment modality when treating patients with low-grade HD. According to our analysis, IS should probably be offered as the first-line treatment option, while RBL should be used in cases of persistent symptomatic second or third-degree anal prolapse.

Since both procedures are not free from relapses and complications, extensive information on efficacy and possible post-operative courses must be given and written consent must be obtained. There is a need for a multicentric RCT to standardize and evaluate the results of these techniques, including separate analysis for second and third-degree HD.

AUTHOR CONTRIBUTIONS

RT gave substantial contribution to the conception of the work. RT, LJKM, ID, PV, MM, and GR gave substantial contribution to the acquisition, analysis and interpretation of data. RT, MM, GM, GS, SB, and GC revised critically the work for important intellectual content. All authors gave their final approval of the version to be published and are co-authors of the present paper.

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Efficacy and Tolerability of a New Formulation in Rectal Ointment Based on Zn-L-Carnosine (Proctilor®) in the Treatment of Haemorrhoidal Disease

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Haemorrhoidal disease (HD) shows high prevalence in western countries, reaching 4.4% per year in the US. Topical preparations are the first-line treatments, which are readily available as "over-the-counter" (OTC) products, often containing a nonstandardised mixture of "natural" remedies, or anaesthetics or cortisol;those latter are not free from undesirable effects. The Zinc-L-Carnosine is a cytoprotective compound, promoting mucosal repair in the gastrointestinal tract and also in mucosal repair, following radiation injuries to the rectum as well as in ulcerative colitis. Our aim was to study the efficacy of Zinc-L-Carnosine in relieving acute symptoms of HD, testing a preparation in the rectal ointment, Proctilor®, in patients complaining of bleeding or thrombosed piles. In a multicentre open trial, 21 patients older than 18 years of age were enrolled. The symptoms of HD were graded according to the Haemorrhoidal Disease Symptoms Score (HDSS) in association with the Short Health Scale (SHS) to assess the influence of HD on quality of life. The pain was assessed with the VAS score, bowel habit by means of the Bristol scale. The patients were evaluated at enrolment (T0) and 2 (T1) and 4 (T2) weeks of treatment with Proctilor® rectal ointment. There were 10 men and 11 women; mean age, 49 years. Pain, bleeding, and thrombosis were all significantly reduced after treatment; the mean VAS score decreased from 4.71 ± 3.05 at T0 to.52 ± 0.87 and.05 ± 0.22 at T1 and T2, respectively; (mean ± SD; $p < 0.001$ in both cases). Similarly, the HDSS score showed to be significantly reduced between T0, T1 (8.05 ± 4.55 vs. 1.14 ± 1.01), and T2 (8.05 ± 4.55 vs. 24 ± 0.44) (mean ± SD; $p < 0.001$ in both cases). Quality of life showed to be improved as the SHS score decreased significantly with treatment (7.90 ± 4.17 at T0 vs. 4.24 ± 0.44 at T1 vs. 4.05 ± 0.22 at T2; mean ± SD; $p < 0.001$ in both cases). The Bristol score of defecation remained substantially unchanged. No side

effects or discontinuation of treatment were reported. Results of our investigation suggest a role of Proctilor® rectal ointment in treating symptomatic HD with good results and an excellent safety profile. However, our preliminary results encourage further studies on a larger number of patients to confirm the role of Zinc-L-Carnosine in the rectal ointment for the topical treatment of HD.

Keywords: haemorrhoids, rectal bleeding, thrombosed piles, topical treatment, Zinc-L-Carnosine

INTRODUCTION

Haemorrhoidal disease (HD) has a high prevalence (1); sedentary life, alimentary habits, constipation or diarrhoea, pregnancy, and physical efforts or straining at defecation may give rise to various clinical features of the haemorrhoidal disease, such as bleeding, prolapse, tenesmus, and anal pain (2). These symptoms may be severe, disabling, and can cause significant worsening of the patient's quality of life, therefore, requiring particular attention. Prevalence of about 4.4% per year has been estimated in the US population, with a peak between 45 and 65 years of age (1). The most common treatments are based upon preparations for topical use, at least in the early phase, and they are generally appreciated by the patient because of the prompt soothing effect.

So far, the topical treatment of HD is not standardised and is based on common anti-inflammatory remedies represented by ointments, enemas, or suppositories containing cortisone or mesalazine and local anaesthetics (3). It is well-known, however, that a prolonged and/or repeated local use of these products is not free from undesirable effects. In addition, the commonly available topical treatments in HD did not show high efficacy both in short-term and long-term remission of symptoms (3).

Hepilor® is an available compound based on Zinc-L-Carnosine, which has shown a significant ability to protect mucous membranes and promote tissue repair. It was extensively tested in the gastro-oesophageal and intestinal areas, without absorption (4–11).

This compound proved to be very effective in treating radiation proctitis, a difficult clinical condition, significantly improving endoscopic pictures and symptoms (12, 13). Furthermore, the product has been effectively tested in ulcerative colitis, where it induced a significant clinical and endoscopic remission (14).

Last but not least, an oral Zn-L-carnosine prevented oesophageal injuries and severe dysphagia in patients with breast cancer who are undergoing radiotherapy (15), resulting in reduced intake of steroids and analgesics.

In summary, the various actions of Zn-L-Carnosine, such as high muco-adhesiveness, increase in mucosal resistance and mucous production, injury repair, and antioxidant radical scavenger action (3–6), are all focused on tissue repair. Thus, based on this background, the compound may exert therapeutic action in HD, counteracting inflammatory changes and tissue damage, and especially relieving acute symptoms.

Abbreviations: HD, Haemorrhoidal disease; VAS, Visual analogue scale; HDSS, Haemorrhoidal disease symptoms score; SHS, Short health scale.

TABLE 1 | Characteristics of the patients enrolled.

	Total ***N* = 21**
Sex, *n* (%)	
Female	10 (47.62)
Male	11 (52.38)
Age, mean ± SD	49.38 ± 14.86
Fissures, *n* (%)	
No	12 (57.14)
Yes	9 (42.86)
Bleeding, *n* (%)	
No	6 (28.57)
Yes	15 (71.43)
Thrombosis, *n* (%)	
No	9 (42.86)
Yes	12 (57.14)

TABLE 2 | Scores values, stratified for time of observation.

	T0	**T1**	**T2**	***p*-value***
VAS, mean ± SD	4.71 ± 3.05	0.52 ± 0.87	0.05 ± 0.22	**0.018**
HDSS, mean ± SD	8.05 ± 4.55	1.14 ± 1.01	0.24 ± 0.44	**<0.001**
Bristol, mean ± SD	2.90 ± 1.67	3.29 ± 0.78	3.43 ± 0.60	0.112
SHSHD, mean ± SD	7.90 ± 4.17	4.24 ± 0.44	4.05 ± 0.22	**0.001**

**One-way repeated measures ANOVA.*
Bold values denote statistical significance.

MATERIALS AND METHODS

This was a multicentre open-label uncontrolled trial. The criteria of the STROBE checklist (16) were fulfilled. Adult patients (>18 years old) with symptomatic HD were enrolled. Written informed consent was obtained from all the patients. Exclusion criteria were: age < 18; pregnancy; inflammatory bowel disease; viral, bacterial, or radiation proctitis; rectal or anal cancer; anal condylomata; proven or suspected intolerance or hypersensitivity to Zn-L-Carnosine or one or more excipients; and inability to return for a control visit.

Demographic data, symptoms of HD, and details of the enrolled patients were collected in a dedicated database.

Enrolled patients underwent clinical examination and anoscopy to assess the degree of HD according to the Goligher

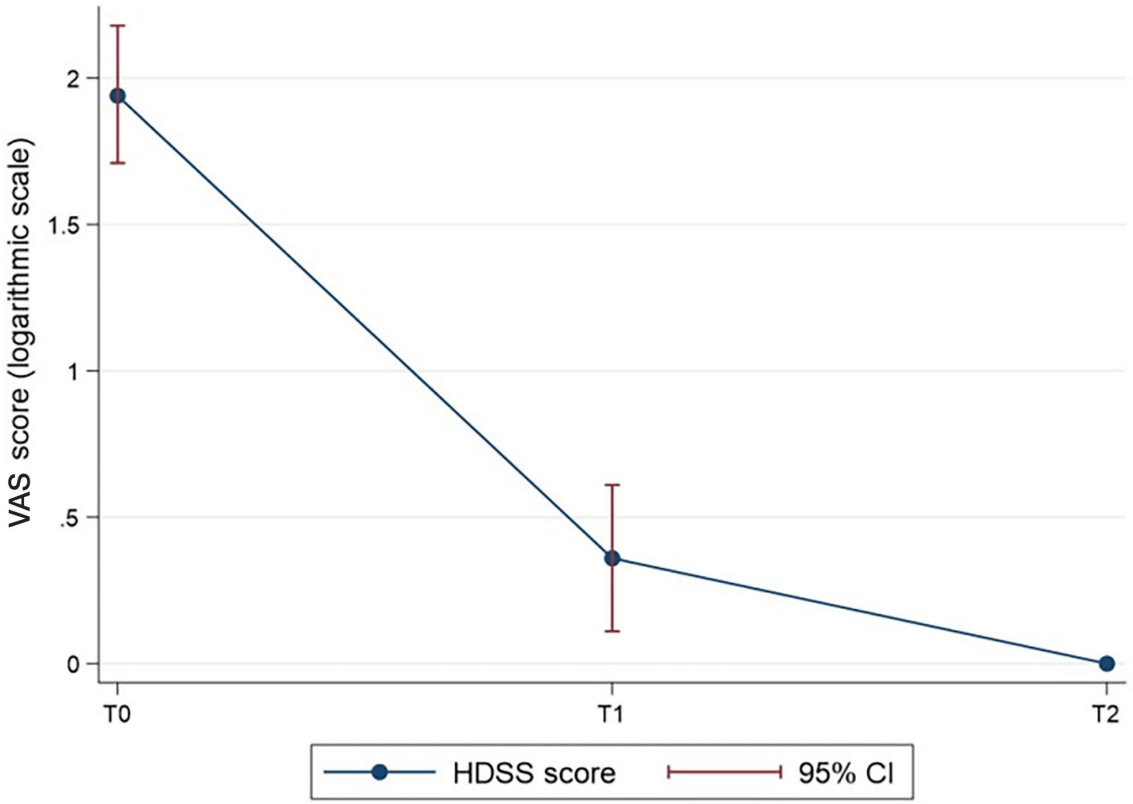

FIGURE 1 | The HDSS score over time (log-transformed for normalisation of the VAS score data). $P < 0.001$ for T1 vs. T0 and T2 vs. T0.

classification and to detect any active bleeding. The presence of thrombosis was registered and was defined as a bulging, swollen perianal vein that is pinkish or bluish in colour. Stool characteristics were assessed using the original version of the Bristol Stool Form Scale (17); severity of symptoms was quantified using the "haemorrhoidal disease symptom score" (HDSS) (18), in which all symptoms were graded with a 5-item scale (0 = never, 1 = <1 time a month, 2 = <1 time a week, 3 = 1–6 days a week, and 4 = every day or always; Minimum = 0, Maximum = 20) in association with "short health scale" (SHS) to assess the burden of HD on quality of life with four questions using a 7-point Likert Scale (minimum = 4, maximum = 28). The pain was recorded using a visual analogue scale (VAS) (the minimum score = 0, maximum = 10). These parameters were recorded at the time of the enrolment (T0) with anthropometric characteristics of the patients and follow-up visits after 2 weeks (T1) and after 4 weeks (T2).

All the patients underwent treatment with the application of Proctilor® rectal ointment 3 ml three times a day. The product was directly provided by the manufacturing company to the Experimentation Centres.

Statistical Analysis

The demographic and clinical characteristics of the sample were analysed using descriptive statistics. The discrete and nominal variables were expressed using frequencies and percentages; continuous variables were expressed as mean values with relative standard deviations (± SDs).

TABLE 3 | *Post-hoc* pairwise comparisons of the scores using Bonferroni's method.

	T0 vs. T1	T0 vs. T2	T1 vs. T2
VAS	**<0.001**	**<0.001**	0.999
HDSS	**<0.001**	**<0.001**	0.485
SHSHD	**<0.001**	**<0.001**	0.999

Bold values denote statistical significance.

The ANOVA for repeated-measures (RM) was used to determine the significance of the difference in scores (VAS, HDSS, Bristol, and SHS) for the time trend after a logarithmic transformation for the normalisation of the data as the non-normal distribution verified through the Shapiro–Wilk test. Logarithmic transformation of the scores over time was represented graphically. *Post-hoc* analysis was performed using Bonferroni's method for pairwise comparisons when the resulting differences were statistically significant. The differences in the clinical characteristics of the sample (bleeding and thrombosis) were analysed using Cochran's *Q*-test for the time trend. *Post-hoc* analysis was performed using McNemar's test. The power of the study was evaluated using the F test, comparing

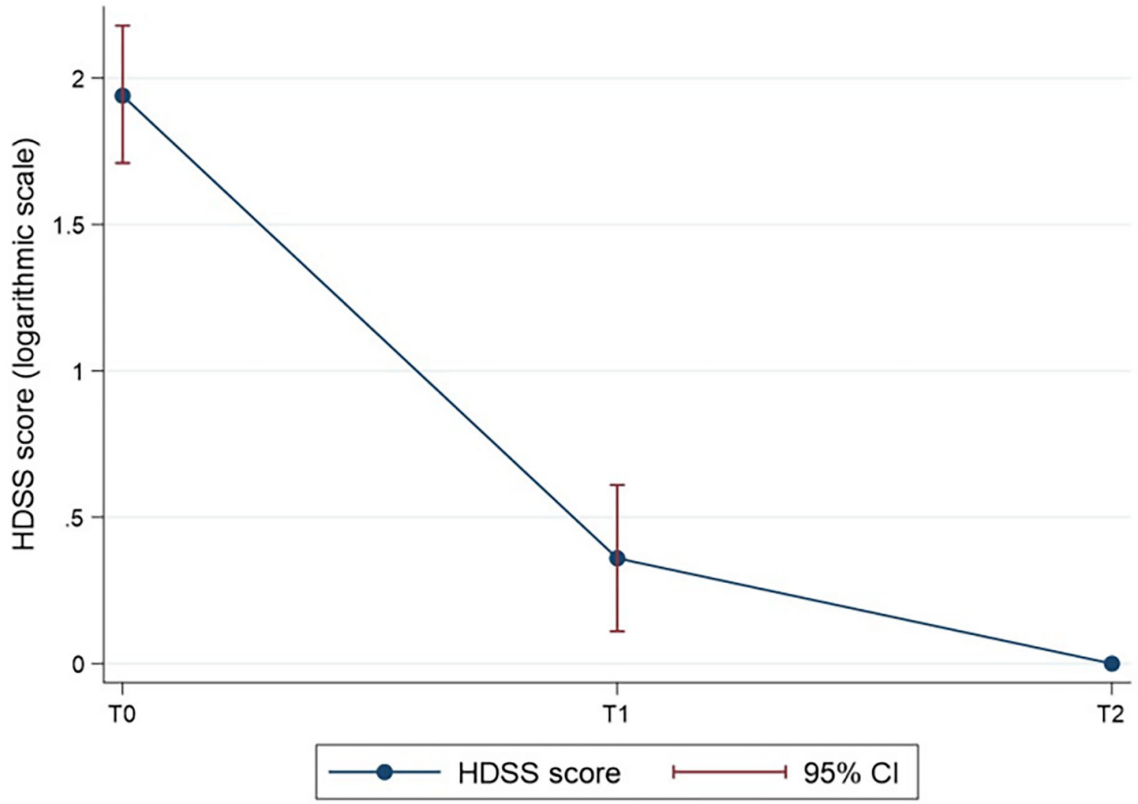

FIGURE 2 | The HDSS score over time (log-transformed for normalisation of the HDSS score data). $P < 0.001$ for T1 vs. T0 and T2 vs. T0.

mean values of VAS at t0 (4.7), t1 (0.5), and t2 (0.04). The estimated power (1–β) was 94%. A prospective analysis with 94% of power and a level of significance $\alpha = 0.05$ identified an estimate of the sample size for a crossover design of at least 21 participants. The data were recorded electronically, and statistical analyses were carried out using Stata Statistical Software, Release 15 (Stata Corp LP, College Station, TX, U.S.A.). All the tests were 2 tailed, and $p < 0.05$ were considered statistically significant.

RESULTS

A total of 21 patients met the criteria to be included in this study. There were 10 men (47.6%) and 11 women (52.4%); the mean age was 49 years (range, 25–74). All of them were diagnosed with symptomatic HD. The f was diagnosed in nine patients (42.9%). In **Table 1**, we reported the demographic characteristics of the sample.

When stratified for time is of observation, the reduction of the VAS score (**Table 2**) was statistically significant ($p = 0.018$). The VAS score over time is shown in **Figure 1**, with logarithmic transformation for the normalisation of the data. The results of the *post-hoc* analysis (**Table 3**) indicated statistically significant differences in the VAS score between time 0 and 1 (4.71 ± 3.05 vs. 52 ± 0.87), and time 0 and 2 (4.71 ± 3.05 vs. 05 ± 0.22) ($p <$ 0.001 in both cases).

The difference in the mean HDSS score (**Table 2**) was statistically significant over time ($p < 0.001$). The HDSS score at a given time is shown in **Figure 2**, with logarithmic transformation for the normalisation of the data. The results of the *post-hoc* analysis (**Table 3**) indicated statistically significant differences of the HDSS score between time 0 and 1 (8.05 ± 4.55 vs. $1.14 \pm$ 1.01), and time 0 and 2 (8.05 ± 4.55 vs. 24 ± 0.44) of observation ($p < 0.001$ in both cases).

The difference in the mean Bristol score (**Table 2**) was not statistically significant over time.

The difference in the mean of the Short Health Scale Haemorrhoidal Disease (SHSHD) score (**Table 2**) was statistically significant over time ($p = 0.001$). The SHSHD score at a given time is shown in **Figure 3**, with a logarithmic transformation for the normalisation of the data. The results of the *post-hoc* (**Table 3**) analysis indicated statistically significant differences of the SHSHD score between time 0 and 1 (7.90 ± 4.17 vs. 4.24 ± 0.44), and time 0 and 2 (7.90 ± 4.17 vs. 4.05 ± 0.22) of observation ($p < 0.001$ in both cases).

Significative differences also emerged for clinical characteristics (bleeding and thrombosis) (**Table 4**). Cochran's *Q*-test showed significant different frequencies of bleeding ($p = 0.005$) and thrombosis ($p < 0.001$) at the various times of observation, with higher percentages of bleeding (71.43 vs.

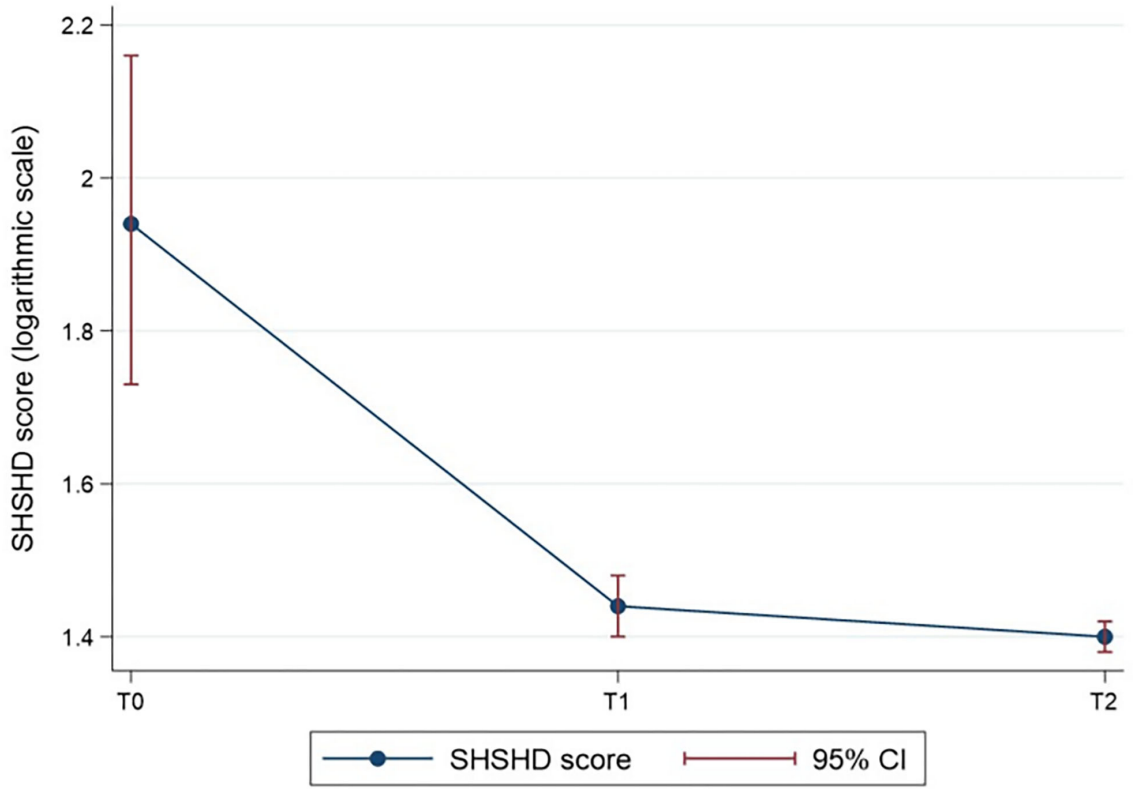

FIGURE 3 | The SHSHD score over time (log-transformed for normalisation of the SHSHD score data). $P < 0.001$ for T1 vs. T0 and T2 vs. T0.

9.52%) and thrombosis (57.14 vs. 9.52%) at time 0 respect to time 2. The results of the *post-hoc* (**Table 5**) analysis indicated statistically significant differences between time 0 and 1, and time 0 and 2 of observation ($p = 0.002$ and $p < 0.001$, respectively) for bleeding.

DISCUSSION

HD is a common complaint affecting ∼40–50% of the adult population (19).

Its pathophysiology has been clarified, and it is characterised by a degenerative process of collagen and fibroelastic supportive fibres of the vascular cushions, resulting in abnormal dilatation, weakness, and displacement of the cushions, resulting in prolapse, bleeding, and thrombosis (20), although many aspects remain controversial (21). Conservative treatments are the first-line options for all degrees of haemorrhoidal disease (3). Conservative treatments are first line options for all degrees of HD (3, 22), and are really helpful in figuring out which patient needs a personalized treatment (23, 24).

A compound based on Zinc-L-Carnosine has shown a significant ability to protect mucous membranes and to promote tissue repair. Zinc is a mineral with many important functions, including the healing of damaged tissue. It seems that insulin-like growth factor-I (IGF-I) could be one of the main factors involved in the healing effect of zinc on gastric ulcers (25).

Hepilor® has been used for the treatment of peptic ulcers in Japan since 1994, and many studies tested it in the gastro-oesophageal and intestinal areas (4–11). In the anorectal field, this compound has proven to be very effective in treating radiation proctitis (12, 13) and ulcerative colitis, where it induced a significant clinical and endoscopic remission (14). Zinc-L-Carnosine induces mucosal repair, stimulating mucus production, antioxidant activity, and membrane-stabilising activity. Its effects are related to different cytoprotective mechanisms, such as the suppression of lipid peroxidation, reduction of the levels of cytokines, and inhibition of superoxide generation. In this way, this compound seems to promote the restoration of the mucosa (25).

Therefore, based on its characteristics and the good results obtained from the use of Zinc-L-Carnosine in tissue repair on the rectal mucosa, it may be possible to hypothesise an effective therapeutic use in the context of other anorectal pathologies. Among these, HD, with its acute or chronic complications, is characterised by a large epidemiological, social, and economic impact.

Although with the limitations due to the small sample of patients, our preliminary study demonstrated the effectiveness of the Zinc-L-Carnosine rectal cream (Proctilor®) in relieving common symptoms of HD, such as bleeding or thrombosis. In fact, we observed a significant reduction in the intensity of the pain at the VAS score, as well as in HDSS and SHSHD scores

TABLE 4 | Clinical characteristics of the sample, stratified for time of observation.

	T0	T1	T2	*p*-value*
Bleeding, *n* (%)				**0.005**
No	6 (28.57)	16 (76.19)	19 (90.48)	
Yes	15 (71.43)	5 (23.81)	2 (9.52)	
Thrombosis, *n* (%)				**<0.001**
No	9 (42.86)	19 (90.48)	19 (90.48)	
Yes	12 (57.14)	2 (9.52)	2 (9.52)	

*Cochran's Q-test.
Bold values denote statistical significance.

TABLE 5 | *Post-hoc* pairwise comparisons clinical characteristics of the sample using McNemar's test.

	T0 vs. T1	T0 vs. T2	T1 vs. T2
Bleeding	**0.002**	**<0.001**	0.257

Bold values denote statistical significance.

in our patients between the time of diagnosis and the last day of treatment.

Constipation and bowel habit are believed to play a role in the development of HD (1–3), and the improvement of bowel habit has a documented therapeutic effect on initial symptoms of HD. The bowel function of our patients ranged from normal to mild constipation and improved after giving pieces of dietary advice. Interestingly, the Bristol stool scale score did not show statistically significant differences between T0 (the mean score, 2.90) and T1 and T2 (mean scores 3.29 and 3.43, respectively). These results further support the role of Proctilor® in treating HD, given the low impact of constipation treatment in our patients as demonstrated by the substantially normal score of the Bristol stool scale.

As for the clinical complaints reported by our patients, the main goal of treatment was to obtain a prompt relief of their symptoms. This goal was reached since significant differences emerged in reduction of pain, improvement of HDSS, and improvement of quality of life (SHSHD), which is already at T1 after 2 weeks of treatment. In addition, a statistically significant improvement was also reported for bleeding and thrombosis between T0–T1 and T0–T2. Zn-L-carnosine rectal ointment seems to show a fast therapeutic effect, as requested commonly by the patients affected by HD, possibly avoiding oral or parenteral administration of substances.

This product showed an excellent safety profile since no patient complained of side effects nor discontinuation of treatment was needed for adverse events. This is important since many topical agents for treatment of HD, containing local anaesthetics or cortisol, are prone to develop local discomfort in chronic use. Four weeks of treatment are quite a long period of topical administration, reasonably sufficient to show adverse events in our patients, thus, reassuring about the high tolerability of Proctilor® rectal ointment.

In conclusion, the very preliminary results of our investigation suggest the effectiveness of Proctilor® ointment for the management of low-grade HD in terms of reduction of pain, bleeding, and relief of thrombosis. It is undoubtedly difficult to draw definitive conclusions due to the small number of patients in this retrospective cohort. However, with these limitations, our study poses the premises for further investigations on a larger number of individuals to confirm the potential therapeutic role of Zn-L-Carnosine in the topical treatment of HD.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RP, AG, AB, and GG recruited patients and made the observational study, selecting patients making diagnosis, treatment, follow-up and they collected data, and elaborated the results. AM and FF made statistical analysis. All authors participated in the elaboration of the manuscript and made final approval of the paper.

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