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Polidocanol foam sclerotherapy in the treatment of hemorrhoidal disease including patients with bleeding disorders

Paulo Salgueiro

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INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR

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POLIDOCANOL FOAM SCLEROTHERAPY IN THE TREATMENT OF HEMORRHOIDAL DISEASE INCLUDING PATIENTS WITH BLEEDING DISORDERS

Thesis applying for **Doctoral Degree** in **Medical Sciences** submitted to **School of Medicine and Biomedical Sciences (ICBAS)** - Oporto University.

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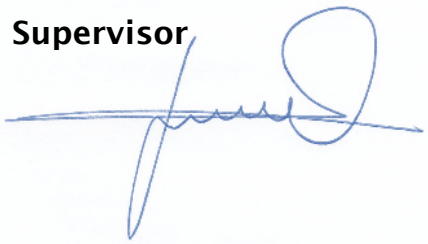

(Fernando Manuel de Castro Poças)

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All the co-authors of my publications, without whom it would not have been possible to complete this project.

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My patients, the main reason for this research.

OUTLINE OF THE THESIS

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In the Summary, a brief description of this thesis is presented.

In Chapter I (GENERAL INTRODUCTION) we present a literature review ("STATE-OF-THE-ART") highlighting the hemorrhoidal disease's physiopathology, epidemiology, diagnosis and classification, as well as the treatment from the more conservative medical approaches to the surgical one. At the end of Chapter I the rationale, research questions and aims are pointed out.

Chapters II and III refer to the work carried out intending to gather the published evidence on the management of hemorrhoidal disease, with a special emphasis on office-based treatments while in Chapters IV and V we seek to add scientific evidence concerning polidocanol foam sclerotherapy.

Thus, in Chapter II, we present the first Portuguese consensus on the diagnosis and management of hemorrhoidal disease ("STANDARD OF CARE") that we created in collaboration with a group of gastroenterologists with expertise in proctology.

Chapter III consists of a systematic review and meta-analysis comparing the two most commonly performed office-based procedures in the management of patients with hemorrhoidal disease ("THE GOLD STANDARD").

Chapter IV ("CHALLENGING THE BEST") includes a paper in which the aim was to compare hemorrhoidal sclerotherapy with polidocanol foam with rubber-band ligation which is currently the most used technique and is referred in the literature as the most effective office-based treatment.

In Chapter V ("A NEW HOPE FOR A VULNERABLE POPULATION") a cohort of patients with bleeding disorders and hemorrhoidal disease treated with polidocanol foam sclerotherapy was prospectively studied.

Chapter VI provides an integrated discussion of all the original articles, focusing on their potential impact on clinical practice.

In Chapter VII we stress out which directions the future investigations addressing polidocanol foam sclerotherapy should take, such as expanding the spectrum of application of this technique to other specific groups of patients as well as comparing it with other treatments. In addition, we have included in this chapter a protocol of a study with cirrhotic patients that we intend to start soon and a pilot study, accepted for publication, comparing polidocanol foam sclerotherapy with hemorrhoid artery ligation and recto-anal repair.

LIST OF PUBLICATIONS

LIST OF PUBLICATIONS

This thesis includes published peer-reviewed articles which were also presented in several meetings.
The list of publications and presentations is listed below.

CHAPTER II - "STANDARD OF CARE"

Portuguese Society of Gastroenterology Consensus on the Diagnosis and Management of Hemorrhoidal Disease
Paulo Salgueiro, Ana Célia Caetano, Ana Maria Oliveira, Bruno Rosa, Miguel Mascarenhas-Saraiva, Paula Ministro, Pedro Amaro, Rogério Godinho, Rosa Coelho, Rúben Gaio, Samuel Fernandes, Vítor Fernandes, Fernando Castro-Poças
GE Portuguese Journal of Gastroenterology. 2020 Feb; 27(2):90-102

CHAPTER III - "THE GOLD STANDARD"

Office-Based Procedures in the Management of Hemorrhoidal Disease: Rubber Band Ligation versus Sclerotherapy – Systematic Review and Meta-Analysis
Paulo Salgueiro, Maria Inês Ramos, Fernando Castro-Poças, Diogo Libânio
GE Portuguese Journal of Gastroenterology. 2022 Feb; 27(2):90-102

CHAPTER IV - "CHALLENGING THE BEST"

Polidocanol Foam Sclerotherapy Versus Rubber Band Ligation in Hemorrhoidal Disease Grades I/II/III: Randomized Trial
Paulo Salgueiro, Mónica Garrido, Ruben Gaio, Isabel Pedroto, Fernando Castro-Poças
Diseases of the Colon & Rectum. 2022 Jul 1;65(7): e718-e727.

- Oral presentation at Semana Digestiva Digital 2020
- Poster presentation at XXX Congresso Nacional de Coloproctologia 2021
- Award: Best oral presentation digestive tract Semana Digestiva Digital 2020
- Award: 1st Prize – Best Research Work in Coloproctology 2020, awarded by the Sociedade Portuguesa de Coloproctologia

LIST OF PUBLICATIONS

CHAPTER V - "A NEW HOPE FOR A VULNERABLE POPULATION"

Polidocanol Foam Sclerotherapy in the Treatment of Hemorrhoidal Disease in Patients with Bleeding Disorders: A Multicenter, Prospective, Cohort Study
Paulo Salgueiro, Andreia Rei, Mónica Garrido, Bruno Rosa, Ana Maria Oliveira, Tiago Pereira-Guedes, Sara Morais, Fernando Castro-Poças
Techniques in Coloproctology 2022 Feb 25:1–11.

- Oral presentation at XXX Congresso Nacional de Coloproctologia 2021
- Award – Best oral presentation (honorable mention) at XXX Congresso Nacional de Coloproctologia 2021

CHAPTER VII - "UPCOMING"

Polidocanol Foam Sclerotherapy Versus Hemorrhoidal Artery Ligation with Recto Anal Repair in Hemorrhoidal Disease Grades II-III: Randomized, Pilot Study
Sara Neves, Daniela Falcão, Ana Povo, Fernando Castro-Poças, Jorge Oliveira, Paulo Salgueiro
Spanish Journal of Gastroenterology 2022 Jun. Epub ahead of print.

ABSTRACT

ABSTRACT

INTRODUCTION

Hemorrhoidal disease (HD) is a prevalent disease with considerable repercussions on patients' quality of life. Nevertheless, some of its treatments are, not infrequently, based on outdated, low-quality literature or from peer learning.

HD treatment varies according to disease severity and local expertise, ranging from conservative diet modifications and medical treatment to office-based procedures and surgery. The most often performed office-based procedures are rubber band ligation (RBL) and sclerotherapy. However, few studies have been published comparing the various types of office-based procedures.

Polidocanol foam has, in recent years, gained attention as a sclerosant for HD. The foam formulation allows the use of lower doses of the sclerosing agent with greater volume, thus increasing the area of contact with the endothelium of the hemorrhoidal vessels. There are no studies comparing polidocanol foam sclerotherapy (PFS) with RBL which has been regarded as the gold standard office-based treatment for HD.

Bleeding is a common HD symptom as well as a complication of HD therapies. Patients with bleeding disorders (BD) are prone to bleed either from the HD itself or as a complication of its treatment. Therefore, some of the more invasive techniques used in the treatment of HD require antithrombotic medication to be discontinued, thus exposing the patient to possible thromboembolic complications. Patients with HD who have concomitant coagulation disorders (either inherited or acquired) would most benefit from treatments with a low incidence of bleeding complications such as PFS. Despite the clinical relevance of this problem, no studies have yet addressed HD therapeutics in this vulnerable population.

AIMS

Review the scientific knowledge concerning the clinical management of HD.

Compare the most often performed office-based procedures RBL and sclerotherapy with liquid sclerosants.

Evaluate the efficacy and safety of PFS compared to RBL.

Assess PFS efficacy and safety in the treatment of HD in patients with BD.

ABSTRACT

METHODS

An expert consensus statement document was developed based on the available scientific evidence to unify the diagnosis and management of HD both in the general population and in some special groups of patients such as patients with BD.

A systematic review and meta-analysis comparing RBL and liquid sclerotherapy was performed.

A randomized trial comparing the efficacy and safety of PFS and RBL in the treatment of HD grades I-III was carried out.

A multicenter, prospective cohort study was conducted to evaluate the efficacy and safety of PFS in the treatment of HD comparing outcomes of patients with and without BD.

RESULTS

The consensus paper stressed that there was an unmet need regarding new outpatient techniques for treating HD. This need was clearly highlighted in the statement that refers to liquid sclerosants as ineffective in more advanced HD, and in the statement that mentions the absence of studies comparing PSF with RBL. Regarding patients with BD, it was consensual that they would benefit from treatments such as sclerotherapy, albeit with only moderate quality evidence.

The meta-analysis carried out with the aim of comparing RBL with liquid sclerotherapy confirmed RBL as the best office-based procedure, demonstrating its superiority in terms of prolapse reduction and hemorrhoidal bleeding control. Despite the higher incidence of pain after RBL, patients undergoing this technique were more satisfied than those treated with liquid sclerosants.

The results obtained in these first two studies were pivotal as they prompted the investigation of the role of PFS in the treatment of HD in the general population and in patients with BD, while demonstrating that a comparison between PFS and RBL is necessary to establish the former as a clinically accepted therapeutic alternative.

In order to fill this evidence gap, 120 patients with HD grades I-III, 60 in each therapeutic arm, were included in a randomized trial aimed at comparing PFS with RBL. Therapeutic success was not significantly different between the groups (PFS: 93.3% vs RBL: 85.0%, p=0.14). However, complete success rate was higher in the PFS group (88.3% vs 66.7%, p=0.009), with fewer therapeutic sessions (mean ± standard deviation: 1.32±0.60 vs 1.62±0.76, p=0.02). Recurrence rates were lower

in the PFS group (16.1% vs 41.2%, p=.004). Complications were mostly minor (91.7%) and were more frequent with RBL (30.0% vs 10.0%, p=0.01). No severe complications were observed.

Regarding the role of PFS in the treatment of patients with BD, a prospective cohort study of 228 patients with HD grades I-III undergoing PFS recruited from 3 centers was carried out. Of the total sample, 73 patients had innate or acquired BD while the remaining 155 had normal coagulation. None of the patients with acquired BD had discontinued antithrombotic therapy, nor patients with congenital BD had prior replacement therapy before PFS. Efficacy and safety outcomes were compared between the two groups. BD patients had more symptomatic HD and had higher bleeding scores. The overall therapeutic success rate was 93.4% with an average number of sessions of 1.51 ± 0.74, significantly higher for the BD group (1.68 ± 0.86 vs 1.43 ± 0.65, p = 0.013). Complications occurred in 11.4% of the patients, with bleeding reported in 4.8%. No significant differences between the two groups were observed for therapeutic success, recurrence, or complications rate, including bleeding complications.

CONCLUSIONS

The scientific literature has scarce evidence concerning the standard of care for HD, particularly in the comparison between the more established outpatient treatments with the most recent and promising PFS. Until our prospective studies were carried out, RBL was regarded as the gold-standard office-based treatment against which emerging treatments should be compared. The role of PFS in BD patients also required further studies specifically aimed at this population.

In the challenge between PFS and RBL, PFS proved to be more effective when considering complete therapeutic success. Patients from the PFS group needed fewer office-based treatment sessions, had lower recurrence rates and were less likely to have complications.

Regarding the treatment of HD in the vulnerable population of patients with BD, PFS showed similar efficacy and safety in patients with BD compared to patients without BD, despite the former having more severe HD.

RESUMO

RESUMO

INTRODUÇÃO

A doença hemorroidária (HD) é muito prevalente e tem forte impacto na qualidade de vida dos doentes. Alguns dos procedimentos utilizados no seu tratamento são, contudo, frequentemente baseados em aprendizagem empírica com evidência científica desatualizada e de baixa qualidade.

O tratamento da HD depende da gravidade da doença variando desde as medidas mais conservadoras, como modificações dietéticas e tratamento farmacológico, até aos procedimentos instrumentais e tratamento cirúrgico. Os procedimentos instrumentais mais comumente realizados na prática clínica são a laqueação elástica (RBL) e a escleroterapia. Não obstante, observa-se uma escassez de publicações comparando os diversos tipos de tratamentos instrumentais.

O polidocanol espumoso tem vindo, nos últimos anos, a atrair a atenção da comunidade científica como um promissor esclerosante. A formulação espumosa permite a utilização de doses menores, mas com um maior volume verificando-se, dessa forma, um aumento da área de contacto do esclerosante com o endotélio dos vasos hemorroidários. Até então, não existiam estudos publicados que comparassem a escleroterapia com o polidocanol espumoso (PFS) com a RBL que tem sido considerada o tratamento instrumental *gold-standard* da HD.

A hemorragia é um sinal cardinal da HD e também uma complicação frequente dos tratamentos efetuados. Os doentes com discrasia hemorrágica têm uma suscetibilidade aumentada para ter complicações hemorrágicas quer da HD, quer dos seus tratamentos. Nesta população, alguns dos procedimentos mais invasivos obrigam à suspensão de medicações antitrombóticas o que aumenta o risco de eventuais eventos tromboembólicos. Assim, os doentes que têm concomitantemente HD e coagulopatias são aqueles que mais poderão beneficiar de técnicas com baixa incidência de complicações hemorrágicas como a PFS. Apesar da elevada relevância clínica desta problemática, não existiam, até à data, estudos com a PFS efetuados especificamente com esta população vulnerável.

OBJETIVOS

Rever e organizar o conhecimento científico sobre a gestão clínica da HD. Comparar os procedimentos instrumentais mais frequentemente realizados, nomeadamente a RBL e a escleroterapia com esclerosantes líquidos. Avaliar a eficácia e segurança da PFS em

comparação com a RBL. Avaliar a eficácia e segurança da PFS no tratamento da HD em doentes com coagulopatias.

MÉTODOS

Com base na evidência científica disponível e na opinião de *experts* foi desenvolvido um documento de consenso com o objetivo de uniformizar o diagnóstico e o tratamento da HD tanto na população geral como em alguns grupos especiais de doentes.

Foi realizada uma revisão sistemática e meta-análise comparando a RBL e a escleroterapia com líquidos.

Foi realizado um ensaio aleatorizado comparando a eficácia e segurança da PFS com a RBL no tratamento da HD graus I a III.

Num estudo de coorte prospetivo, multicêntrico, foram avaliadas a eficácia e segurança da PFS no tratamento da HD comparando os resultados em doentes com e sem discrasia hemorrágica.

RESULTADOS

O consenso destacou a pertinência clínica de investigar novas técnicas instrumentais no tratamento da HD. Essa necessidade foi claramente demonstrada na recomendação que se refere aos esclerosantes líquidos como ineficazes na HD mais avançada, bem como na recomendação que menciona a ausência de estudos comparando a PSF com a RBL. Em relação aos pacientes com coagulopatia, foi consensual que estes beneficiariam de tratamentos como a escleroterapia, embora com base em evidência de qualidade moderada.

A meta-análise realizada com o objetivo de comparar a RBL com a escleroterapia com líquidos reafirmou a RBL como o melhor procedimento instrumental, demonstrando a sua superioridade na redução do prolapso e controlo da hemorragia hemorroidária. Apesar da maior incidência de dor após RBL, os doentes submetidos a esta técnica ficaram mais satisfeitos do que aqueles tratados com esclerosantes líquidos.

Os resultados dos dois primeiros estudos foram muito importantes na construção da tese pois inspiraram a investigação do papel da PFS no tratamento da HD na população geral e em doentes com coagulopatias. Serviram também para demonstrar que a afirmação da PFS como alternativa terapêutica da HD implicava, inevitavelmente, a sua comparação com a RBL.

Nesse sentido, 120 doentes, 60 em cada braço terapêutico, com HD graus I-III, foram incluídos num estudo aleatorizado visando comparar a PFS com a RBL. O sucesso terapêutico global não foi significativamente diferente entre os grupos (PFS: 93,3% vs RBL: 85,0%, p=0,14). No entanto, a taxa de sucesso completo foi maior no grupo da PFS (88,3% vs 66,7%, p=0,009), com menor número de sessões terapêuticas (média ± desvio padrão: 1,32±0,60 vs 1,62±0,76, p=0,02). A recorrência ao final de 1 ano foi menor no grupo PFS (16,1% vs 41,2%, p = 0,004). As complicações, maioritariamente ligeiras (91,7%), foram mais frequentes com a RBL (30,0% vs 10,0%, p=0,01). Não foram observadas complicações graves em nenhum dos grupos terapêuticos.

Em relação ao papel da PFS no tratamento de doentes com discrasia hemorrágica, foi realizado um estudo de coorte prospetivo que incluiu 228 doentes com HD graus I-III submetidos a PFS, recrutados em 3 centros. Do total da amostra, 73 participantes apresentavam coagulopatia inata ou adquirida enquanto os restantes 155 não apresentavam essa comorbilidade. Nenhum dos participantes com discrasia hemorrágica adquirida descontinuou a medicação antitrombótica, nem os pacientes com coagulopatias congénitas efetuaram qualquer profilaxia de hemorragia antes da PFS. Os resultados de eficácia e segurança foram comparados entre os dois grupos. Os doentes com coagulopatia apresentavam, à partida, HD mais sintomática e com scores de hemorragia mais elevados. A taxa global de sucesso terapêutico foi de 93,4% com número médio de sessões de 1,51 ± 0,74, significativamente maior para o grupo dos doentes com coagulopatia (1,68 ± 0,86 vs 1,43 ± 0,65, p = 0,013). Ocorreram complicações em 11,4% dos doentes, entre as quais complicações hemorrágicas em 4,8%. Não se observaram diferenças estatisticamente significativas entre os dois grupos no que respeita ao sucesso terapêutico, recorrência da HD ou taxa de complicações, incluindo complicações hemorrágicas.

CONCLUSÕES

A literatura científica apresenta algumas limitações no que concerne ao *standard of care* da HD, principalmente lacunas na comparação entre os tratamentos instrumentais estabelecidos com a mais recente e promissora PFS. Até à realização dos nossos estudos prospetivos, a RBL era considerada o tratamento instrumental *gold-standard,* com o qual os tratamentos emergentes devem ser comparados. O papel da PFS em doentes com coagulopatias também carecia de mais estudos direcionados especificamente para essa população.

RESUMO

Na comparação entre a PFS e a RBL, a PFS demonstrou maior eficácia considerando o sucesso terapêutico completo. Os doentes do grupo da PFS precisaram de menos sessões de tratamento, tiveram menores taxas de recorrência e menos complicações decorrentes da intervenção.

Em relação ao tratamento da HD na população vulnerável de doentes com coagulopatia, a PFS mostrou eficácia e segurança equivalentes quando comparados os resultados dos doentes com coagulopatia com doentes sem esta comorbilidade, mesmo tendo, os primeiros, HD mais grave.

CHAPTER I – GENERAL INTRODUCTION

CHAPTER I – GENERAL INTRODUCTION

"*STATE-OF-THE-ART*"

HISTORY OF HEMORRHOIDAL DISEASE

The history of proctology goes back to the origins of mankind (Rivera, 1989; Sobrado, 2020). There are several historical writings that address HD subject, such as those of ancient Egypt where there was a Pharaoh's personal doctor called "guardian of the Pharaoh's anus". Historical records of Hippocrates' work describe the healthy benefits of hemorrhoidal bleeding and even some treatments that were advocated at that time "force out the anus as much as possible with the fingers, and make the irons red-hot, and burn the pile until it be dried up, and so as that no part may be left behind" (Adams, 1849). We can also find biblical references to hemorrhoids in Deuteronomy 28:27 *"The LORD will smite thee with the boils of Egypt, and with the emerods, and with the scab, and with the itch, whereof thou canst not be healed"* (New King, 1985). More recently, in 1376, the first book on proctology was published by John Arderne "Clinic and Treatment of Fistulas". (Sobrado, 2020). A historical milestone that must not go unreported is the fact that HD was responsible for a serious event in the political life of Europe: the loss of the Napoleon's empire in 1815. There are historical facts indicating that, on the morning of the Battle of Waterloo, Napoleon Bonaparte was struggling with a hemorrhoidal thrombosis which caused him excruciating pain. This event prevented him from riding the horse and, as such, he was unable to lead the French army, which culminated in his defeat for the English forces commanded by the Duke of Wellington (Welling, Wolff, & Dozois, 1988).

Concerning instrumental procedures there are references in the literature dating back to the time of Aulus Cornelius Celsus (1st century AD) that recommended the ligation of hemorrhoids with flax followed by the excision of the ligated nodule (Celsus, 1938). Galen (130−200 AD), the Greek physician, surgeon and philosopher suggested a conservative management based on laxatives, leeches, and ointment (Ellesmore S, 2022), proposing ligation by a tight thread as the only surgical option. Already in modern times, proctology became an emerging specialty, especially after the foundation of St. Mark's hospital in London (Pata et al., 2021). Frederick Salmon, founder of the institution "Benevolent Dispensary for the Relief of the Poor

Afflicted with Fistula, Piles and other Diseases of the Rectum and Lower Intestines" that became in 1853 the "St Mark's Hospital for Fistula and other Diseases of the Rectum" (Granshaw, 1985) was the first to propose anal stretching to treat HD (Salmon, 1828). This technique was popularized by Lord (Lord procedure) (Lord, 1969) and was still advocated in the 1980s (Vellacott & Hardcastle, 1980). It was later abandoned because it frequently caused injuries to the anal sphincters.

In 1869, John Morgan (Irish surgeon), published the first description of the use of iron sulfate as a HD sclerosing agent (Morgan, 1869).

In the 20th century 1920s, 5% phenol oil started to be used in sclerotherapy, although other agents, such as urethane, nitric acid, iodine, alum, or quinine, were reported (CE Blanchard, 1928; Holley, 1946).

In 1963, James Barron, inspired by Blaisdell who performed hemorrhoidal ligation using an umbilical cord ligator (Blaisdell, 1958), described rubber banding reporting a series of 200 treated patients (Barron, 1963).

Other office-based treatments such as cryotherapy (Lewis, De la Cruz, Gazzaniga, & Ball, 1969) and infrared coagulation (Neiger, Moritz, & Kiefhaber, 1977) were introduced in clinical practice in 1969 and 1977, respectively.

PATHOPHISIOLOGY AND EPIDEMIOLOGY OF HEMORRHOIDAL DISEASE

Hemorrhoids are vascular cushions located in the submucosa that are composed of blood vessels, smooth muscle and connective tissue. They can also be described as arteriovenous communications between terminal branches of the upper and middle rectal arteries and upper, middle and lower rectal veins. Their main function is to maintain anal continence, contributing in about 15-20% to anal resting pressure. In addition, when engorged with blood, they serve as a protection for the anal sphincters during the act of defecation. Lastly, hemorrhoids have a sensory function, allowing to differentiate liquids, solids or gases and to signal defecation (Sneider & Maykel, 2010). During the normal defecation process, the fibroelastic component contracts and the hemorrhoidal pads are depleted of blood which decreases their size and increases the lumen diameter of the anal canal (Arora et al., 2016; Rakinic & Poola, 2014).

The pathophysiology of HD is not fully understood. The theories meanwhile discarded for the development of the disease include the existence of arteriovenous fistulas in the anal submucosa or the existence of varicose veins and

deep venous thrombosis (Arora et al., 2016). It is now common knowledge that abnormal dilation and vascular distortion, together with degenerative changes in connective tissue are the main features of HD. In this way the venous drainage is compromised and the hemorrhoids dilate (Lohsiriwat, 2012, 2013; Sud & Khan, 2014). The HD develops when the supporting tissues of hemorrhoidal cushions deteriorate due to various processes such as abnormal venous dilation, vascular thrombosis, degenerative processes of collagen and fibroelastic tissue, distortion and rupture of anal subepithelial muscle, hyperperfusion of the hemorrhoidal plexus, inflammatory phenomena, and hormonal changes (typical of pregnancy) (Lohsiriwat, 2012, 2013; Silva, 2010).

Several factors contribute to the dysfunction of normal physiology observed in HD, including prolonged defecation effort, increased intra-abdominal pressure, irregular intestinal transit (constipation/diarrhea), genetic factors, absence of valves in the hemorrhoidal veins, and aging (Peery et al., 2015; Sneider & Maykel, 2010). Other factors, particularly dietetic ones, such as low-fiber diets, spicy foods or alcohol consumption have been implicated in disease onset and progression, though scientific evidence is still lacking. It should also be noted that the role of constipation in the development of HD has been questioned by some studies (Faccini et al., 2001; Pigot, Siproudhis, & Allaert, 2005). Even so, the increase in defecation effort seems to precipitate the development of symptoms such as bleeding and prolapse (Lohsiriwat, 2012).

HD occurs frequently in the adult population and a considerable number of patients are asymptomatic (Riss et al., 2012). Ten million people suffer from HD in the United States, amounting to a prevalence of 4.4% (Johanson & Sonnenberg, 1990). Both sexes are similarly affected (Cirocco, 2007; Johanson & Sonnenberg, 1990; Riss et al., 2012). Some studies suggest a higher prevalence of the disease with higher socioeconomic status and in caucasians (Cirocco, 2007; Johanson & Sonnenberg, 1990). The peak incidence occurs between 45-65 years, being rare before the age of 20 (Johanson & Sonnenberg, 1990). Epidemiological studies of the prevalence of HD in Portugal are lacking.

DIAGNOSIS, CLASSIFICATION AND SEVERITY OF HEMORRHOIDAL DISEASE

Anamnesis and physical examination are the initial steps in the assessment of HD. The most common manifestations are painless rectal bleeding associated with

defecation, pruritus, prolapse, and perianal pain or discomfort. Bleeding is typically bright red and not mixed with feces (Lohsiriwat, 2015). Pain may occur but is usually associated with external thrombosed hemorrhoids, otherwise it is more common in other pathologies such as anal fissures or perianal abscesses (Lohsiriwat, 2012). Less common symptoms include feeling of incomplete evacuation and expulsion of mucus (Sneider & Maykel, 2010).

Physical examination should include anal inspection, rectal examination and anoscopy (Silva, 2010). Using flexible sigmoidoscopy in the investigation of rectal bleeding results in a diagnosis of a pre-malignant or malignant condition in less than 10% of patients and should be considered a default investigation (Hollingshead & Phillips, 2016). The use of colonoscopy is warranted in patients older than 50 years (unless recently performed) (Sun & Migaly, 2016) or in younger patients with a family history of colorectal neoplasia, iron deficiency anemia, a positive occult blood test or a suspicion of inflammatory bowel disease (Silva, 2010).

Differential diagnoses include anal fissure, perianal abscess, anal fistula, anal stricture, neoplasia, irritable bowel syndrome, inflammatory bowel disease, anal pruritus, anal wart, rectal prolapse, hypertrophied anal papilla, and perianal skin tags (Sneider & Maykel, 2010).

Hemorrhoids can be classified according to their relation to the pectineal line into internal or external; the former are located proximally to the dentate line and covered by columnar epithelium, while the latter are distal to the dentate line and are covered by modified squamous epithelium, being richly innervated and therefore painful when there is associated thrombosis (Sneider & Maykel, 2010).

Internal HD is further classified based on the degree of prolapse according to the Goligher classification: grade I, without prolapse (potential to bleed but not visualized without the aid of an anoscope); grade II, prolapse with defecation, but reduced spontaneously; grade III, prolapse with defecation requiring manual reduction and grade IV, prolapsed and non-reducible (Qureshi, 2018).

New classifications have emerged, notably the PATE 2001(Gaj & Trecca, 2004), PATE 2006 (Gaj & Trecca, 2007) or the Single Pile Classification (Elbetti, Giani, Novelli, Fucini, & Martellucci, 2015) scores, but the Goligher classification remains the most commonly used in clinical practice.

Since HD is a benign pathology, its treatment should be guided by the symptoms and the impact of the disease on quality of life. A prospective study developed and validated the Sodergren scale, which is based on a set of symptoms to assess the

severity of HD. This scale can be used to compare treatments and monitor disease activity and, thus, is helpful in the choice of the best therapeutic option (Pucher et al., 2015).

THERAPY OF HEMORRHOIDAL DISEASE

Treatment of HD can be divided into conservative measures, office-based procedures, and surgical treatments.

First line therapy should be conservative and embraces a set of lifestyle and dietary changes, laxatives, phlebotonics and/or topical anti-inflammatory drugs. These measures produce beneficial effects and should be implemented even in the highest grades of HD or in patients undergoing instrumental or surgical treatment (Hollingshead & Phillips, 2016).

The instrumental office-based treatment is usually indicated for HD grades I and II (Sandler & Peery, 2019), though it can also be used in grade III HD (Lohsiriwat, 2013). It is aimed at decreasing hemorrhoidal vascularization, reducing redundant tissue and promoting the fixation of hemorrhoids to the rectal wall in order to prevent or reduce prolapse (Ganz, 2013).

Surgical treatment is reserved for refractory cases to conservative and instrumental treatment, grade IV or mixed HD (internal and external) (Sun & Migaly, 2016), symptomatic HD with the concomitant presence of another anorectal condition requiring surgery and lastly if it is the patient's choice (Clinical Practice Committee, 2004). Although surgical approach is apparently more effective than instrumental treatment, it is also associated with a higher rate of complications (Brown et al., 2016; Conaghan & Farouk, 2009; Ohning, Machicado, & Jensen, 2009; Peng, Jayne, & Ho, 2003; Yano, Asano, Tanaka, Oda, & Matsuda, 2014). Several surgical methods have been described which range from conventional hemorrhoidectomy and its variants to more recent methods such as doppler guided hemorrhoidal artery ligation or hemorrhoidectomy stapler. The choice of each method should consider various specificities, namely the degree of HD and the experience of the center (Yeo & Tan, 2014).

– CONSERVATIVE TREATMENT

The first line approach should focus on diet and lifestyle changes. The adoption of measures such as an adequate fluid intake, increased fiber consumption, and advice on healthy habits of defecation should be the main goals for the prevention and treatment of HD. These measures are useful in all grades of the disease, including after an acute event such as thrombosis or non-reducible prolapse (Sun & Migaly, 2016). Increased water intake allows stool to become softer, contributing to a decrease in constipation, while increased fiber intake contributes to an easier expulsion of fecal matter (Sun & Migaly, 2016). Fiber supplements (7-20 g/day) reduce the risk of bleeding in up to 50% of cases with no effect on the improvement of prolapse, pain or pruritus (Alonso-Coello, Mills, et al., 2006). However, higher doses of fiber (20-25 g/day) ingested with 500 ml of water prevent progression and decrease the size of the hemorrhoidal prolapse avoiding surgery in patients with advanced HD (Garg, 2016, 2017; Garg & Singh, 2017). The use of other types of laxatives (as osmotic agents or stimulants) is controversial and requires more evidence (Alonso-Coello et al., 2005; Hollingshead & Phillips, 2016).

Patients should be advised to avoid strong and prolonged defecation efforts by limiting the time spent during defecation (once a day, at most 3 minutes) since these factors contribute significantly to the development and worsening of HD (Garg & Singh, 2017). It is likely that a significant portion of patients with HD meet criteria for irritable bowel syndrome with predominance of constipation (Johannsson, Graf, & Påhlman, 2005).

The use of topical drugs and suppositories with corticosteroids, anesthetics, antiseptics and barrier ointments may be instituted for temporary symptomatic relief, particularly pruritus, but their use may be associated with cutaneous allergic reactions (Davis, Lee-Kong, Migaly, Feingold, & Steele, 2018). In addition, prolonged use of steroid ointments should be avoided since it is associated with risk of ulceration or other lesions in the perianal skin. There are no randomized trials supporting the use of ointments in HD (Acheson & Scholefield, 2008). Recently other types of topical preparations have been studied, namely creams containing hyaluronic acid, nitric oxide donors, phytotherapeutic preparations, combinations of polidocanol and allantoin and suspensions of *Escherichia coli*. In all cases, more studies are needed to draw definitive conclusions about the efficacy and safety of its use in the setting of HD (Altomare & Giannini, 2013). The use of intra-anal topical iferanserin, a selective serotonin receptor antagonist, decreases

the severity of pruritus and hemorrhage in grade I, II and III HD when compared to placebo (Herold, Dietrich, & Aitchison, 2012). The use of salty baths (tepid salt water for 10 minutes twice daily) has been shown to relieve symptoms in pregnant women more effectively when compared to the topical application of an antiseptic and emollient cream (Shirah, Shirah, Fallata, Alobidy, & Hawsawi, 2018).

The use of phlebotonics is very common in continental Europe. These drugs reduce the vascular permeability, improve venous tone, increase lymphatic drainage, and reduce inflammation (Acheson & Scholefield, 2008). Its use in HD is safe, although its benefits appear to be modest. Most studies concerning this topic suffer from publication biases and other methodological issues (Alonso-Coello, Zhou, et al., 2006; Perera et al., 2012). The use of a mixture of flavonoids (diosmin, troxerutin and hesperidin) has been shown to improve pain and bleeding symptoms in patients with acute hemorrhoidal crisis when compared to placebo (Giannini et al., 2015). However, there is evidence of the superiority of instrumental office treatment when compared to the use of oral flavonoids (Yuksel et al., 2008).

- NON-SURGICAL OFFICE-BASED TREATMENT

All the office-based treatments used in the HD act by decreasing vascularization and increasing hemorrhoidal fixation to the deep layers of the rectal wall, which reduces prolapse as well as the remaining symptoms associated with this pathology (Davis et al., 2018). It is important to reinforce that, before using this type of treatment, the patient should try to control the symptoms with conservative measures, and only after these measures fail, an instrumental procedure should be considered. Since these procedures do not interfere with the external components (Jacobs, 2014), the non-surgical procedures are reserved for the internal HD (grades I to III) (Sanchez & Chinn, 2011) and are not recommended for the treatment of external hemorrhoids, perianal skin tags or internal hemorrhoids grade IV (Rakinic & Poola, 2014).

The main office procedures for HD include RBL, sclerotherapy, IRC, electrocoagulation, cryotherapy, radiofrequency ablation and laser.

All these procedures are relatively well tolerated, but often require reintervention due to high recurrence rates of HD (Davis et al., 2018).

RUBBER BAND LIGATION

RBL causes the strangulation of the hemorrhoids and, consequently, their blood flow. This technique consists in the application of small elastic bands at the base of the internal hemorrhoids, at least half a centimeter above the dentate line resulting in ischemia and subsequent necrosis of the prolapsed mucosa followed by cicatricial fixation to the rectal wall. It is a fast and well tolerated procedure (Davis et al., 2018). It is an appropriate option for patients with grade I and II as well as selected patients with grade III HD (Sun & Migaly, 2016).

Patients are placed on the left lateral position or jackknife position and the procedure is performed through an anoscope (Sun & Migaly, 2016). Ligation instruments include McGivney forceps and its variants, suction lacing (such as the McGown suction instrument), endoscopic techniques, and single-use devices.

McGivney-type instruments, less commonly used in clinical practice, require the use of two hands and an assistant to hold the anoscope. They involve the use of a crocodile forceps and a trigger that, when activated, places the elastic band in the desired location. The most commonly used McGown instruments use suction to prolapse the hemorrhoid into the device and can be performed with only one hand, allowing only one user to execute the technique. Ligation may also be performed with a variceal endoscopic ligator applied on a flexible endoscope enabling concomitant diagnostic endoscopy and rubber ligation. There are two varieties of single-use devices developed for ligation: the ShortShot Saeed Hemorrhoidal Multi-band Ligator® (similar to a McGown device with 4 preloaded elastic bands) and the O'Reagan Ligating System® (syringe type device) (Singer, 2014). The suction-ligation instruments are superior to the forceps ligator since they cause less pain and are associated with less intra-procedural bleeding (Ramzisham, Sagap, Nadeson, Ali, & Hasni, 2005). In a study involving 60 patients, the O'Reagan device proved to be safe and effective (Paikos et al., 2007). The success rates are around 80% at 5 years and 70% at 10 years, with recurrences responding well to subsequent ligations (Moss & Bordeianou, 2013).

Complications associated with RBL include bleeding (ranging from mild to severe), pain, urinary symptoms, priapism, vagal symptoms, hemorrhoidal thrombosis, sepsis, fistulation or even death (Albuquerque, 2016). Hemorrhage and pain are among the most frequent (Albuquerque, 2016; Cocorullo et al., 2017). Post-ligation bleeding typically occurs 10 to 14 days after treatment (although it may occur immediately after the procedure) (Hollingshead & Phillips, 2016), with rates ranging from 1.2% to 50% of the treated patients (Cocorullo et al., 2017). The risk of

bleeding is more significant in patients under antiplatelet or anticoagulation medications, although the risk with the use of aspirin is considered low (Iyer, Shrier, & Gordon, 2004). Thus, this technique is not indicated in this subgroup of patients. RBL in cirrhotic patients with coagulopathy is not contraindicated, but further studies are warranted (Albuquerque, 2016). The use of RBL is not advised in HIV-positive patients with CD4+ lymphocyte count below 200 and as first-line treatment in pregnant women (Martel & Boushey, 2007). Furthermore, its use in Crohn's disease patients is controversial (Albuquerque, 2016; D'Ugo et al., 2013). Relative contraindications include anal fissures, fistulas and spasm of the internal anal sphincter (Forlini, Manzelli, Quaresima, & Forlini, 2009).

SCLEROTHERAPY

Hemorrhoidal sclerosis is a procedure commonly used to treat grade I and II HD (Acheson & Scholefield, 2008; Sneider & Maykel, 2010). Additionally, it has been used in internal grade III hemorrhoids, although in these cases there is little scientific evidence supporting its efficacy (Cocorullo et al., 2017).

In this technique a needle is introduced through an endoscope or anoscope and the sclerosing agent is injected into the submucosa at the base of the hemorrhoid above the anterolateral line (Blanchard technique) (CE Blanchard, 1928). This causes an inflammatory response and fibrosis that interrupts the vascular blood supply (Siddiqui et al., 2014).

A variety of sclerosing agents such as 5% phenol in vegetable oil (Brown, 2017; Sun & Migaly, 2016), quinine, tetradecyl sodium sulfate, sodium morphate (Moss & Bordeianou, 2013) or potassium aluminum sulfate and tannic acid (ALTA) have been used (Hachiro, Kunimoto, Abe, Kitada, & Ebisawa, 2011; Herold et al., 2012). The use of ALTA proved to be more effective than the use of 5% phenol in grade III HD (Yano & Yano, 2015). More recently, a new sclerosing substance, polidocanol, a non-ionic detergent consisting of two chains, a polar hydrophilic and a non-polar hydrophobic (Hussar & Stevenson, 2010), started to be employed in the treatment of HD. The experience of its use in sclerotherapy comes mainly from the treatment of varicose veins in the lower extremities and it can be used in its liquid form or in the form of foam. Several studies reported the efficacy of the use of sclerotherapy with liquid polidocanol in HD. It is considered a sclerosing agent with anesthetic properties, well tolerated, with low necrotic potential and a promising agent for the treatment of grade I HD (Aakerud, 1995; Mukhopadhyay et al., 2014; Yuksel et al.,

2008). The foam formulation allows for greater efficacy and use of lower doses of sclerosing agent. One of the most widely used methods for foam formation is based on the Tessari technique. Described by Lorenzo Tessari in 1999, this technique uses a device that combines two syringes and a three-way tap in which the polidocanol is mixed with air under mechanical force ("Tourbillon technique") (Cavezzi & Tessari, 2009; Tessari, Cavezzi, & Frullini, 2001). This method applies different amounts of air mixture and sclerosant depending on the target site and is relatively easy to perform (Wollmann, 2004). The use of polidocanol foam in the treatment of varicose veins is safe and effective and has been shown to be superior to the use of liquid polidocanol (Hamel-Desnos et al., 2003; Jia et al., 2007). Its use is not indicated in cases of acute thromboembolism and allergy to polidocanol (Aakerud, 1995). There is only one study showing the superiority of polidocanol foam compared to its liquid formulation in the treatment of grade I HD (Moser et al., 2013). In a recently published non-controlled study, 2000 patients with HD grades I to IV were treated with polidocanol foam and the authors concluded that this therapy was very successful, with 98% of the patients reporting satisfaction regarding bleeding control and prolapse reduction. Complications were rare and usually minor (Fernandes & Fonseca, 2019). Data comparing polidocanol foam with other HD ablative techniques is lacking. The most common complications of sclerotherapy include mild anal discomfort and bleeding. However, the bleeding risk is lower compared to that observed with RBL (Moss & Bordeianou, 2013). Rare complications include erectile dysfunction, mucosal ulceration, necrosis, prostatic abscess, retroperitoneal sepsis and transient bacteremia (Davis et al., 2018). Sclerotherapy is a valid alternative for the treatment of patients in whom hemorrhage is the main symptom and where conservative therapy has not been effective, as well as for patients on anticoagulant medication, and for cirrhotic or immunocompromised patients (Fernandes & Fonseca, 2019).

OTHER OFFICE-BASED THERAPIES

Infrared photocoagulation (IRC) can be used for treatment of grade I and II and, in selected patients with grade III HD (Sun & Migaly, 2016; Trompetto et al., 2015). It is a safe and non-invasive procedure and, in a few studies, showed similar efficacy to that of band ligation (Gupta, 2003a; Marques et al., 2006). Since it is less painful and rarely complicates with bleeding, this technique can be recommended for

patients in whom band ligation is not indicated (Marques et al., 2006; Poen, Felt-Bersma, Cuesta, Deville, & Meuwissen, 2000; Singal, Gupta, Dalal, Dalal, & Attri, 2013). However, it is more expensive, requires more training (Brown, 2017), and is associated with higher rates of recurrence and persistence of the disease (Scaglia, Delaini, Destefano, & Hultén, 2001; Sun & Migaly, 2016).

Electrocoagulation by monopolar or bipolar current consists in the application of an electric current that causes the coagulation of the tissues, with subsequent occlusion, fibrosis, and hemorrhoid necrosis. In bipolar diathermy, a 20W pulse is applied for about 30 seconds in multiple discharges at the same site. The most frequent adverse events include pain, bleeding, fissure and spasm of the internal sphincter (Bharucha, Pemberton, & Locke, 2013). Its usefulness is greater in HD grades I to III. Direct current electrotherapy requires an extended time (up to 14 minutes) of application of 110 V at the hemorrhoid base. It may involve multiple treatments at the same site. The most common complications include pain, ulceration and hemorrhage (Gami, 2011). Despite some success with the employment of these techniques (Izadpanah, Hosseini, & Mahjoob, 2010; Izadpanah & Hosseini, 2005; Olatoke, Adeoti, Agodirin, Ajape, & Agbola, 2014), they do not appear to offer advantages over RBL or sclerotherapy (Brown, 2017; Izadpanah et al., 2010; Silva, 2010).

Laser treatment consists of photocoagulation through a diode laser with the help of a doppler probe (Giamundo, Cecchetti, et al., 2011). The diode laser, with a wavelength of 980 nm, has a remarkable coagulating effect allowing the photocoagulation of the submucosal branches of the hemorrhoidal arteries (Salfi, 2009). Thus, it causes a decrease in the blood supply which leads to a reduction in hemorrhoidal plexus volume (De Nardi et al., 2016). The treatment is effective in stopping the rectal bleeding and diminish the occurrence of pain in HD grades I to III (Crea et al., 2014; De Nardi et al., 2016). It is associated with a low complication rate and high patient satisfaction (Boarini, Boarini, Candelaria, Lima, & Boarini, 2017). In a comparison between this method and RBL, the laser treatment caused less pain and was more effective. However, it is a costlier procedure (Giamundo, Salfi, et al., 2011). Also, the technique lacks trials with a desirable follow-up (more than one year) (Giamundo, Salfi, et al., 2011) and was not yet approved by the Food and Drugs Administration (FDA) in United States of America (Siddiqui et al., 2014).

Cryotherapy involves the use of probes through which liquid nitrogen or nitric oxide is applied to the hemorrhoidal tissue causing necrosis and tissue destruction.

This technique was practically abandoned due to frequent post-procedure complications, namely pain and anal incontinence (Lohsiriwat, 2012).

Radiofrequency ablation works by creating thermal energy from radio waves, resulting in coagulation necrosis (Gupta, 2003b). The results are similar to those obtained with RBL (Gupta, 2005) but the equipment required for the procedure is very expensive (Brown, 2017). Although it is almost painless, the procedure is associated with high rates of bleeding and prolapse (Lohsiriwat, 2012).

COMPARISON BETWEEN DIFFERENT OFFICE-BASED TREATMENTS

Among the most commonly used procedures – RBL, sclerotherapy and IRC – a significant difference is almost negligible in terms of long-term efficacy, although some studies suggest a higher effectiveness for RBL (Jutabha, Jensen, & Chavalitdhamrong, 2009; Siddiqui et al., 2014), while others report a lower effectiveness for sclerotherapy (Cocorullo et al., 2017; Moss & Bordeianou, 2013). Poen et al. (Poen et al., 2000) in a prospective and randomized study comparing the effectiveness between RBL and photocoagulation, showed that both methods are equally effective, with rubber band being more painful but also more adequate to treat HD grade III. These results have been confirmed by Marques et al. (2006), with the additional information that both techniques are relatively safe of complications even though RBL causes more pain in the 24 hours post procedure (Marques et al., 2006). In another prospective study comparing IRC with RBL in 100 patients with grade II HD, the results showed a greater effectiveness of RBL. However, the authors recommended photocoagulation since it is a less painful procedure (Gupta, 2003a). In a meta-analysis that included 18 randomized clinical trials, RBL proved to be more effective than sclerotherapy for all degrees of HD (MacRae & McLeod, 1995).

To our knowledge, there have been no comparative studies between RBL and PFS to date, though the later seems to be more effective than sclerosis with liquid agents (Moser et al., 2013).

Patient satisfaction appears to be greater with banding (Cocorullo et al., 2017; MacRae & McLeod, 1995), and this technique has a lower incidence of recurrent symptoms and need for retreatment (Cocorullo et al., 2017; Lohsiriwat, 2015; Siddiqui et al., 2014). However, it is the most painful method and the most likely to cause rectal bleeding. Both sclerotherapy and IRC should be considered in

patients who cannot discontinue antithrombotic medications (Cocorullo et al., 2017; Moss & Bordeianou, 2013; Siddiqui et al., 2014).

– NON-SURGICAL ENDOVASCULAR TREATMENT

Recently new endovascular techniques evolved for the treatment of HD, namely the embolization of superior rectal arteries (SRA) (Eberspacher et al., 2021). The "emborrhoid" technique (endovascular arterial occlusion of the terminal branches of the SRA) using micro-coils was first described in 2014 by Vidal et al. (Vidal, Louis, Bartoli, & Sielezneff, 2014) for the treatment of chronic hemorrhoidal bleeding. It provides complete visualization of superior rectal artery branches and its anastomosis with middle and inferior rectal arteries (Eberspacher et al., 2021; Talaie et al., 2022). This outpatient procedure maintains the hemorrhoidal tissue in place and avoids direct anorectal trauma, preserving the anal tone (Talaie et al., 2022). A recent meta-analysis demonstrated the clinical efficacy of this technique, defined by improvement in post procedural scores (including bleeding score and Goligher grade), significant pain reduction and better functional status. Clinical success in published studies ranged between 84% and 94% for patients with grades I-III HD, although using different evaluation scales and small groups of patients (Rebonato et al., 2021). Moussa et al. (Moussa et al., 2017) described a success rate of 68% using combined embolization of particles and coils, and a clinical score (bleeding severity, Goligher grade and quality of life score) improvement in 72% of the patients after a single embolization. Bleeding rate did not improve in 28% of the patients. Also, low rates of peri-procedural complications and morbidity have been reported (Nguyenhuy et al., 2022; Talaie et al., 2022). Moggia et al. (Moggia et al., 2021) described in their preliminary results of the "emborrhoid" technique no post-procedure and short-term complications in a 12-month follow-up period.
Therefore, this technique may constitute a feasible alternative for patients not eligible for surgery or under antithrombotic treatment, despite the limited experience and undefined role among other treatment modalities (Eberspacher et al., 2021; Nguyenhuy et al., 2022). Robust data regarding clinical efficacy, long-term safety and recurrence rates still needs to be demonstrated. Also, further research is warranted to evaluate comparative outcomes, feasibility, and cost-effectiveness relative to the more established office-based procedures (Talaie et al., 2022).

– SURGICAL TREATMENT

The surgical management of HD has been extensively implemented and studied, with several well-established indications. Traditionally, surgery should be considered when conventional medical and office-based procedures failed to achieve acceptable outcomes or are contraindicated. Grade IV and large grade III HD, acute hemorrhoidal complications (like pain, necrosis and thrombosis), refractory symptomatic internal HD and external HD with bothersome hypertrophic tags (De Schepper et al., 2021; Singer, 2014) are also indications for surgery (Davis et al., 2018; De Schepper et al., 2021; van Tol et al., 2019). Also, surgical treatment should be discussed in cases of severe anemia resulting from hemorrhoidal bleeding (regardless of grade of the disease) and for symptomatic internal hemorrhoids that present with another proctological disease such as anal fissure, fistula or condyloma.

Five to ten percent of the patients with HD are estimated to require hemorrhoidectomy (Singer, 2014).

Hemorrhoidectomy can be performed as an open (Milligan-Morgan) or closed procedure (Ferguson), with a variety of surgical devices (Davis et al., 2018; Singer, 2014). The most common reported complications are postoperative bleeding, pain and acute urinary retention (Davis et al., 2018). Other possible complications are infection, anal stenosis and fecal incontinence (Singer, 2014). In a meta-analysis of eleven randomized clinical trials (RCT) (Bhatti, Sajid, & Baig, 2016) the closed technique was associated with lesser risk of post-operative bleeding and decreased pain, with faster wound healing comparing to the open procedure. Recurrence rate and infectious complications were similar (Davis et al., 2018). The use of bipolar energy devices such as Harmonic® scalpel, LigaSure TM, or EnSeal® may shorten the procedure time and cause less post-operative pain (Davis et al., 2018; Singer, 2014).

The surgical hemorrhoidal management has evolved in the last twenty years from the conventional excisional hemorrhoidectomy into the development of several minimally invasive procedures that result in less post-operative pain and improved recovery. These include stapled hemorrhoidopexy and transanal hemorrhoidal dearterialization or doppler-guided hemorrhoidal artery ligation with rectoanal repair (HAL-RAR) (Altomare et al., 2018; Singer, 2014; van Tol et al., 2019). These new techniques have been widespread, however their superiority over traditional hemorrhoidectomy in terms of recurrence and long-term complications was not

clearly established by RCT. In stapled hemorrhoidopexy, a circumferential rectal mucosectomy above the hemorrhoidal complex is performed causing disruption of the hemorrhoidal plexus blood supply, reducing engorgement and hemorrhoidal prolapse, and restoring the normal anatomy of the anal canal. Comparing to conventional hemorrhoidectomy, stapled hemorrhoidopexy is associated with less procedure time, less postoperative pain, bleeding, and wound complications, and faster functional return to normal activities. However, the cost of the procedure and the recurrence rate are higher (De Schepper et al., 2021; Gallo et al., 2020).

The transanal hemorrhoidal dearterialization or doppler-guided hemorrhoidal artery ligation is performed for grades II-III HD (Gallo et al., 2020) with a doppler-equipped anoscope to identify and ligate the arteries supplying internal hemorrhoids, and often includes the mucopexy with recto-anal repair. The aim is to reduce hemorrhoidal engorgement and to reposition the prolapsing tissue to its normal anatomical site (De Schepper et al., 2021). HAL-RAR is associated with little postoperative pain (less than 10%) (Gallo et al., 2020), due to absence of surgical wound or sutures above the dentate line, when compared to conventional hemorrhoidectomy and stappled hemorrhoidopexy (De Schepper et al., 2021). The decreased postoperative bleeding rate (up to 18%) (Gallo et al., 2020) is reported as the best outcome of this procedure compared to open and stapled procedures. This technique also has lower reoperation rate compared to open, closed or LigaSure® hemorrhoidectomies and stapled hemorrhoidopexy (Simillis et al., 2015). The drawback is the higher recurrence rate compared to stapled hemorrhoidopexy, ranging from 3-24%, with a reintervention rate of 2.7–22% (Gallo et al., 2020).

Recently, Aibuedefe et al. compared the clinical outcomes, including recurrence rates and complications, of 14 surgical treatments for HD grades III and IV. They reported less recurrence with Starion™ and Harmonic Scalpel™ compared to IRC and transanal hemorrhoidal dearterialization. There were fewer post-operative complications with IRC and LigaSure® compared to suture ligation and open hemorrhoidectomy. Post-operative pain rate was lower in laser, IRC and stapling compared to open and closed hemorrhoidectomies. The return to work was earlier with HAL-RAR and stapled techniques than with laser and open hemorrhoidectomy (Aibuedefe, Kling, Philp, Ross, & Poggio, 2021).

In summary, a tailored management plan for the surgical treatment of HD should be discussed with the patient and implemented according to the grade of the disease and main symptoms. Stapled hemorrhoidopexy and HAL-RAR typically are

not recommended for grade IV HD and conventional hemorrhoidectomy still performs as the treatment of choice for HD refractory to instrumental procedures. Stapled hemorrhoidopexy and HAL-RAR are associated with less post-operative pain and faster recovery, but higher recurrence rates have been reported, with reintervention rate and quality-of-life measures favoring conventional hemorrhoidectomy (De Schepper et al., 2021). In line with this data, Altomare et al. in their Italian survey regarding HD treatment of over 32000 patients for 17 years, showed that Milligan-Morgan hemorrhoidectomy remained the most frequently performed surgery for grade III-IV HD, despite the drawback of post-operative pain. Also, that stapled hemorrhoidopexy has become much less popular in contrast to HAL-RAR which is being performed much more frequently (Altomare et al., 2018; Singer, 2014).

- HEMORRHOIDAL DISEASE TREATMENT IN SPECIAL GROUPS OF PATIENTS

PATIENTS WITH IMMUNOSUPPRESSIVE CONDITIONS

In general, immunocompromised patients have poor tissue healing and higher risk of anorectal sepsis after any intervention, including hemorrhoidal treatment. Surgical treatment should therefore be carefully considered. Data concerning efficacy and safety of outpatient procedures is scarce (van Tol et al., 2019).

HD is described in up to 10% of patients infected with human immunodeficiency virus (HIV) (Luma et al., 2017). Conservative measures should remain the first-line treatment for hemorrhoidal treatment in these patients (Fan & Zhang, 2017). In a systematic review evaluating the prevalence and predisposing factors for significant sepsis following hemorrhoid treatment (McCloud, Jameson, & Scott, 2006), only 2 of the 38 patients had abnormal immunity (one with agranulocytosis and another with HIV infection) and both patients improved significantly following surgery. Anecdotal reports have shown significant complications in HIV patients following RBL (Buchmann & Seefeld, 1989). However, sclerotherapy may be an attractive alternative in these patients. In a prospective study, 22 patients with acquired immunodeficiency syndrome were successfully treated with sclerotherapy for grade II-IV HD. No complications were recorded (Scaglia et al., 2001). While controversial, older studies have suggested a potential benefit of antibiotic prophylaxis in these patients owing to the risk of bacteremia after sclerotherapy (Adami, Eckardt, Suermann, Karbach, & Ewe, 1981). The American Society of

Gastroenterology (ASGE) guidelines also recommend antibiotic prophylaxis in patients with severe neutropenia (absolute neutrophil count <500 cells/mL) and advanced hematologic malignancies (Khashab et al., 2015).

Due to the high incidence of delayed wound healing in HIV-positive patients, surgical treatment with hemorrhoidectomy needs to be carefully considered, although evidence does not suggest an increase in complication rate for patients with a low CD4 + T-cell count (< 200/μL) (De Schepper et al., 2021; Fan & Zhang, 2017; Gallo et al., 2020). A modified stapled hemorrhoidopexy technique (tissue-selecting therapy stapler) (Fan et al., 2017) was reported to be safe and effective in HIV-infected patients with prolapsing hemorrhoids (Fan & Zhang, 2017).

PATIENTS WITH INFLAMMATORY BOWEL DISEASE

HD can occur in up to 20% of the patients with inflammatory bowel disease (IBD) but the prevalence may be underestimated due to other clinical features of IBD and few published data (De Schepper et al., 2021; van Tol et al., 2019). Several guidelines support the conservative medical treatment as the first-line management in IBD patients with HD (De Schepper et al., 2021; Gallo et al., 2020). Office-based procedures and surgical treatment can be considered in carefully selected patients and whether the inflammatory disease is quiescent (with no sign of active disease) (De Schepper et al., 2021; Gallo et al., 2020; van Tol et al., 2019). In active anorectal IBD, RBL and IRC should not be performed (De Schepper et al., 2021*).* Also, there appears to be a higher risk of severe complications after hemorrhoidectomy in IBD patients, that is threefold higher for Crohn´s disease than for ulcerative colitis *(17.1% vs. 5.5%).* In a prospective study of 86 patients with Crohn´s disease following conservative failure of hemorrhoidal treatment, the authors reported a high complication rate of 41.2% after hemorrhoidectomy (15 patients) and RBL (2 patients) (D'Ugo et al., 2013). The risk of complications was significantly higher for patients without a definitive IBD diagnosis, so when there is clinical suspicion, it is advisable to exclude IBD prior to any proctological intervention (De Schepper et al., 2021). Further randomized trials are needed to establish more robust conclusions regarding the safety of office-based and surgical approaches to HD in IBD patients.

PATIENTS WITH LIVER CIRRHOSIS

For patients with compensated liver cirrhosis (Child-Pugh A), RBL was proposed as a safe procedure for the treatment of HD (De Schepper et al., 2021). However, this outpatient procedure is discouraged in patients with advanced cirrhosis (Child Pugh B or C) due to the bleeding risk. In a prospective randomized comparative study, 120 patients with liver cirrhosis matched by age, sex, and Child score (mean ± SD 7.82 ± 2.63 and 7.85 ± 2.9) were randomized to receive RBL or sclerotherapy for the treatment of symptomatic HD. Both therapies demonstrated to be safe and effective with low re-bleeding (10-13%) and recurrence (20%) rates (Awad et al., 2012). Further randomized studies are clearly needed to elucidate the best treatment for these patients since the available evidence is limited.

PREGNANCY AND LACTATION

The prevalence of HD during pregnancy ranges from 25% to 35% of the woman (Abramowitz et al., 2002; De Schepper et al., 2021; Gallo et al., 2020). It is higher in the third trimester and first month after delivery, with thrombosed external hemorrhoids occurring up to 7.8% and 20% respectively (Gallo et al., 2020). Several physiologic changes and predisposing factors contribute to the development of HD in this phase including increased intra-abdominal pressure from uterine growth, hormonal changes, and constipation (Ferdinande, Dorreman, Roelens, Ceelen, & De Looze, 2018). Considering delivery, spontaneous vaginal delivery, high birth weight, and prolonged straining are also risk factors (De Schepper et al., 2021). The conservative management of HD with dietary and lifestyle modification is the first-line recommended treatment. (De Schepper et al., 2021; Gallo et al., 2020) Sitz baths have been shown to improve symptoms, to achieve complete hemorrhoidal healing, and to be more efficient than anorectal topics (De Schepper et al., 2021; Gallo et al., 2020; Shirah et al., 2018). Concerning medical treatment, a cohort study in 2015 showed no adverse outcomes among pregnant women exposed to venotropics (Lacroix et al., 2016), and several authors reported that oral rutosides may also improve symptoms in pregnant patients with HD grades I and II. However, there is no definitive data concerning safety of these medications precluding its recommendation in pregnancy and lactation (De Schepper et al., 2021; Gallo et al., 2020).

Also, there are no trials evaluating office-based procedures for HD treatment in these patients. The Belgian consensus guideline on the management of HD (De Schepper et al., 2021) states as an expert opinion that IRC should be avoided during pregnancy, due to lack of evidence on safety, and RBL is contra-indicated. Although (closed) hemorrhoidectomy has been safely performed in pregnant women with severe symptomatic HD, surgery should only be considered in extensively thrombosed hemorrhoids or with intractable bleeding (De Schepper et al., 2021; Gallo et al., 2020; Saleeby et al., 1991). These patients should be reevaluated in the post-partum period acknowledging that most symptoms will resume within the first month after delivery. Conservative dietary and lifestyle management generally allow for improvement without safety concerns and are the consensual approach (Gallo et al., 2020). There is agreement that more data is needed concerning the safety of HD treatment during pregnancy (De Schepper et al., 2021; Gallo et al., 2020).

PATIENTS WITH COAGULATION DISORDERS

Hemorrhoidal bleeding is a potential major complication of instrumental hemorrhoidal treatment (Moser et al., 2013). Patients with coagulation disorders, whether congenital or acquired/ induced by antithrombotic therapy, are more prone to rectal bleeding. Antiplatelet and anticoagulant therapies are increasingly used for thromboembolism prevention particularly in the older population (Albrecht et al., 2019; Gallo et al., 2020; Swan, Loughran, Makris, & Thachil, 2020). These medications are associated with a general risk of GI bleeding ranging from 1.5%-4.5% (Pannach et al., 2017; Sorensen et al., 2009). The risk of gastrointestinal bleeding is higher for anticoagulants compared to antiplatelet therapy or nonsteroidal anti-inflammatory drugs. Although there is conflicting data, this risk appears to be higher for new oral anticoagulants compared to vitamin K antagonists (Lanas et al., 2015; Pannach et al., 2017). Pannach et al. described a higher frequency of lower gastrointestinal bleeding in patients under direct anticoagulants, respectively of 33.3%, 10.6% and 8.7% in patients under direct oral anticoagulants, vitamin K antagonists and antiplatelet therapy (Pannach et al., 2017).

In patients with coagulation disorders, the management of HD and the indications for surgery are not well defined (Gallo et al., 2020). Considering the bleeding risk, some office-based procedures like RBL or surgery are generally contraindicated, or

antithrombotic therapy should be suspended several days before the procedure, increasing the thrombotic risk (Gallo et al., 2020; Lanas et al., 2015; Miller, Dorreen, Martel, Huynh, & Barkun, 2017; Pengo, Pegoraro, Cucchini, & Iliceto, 2006). In a large retrospective study of 805 patients undergoing RBL, higher bleeding rates were described in patients on warfarin and aspirin (7.5%) compared with patients not taking these medications (2.9%) (Iyer et al., 2004). Another retrospective case-controlled cohort study showed similar 30-day bleeding rates in patients taking clopidogrel and controls (Hite et al., 2018). The highest risk of bleeding occurs between 10 to 14 days after the procedure, mostly due to the sloughing of the ligated hemorrhoids (Albuquerque, 2016; Beattie, Rao, & Campbell, 2004; Odelowo, Mekasha, & Johnson, 2002). This has led many authors to recommend patients to suspend medication 7 to 10 days before RBL, followed by a further 7 to 10 days thereafter (Beattie et al., 2004; Nelson et al., 2008). In a large retrospective observational study including 364 patients undergoing RBL, withholding antiplatelet medication 7-10 days after the procedure appeared to equalize the risk of bleeding to that of patients not taking antithrombotic medications (Nelson et al., 2008).

Patients with congenital BD are also predisposed to spontaneous, traumatic, and intervention-related hemorrhagic complications (Ingerslev & Hvid, 2006; Tomaszewski et al., 2019). Hemophilia represents the main cause of inherited defects of clotting factors VIII and IX. Although the perioperative mortality in this subgroup decreased significantly with the advent of clotting factors concentrates, there is a persistent risk of bleeding, delayed wound healing and postoperative infections (Ingerslev & Hvid, 2006). In patients with Von Willebrand disease, gastrointestinal bleeding is 2.5 times more prevalent than in controls and can account for up to 53% of all bleeding-related hospitalizations (Tsagianni, Comer, Yabes, & Ragni, 2019). Considering the persistent bleeding risk, it is imperative to define more optimally the efficacy and safety of the management of HD in patients with BD.

RATIONALE

HD is very prevalent on the clinical setting. Nevertheless, some of the treatments that are used in the management of this disease are, not infrequently, based in outdated, low-quality literature or from peer learning. Despite the publication of some guidelines addressing HD (Davis et al., 2018; Trompetto et al., 2015) no comprehensive approach to this matter was available for the Portuguese reality.

HD treatment vary according to disease's severity and local expertise ranging from the conservative diet modifications and medical treatment to office-based procedures and surgery (Cengiz & Gorgun, 2019). Internal HD grades I to III are most commonly treated with medical treatment and/or office-based procedures, being surgery reserved for refractory cases, patients with external hemorrhoids, and grade IV internal HD (Lohsiriwat, 2015). Nowadays, the most often performed office-based procedures are RBL, sclerotherapy, and less often IRC (Lohsiriwat, 2015). We found, however, that few studies have been published comparing the various types of office-based procedures. The latest meta-analysis comparing various hemorrhoidal therapeutic modalities was published in 1995 (MacRae & McLeod, 1995). This meta-analysis showed that, among office-based therapies, RBL was the most effective, although more painful and more prone to bleeding complications. From this publication until now RBL is consensually considered the first-line office-based treatment for HD grades I to III (MacRae & McLeod, 1995).

However, other studies were published, and other techniques began to emerge, making it imperative to reassess the comparison between the most used techniques in clinical practice, namely RBL and sclerotherapy.

In most published studies addressing HD sclerotherapy, sclerosants are used in liquid formulation (He & Chen, 2022; Moser et al., 2013). Polidocanol, a non-ionic detergent made up of two chains, one hydrophilic and one hydrophobic, can be used has a sclerosant in liquid or foam formulations (Hussar & Stevenson, 2010). The experience of its use in sclerotherapy comes from the treatment of varicose veins where it proved to be safe and effective being, the foam formulation, superior to the liquid one (Hamel-Desnos et al., 2003; Jia et al., 2007). In fact, foam formation allows the use of lower doses of sclerosing agent, since the greater volume increases the area of contact with the endothelium (Nastasa et al., 2015). Polidocanol foam has, in recent years, drawn attention to its use in the treatment of HD. In a randomized trial including patients with HD grade I, polidocanol foam

performed better than liquid polidocanol (Moser et al., 2013). Four retrospective cohort studies have shown that polidocanol foam injection is effective and safe in HD grades I to IV with minor complications (Fernandes & Fonseca, 2019; Figueiredo, Bordalo Ferreira, Rafael, & Oliveira, 2022; Lobascio et al., 2021; Ronconi M, 2019). In one prospective small series, 10 patients with HD grades III-IV were successfully treated with PFS as a bridge for hemorrhoidal surgery (Lisi, Campanelli, Grande, Milito, & Grande, 2021). More recently, a multicenter, prospective cohort study concluded that 3% polidocanol foam is an effective, safe, repeatable, and low-cost procedure in patients with HD grade II (Gallo et al., 2022). Until now, there were no studies comparing PFS with RBL which, as mentioned above, is considered the current gold standard among office-based treatments for HD.

Bleeding is both a HD symptom and a complication from HD office-based therapies (Lohsiriwat, 2012; Sun & Migaly, 2016). It is of common knowledge that BD patients are susceptible to hemorrhagic complications arising from HD as well as from its treatment. Therefore, the treatment of these patients remains a clinical challenge, not only because of the imperative need to treat them, but also because of the limitation we face when choosing the type of treatment. In fact, some more invasive techniques, such as surgery, may be contraindicated or require withdrawal of antithrombotic medication, which can substantially increase the risk of thromboembolic events (Atallah et al., 2016; Gallo et al., 2020; Nelson et al., 2008). With the aging of the population and the consequent rise in cardiovascular pathologies, we are witnessing an increase in the need for anticoagulant and antiplatelet medications which increases the risk of gastrointestinal bleeding (Albrecht et al., 2019; Lanas et al., 2015; Miller et al., 2017; Pannach et al., 2017; Pengo et al., 2006; Rothberg, Celestin, Fiore, Lawler, & Cook, 2005; Sherwood et al., 2015; Sorensen et al., 2009; Swan et al., 2020; Yusuf et al., 2011). Likewise, patients with congenital coagulopathies such as hemophilia A and von Willebrand disease, are also predisposed to intervention related bleeding. Gastrointestinal bleeding is at least two times more frequent and can account for half of all bleeding related events in patients with inherited coagulopathies (Ingerslev & Hvid, 2006; Tomaszewski et al., 2019; Tsagianni et al., 2019). Despite of being a widely recognized problem, the treatment of HD in patients with BD is paradoxically poorly studied. Given the particularly high risk of bleeding complications associated with interventions in this subgroup of patients, we believe that these would be the ones who would most benefit from less invasive office-based procedures such as PFS. To

date, there are only two non-controlled studies with polidocanol foam that included patients on antithrombotic medication (Fernandes & Fonseca, 2019; Figueiredo et al., 2022). Thus, there is an urgent need for more robust studies to assess the efficacy and safety of PFS in the treatment of HD in patients with BD.

The aforementioned shortcomings in the published literature compelled us to formulate the research questions that we address in the next section.

RESEARCH QUESTIONS AND AIMS

Research question 1

What is the current standard of care for patients with hemorrhoidal disease?

Aim

To develop consensus statements aggregating current scientific evidence in order to standardize and guide the management of hemorrhoidal disease both in the general population and in some special groups of patients.

Research question 2

Concerning hemorrhoidal disease's office-based procedures, what is the current gold standard?

Aim

To carry out a systematic review and meta-analysis comparing the efficacy and safety of the most often performed office-based procedures: RBL and sclerotherapy

Research question 3

How is the clinical performance of polidocanol foam sclerotherapy compared to the currently most effective office-based treatment?

Aim

To evaluate the efficacy (therapeutic success and recurrence) and safety (occurrence of complications) of polidocanol foam sclerotherapy compared to rubber band ligation.

Research question 4

Is polidocanol foam sclerotherapy effective and safe in the treatment of hemorrhoidal disease in patients with bleeding disorders?

Aim

To assess efficacy and safety outcomes of polidocanol foam sclerotherapy in the treatment of hemorrhoidal disease, comparing the results of its use in patients with and without bleeding disorders.

CHAPTER II - “STANDARD OF CARE”

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Portuguese Society of Gastroenterology Consensus on the Diagnosis and Management of Hemorrhoidal Disease

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Guidelines

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Portuguese Society of Gastroenterology Consensus on the Diagnosis and Management of Hemorrhoidal Disease

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Keywords
Hemorrhoidal disease · Consensus · Portugal

Abstract
Hemorrhoidal disease (HD) is a frequent health problem with considerable repercussions on patients' quality of life. However, much of the clinical practice related to HD is based on knowledge without scientific evidence and supported largely by empirical experience of the physician who deals with this pathology. As in other countries, the goal of this consensus is to establish statements supported by solid scientific evidence and whose purpose will be to standardize and guide the diagnosis and management of HD both in the general population and in some particular groups of patients.

Consenso da Sociedade Portuguesa de Gastrenterologia sobre o Diagnóstico e Tratamento da Doença Hemorroidária

Palavras Chave
Doença Hemorroidária · Consenso · Portugal

Resumo
A doença hemorroidária é uma patologia prevalente com repercussões consideráveis na qualidade de vida dos doentes. No entanto, muita da prática clínica relacionada com a doença hemorroidária é baseada em conhecimentos sem evidência científica e apoiada largamente por uma experiência empírica por parte do médico que lida com esta patologia. À semelhança do que tem sido feito noutros países, o objetivo deste consenso foi estabelecer

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statements suportados por evidência científica sólida e cuja finalidade será o de uniformizar e orientar o diagnóstico e tratamento da doença hemorroidária quer na população em geral quer em grupos particulares de doentes.

Introduction

Hemorrhoidal disease (HD) is a prevalent condition among industrialized societies. It is one of the leading causes for a visit to a coloproctology's office. Given the large number of symptoms and associated patient distress, it is important that this disease is correctly diagnosed and treated.

Several guidelines and consensus have been published in recent years, addressing this issue [1, 2]. Nevertheless, a national guideline has not been published to date. Therefore, this workgroup was developed to elaborate statements that should aid in clinical practice.

Given that a lot of information regarding this field is either outdated or without published evidence, an effort was made to select a group of participants considered as experts in HD.

Prior to this meeting, an invitation was sent to 12 prominent gastroenterologists with interest in proctology asking for the elaboration of statements addressing the different subthemes included in this document and, through research in scientific literature and/or clinical experience, the statements were revised and classified according to the quality of evidence [3] (online suppl. Appendix 1; for all online suppl. material, see www.karger.com/doi/10.1159/000502260).

On the consensus meeting, each statement was voted (anonymously, through an electronic application) with the options A (Agree) and B (Disagree). A minimum of 10 votes (80%) on the option A was necessary to obtain consensus. If the statement did not reach 10 votes, it was either changed until a consensus was obtained or excluded.

The meeting was held in Curia, Portugal, on February 24, 2019 with the scientific support of SPG – Sociedade Portuguesa de Gastrenterologia.

A summary of the consensus is provided in online supplementary Appendix 2 and an algorithm for the management of patients with suspected HD in Figure 1.

Physiopathology of HD

The functional anal canal is approximately 4 cm in length (from the anal verge to distal rectum) [4–7]. The dentate line, approximately 2 cm above the anal verge, is a major anatomic point when considering the physiology and physiopathology of HD since, distal to the dentate line, the anal canal is lined with squamous epithelium covering the external hemorrhoidal plexus that is innervated by the somatic nervous system and highly sensitive to pain [4–7]. Internal hemorrhoids are located proximal to the dentate line, where the anal canal is lined with columnar epithelium as in the rectum. This tissue lacks sensitivity due to its innervation by the sympathetic and parasympathetic nervous systems, primarily distinguishing only fullness and pressure [4–7]. There are typically 3 major anal cushions above the dentate line (right anterior, right posterior, and left lateral) often with some minor accessory cushions between them [8].

The pathogenesis of HD is most likely multifactorial including deterioration of anchoring connective tissue of anal cushions, downward displacement or prolapse of the hemorrhoidal tissue [9], hyperperfusion state and neovascularization with abnormal distention of the arteriovenous anastomoses and veins of the internal hemorrhoidal venous plexuses [10], overexpression of inflammatory mediators [11], and increased resting anal pressure [12, 13].

Chronic constipation is usually considered to contribute to the occurrence of HD by causing an increased shearing force on the anal cushions and decreased venous return leading to degeneration of the supportive tissue in the anal canal and distal displacement of anal cushions [14–16]. Although this concept has been recently challenged [17], it remains one of the most consistently accepted risk factor for HD. Other conditions associated with increased intra-abdominal pressure, such as pregnancy [18], prolonged sitting, or heavy lifting are believed to cause HD as a result of compromised venous drainage of hemorrhoid plexus [19]. Advancing age, obesity, and sedentarism have also been reported to contribute to symptoms onset [4, 20–23]. Chronic diarrhea is also a risk factor for developing HD due to frequent stool passage causing local trauma and weakening of the anal canal lining [13, 24]. Data are inconsistent regarding the presumed correlation between HD and habits such as smoking, spicy foods, or alcohol consumption [7, 25]. There is currently no consistent scientific evidence regarding any genetic predisposition to HD [26].

Epidemiology

HD is commonly diagnosed in clinical practice [26]. The reported prevalence in adults is highly variable, from 4.4% in self-reporting surveys [27] to 38.9% in screening

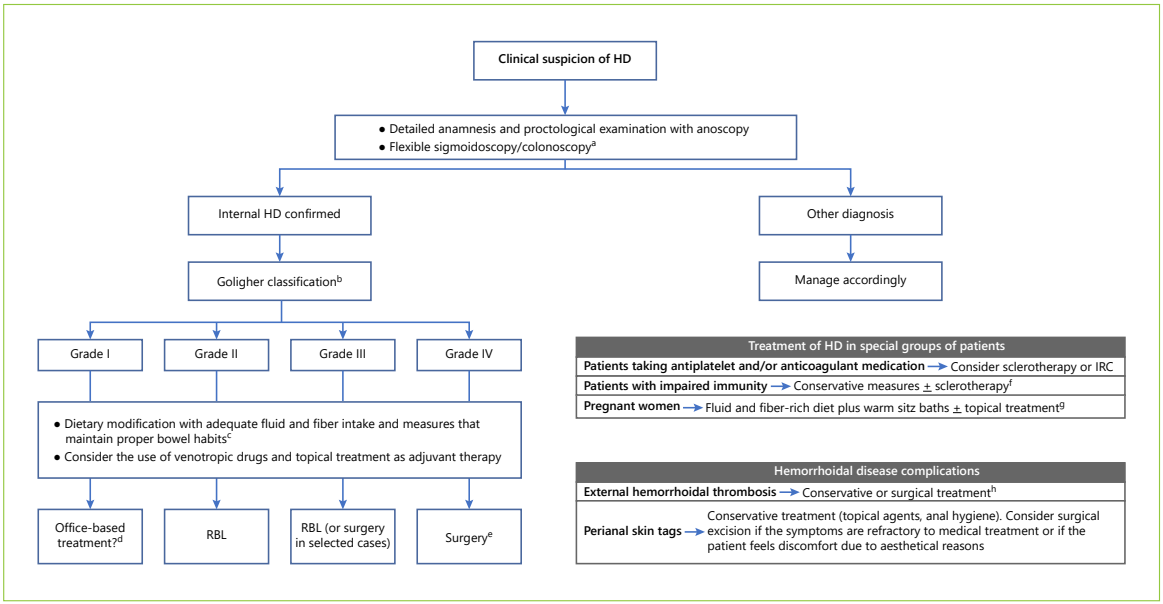

Fig. 1. Algorithm for the management of patients with suspected hemorrhoidal disease. [a] Colonoscopy is indicated in patients over the age of 50 years (earlier if there is family history of CRC or another condition predisposing to CRC) or if any alarm symptom is present; [b] consider using a symptom-based score, such as Sodergren score, to evaluate the severity of the HD; [c] advise avoiding excessive straining and limit the time at defecation; [d] medical management is enough for most patients. Some cases may require office-based treatment. RBL may be difficult to perform in such small vascular cushions; [e] the adopted type of surgical technique will depend on local expertise and should be a joint decision between the doctor and the patient; [f] studies have suggested a potential benefit of antibiotic prophylaxis in these patients owing to the risk of bacteremia after sclerotherapy; [g] there are no trials evaluating office-based therapies in pregnant women; therefore, they should probably be avoided during this period; [h] surgical treatment is effective in the prevention of recurrence and symptom control when applied during the first 48–72 h after symptoms onset. HD, hemorrhoidal disease; RBL, rubber band ligation; IRC, infrared coagulation.

colonoscopy setting [23]. HD affects both sexes equally, with a peak prevalence occurring between the ages of 45–65 years, being unusual before the third decade [27].

Clinical Evaluation and Diagnostic Tests

Statement 1

A detailed history and proctological examination are mandatory in patients with suspicion of symptomatic HD *(high-quality evidence)*.

Agreement: 100%.

Statement 2

Anoscopy is the gold standard for the evaluation of the anus if HD is suspected *(moderate-quality evidence)*.

Agreement: 100%.

Statement 3

Flexible sigmoidoscopy should be performed in patients with rectal bleeding. Colonoscopy is indicated in patients over the age of 50 years (earlier if there is family history of colorectal cancer [CRC] or another condition predisposing to CRC) or if any alarm symptom is present *(moderate-quality evidence)*.

Agreement: 100%.

Rationale

Internal HD is associated with painless bleeding (usually related to bowel movement), mucus discharge, soiling, and pruritus [5].

When patients complain of a significant anal pain, other diagnosis must be considered, such as anal fissure or inflammatory bowel disease (IBD) [5, 27].

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Patient history must include information regarding the presence of alarm symptoms, whether constipation or diarrhea coexist and relationship between symptoms and defecation. Family history must also be included with a detailed cancer history to stratify CRC risk and history of IBD.

A proctological examination should be performed allowing the evaluation of the anal verge and its structures excluding a distal rectal mass or an anorectal abscess [8, 28]. Moreover, anoscopy seems to be the most accurate method to diagnose HD and can be performed in the office setting with no prior preparation [28, 29].

Patients over the age of 50 years or with alarm symptoms/signs (anemia, iron deficiency, abdominal pain, diarrhea, weight loss, or fever) or with risk factors for CRC/IBD should undergo colonoscopy. It also should be highlighted that HD alone does not affect the prevalence of positive occult blood tests so, in case of a positive result, it should not be attributed to HD until a colonoscopy is performed [30–32].

Flexible sigmoidoscopy should be considered in patients who do not meet any of the criteria described above.

HD Grading

Statement 4

Although never validated, the most widely used score is the Goligher classification. Other classification systems were proposed, however, never gained widespread acceptance *(low-quality evidence)*.

Agreement: 100%.

Statement 5

A symptom-based score, such as Sodergren score, can be used to evaluate the severity of the HD *(moderate-quality evidence)*.

Agreement: 83%.

Rationale

No unified tool exists to classify the severity of HD [2, 33]. The most widely used is the Goligher classification [34]. It categorizes only internal hemorrhoids and defines 4 grades of HD according to the most prolapsed pile. However, there is a frequent disparity between worsening symptoms and Goligher grade increment.

New classification systems for HD were proposed over the past 3 decades [35–38]. Some authors categorized HD in bleeding, prolapsing, thrombotic, and mixed HD [37]. This classification, based on histological evaluation of the anal canal in different stages of life, shed new light on the pathophysiology of HD. Other authors, using a retroflexed colonoscope, proposed a classification based on a detailed anatomical description [38]. Their algorithm included the degree of mucosal elevation of the rectal columns, changes in color, and the existence and size of hypertrophied anal papillae evaluated by colonoscopy. The Sodergren score [39] was developed and validated in 2015 using a simple symptom-based scoring system to quantify the severity of HD. In this study, 50 patients were scored with rectal bleeding according to the severity and frequency of pruritus, pain at rest, pain at defecation, and prolapse.

The single pile hemorrhoid classification (2015) is a new tool that considers the number of pathological piles, the characteristics of each internal pile (incorporating here the Goligher classification), and the characteristics of each external pile [33].

Although interesting from a descriptive point of view, these new classification systems are not widely used, perhaps because of their complexity. Probably no scoring system will ever be completely satisfactory.

Medical Management of HD

Diet, Transit Modifiers, and Laxatives

Statement 6

Dietary fiber (in food or as supplement) decrease bleeding and the recurrence of symptoms. The use of fiber is recommended in the treatment of acute episodes and to prevent recurrence *(high-quality evidence)*.

Agreement: 92%.

Statement 7

Patients with HD benefit from measures that maintain proper bowel habits such as avoiding straining and limiting the time at defecation *(moderate-quality evidence)*.

Agreement: 100%.

Rationale

As discussed above, HD has been considered to be caused by a low-fiber diet and constipation [40, 41]. Medical therapy involves dietary modification with adequate fluid and fiber intake, along with avoiding straining as well as diarrhea [42]. Data on fiber have been assessed in a systematic review and meta-analysis of 7 trials, which included 378 patients randomized in 2 groups: fiber group versus nonfiber group [43]. The results suggested that fiber has an apparent beneficial effect. Alongside with dietary supplementation, patients benefit from mea-

sures that maintain proper bowel habits such as avoiding straining during passing motions, limiting the time at defecation, and once a day defecation [44]. There is lack of supporting evidence for the efficacy of other laxatives in the treatment of HD.

Venotropic Drugs and Topical Treatment

Statement 8

Venotropic drugs seem to be effective in the treatment of symptomatic HD. There is a lack of evidence about optimal dosage, duration of treatment, or superiority of a specific drug *(moderate-quality evidence)*.

Agreement: 100%.

Statement 9

Topical treatment may be useful in the short-term treatment of symptoms of HD but, so far, its use is not supported by well-designed, robust studies *(moderate-quality evidence)*.

Agreement: 92%.

Rationale

The main goal of pharmacological treatment is to relieve acute symptoms of HD rather than reverting its chronic structural changes. Venotropics are a heterogeneous class of drugs used to treat chronic venous insufficiency [45] that have also been proposed for the treatment of HD [46]. Most of these drugs are derived from natural products extracted from plants, predominantly bioflavonoids. The precise mechanism of action has not been well established. There is some evidence in the literature that this class of drugs plays a role in the control of symptoms from HD [46]. A meta-analysis of 14 randomized controlled trials involving 1,514 patients and comparing various flavonoids formulations (diosmin + hesperidin micronized purified flavonoid fraction, diosmin, and rutosides) with placebo or no therapy reported an overall significant symptomatic improvement, namely, a beneficial effect on bleeding, pain, and itching. Moreover, the few studies evaluating symptom recurrence also showed a favorable effect [47]. A more recent Cochrane review expanded this evaluation to 24 trials involving 2,334 patients comparing venotropics (mostly flavonoids with some studies also evaluating calcium dobesilate) with a control intervention or no treatment and found relatively similar favorable results in overall improvement and in each symptomatic parameter [48]. No serious adverse events were reported with bioflavonoids besides mild gastrointestinal disturbances [47, 48]; however, agranulocytosis has been described with calcium dobesilate [49].

Despite these encouraging results, both the Cochrane review and the meta-analysis emphasize the limitations in methodological quality and the heterogeneity of data among trials, leaving uncertainty about the real efficacy of venotropics in the treatment of symptomatic HD and advising that larger and better designed trials are necessary to achieve high-quality evidence.

Drugs available for topical application (mostly ointments or creams and suppositories) may contain analgesics/anesthetics (e.g., cinchocaine), steroids (e.g., hydrocortisone), venotropics (e.g., ruscogenin), spasmolytics (e.g., trimebutin), vasoconstrictors (e.g., phenylephrine), antiseptics, and emollients, either isolated or in association. The mechanism of action of some of these drugs has not been clarified. Evidence of efficacy has not been adequately demonstrated as most studies involve few patients and centers, have not been adequately designed or are outdated, and have not been replicated. Even though some studies involved significant number of patients, such as the review on policresulen plus cinchocaine reporting beneficial effect in 1,904 (83.2%) out of 2,287 patients [50] or the review on several studies of tribenoside plus lidocaine [51], strong evidence cannot be drawn from the studies designed to provide a clear recommendation. Caution must be taken with prolonged or iterative use of topical medication because allergic reactions or sensitization may occur [52–54].

A few more recent and so far isolated reports of randomized clinical trials showed benefit from a gel containing hyaluronic acid with tea tree oil and methyl-sulfonylmethane in a single-center study with a small number of patients [55] and from an intra-anal ointment with iferanserin, a selective serotonin receptor antagonist, evaluated in a multicentric study [56].

A Cochrane review on traditional Chinese medicine herbs found no evidence to support its use in HD [57].

Office-Based Treatment of HD

Rubber Band Ligation

Statement 10

Rubber band ligation (RBL) is recommended as first-line treatment for internal grade II HD and for selected patients with grade III that do not respond to medical treatment. This technique is more effective and equally safe compared to sclerotherapy (liquid sclerosants) and infrared coagulation (IRC; *high-quality evidence)*.

Agreement: 92%.

Statement 11

For internal grade II HD, RBL has similar efficacy but fewer side effects than excision hemorrhoidectomy *(moderate-quality evidence)*.

Agreement: 100%.

Rationale

Interventional management of HD can be divided in office-based or surgical procedures [58, 59].

The various nonsurgical treatments can be performed as outpatient procedures without anesthesia [59].

RBL involves placing rubber bands around hemorrhoids until they eventually fall off. It is a quick, simple, inexpensive procedure [59]. The elastic bands are applied on an insensitive area just above the dentate line to strangulate the piles leaving an area where inflammation fixes the mucosa to the submucosa preventing subsequent development of new hemorrhoidal tissue and is the most widely used nonsurgical treatment for patients with grade II or III HD [60]. Data regarding efficacy of RBL in grades I and IV are occasionally reported. The overall subjective improvement with RBL ranges from 73 to 84% [60]. A meta-analysis of 18 randomized trials comparing various treatment methods for grades I to III HD concluded that RBL was more effective than sclerotherapy and that patients who underwent ligation were less likely to need subsequent therapy [61]. Also, compared to excision hemorrhoidectomy, RBL has similar results but without the side effects of excision hemorrhoidectomy for the treatment of grade II HD [59]. Although RBL is more painful than other outpatient modalities, complication rates are similar [61]. Postoperative pain ranges from 8 to 80% in different randomized controlled trials (RCT) [60]. Postoperative bleeding ranges from 1.20 to 36% in the majority of RCT, but there is one trial that reported 50% [60, 62–64]. Other complications include vagal symptoms, chronic ulcers, priapism, difficulty in urination, hemorrhoidal thrombosis, and, although extremely uncommon, severe pelvic sepsis [58]. Recurrences of bleeding and prolapse at follow-up occur, respectively, in 10–18% and in 2.2% of patients; 1 RCT reported higher percentages (46 and 34%, respectively) [60].

Sclerotherapy

Statement 12

Sclerotherapy with liquid sclerosants is safe but poorly effective and therefore should be used only for grade I internal HD *(high-quality evidence)*. Since postprocedural bleeding is uncommon, it should be considered for patients who have higher bleeding risk *(moderate-quality evidence)*.

Agreement: 92%.

Statement 13

The use of other sclerosing techniques, such as polidocanol foam and aluminum sulfate and tanic acid (ALTA), seems to be safe and effective even in patients under anticoagulation and/or antiplatelet therapy. The efficacy and safety compared to other office-based procedures are yet to be defined *(low-quality evidence)*.

Agreement: 100%.

Rationale

Internal HD can be fulgurated or sclerosed through injection [65]. As with RBL, sclerotherapy does not require anesthesia (local or intravenous). The procedure is performed through an anoscope, being the sclerosant injected into the hemorrhoidal cushions above the dentate line [7, 60].

Sclerotherapy (with liquid sclerosants) is considered safe but poorly effective and, therefore, used only for small hemorrhoids. Postprocedural bleeding is uncommon and so should be considered for patients who have an elevated bleeding risk, such as those receiving anticoagulants.

The interpretation of published studies comparing sclerotherapy with elastic banding and hemorrhoidectomy is not always easy. Sclerosants used vary, as does the dose, injection method, puncture site, and the type of needle used. On the other hand, subjective evaluation of prolapse reduction, intermittent blood loss, and recurrence of HD make the analysis difficult.

Among the various sclerosing agents described, 2 have stood out in recent years for their effectiveness and safety: ALTA and polidocanol foam. An RCT with ALTA reported resolution of bleeding in 69–88% of grade I HD [66], while 3 case series showed an improvement of bleeding in 100% of grades II and III HD [65, 67, 68]. More than 90% of prolapses resolution in grade II HD is reported in an RCT and 2 case series [66, 68, 69]. Good results are shown also for grade III, but data are reported only by case series. A prospective study showed an overall prolapse improvement in 100% of patients [70], while Yano reported 52% of improvement of prolapse in III degree [71]. Miyamoto et al. [69] and Tokunaga [72] in their case series showed an improvement for grade IV, too.

In Portugal, liquid polidocanol 1 or 2% is commonly injected through the anoscope in low doses. However,

polidocanol foam seems to be a better sclerosant than the liquid form [73, 74].

In a recently published Portuguese study, 2,000 patients were treated with polidocanol foam (without control group). The authors concluded that this therapy was very successful, with 98% of the patients reporting satisfaction regarding bleeding control and prolapse reduction. Complications were rare and usually minor [75].

Complications of sclerotherapy are uncommon, with the most frequent being minor discomfort, tenesmus, or bleeding with the injection. The major complications are most often iatrogenic, owing to misplaced injections into nonhemorrhoidal tissues or with systemic injections into the vasculature. Urinary retention, rectourethral fistulas, rectovaginal fistulas, rectal perforations, infections, necrotizing fasciitis, sepsis, and death are rare complications [76–78].

Other Techniques: IRC, Cryotherapy, Eletrocoagulation, and Heater Probe

Statement 14

IRC is an effective procedure in the treatment of grades I and II HD. When compared to RBL, IRC shows less postoperative pain but higher probability of recurrence *(high-quality evidence)*.

Agreement: 100%.

Statement 15

Other office-based procedures have shown inconsistent results, namely, electrotherapy *(moderate-quality evidence)*, cryotherapy, heater probe, and argon plasma coagulation *(high-quality evidence)*. Their use is not supported by recent evidence.

Agreement: 92%.

Rationale

In addition to the techniques described earlier, a variety of procedures can be used for HD: IRC, bipolar diathermy (BD), direct current electrotherapy (DCE), cryotherapy, and heater probe. For these therapeutic techniques, there are not enough controlled studies, particularly recent, and many authors consider that they should be regarded as obsolete [79].

IRC focuses infrared radiation from a tungsten-halogen lamp via a polymer probe tip, resulting in protein necrosis within the hemorrhoid. One RCT evaluated the efficacy of IRC, flavonoids, and combination therapy for 5 days: the percentages of improvement of IRC for different grades of HD were 78, 51, and 22% for grades I, II, and III HD, respectively, and efficacy increased when the technique was associated with flavonoids; interestingly, the efficacy of IRC alone was similar to 5 days of flavonoids alone [80]. RCTs comparing IRC with RBL [81–84] showed that both were well-accepted and highly efficacious methods for the treatment of internal hemorrhoids; in general, RBL was more effective in controlling symptoms and needs fewer additional treatments but is associated with more pain than IRC.

BD is a studied treatment for grades I, II, and III HD. Success rates range from 88 to 100% in randomized trials but do not eliminate prolapsing tissue [31]. About 12% of patients experience pain, bleeding, fissure, or spasm of the internal sphincter [31]. Compared with IRC, BD has some practical advantages but results are similar [85]. Comparing BD with heater probe efficacy was the same, but pain was more common and the time to symptom relief was shorter with heater probe [86].

DCE has no advantage compared with standard medical therapy in an RCT [87] and a limited control of prolapse in higher grade HD [88]. In another RTC, although more painful than sclerotherapy, DCE is a safe and a highly satisfactory procedure for treating early HD [89]. However, DCE has not been widely accepted because of the lengthy treatment time and similar efficacy compared with BD [90–92], RBL [87], and sclerotherapy [88].

As for cryotherapy, the cryoprobe of liquid nitrogen is applied to the hemorrhoid for about 3 min to produce liquefaction of frozen tissue, over the ensuing 2–3 weeks. Despite initial enthusiasm, this procedure is now only rarely used because of prolonged pain, foul-smelling discharge, and a greater need for additional therapy than closed hemorrhoidectomy [31].

Treatment of HD in Special Groups of Patients

Statement 16

In patients taking antiplatelet and/or anticoagulant medication, the risk of bleeding is increased after RBL *(low-quality evidence)*. In these patients, sclerotherapy appears to be safe *(moderate-quality evidence)*.

Agreement: 100%.

Statement 17

Instrumental interventions should be used with caution in patients with impaired immunity. Antibiotic prophylaxis might be beneficial after office-based procedures *(low-quality evidence)*.

Agreement: 100%.

Statement 18

The first-line treatment of symptomatic HD during pregnancy should include a fluid and fiber-rich diet *(moderate-quality evidence)*. Warm sitz baths are also helpful *(high-quality evidence)*.

Agreement: 100%.

Statement 19

In pregnant women, rutosides *(high-quality evidence)*, combination of tribenoside and lidocaine *(moderate-quality evidence)*, and hydrocortisone creams *(low-quality evidence)* seem effective in reducing symptoms of HD. Although preliminary data suggest no increased risk during pregnancy, these therapies should be avoided during the first trimester *(low-quality evidence)*.

Agreement: 92%.

Rationale

Antiplatelet and anticoagulant medication appear to increase the risk of bleeding after RBL with published reports of massive and life-threatening hemorrhage [93–96]. In a large retrospective study of 805 patients undergoing RBL, higher bleeding rates were encountered in patients on warfarin (25%) and acetylsalicylic acid (7.5%) compared with patients not taking these medications (2.9%) [64]. It is believed that the highest risk of bleeding occurs between 10 and 14 days after the procedure [62, 93, 94]. This has led many authors to recommend patients to stop their medication 7–10 days before banding, followed by a further 7–10 days thereafter [93, 97]. In a large retrospective observational study including 364 patients undergoing RBL, withholding antiplatelet medication 7–10 days after the procedure appeared to equalize the risk of bleeding to that of patients not taking antithrombotic medications [97].

In a case-matched series of 37 patients receiving sclerotherapy for symptomatic HD while on antiplatelet and/or anticoagulant therapy, there was no difference in post-procedure bleeding rates [65].

In a prospective study, 120 patients with liver cirrhosis without coagulation disorders were randomized to receive RBL or sclerotherapy for the treatment of HD. Both therapies proved to be safe and effective [98]. In another prospective randomized trial of 26 patients with cirrhosis and HD, resolution of symptoms and complications were similar between patients receiving RBL and stapled hemorrhoidopexy [99]. Even though studies seem to suggest that office-based therapy is beneficial in patients with liver cirrhosis, the authors have considered that there is not enough solid evidence to elaborate a statement on this matter.

HD is present in up to 10% of patients infected with human immunodeficiency virus [100]. Older studies have reported impaired tissue healing and an increased risk of anorectal sepsis in immunocompromised patients [101]. Wound healing may be specially compromised in patients with low CD4 counts [102]. This had led to the general belief that interventions should be avoided or performed with careful consideration in immunocompromised patients. Other reports, however, have demonstrated that surgery for HD is safe in these patients [103]. At this moment, it seems wiser to use conservative measures (fluid and fiber-rich diet, laxatives, warm *sitz* baths) as the first-line treatment [104]. There is a paucity of data evaluating the safety and efficacy of instrumental techniques in immunocompromised patients with HD. Anecdotal reports have shown significant complications in human immunodeficiency virus patients following RBL [105]. However, sclerotherapy may be an attractive alternative in these patients [70]. Studies have suggested a potential benefit of antibiotic prophylaxis in these patients owing to the risk of bacteremia after sclerotherapy [106].

The prevalence of HD during pregnancy can reach 85% during the third trimester [107, 108]. Treating constipation by increasing fluid and fiber intake and taking a warm *sitz* bath 3 times a day may be helpful in improving symptoms from HD. In a prospective comparative study, relief of HD symptoms was achieved in all 284 patients in the warm *sitz* bath group but only in 179/211 patients in the control group [109].

Two randomized controlled trials including over 150 pregnant women have shown that rutosides are effective in treating symptomatic HD [110, 111]. The safety of rutosides was demonstrated in another randomized controlled trial including 69 pregnant women with venous insufficiency [112]. The combination of tribenoside and lidocaine suppositories has been studied in an old randomized parallel double-blind randomized trial versus lidocaine suppositories (n = 21 vs. 20) and hydrocortisone suppositories (n = 13 vs. 13) [113]. In both occasions, the combination of tribenoside and lidocaine appeared to be safe and to relieve HD symptoms. In an observational study, 82.5% of 33 pregnant women reported clinical improvement with oral tribenoside or a combination of tribenoside and lidocaine suppositories [114]. Again, no adverse events were reported. Finally, in a population-based study, oral tribenoside was associated with a higher risk of congenital hydrocephalus in children. However, this finding was based on only 4 cases [115]. Topical hydrocortisone has shown modest effectiveness in controlling hemorrhoidal symptoms in a randomized controlled

study against a modified toilet seat device [116]. No side effects were reported in the study. In a prospective observational study, topical hydrocortisone cream was effective in decreasing HD symptoms in 88 pregnant women [117]. Side effects were not reported in both studies. The safety of topical hydrocortisone has been evaluated in a prospective nonrandomized multicenter study comparing 204 treated pregnant women with 204 controls. No differences were found in birth weight or rates of prematurity [118]. In an open study of 50 pregnant women, a combination of diosmin and hesperidin proved effective in treating HD. Although lack of a control group precludes conclusions, significant adverse events were not noted [119].

We could not find any studies addressing the safety of any of the former drugs in lactating women.

There are no trials evaluating office instrumental therapies in pregnant or lactating women. As concerns regarding their safety during pregnancy or lactation exist, they should probably be avoided during this period.

Lastly, we should mention a specific group of patients, those with Crohn's disease. HD has been estimated in a 2012 study as affecting 1.6% of patients with Crohn's disease [120], but higher rates of prevalence (7%) have been reported [121]. Surgery is usually not indicated in these patients, especially if the disease is not quiescent [122]. Conservative management is usually advised but nonetheless is often not effective in resolving HD. There is a paucity of studies involving the office-based treatment of HD in Crohn's disease [121], and as such, the authors have decided not to elaborate a statement on the matter.

HD Complications

Statement 20

The treatment of irreducible hemorrhoidal prolapse should be surgical *(high-quality evidence)*. New sclerosing techniques may be a promising alternative *(low-quality evidence)*.

Agreement: 100%.

Statement 21

Treatment of external hemorrhoidal thrombosis can be conservative or surgical *(high-quality evidence)*.

Agreement: 92%.

Rationale

The treatment of irreducible hemorrhoidal prolapse (Goligher grade IV) is surgical [123]. Although excisional hemorrhoidectomy is the most widely used technique in the world for irreducible hemorrhoidal prolapse, the comparison between surgical techniques for the treatment of grade IV HD does not show superiority of one method over another and is mainly a joint decision between the doctor and the patient [123, 124].

Although surgical treatment is quite effective in the treatment of external hemorrhoidal thrombosis, allowing the prevention of recurrence and symptom control, there is a clear lack of randomized prospective studies that allow to establish surgery as the gold standard in the treatment of this condition [125–127]. Surgical excision of external hemorrhoidal thrombosis relieves symptoms markedly on the fourth postoperative day when compared to conservative treatment [125]. One of the main doubts that remain is the optimal timing for surgery. Also, there is no evidence in the literature to support conservative treatment in the first 48–72 h of symptoms; however, clinical practice seems to favor this approach [126]. Thus, choosing between conservative treatment and surgery should take into account the patient's will and the clinician's experience [127].

There is a lack of studies aimed at the treatment of anal skin tags in patients with no other rectal pathology. Reference should be made to the existence of guidelines (which take the form of a systematic review) of the German Society of Coloproctology in conjunction with the German Society of Dermatology, but these guidelines are mostly based on studies over 30 years old [128]. In these guidelines, anal skin tags are considered to be mainly an esthetic problem, which only becomes more burdensome when it interferes with the hygiene of the patient. Thus, asymptomatic anal skin tags should not be treated, and careful hygiene should be carried out with water. The treatment of symptomatic anal skin tags should be made conservatively, with topical agents, anal hygiene, and regular habits of defecation. Fibrous skin tags that cause skin irritation or pressure on contralateral areas can be removed surgically.

Final Thoughts

HD is a common disorder that appears very often on the clinical setting. Nevertheless, from our experience, most of the knowledge and techniques that gastroenterologists use in the management of this disease are based in somewhat outdated literature or from peer learning, and no comprehensive approach to this matter is available for the Portuguese reality.

Our goal was to elaborate statements based on the most recent literature paying attention to evidence level. This way, we aimed to reinforce correct patterns of knowledge and practice to meet the standards of published evidence also trying to highlight new information on the subject. Another end point we would like to achieve is the uniformization of clinical practice regarding this disease among gastroenterologists.

It should be noted, however, that some of the topics need further research and emphasis should be made on more studies regarding several of the office-based methods available, such as sclerotherapy.

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APPENDIX 1.

Evidence level	
High quality	One or more well-designed and well-executed randomized controlled trials (RCTs) that yield consistent and directly applicable results. This level also means that further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality	RCTs with important limitations (i. e., biased assessment of the treatment effect, large loss to follow-up, lack of blinding, unexplained heterogeneity), indirect evidence originating from similar (but not identical) populations of interest, and RCTs with a very small number of participants or observed events. In addition, evidence from well-designed controlled trials without randomization, from well-designed cohort or case – control analytic studies, and from multiple time series with or without intervention is in this category. This level also means that further research will probably have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality	Observational studies would typically be rated as low quality because of the risk for bias. This level also means that further research is very likely to have an important impact on our confidence in the estimate of effect and will probably change the estimate.
Very low quality	Evidence is conflicting, of poor quality, or lacking, and hence the balance of benefits and harms cannot be determined. Any estimate of effect is very uncertain as evidence is either unavailable or does not permit a conclusion.

APPENDIX 2.

CLINICAL EVALUATION AND DIAGNOSTIC TESTS
STATEMENT 1. A detailed history and proctological examination are mandatory in patients with suspicion of symptomatic hemorrhoidal disease ***[high quality evidence]*** AGREEMENT: 100%
STATEMENT 2. Anoscopy is the gold standard for the evaluation of the anus if hemorrhoidal disease is suspected ***[moderate quality evidence]*** AGREEMENT: 100%
STATEMENT 3. Flexible sigmoidoscopy should be performed in patients with rectal bleeding. Colonoscopy is indicated in patients over the age of 50 years (earlier if there is family history of colorectal cancer or another condition predisposing to colorectal cancer) or if any alarm symptom is present ***[moderate quality evidence]*** AGREEMENT: 100%
HEMORRHOIDAL DISEASE GRADING
STATEMENT 4. Although never validated the most widely used score is the Goligher classification. Other classification systems were proposed, however, never gained widespread acceptance ***[low quality evidence]*** AGREEMENT: 100%
STATEMENT 5. A symptom-based score, such as Sodergren score, can be used to evaluate the severity of the hemorrhoidal disease ***[moderate quality evidence]*** AGREEMENT: 83%

MEDICAL MANAGEMENT OF HEMORRHOIDAL DISEASE
DIET, TRANSIT MODIFIERS AND LAXATIVES
STATEMENT 6. Dietary fiber (in food or as supplement) decrease bleeding and the recurrence of symptoms. The use of fiber is recommended in the treatment of acute episodes and to prevent recurrence ***[high quality evidence]*** AGREEMENT: 92%
STATEMENT 7. Patients with hemorrhoidal disease benefit from measures that maintain proper bowel habits such as avoiding straining and limiting the time at defecation ***[moderate quality evidence]*** AGREEMENT: 100%
VENOTROPIC DRUGS AND TOPICAL TREATMENT
STATEMENT 8. Venotropic drugs seem to be effective in the treatment of symptomatic hemorrhoidal disease. There is a lack of evidence about optimal dosage, duration of treatment or superiority of a specific drug ***[moderate quality evidence]*** AGREEMENT: 100%
STATEMENT 9. Topical treatment may be useful in the short-term treatment of symptoms of hemorrhoidal disease but, so far, its use is not supported by well-designed, robust studies ***[moderate quality evidence]*** AGREEMENT: 92%

OFFICE-BASED TREATMENT OF HEMORRHOIDAL DISEASE
RUBBER BAND LIGATION
STATEMENT 10. Rubber band ligation is recommended as first-line treatment for internal hemorrhoidal disease grade II and for selected patients with grade III that do not respond to medical treatment. This technique is more effective and equally safe compared to sclerotherapy (liquid sclerosants) and infrared coagulation ***[high quality evidence]*** AGREEMENT: 92%
STATEMENT 11. For internal hemorrhoidal disease grade II, rubber band ligation has similar efficacy but fewer side effects than excision hemorrhoidectomy ***[moderate quality evidence]*** AGREEMENT: 100%
SCLEROTHERAPY
STATEMENT 12. Sclerotherapy with liquid sclerosants is safe but poorly effective and therefore should be used only for grade I internal hemorrhoidal disease ***[high quality evidence].*** Since postprocedural bleeding is uncommon it should be considered for patients who have higher bleeding risk ***[moderate quality evidence]*** AGREEMENT: 92%
STATEMENT 13. The use of other sclerosing techniques, such as polidocanol foam and aluminum sulfate and tanic acid (ALTA), seem to be safe and effective, even in patients under anticoagulation and/or antiplatelet therapy. The efficacy and safety compared to other office-based procedures is yet to be defined ***[low quality evidence]*** AGREEMENT: 100%

OTHER TECHNIQUES: INFRARED COAGULATION, CRYOTHERAPY, ELETROCOAGULATION AND HEATER PROBE
STATEMENT 14. Infrared coagulation is an effective procedure in the treatment of hemorrhoidal disease grades I and II. When compared to rubber band ligation, infrared coagulation shows less postoperative pain but higher probability of recurrence ***[high quality evidence]*** AGREEMENT: 100%
STATEMENT 15. Other office-based procedures have shown inconsistent results, namely electrotherapy ***[moderate quality evidence]***, cryotherapy, heater probe and argon plasma coagulation ***[high quality evidence]***. Their use is not supported by recent evidence. AGREEMENT: 92%
TREATMENT OF HEMORRHOIDAL DISEASE IN SPECIAL GROUPS OF PATIENTS
STATEMENT 16. In patients taking antiplatelet and/or anticoagulant medication the risk of bleeding is increased after rubber band ligation ***[low quality evidence]***. In these patients, sclerotherapy appears to be safe ***[moderate quality evidence]*** AGREEMENT: 100%
STATEMENT 17. Instrumental interventions should be used with caution in patients with impaired immunity. Antibiotic prophylaxis might be beneficial after office-based procedures ***[low quality evidence]*** AGREEMENT: 100%
STATEMENT 18. The first-line treatment of symptomatic hemorrhoidal disease during pregnancy should include a fluid and fiber-rich diet ***[moderate quality evidence].*** Warm *sitz* baths are also helpful ***[high quality evidence]*** AGREEMENT: 100%
STATEMENT 19. In pregnant women, rutosides ***[high quality evidence],*** combination of tribenoside and lidocaine ***[moderate quality evidence]*** and hydrocortisone creams ***[low quality evidence]*** seem effective in reducing symptoms of hemorrhoidal disease. Although preliminary data suggest no increased risk during pregnancy, these therapies should be avoided during the first trimester ***[low quality evidence]*** AGREEMENT: 92%

HEMORRHOIDAL DISEASE COMPLICATIONS
STATEMENT 20. The treatment of irreducible hemorrhoidal prolapse should be surgical ***[high quality evidence]***. New sclerosing techniques may be a promising alternative ***[low quality evidence]*** AGREEMENT: 100%
STATEMENT 21. Treatment of external hemorrhoidal thrombosis can be conservative or surgical ***[high quality evidence]*** AGREEMENT: 92%

CHAPTER III - “THE GOLD STANDARD”

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Office-Based Procedures in the Management of Hemorrhoidal Disease: Rubber Band Ligation versus Sclerotherapy – Systematic Review and Meta-Analysis

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Office-Based Procedures in the Management of Hemorrhoidal Disease: Rubber Band Ligation versus Sclerotherapy – Systematic Review and Meta-Analysis

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Keywords
Hemorrhoidal disease · Rubber band ligation · Sclerotherapy

Abstract

Introduction: The most frequently used office-based procedures in hemorrhoidal disease (HD) are rubber band ligation (RBL) and sclerotherapy. Few studies have been published comparing the various types of instrumental therapy. The aim of this systematic review and meta-analysis was to compare the efficacy and safety of sclerotherapy and RBL. ***Methods:*** Three online databases were searched. Efficacy (control of symptoms, prolapse, bleeding and pain, patients' satisfaction, and disease recurrence) and safety (complications, such as pain and bleeding) were the assessed outcomes. Pooled relative risks (RR) were computed for each outcome using a random-effects model, and heterogeneity was assessed by Cochran's Q test and I^2. ***Results:*** Six RCTs and three cohort studies were included. Control of prolapse and bleeding was significantly higher with RBL (93.1% RBL vs. 66.4% sclerotherapy, RR 1.34, 95% CI 1.12–1.60 and 89.1% RBL vs. 78.7% SCL, RR 1.17, 95% CI 1.02–1.34, respectively). Both techniques had similar results in terms of pain relief, overall control of symptoms, and risk of recurrence at 3 months. Although patient satisfaction was significantly higher with RBL (77.8% RBL vs. 46.7% sclerotherapy, RR 1.59, 95% CI 1.01–2.50), post-procedural pain was significantly higher with this technique (24% RBL vs. 14% sclerotherapy, RR 1.74, 95% CI 1.32–2.28). There was no significant difference regarding post-procedure bleeding (11.1% RBL vs. 8.7% sclerotherapy, RR 1.29, 95% CI 0.86–1.94). In the subgroup analysis, according to the HD grade, post-procedure pain was higher with RBL only in HD grade II (vs. HD grade I–III). ***Conclusions:*** RBL performs better than sclerotherapy in controlling HD symptoms, specifically prolapse and bleeding, although post-procedural pain is a frequent complication. Recurrence is similar with both procedures. While waiting for the publication of results with sclerotherapy with new sclerosants, RBL remains the office-based treatment of choice in HD.

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Tratamento Instrumental da Doença Hemorroidária: Laqueação Elástica versus Escleroterapia – Revisão sistemática e Meta-análise

Palavras Chave
Doença hemorroidária · Laqueação elástica · Escleroterapia

Resumo
Contexto/Objetivos: Os tratamentos instrumentais mais frequentemente realizados na doença hemorroidária (DH) são a laqueação elástica (LE) e a escleroterapia. Existem poucos estudos publicados que comparem os vários tipos de tratamento instrumental. O objetivo desta revisão sistemática e meta-análise foi comparar a eficácia e a segurança da escleroterapia e da LE. ***Métodos:*** A pesquisa foi feita em três bases de dados. A eficácia (controlo dos sintomas, do prolapso, da hemorragia e da dor, satisfação dos doentes e recorrência da DH) e a segurança (complicações, tais como dor e hemorragia) foram os resultados avaliados. Os riscos relativos (RR) foram calculados para cada resultado, com recurso a um modelo de efeitos aleatórios, e a heterogeneidade foi avaliada pelo teste Q de Cochran e I^2. ***Resultados:*** Foram incluídos seis estudos clínicos randomizados e três estudos de coorte. O controlo do prolapso e da hemorragia foi significativamente mais elevado com a LE (93,1% LE *VS* 66,4% escleroterapia, RR 1,34, 95% CI 1,12-1,60 e 89,1% LE *VS* 78,7% escleroterapia, RR 1,17, 95% CI 1,02-1,34, respetivamente). Ambas as técnicas tiveram resultados semelhantes em termos de alívio da dor, controlo global dos sintomas e risco de recidiva aos 3 meses. Embora a satisfação dos doentes fosse significativamente maior com LE (77,8% LE *VS* 46,7% escleroterapia, RR 1,59 95% CI 1,01-2,50), a dor pós-procedimento foi significativamente maior com esta técnica (24% LE *VS* 14% escleroterapia, RR 1,74, 95% CI 1,32-2,28). Não houve diferença significativa na hemorragia pós-procedimento (11,1% LE *VS* 8,7% escleroterapia, RR 1,29, 95% CI 0,86-1,94). Na análise de subgrupos, de acordo com o grau da DH, a dor pós-procedimento foi mais elevada com a LE apenas na DH grau II (*VS* DH graus I-III). ***Conclusões:*** A LE tem melhores resultados do que a escleroterapia no controlo dos sintomas, mais concretamente na resolução do prolapso e da hemorragia hemorroidária, embora a dor pós-procedimento seja uma complicação mais frequente com a LE. A recorrência é semelhante em ambos os procedimentos. Enquanto se aguarda a publicação dos resultados de estudos com novos esclerosantes, a LE deverá ser considerado o tratamento instrumental de primeira linha na DH.

Introduction

Hemorrhoidal disease (HD) is very common among adults and is defined as the symptomatic enlargement and distal displacement of the normal vascular structures in the anal canal [1].

Treatment options depend on the type and severity of the disease, patients' preferences, and physician's expertise. There are several approaches such as lifestyle and diet modification, medical treatment (systemic and topical drugs), office-based procedures, and surgical treatments [2]. Internal HD grades I to III are usually treated with medical treatment and/or office-based procedures, with surgery being reserved for grade IV hemorrhoidal disease, external hemorrhoids, and disease refractory to office-based treatment [3].

The most used office-based procedures are rubber band ligation (RBL), sclerotherapy, and infrared coagulation [3]. However, few studies have been published comparing the various types of instrumental therapy. The latest meta-analysis comparing various hemorrhoidal therapeutic modalities was published 26 years ago (in 1995) [4]. In this meta-analysis the authors concluded that, among office-based therapies, RBL was the most effective, although more painful and more prone to bleeding. Since this publication, RBL is seen as the gold-standard office-based procedure and is recommended as the first-line treatment for hemorrhoidal disease grades I to III [4]. Since then, other alternatives have emerged, namely sclerotherapy with safer and more effective sclerosing agents, raising the need of reassessing the comparison of different office-based procedures. There are also patients with special conditions such as pregnancy, bleeding disorders, immunosuppression, inflammatory bowel disease, and liver cirrhosis, which require a targeted and specific approach [1]. Regarding these groups there is still little information on the efficacy and safety of these approaches.

In this systematic review and meta-analysis, our aim was to compare the efficacy and safety of sclerotherapy and RBL, as these are the two most performed procedures in daily practice.

Methods

Search and Selection

This systematic review and meta-analysis was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [5]. We included fully published randomized controlled trials and prospective cohort studies including patients with HD submitted to the non-surgical treatments sclerotherapy and RBL, and evaluating efficacy and safety outcomes (detailed below).

Study search was performed through scanning of three electronic databases: MEDLINE through PubMed, ISI Web of Knowledge, and Scopus Preview, from inception to March, 2021.

The following search query was used for PubMed: ((hemorrhoid) OR (haemorrhoid) OR ("hemorrhoidal disease") OR ("haemorrhoidal disease")) AND ((band ligation) OR (ligation) OR "rubber band))) AND ("sclerotherapy" OR polidocanol). The search terms for other databases were adapted from this query. Additional studies were identified by checking the list of references of all included studies and also review articles on this topic.

After removal of duplicates, two authors (P. Salgueiro and M.I. Ramos) independently screened all titles and abstracts for relevance. The full text of relevant studies was then evaluated by the same researchers to apply the inclusion/exclusion criteria described below. Disagreements among the two authors were solved by intervention of a third investigator (D. Libânio).

This systematic review was registered at International Prospective Register of Systematic Reviews (PROSPERO) with the identifier CRD42021275047.

Inclusion/Exclusion Criteria and Outcomes

We included studies enrolling patients with symptomatic HD of any grade undergoing RBL or sclerotherapy, without distinction for age or gender. Only studies comparing RBL and sclerotherapy were included. All types of sclerosant (ethanolamine + almond oil, polidocanol, dextrose, etc.) and also endoscopic or anoscopic techniques were considered. Regarding RBL, neither the type of instrument used for the application nor the number of rubber bands applied were exclusion criteria.

For being included in this systematic review, the studies had to report at least one of the following outcomes: for efficacy, we considered overall control of symptoms, hemorrhoidal prolapse reduction (according to Goligher score), bleeding control, pain relief, patients' satisfaction, and disease recurrence; regarding safety, complications related to the office-based procedures, such as pain and bleeding, were assessed. Length of follow-up was not an exclusion criteria.

Pain assessments differ between studies with the use of different scores (VAS-scale, Numeric Pain Rating Scale, and Wong Baker scale); therefore, for the analysis, pain as a HD symptom, was categorized into a dichotomous output: present or absent. We excluded from the meta-analysis studies that only reported the average pain, based on the chosen score.

As reports of patients' satisfaction also differ between studies, this outcome was categorized into a dichotomous output: cured/improved (symptom free or mild residual symptoms but not requiring further treatment) or unchanged/worse (no symptom improvement and/or requiring further treatment).

Quality Assessment

Quality evaluation of included studies was performed through consensus by M.I. Ramos and D. Libânio using the Cochrane risk of bias tool for randomized studies and Newcastle-Ottawa Scale (NOS) for prospective cohort studies. Cochrane risk of bias tool is based on 7 domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Studies were classified into high risk or low risk of bias. Trials with low risk of bias were considered as high-quality trials. NOS is based on a "star system," in which a study is judged on three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of outcome of interest for cohort studies. The total maximum score is 9 and a study with a score from 7 to 9 has high quality.

Data Extraction and Analysis

P. Salgueiro and M.I. Ramos extracted data from all the included studies, which were analyzed for the above methodological quality and for details regarding participants, interventions, and outcomes. Data entry was performed by M.I. Ramos and checked by P. Salgueiro and D. Libânio. Relative risks (RR) along with 95% confidence intervals (CI) were calculated for the dichotomous outcomes. Pooled RRs were then calculated using Review Manager (RevMan Version 5.4.1). Heterogeneity was evaluated with the Cochran's Q test and I^2. Significant heterogeneity was defined as $I^2 > 50\%$ or Cochran's Q test $p < 0.05$. Subgroup analysis was planned according to inclusion of different grades of hemorrhoidal disease (grade II only vs. grade I–III), according to the sclerosant used and study design and quality. In case of significant heterogeneity, sensitivity (leave-one-out meta-analysis) was performed to explore the reasons for heterogeneity.

Results

Description of Studies

A total of 791 records were identified in PubMed (n = 157), ISI Web of Knowledge (n = 107), and Scopus (n = 527). After exclusion of duplicates, 667 were screened for relevance and 88 were assessed for full-text eligibility. Nine studies comparing RBL with sclerotherapy met the inclusion criteria (Fig. 1).

Of these, six [6–11] were RCTs and three [12–14] were prospective cohort studies. Baseline characteristics of the included studies are displayed in Table 1.

All the studies compared patients with grade II hemorrhoids, but some of them also included grades I and/or III and/or IV [6, 7, 13] according to Goligher Prolapse Score. Six studies [8–12, 14] only included patients with grade II hemorrhoids.

In the sclerotherapy group, different sclerosants were used: dextrose in water (1 study [6]), phenol in almond oil (4 studies [9, 10, 12, 14]), ethanolamine in almond oil (2 studies [8, 9]), and polidocanol (1 study [8]). In the

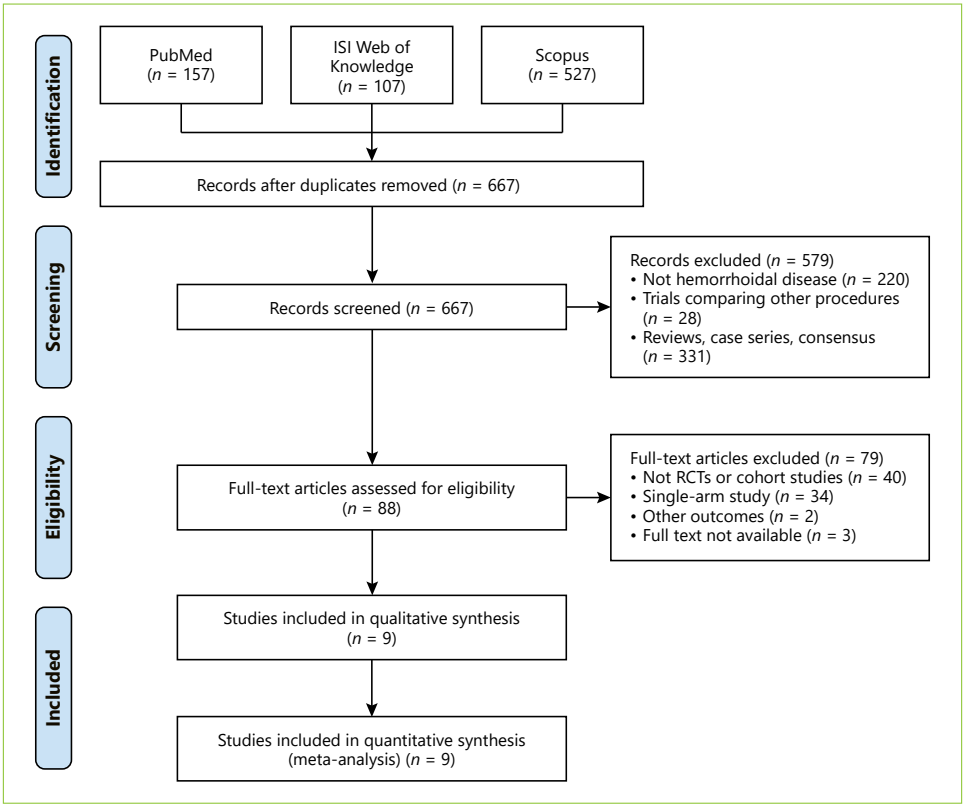

Fig. 1. Flowchart of the study selection.

RBL group, one or more bands were used: one band (4 studies [10, 12–14]), two bands (2 studies [8, 9]), one or two (1 study [6]), two to four (1 study [7]).

Regarding risk of bias, 2 [12, 14] of the 3 cohort studies were classified as high-quality articles according to the Newcastle-Ottawa Quality Assessment Scale (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000522171). The results of the RCTs [6–11] are favorable, with a low risk of bias (online suppl. Fig. 1). However, there is a high risk of performance bias since the blinding of participants and medical staff was not possible in these studies (online suppl. Fig. 2).

Outcomes

Table 2 includes all the outcomes. Online supplementary Table 2 includes analysis by subgroups according to the HD grade (grade II and other grades versus RBL), in the outcomes in which this sub-analysis was possible to perform (post-procedural pain and bleeding).

Online supplementary Table 3 includes a subanalysis according to the type of injected sclerosant (phenol in almond oil and other sclerosants versus RBL). It was possible to compare the efficacy outcomes "overall control of symptoms" and "bleeding control" and the safety outcomes "post-procedural pain" and "post-procedural bleeding."

Efficacy Outcomes

Both RBL and sclerotherapy had similar efficacy in overall control of HD symptoms (RBL 77.6% vs. sclerotherapy 61.9%, RR 1.32, 95% CI 0.86–2.03) (Fig. 2a). However, if Kanellos, 2002 [9] and Khan, 2017 [14] (cohort study and RCT with high risk of bias, respectively) are excluded, heterogeneity reduces from 97% to 0% and

Table 1. Characteristics of included studies

Author, year	Study design, follow-up period	Number of patients		Mean age, % males		Intervention		Outcomes assessed	HD grade	Adjuvant medical therapy
		RBL	SCL	RBL	SCL	RBL (number of bands)	SCL			
Abiodun, 2020 [6]	RCT, 11 months	30	30	42.1, 80%	43.4, 73%	1–2	50% dextrose in water	Hemorrhoidal prolapse reduction, patient satisfaction, disease recurrence, post-procedural pain and bleeding	II and III	Diclofenac sodium 50 mg if moderate to severe pain
Adnan, 1991 [12]	Cohort study, 2 years	470	280	36.6%, no description	34.6%, no description	1	5% phenol in almond oil	Hemorrhoidal prolapse reduction, bleeding control, pain relief	II	Laxatives and corticosteroids suppositories ("on-demand")
Awad, 2012 [7]	RCT, 6 months	60	60	48.9, 75%	46.6, 83%	2–4	5% ethanolamine oleate	Patient satisfaction, post-procedural bleeding	II, III, and IV	Oral lactulose and analgesic (not specified)
Awan, 2017 [13]	Cohort study, 7 days	30	30	40.9, 57%	40.4, 63%	1	Ethanolamine in almond oil	Post-procedural pain, post-procedural bleeding	I and II	Co-trimoxazole 500 mg/day, metronidazole 400 mg/day, and povidone-iodine sitz bath (for 5 days)
Cestaro, 2013 [8]	RCT, 2 years	36	36	36.7, ratio m/f 1.3	37.2, ratio m/f 1.4	2	Polidocanol 3%	Overall control of symptoms, disease recurrence, post-procedural pain and bleeding	II	Not specified
Kanellos, 2003 [9]	RCT, 3 years	81	80	53.4, 67%	54.1, 63%	2	5% phenol in almond oil	Overall control of symptoms, post-procedural pain and bleeding	II	Not specified
Khan, 2017 [14]	Cohort study, 2 years and 2 months	65	65	45, 43%	45, 46%	1	5% phenol in almond oil	Overall control of symptoms, post-procedural pain and bleeding	II	Diclofenac 50 mg and liquid paraffin plus milk of magnesia solution
Nauman, 2018 [10]	RCT, 6 months	58	58	43.1, ratio m/f 4.8	44.1, ratio m/f 8.6	1	5% phenol in almond oil	Overall control of symptoms, bleeding control, post-procedural pain and bleeding	II	Mefenamic acid 500 mg for pain
Shah, 2011 [11]	RCT, 2 years	50	50	49.0, 84%	40.98, 56%	No description	No description	Bleeding control, pain relief, hemorrhoidal prolapse reduction, overall control of symptoms, post-procedural pain and bleeding	II	Diclofenac sodium or paracetamol (for pain) and metronidazole 400 mg/day and glycerol trinitrate 0.2%

RCT, randomized controlled trial; RBL, rubber band ligation; SCL, sclerotherapy.

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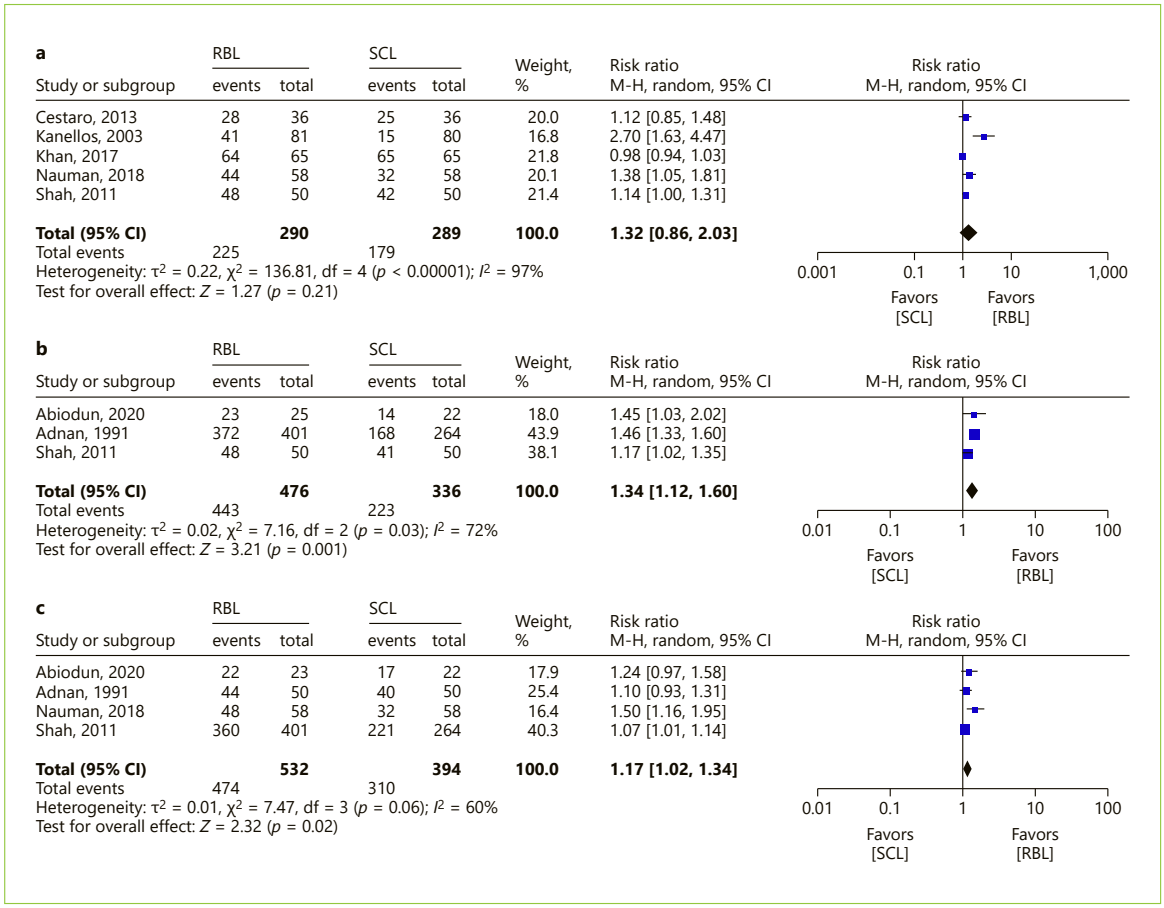

Fig. 2. Comparison 1: rubber band ligation versus sclerotherapy for hemorrhoidal disease; outcome 1: overall control of symptoms (**a**); outcome 2: prolapse reduction (**b**); outcome 3: bleeding control (**c**).

Table 2. Comparison 1: rubber band ligation versus sclerotherapy for hemorrhoidal disease

Outcome	Studies, *n* [references]	Participants	RBL, *n*/total (%)	SCL, *n*/total (%)	RR [95% CI]	I^2
1. Overall control of symptoms	5 [8–11, 14]	579	225/290 (77.6)	179/289 (61.9)	1.32 [0.86, 2.03]	97%
2. Hemorrhoidal prolapse reduction	3 [6, 11, 12]	812	443/476 (93.1)	223/336 (66.4)	1.34 [1.12, 1.60]	72%
3. Bleeding control	4 [6, 10–12]	926	474/532 (89.1)	310/394 (78.7)	1.17 [1.02, 1.34]	60%
4. Pain relief	2 [11, 12]	765	392/451 (87)	260/314 (82.8)	1.04 [0.98, 1.10]	0%
5. Patient satisfaction	2 [6, 7]	180	70/90 (77.8)	42/90 (46.7)	1.59 [1.01, 2.50]	74%
6. Disease recurrence	2 [6, 8]	112	6/59 (10.2)	8/53 (15.1)	0.72 [0.27, 1.93]	0%
7. Post-procedural pain	7 [6, 8–11, 13, 14]	699	84/350 (24)	49/349 (14)	1.74 [1.32, 2.28]	0%
8. Post-procedural bleeding	7 [7–11, 13, 14]	759	42/380 (11.1)	33/379 (8.7)	1.29 [0.86, 1.94]	0%

Statistical method: risk ratio (M-H, random, 95% CI). RBL, rubber band ligation; SCL, sclerotherapy.

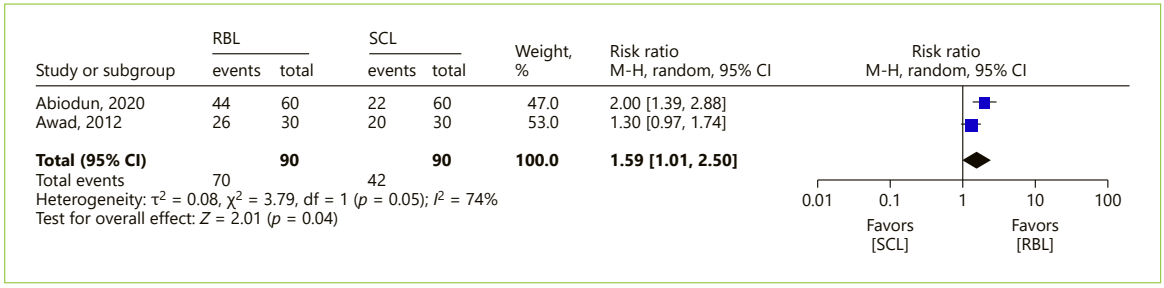

Fig. 3. Comparison 1: rubber band ligation versus sclerotherapy for hemorrhoidal disease; outcome 5: patient satisfaction.

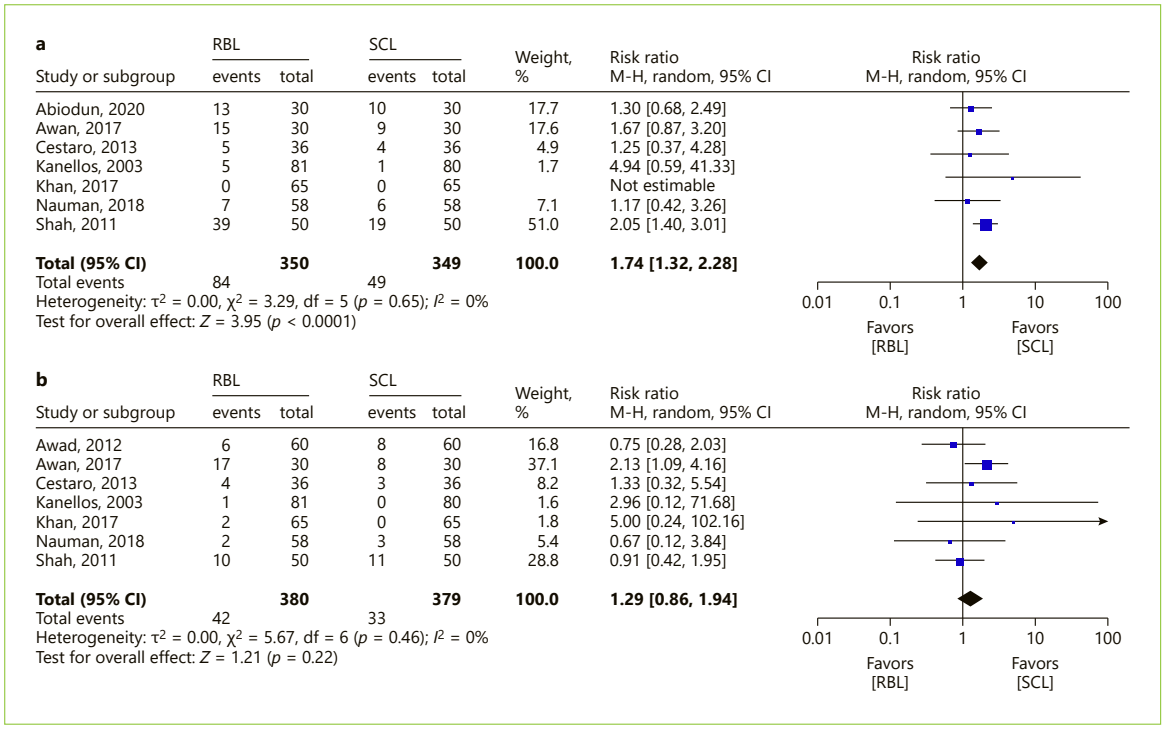

Fig. 4. Comparison 1: rubber band ligation versus sclerotherapy for hemorrhoidal disease; outcome 7: post-procedural pain (**a**); outcome 8: post-procedural bleeding (**b**).

RBL is associated with a significantly higher control of HD symptoms (RBL 83.3% vs. sclerotherapy 68.8%, RR 1.17, 95% CI 1.05–1.31).

Prolapse reduction was significantly better with RBL vs. sclerotherapy (93.1% vs. 66.4%, RR 1.34, 95% CI 1.12–1.60) (Fig. 2b). Excluding Shah, 2011 [11], an RCT that did not report the number of bands nor the type of sclerosant used, heterogeneity decreases from I^2 of 72% to 0%, without significant alteration in the pooled estimate (RBL 92.7% vs. sclerotherapy 63.6%, RR 1.46, 95% CI

1.33–1.60). Bleeding control was also significantly higher with RBL (89.1% vs. 78.7%, RR 1.17, 95% CI 1.02–1.34) (Fig. 2c). Regarding pain relief there was no significant difference between the two interventions (RBL 87% vs. sclerotherapy 82.8%, RR 1.04, 95% CI 0.98–1.10) (online suppl. Fig. 3).

Patient satisfaction was significantly higher with RBL (77.8% vs. 46.7%, RR 1.59, 95% CI 1.01–2.50, I^2 = 74%) (Fig. 3).

The risk of disease recurrence at 3 months was similar between the two groups (RBL 10.2% vs. sclerotherapy 15.5%, RR 0.72, 95% CI 0.27–1.93) (online suppl. Fig. 4).

Concerning the efficacy outcomes, it was not possible to make subgroup analysis by HD grade. Yet, it is important to mention that the studies included in the "overall control of symptoms" and "pain relief" analysis enrolled only patients with grade II HD.

In the other subgroup analysis, according to the type of sclerosant, it was possible to compare the efficacy outcomes "overall control of symptoms" and "bleeding control." Regarding overall control of symptoms, there was no significant difference between the phenol in almond oil subgroup and RBL (RBL 73% vs. phenol sclerotherapy 55.2%, RR 1.53, 95% CI 0.38–6.20). However, RBL was significantly better than the "other sclerosants" subgroup (88.4% vs. 77.9%, RR 1.14, 95% CI 1.01–1.28) (online suppl. Fig. 5). It is important to highlight that the results were quite heterogeneous in the phenol in almond oil group (I^2 = 99%). There was no difference between RBL and each subgroup concerning bleeding control (online suppl. Fig. 6).

In the remaining outcomes, subgroup analysis according to study design/study quality was not possible.

Safety Outcomes

The risk of post-procedural pain was significantly higher with RBL (24% vs. 14%, RR 1.74, 95% CI 1.32–2.28) (Fig. 4a). However, there was no significant difference between the two interventions regarding post-procedural bleeding (RBL 11.1% vs. sclerotherapy 8.7%, RR 1.29, 95% CI 0.86–1.94) (Fig. 4b).

In the subgroup analysis according to HD grades, post-procedural pain was higher with RBL (19.3 % vs. 10.4%, RR 1.90, 95% CI 1.35–2.67) in "grade II HD" subgroup and there was no significant difference between the two interventions in the "other grades" subgroup (RBL 46.7% vs. sclerotherapy 31.7%, RR 1.47, 95% CI 0.93–2.33) (online suppl. Fig. 7). With regard to post-procedural bleeding, there were no significant differences in the two subgroups (online suppl. Fig. 8).

At last, in the type of sclerosant subgroup analysis, we observed that, regarding post-procedural pain, RBL was similar to phenol in almond oil (RBL 5.9% vs. phenol sclerotherapy 3.4%, RR 1.78, 95% CI 0.48–6.57). Nevertheless, when comparing "other sclerosants" subgroup with RBL, post-procedural pain was more common in the RBL group (49.3% vs. 28.8%, RR 1.76, 95% CI 1.32–2.34) (online suppl. Fig. 9). Concerning post-procedural bleeding, there were no significant differences between RBL with either phenol in almond oil or other sclerosants (online suppl. Fig. 10).

Discussion

This systematic review and meta-analysis compared the efficacy and safety of the most commonly performed office-based procedures in the treatment of HD, RBL and sclerotherapy**.** We found that RBL is associated with a better overall control of symptoms, namely hemorrhoidal prolapse and bleeding, but at the expense of higher post-procedural pain. Despite this higher incidence of pain after the procedure, patients undergoing RBL are more satisfied with this treatment than those treated with sclerotherapy. These findings suggest that RBL should be the first-line office-based procedure for patients with HD.

The range of treatment options for hemorrhoidal disease can vary and they are divided into conservative measures, office-based procedures, and surgical treatments.

Lifestyle changes, dietary changes, laxatives and phlebotonic medications and topical anti-inflammatory drugs are effective in controlling HD symptoms in the short term. Since these measures produce beneficial effects, they should be implemented in all patients with HD [15].

The minimally invasive office-based procedures are alternatives to the traditional hemorrhoidectomy and hemorrhoidopexy for symptomatic patients with low-grade HD, especially because of higher rate of surgical complications. In this way, surgical treatment should be reserved for refractory cases, grade IV, or mixed HD [16].

The instrumental office-based treatment is usually indicated for hemorrhoidal disease grade I and II [17], though it can also be used in grade III hemorrhoidal disease [18].

RBL is usually the preferred office-based treatment for grades I to III hemorrhoids because of its effectiveness when compared with other office-based procedures [16, 19]. This technique is performed using an anoscope or an endoscope in retroversion in the patient's rectum and consists in positioning elastic bands above the dentate line

to strangulate the hemorrhoidal piles, resulting in ischemia and subsequent necrosis of the prolapsed mucosa. It is a fast, easy-to-learn, and well-tolerated procedure [20].

Bleeding and pain are among the most frequent complications of RBL [21, 22]. Post-ligation bleeding typically occurs 10 to 14 days after treatment, but it may occur immediately after the procedure [15]. The risk of bleeding is more significant in patients under antiplatelet or anticoagulation medications, so it is not indicated in this subgroup of patients [23]. Although RBL may be more painful historically, the differences to other office-based treatments are smaller in more recent studies [24].

Hemorrhoidal sclerotherapy is a procedure commonly used to treat grade I and II hemorrhoidal disease [25, 26]. It has also been used in internal grade III hemorrhoids [20] although, in these cases, there is little scientific evidence supporting its efficacy [22]. The hemorrhoidal injection with sclerosant agents interrupts the vascular blood supply and leads to scarring, which prevents further bleeding and prolapse of the hemorrhoidal tissue [27, 28].

Many sclerosant agents have been used over time. Sclerotherapy with older sclerosing agents seems to be less effective than RBL, which is why some authors recommend that this technique, at least with those sclerosing agents, should only be used in grade I HD [19]. More recently, the sclerosing substance polidocanol started to be employed in the form of foam [29]. The foam formulation allows for greater efficacy and use of lower doses of sclerosing agent [30]. Although it is a sclerosing substance with very promising results, data comparing polidocanol foam with other hemorrhoidal disease ablative techniques is lacking. Since there are no comparative studies between RBL and polidocanol foam sclerotherapy, none of the studies included in this meta-analysis used polidocanol foam as a sclerosing agent.

The most common complications of sclerotherapy include mild anal discomfort and bleeding. However, the bleeding risk is often described as being inferior to that observed with RBL [31].

A previous meta-analysis compared various HD treatment modalities [31]. The outcomes evaluated included response to therapy, need for further therapy, and complications. In that review, patients treated with RBL were less likely to require further therapy than those treated with sclerotherapy, although pain was significantly more likely to occur following RBL. Therefore, it was concluded that RBL was better than sclerotherapy in response to treatment for all hemorrhoids, so RBL was recommended as the initial treatment for grades I to III HD [4].

Twenty-six years later, in this systematic review, we have expanded the outcomes by including patient satisfaction and discriminating the effect of the office-based procedures in the most frequent HD symptoms (prolapse, bleeding, and pain). It is also important to mention that the studies included in our meta-analysis are different from those included in the previous one.

The control of the hemorrhoidal symptoms is the most obvious measure of success for any procedure, so it is a very important and relevant aspect when choosing the primary treatment. In our review, both RBL and sclerotherapy were effective in controlling overall HD symptoms; however, control of prolapse and bleeding was significantly better with RBL. Pain relief was equally effective with both techniques.

The safety of the interventions is also an extremely important aspect, particularly when dealing with a benign disease such as HD. In this situation, the occurrence of serious complications is especially unwanted and unacceptable. Post-procedural complications, such as pain and bleeding, are crucial factors that can influence a patient's decision to accept or not a specific type of treatment. In the present study, the risk of post-procedural pain was greater with RBL; however, in the group of grade II HD, the results were similar.

Recurrence was similar with both procedures and was less than 20%.

Finally, patient satisfaction is determined by the efficacy and safety of each procedure and, in our study, was higher with RBL.

This systematic review and meta-analysis has some limitations. First, the lack of standardization of therapies concerning the number of bands used in each session, the type and volume of the injected sclerosant, the number of hemorrhoidal cushions treated in each session, as well as the adjuvant medical therapy (not always specified in all studies included, see Table 1) could contribute to the heterogeneity of the results. Second, significant heterogeneity was found in some outcomes, which can be explained by the type of sclerosant used: phenol in almond oil subgroup was associated with 99% heterogeneity in the outcome "overall control of symptoms" and with 77% heterogeneity in "control of bleeding." Also, when we performed subgroup analyses, for some of the outcomes, it was possible to include only a small number of studies. Third, even though we are aware of the importance of including studies published only as conference abstract, we decided not to do so since, in most abstracts, perhaps due to restrictions on the number of words allowed, extractable data (inclusion/exclusion criteria, technique used,

type of sclerosant, etc.) are rarely reported for carrying out meta-analysis. Lastly, in most centers, as in ours, it is usual to refer grade IV HD patients directly to surgical treatment. In our meta-analysis, since the grade of hemorrhoidal disease was not considered an exclusion criterion, among the included studies, one included patients with grade IV HD [18]. It refers to a randomized trial including patients with liver cirrhosis and hemorrhoidal disease grades II to IV that compared RBL and sclerotherapy (60 patients included in each therapeutic arm). Patients with grade IV HD included in that study represent only 2.5% of the sample (2 patients in the ligation group and 1 patient in the sclerotherapy group); therefore, we do not believe that the inclusion of participants with such an advanced HD had a significant influence on the results obtained.

Additionally, it is important to mention that in our research we did not find comparative studies between RBL and the most recent and promising sclerosing agents polidocanol foam and aluminum potassium sulfate and tannic acid. If, at the time of our research, comparative studies with these sclerosing agents were published, their inclusion in the meta-analysis could possibly influence the results in terms of benefiting sclerotherapy. At this time, it is not possible to draw conclusions about comparing RBL with these new sclerosing agents.

Conclusion

RBL is currently the best office-based treatment for HD grades I to III since it is more effective than sclerotherapy with regard to overall control of HD symptoms, specifically prolapse and bleeding. Despite the higher incidence of pain after performing RBL, patients undergoing this technique have higher rates of satisfaction than those treated with sclerotherapy. Recurrence is similar for both procedures.

While waiting for the publication of comparative trials with new sclerosants, RBL remains the office-based treatment of choice.

Statement of Ethics

Our paper refers to a systematic review and meta-analysis of previously published data, which is why ethics approval does not apply.

Conflict of Interest Statement

The authors declare no conflicts of interest of any kind regarding the content of the manuscript.

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None.

Author Contributions

Paulo Salgueiro (conceptualization; methodology; investigation; formal analysis; writing – original draft); Maria Inês Ramos (conceptualization; methodology; investigation; formal analysis; writing – original draft); Fernando Castro-Poças (writing – review and editing); Diogo Libânio (conceptualization; methodology; writing – review and editing; supervision). All authors approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and/or its supplementary material files. Further enquiries can be directed to the corresponding author.

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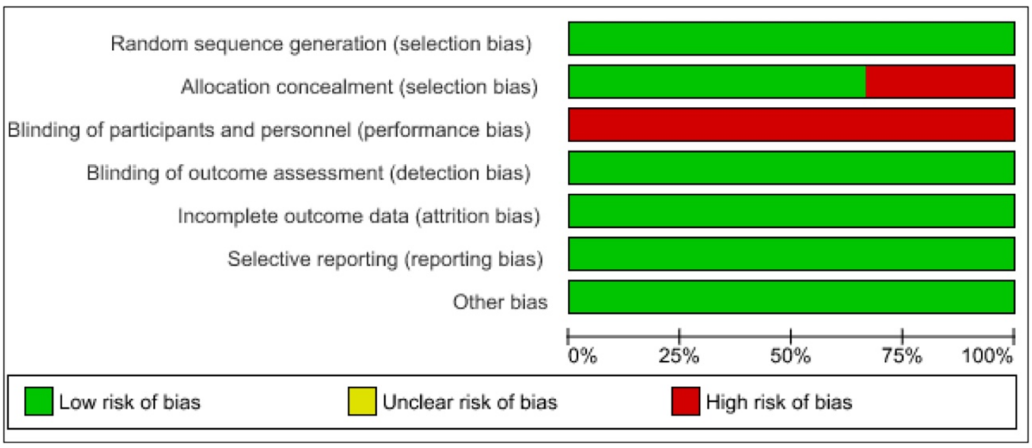
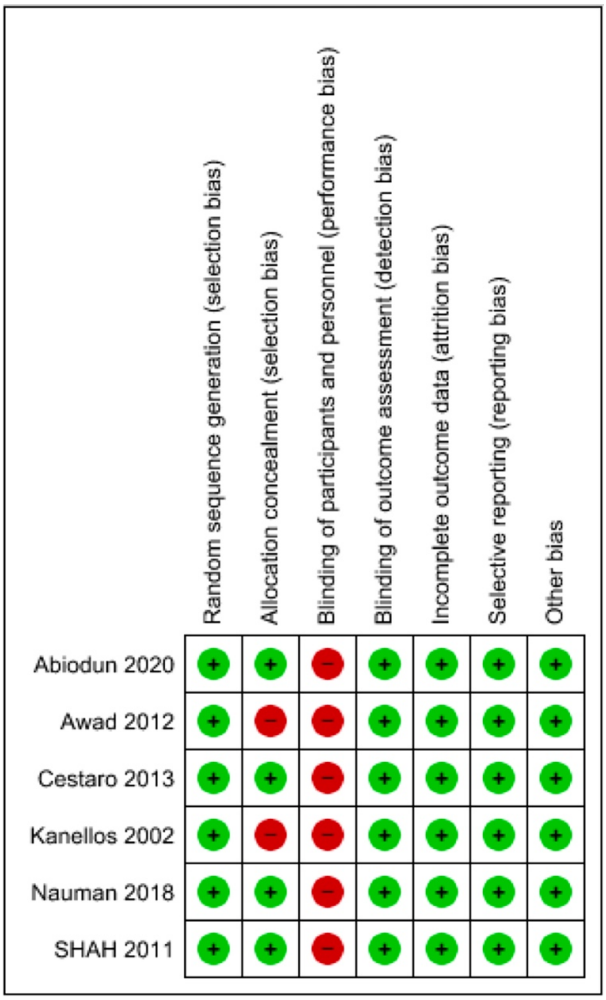
Supp material Fig. 1. RCTs' risk of bias graph



Supp material Fig. 2. RCTs' risk of bias summary



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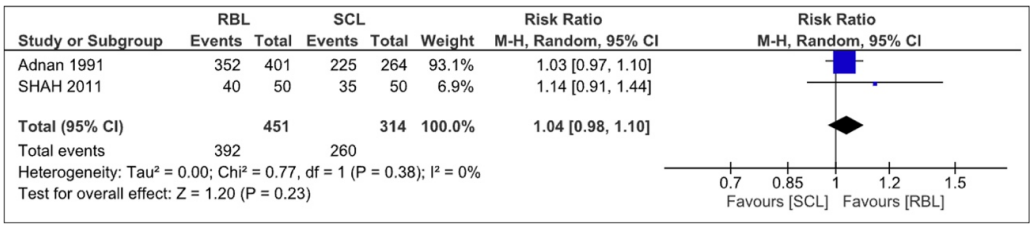
Supp material Fig. 3. Comparison 1: Rubber band ligation versus sclerotherapy for hemorrhoidal disease; Outcome 4: Pain relief



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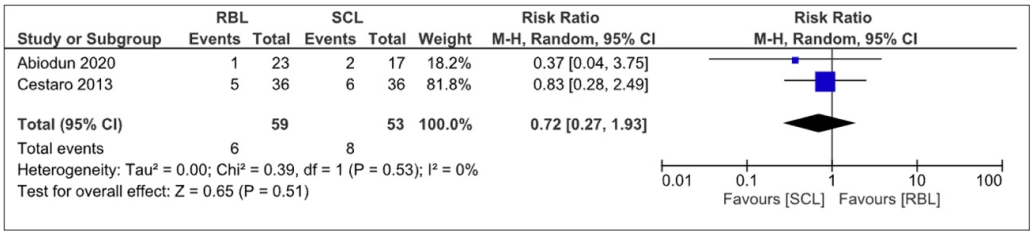
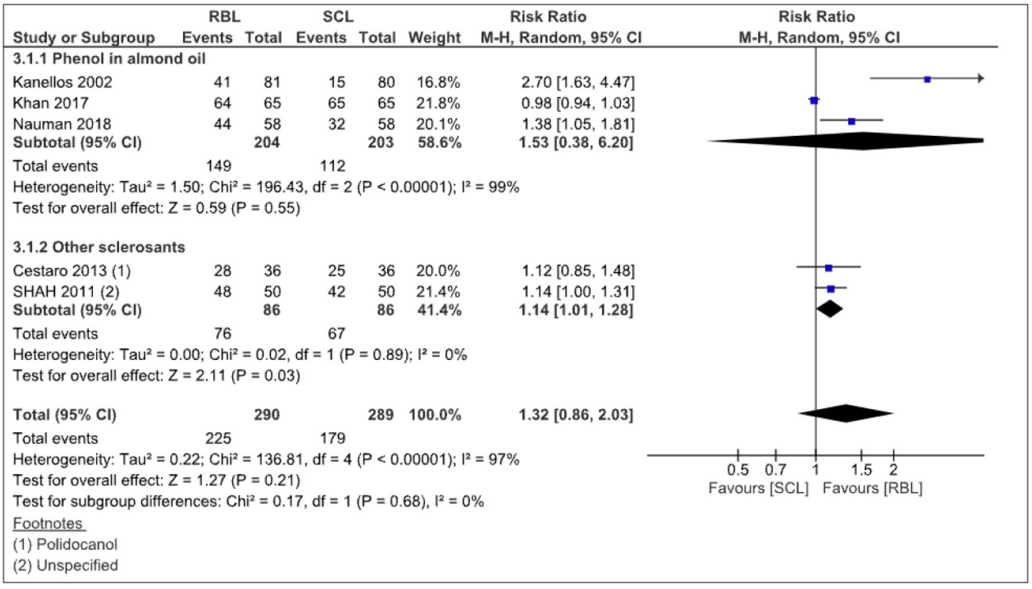
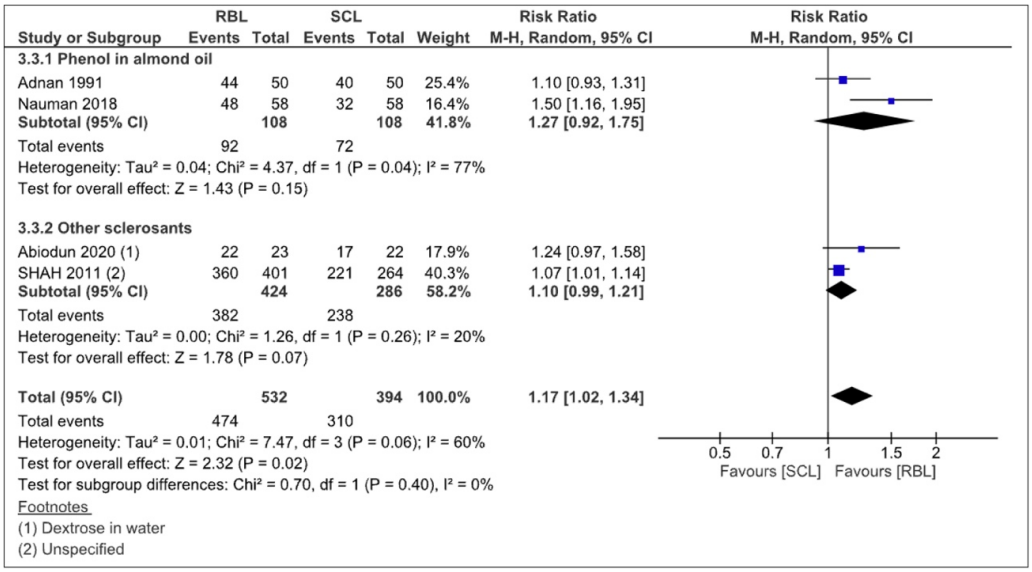


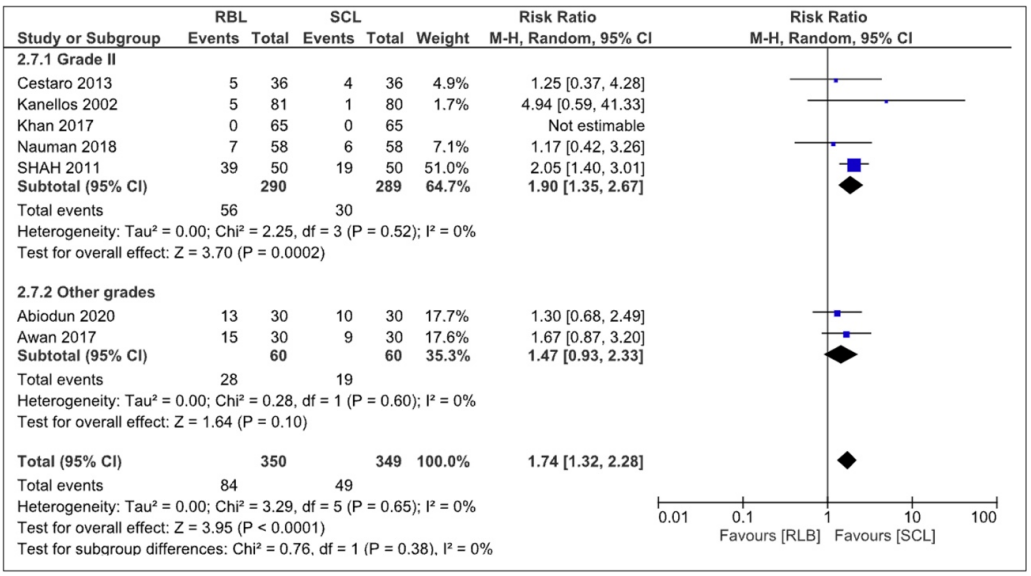
Supp material Fig. 5. Comparison 3. Rubber band ligation versus sclerotherapy for hemorrhoidal disease according to sclerosants; Outcome 1: Overall control of symptoms



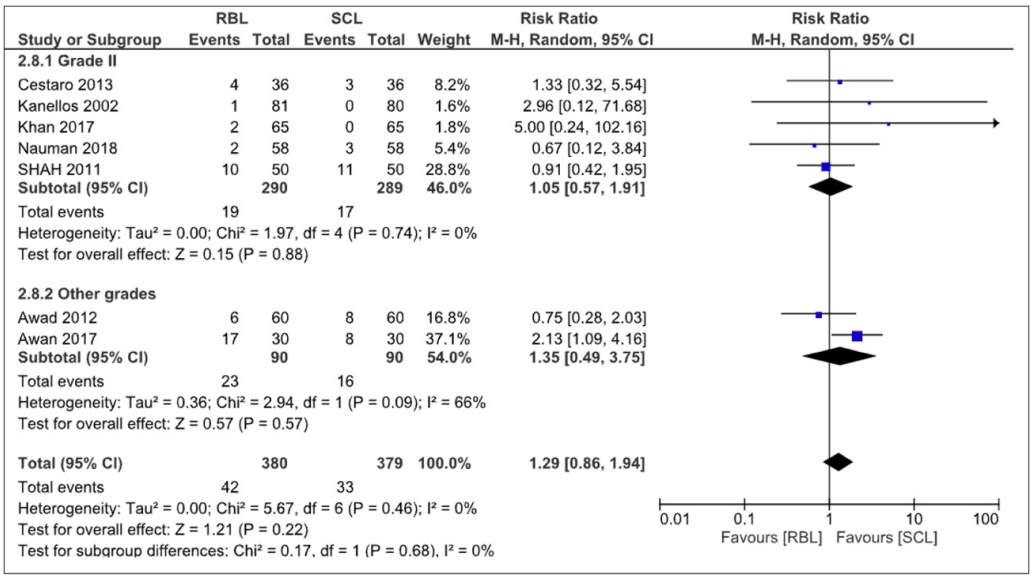
Supp material Fig. 6. Comparison 3. Rubber band ligation versus sclerotherapy for hemorrhoidal disease according to sclerosants; Outcome 3: Bleeding control



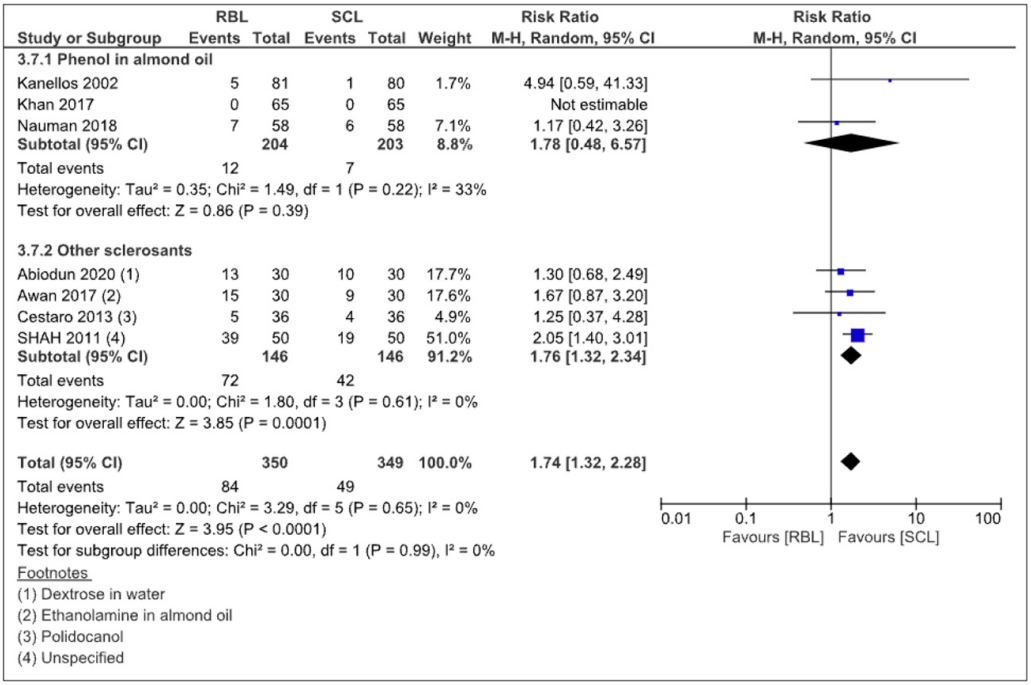
Supp material Fig. 7. Comparison 2: Rubber band ligation versus sclerotherapy for hemorrhoidal disease according to grades; Outcome 7: Post procedural pain



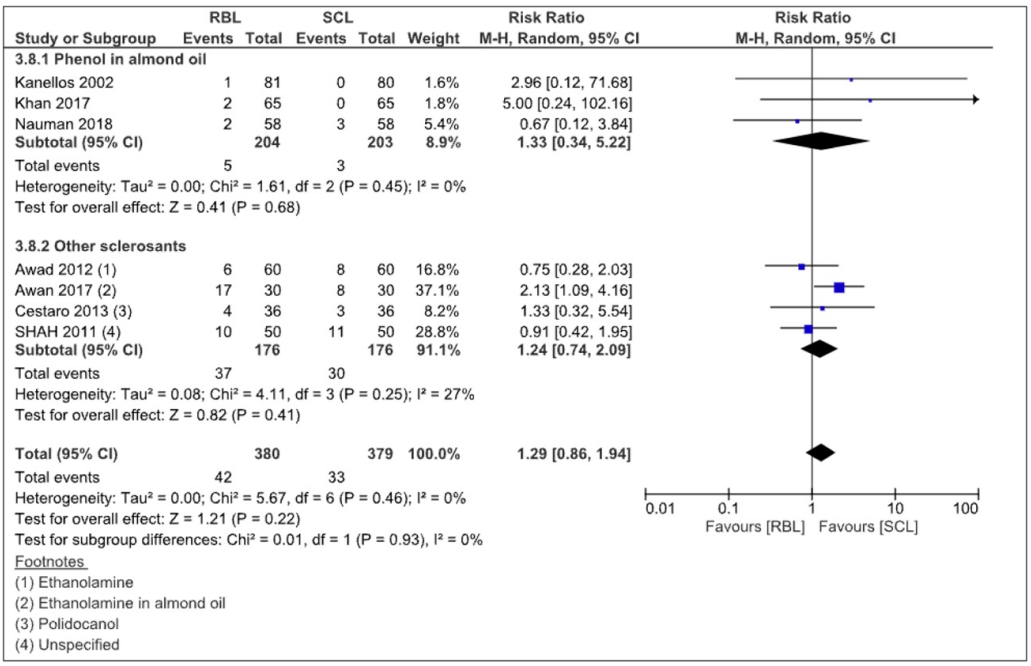
Supp material Fig. 8. Comparison 2. Rubber band ligation versus sclerotherapy for hemorrhoidal disease according to grades; Outcome 8: Post-procedural bleeding



Supp material Fig. 9. Comparison 3. Rubber band ligation versus sclerotherapy for hemorrhoidal disease according to sclerosants; Outcome 7: Post-procedural pain



Supp material Fig. 10. Comparison 3. Rubber band ligation versus sclerotherapy for hemorrhoidal disease according to sclerosants; Outcome 8: Post-procedural bleeding



Supp material Table 1. Newcastle - Ottawa Quality Assessment Scale for cohort studies

Study ID	Selection	Comparability	Outcome	Total (9*)
Adnan 1991	****	**	**	8 (high-quality)
Awan 2017	****	*	*	6
Khan 2017	****	*	**	7 (high quality)

Supp material Table 2. Comparison 2. Rubber band ligation versus sclerotherapy for hemorrhoidal disease according to grades

Outcome	Studies (references)	Participants	RBL No/Total (%)	SCL No/Total (%)	RR (95% CI)	I^2
2.7 Post-procedural pain	7 (6,8-11,13,14)	699	84/350 (24)	49/349 (14)	1.74 [1.32, 2.28]	0%
2.7.1 Grade II	5 (8-11,14)	579	56/290 (19.3)	30/289 (10.4)	1.90 [1.35, 2.67]	0%
2.7.2 Other grades	2 (6,13)	120	28/60 (46.7)	19/60 (31.7)	1.47 [0.93, 2.33]	0%
2.8 Post-procedural bleeding	7 (7-11,13,14)	759	42/380 (11.1)	33/379 (8.7)	1.29 [0.86, 1.94]	0%
2.8.1 Grade II	5 (8-11,14)	579	19/290 (6.6)	17/289 (5.9)	1.05 [0.57, 1.91]	0%
2.8.2 Other grades	2 (7,13)	180	23/90 (25.6)	16/90 (17.8)	1.35 [0.49, 3.75]	0%

Statistical Method: Risk Ratio (M-H, Random, 95% CI)
RBL: rubber band ligation
SCL: sclerotherap

Supp material Table 3. Comparison 3. Rubber band ligation versus sclerotherapy for hemorrhoidal disease according to sclerosants

Outcome	Studies n (references)	Participants	RBL No/Total (%)	SCL No/Total (%)	RR (95% CI)	I^2
3.1 Overall control of symptoms	5 (8-11,14)	579	225/290 (77.6)	179/289 (61.9)	1.32 [0.86, 2.03]	97%
3.1.1 Phenol in almond oil	3 (9,10,14)	407	149/204 (73)	112/203 (55.2)	1.53 [0.38, 6.20]	99%
3.1.2 Other sclerosants	2 (8,11)	172	76/86 (88.4)	67/86 (77.9)	1.14 [1.01, 1.28]	0%
3.3 Bleeding control	4 (6,10-12)	926	474/532 (89.1)	310/394 (78.7)	1.17 [1.02, 1.34]	60%
3.3.1 Phenol in almond oil	2 (10,12)	216	92/108 (85.2)	72/108 (66.7)	1.27 [0.92, 1.75]	77%
3.3.2 Other sclerosants	2 (6,11)	710	382/424 (90.1)	238/286 (83.2)	1.10 [0.99, 1.21]	20%
3.7 Post-procedural pain	7 (6,8-11,13,14)	699	84/350 (24)	49/349 (14)	1.74 [1.32, 2.28]	0%
3.7.1 Phenol in almond oil	3 (9,10,14)	407	12/204 (5.9)	7/203 (3.4)	1.78 [0.48, 6.57]	33%
3.7.2 Other sclerosants	4 (6,8,11,13)	292	72/146 (49.3)	42/146 (28.8)	1.76 [1.32, 2.34]	0%
3.8 Post-procedural bleeding	7 (7-11,13,14)	759	42/380 (11.1)	33/379 (8.7)	1.29 [0.86, 1.94]	0%
3.8.1 Phenol in almond oil	3 (9,10,14)	407	5/204 (2.5)	3/203 (1.2)	1.33 [0.34, 5.22]	0%
3.8.2 Other sclerosants	4 (7,8,11,13)	352	37/176 (21)	30/176 (17)	1.24 [0.74, 2.09]	27%

Statistical Method: Risk Ratio (M-H, Random, 95% CI)
RBL: rubber band ligation
SCL: sclerotherapy

CHAPTER IV - “CHALLENGING THE BEST”

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Polidocanol Foam Sclerotherapy Versus Rubber Band Ligation in Hemorrhoidal Disease Grades I/II/III: Randomized Trial

Paulo Salgueiro, Mónica Garrido, Ruben Gaio, Isabel Pedroto, Fernando Castro-Poças

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ORIGINAL CONTRIBUTION

Polidocanol Foam Sclerotherapy Versus Rubber Band Ligation in Hemorrhoidal Disease Grades I/II/III: Randomized Trial

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BACKGROUND: Rubber band ligation and sclerotherapy are considered the office-based procedures of choice in hemorrhoidal disease. However, there are no studies comparing rubber band ligation and polidocanol foam sclerotherapy.

OBJECTIVE: We aimed to evaluate the efficacy and safety of polidocanol foam sclerotherapy compared with rubber band ligation.

DESIGN: This study was a randomized open-label study with 1-year follow-up.

SETTINGS: The study was conducted in the colorectal unit of a tertiary hospital.

PATIENTS: One hundred twenty patients with hemorrhoidal disease grades I to III were included.

INTERVENTIONS: Patients were stratified by hemorrhoidal disease grade and randomly assigned (1:1) to treatment with either rubber band ligation (n = 60) or polidocanol foam sclerotherapy (n = 60).

MAIN OUTCOME MEASURES: Efficacy outcomes included therapeutic success and recurrence. Safety outcomes included the occurrence of complications related to the procedures.

RESULTS: Therapeutic success was not significantly different between the groups (polidocanol foam sclerotherapy 93.3% vs rubber band ligation 85.0%, $p = 0.14$). However, complete success rate was higher in the polidocanol foam sclerotherapy group (88.3% vs 66.7%, $p = 0.009$) with fewer office-based sessions (mean ± SD: 1.32 ± 0.60 vs 1.62 ± 0.76, $p = 0.02$). Recurrence rates were lower in the polidocanol foam sclerotherapy group (16.1% vs 41.2%, $p = 0.004$). Most recurrences were mild (83.3%). Complications were more frequent in the rubber band ligation group (30.0% vs 10.0%, $p = 0.01$) and were mostly minor (91.7%). No severe complications were observed in either group.

LIMITATIONS: This study was performed in a single center, and both patients and investigators were not blinded to the treatment group.

CONCLUSIONS: Both procedures are effective in the treatment of hemorrhoidal disease grades I to III. Polidocanol foam sclerotherapy was more effective than rubber band ligation when considering complete success. Patients in the polidocanol foam sclerotherapy group needed fewer treatment sessions, had lower recurrence rates, and were less likely to have complications. See **Video Abstract** at http://links.lww.com/DCR/B816.

REGISTRATION: https//www.clinicaltrials.gov; Identifier: NCT04091763.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML and PDF versions of this article on the journal's website (www.dcrjournal.com).

Poster presentation at the UEG Week Virtual 2020, October 11 to 13, 2020; presented at the Portuguese Gastroenterology Congress, November 20 to 21, 2020; awarded first prize for "Research in Coloproctology" attributed by the Portuguese Coloproctology Society, for the year 2021.

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ESCLEROTERAPIA CON ESPUMA DE POLIDOCANOL VERSUS LIGADURA CON BANDA DE GOMA EN LOS GRADOS I / II / III DE ENFERMEDAD HEMORROIDAL: ENSAYO ALEATORIZADO

DISEASES OF THE COLON & RECTUM VOLUME 65: 7 (2022)

ANTECEDENTES: La ligadura con banda elástica y la escleroterapia se consideran los procedimientos de elección en el consultorio para la enfermedad hemorroidal. Sin embargo, no hay estudios que comparen la ligadura con bandas elastica y la escleroterapia con espuma de polidocanol.

OBJETIVO: Nuestro objetivo fue evaluar la eficacia y seguridad de la escleroterapia con espuma de polidocanol en comparación con la ligadura con bandas elastica.

DISEÑO: Estudio aleatorizado randomizado, abierto, con seguimiento de 1 año.

AJUSTES: El estudio se realizó en una unidad colorrectal de un hospital terciario.

PACIENTES: Se incluyeron 120 pacientes con enfermedad hemorroidal grados I a III.

INTERVENCIONES: Los pacientes fueron estratificados por grado de enfermedad hemorroidal y asignados al azar (1: 1) al tratamiento con ligadura con banda elastica (n = 60) o escleroterapia con espuma de polidocanol (n = 60).

PRINCIPALES MEDIDAS DE RESULTADO: Los resultados de eficacia incluyeron el éxito terapéutico y la recurrencia. Los resultados de seguridad incluyeron la aparición de complicaciones relacionadas con los procedimientos.

RESULTADOS: El éxito terapéutico no fue significativamente diferente entre los grupos (escleroterapia con espuma de polidocanol 93,3% vs ligadura con banda de goma 85,0%, $p = 0,14$). Sin embargo, la tasa de éxito completo fue mayor en el grupo de escleroterapia con espuma de polidocanol (88,3% vs 66,7%, $p = 0,009$), con menos sesiones en el consultorio (media ± desviación estándar: 1,32 ± 0,60 vs 1,62 ± 0,76, $p = 0,02$). Las tasas de recurrencia fueron más bajas en el grupo de escleroterapia con espuma de polidocanol (16,1% vs 41,2%, $p = 0,004$). La mayoría de las recurrencias fueron leves (83,3%). Las complicaciones fueron más frecuentes en el grupo de ligadura con bandas elastica (30,0% vs 10,0%, $p = 0,01$) y fueron en su mayoría menores (91,7%). No se observaron complicaciones graves en ninguno de los grupos.

LIMITACIONES: Este estudio se realizó en un solo centro y ni los pacientes ni los investigadores estaban cegados al grupo de tratamiento.

CONCLUSIONES: Ambos procedimientos son efectivos en el tratamiento de la enfermedad hemorroidal grados I a III. La escleroterapia con espuma de polidocanol fue más eficaz que la ligadura con banda de goma cuando se consideró el éxito completo. Los pacientes del grupo de escleroterapia con espuma de polidocanol necesitaron menos sesiones de tratamiento, tuvieron tasas de recurrencia más bajas y menos probabilidades de tener complicaciones. Consulte **Video Resumen** en http://links.lww.com/DCR/B816. *(Traducción—Dr Yolanda Colorado)*

ClinicalTrials.gov, número NCT04091763.

KEY WORDS: Hemorrhoidal disease; Polidocanol foam; Rubber band ligation; Sclerotherapy.

Hemorrhoidal disease (HD) affects up to 38.9% of the adult population.[1–3] Office-based treatments are indicated for HD grades I to III[4–6] and include rubber band ligation (RBL) and sclerotherapy, among others. Rubber band ligation has been recommended as the first-line office-based treatment in several guidelines and consensus statements,[7–9] given its higher effectiveness compared with liquid sclerotherapy.[10] However, it is more painful and more prone to bleeding complications.[10,11] Hemorrhoidal sclerosis is a procedure used to treat grades I to III HD.[2,8,11,12] Despite the wide variety of sclerosing agents described in this setting, most studies report the efficacy of liquid agents.[6,13–16]

Polidocanol has recently started to be used in the treatment of HD in liquid or foam formulation. The foam formulation allows for higher efficacy with lower doses of sclerosing agent, because the greater volume increases the area of contact with the vascular endothelium,[17] as demonstrated in a randomized study that included patients with first-degree HD.[18] Two recent nonrandomized studies have shown that polidocanol foam injection is effective in HD grades II to IV and has only rare and usually minor complications.[19,20] To date, no studies have compared polidocanol foam sclerotherapy (PFS) with RBL.

We conducted a clinical study comparing the efficacy and safety of PFS and RBL.

MATERIALS AND METHODS

Study Design

We conducted an open-label, randomized, controlled study. We recruited patients referred to the proctology outpatient clinic of the Gastroenterology Department of Centro Hospitalar Universitário do Porto, a tertiary hospital in Porto, Portugal.

The study was approved by the Ethics Committee of Centro Hospitalar Universitário do Porto (reference 2018.135(116-DEFI/115-CES)) and was registered at https://www.clinicaltrials.gov (identifier NCT04091763).

All authors had access to the study data and approved the final manuscript.

Patients, Randomization, and Masking

Adult patients were included if they had had internal HD with a Goligher grade I to III that was refractory to conservative management (defined as 900 mg of diosmin, oral capsules, and ruscogenin 5 mg/g + trimebutine 5.8 mg/g, rectal cream, plus fiber or laxatives if necessary) for at least 4 weeks.

Patients were randomly assigned (1:1) into one of the groups (PFS or RBL) and stratified according to the Goligher classification. The randomization list was computer generated, and assignments were kept in sequentially numbered and concealed envelopes. Because the studied procedures have different techniques, it was not possible to blind either the patient or the clinician who applied the treatment.

All patients had a colonoscopy before enrollment. Exclusion criteria were known allergy to polidocanol, liver cirrhosis, IBD, immunosuppression, inherited or acquired bleeding disorders, pregnancy/breastfeeding, concomitant perianal diseases, and office-based or surgical treatments for HD within the past 6 months.

All patients provided written consent.

Procedures and Techniques

Patients underwent a cleansing enema before the procedures. Treatment was performed with the patient in the knee-chest position. All procedures were performed on an outpatient basis, without the use of sedation or local anesthesia, by 2 experienced proctologists. In each session, treatment of more than 1 hemorrhoid cushion was allowed. All patients received systemic phlebotonic and topical medications (900 mg diosmin, oral capsules, daily; ruscogenin 5 mg/g + trimebutine 5.8 mg/g, rectal cream, twice daily, for 2 weeks) after each intervention. Prophylactic antibiotics were not administered.

The PFS technique (Fig. 1A) was as follows: 1) preparation of the polidocanol foam using 4 mL of liquid polidocanol 3% (Aethoxysklerol Kreussler Pharma) mixed with 16 mL of air, using a 3-way tap adapted to two 20-mL syringes, according to the Tessari method[21] (Fig. 2); 2) intravascular application above the dentate line through an anoscope using a reusable 10-cm syringe extender adapted to an intravenous needle; 3) the maximum dose of polidocanol foam was 20 mL (4 mL of liquid polidocanol 3% mixed with 16 mL of air) per treatment session (Fig. 3A, B).

The RBL technique (Fig. 1B) was as follows: 1) use of a reusable metal ligation device connected to a vacuum system (McGown suction method) to apply the rubber bands above the dentate line through an anoscope; 2) more than 1 band per session could be applied (Fig. 3C, D).

Visits and Data Collection

At every visit, the severity of HD was assessed using the Goligher Classification[22] (Supplemental Digital Content 1 at http://links.lww.com/DCR/B817), Sodergren hemorrhoid symptom severity score (SHSS)[23] (Supplemental Digital Content 2 at http://links.lww.com/DCR/B817), and hemorrhoidal disease bleeding grade (HDBG)[24] (Supplemental Digital Content 3 at http://links.lww.com/DCR/B817). A proctologic examination was performed at each visit.

Two distinct periods were considered in the study: intervention and follow-up.

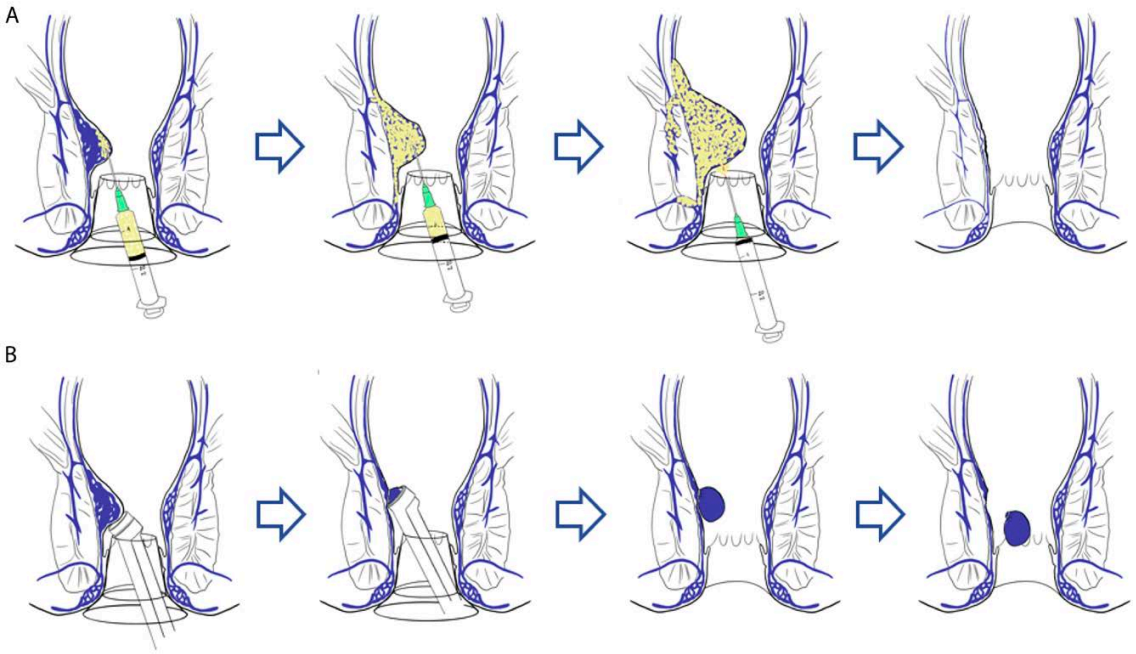

FIGURE 1. Schematic representation of polidocanol foam sclerotherapy (A) and rubber band ligation (B) procedures.

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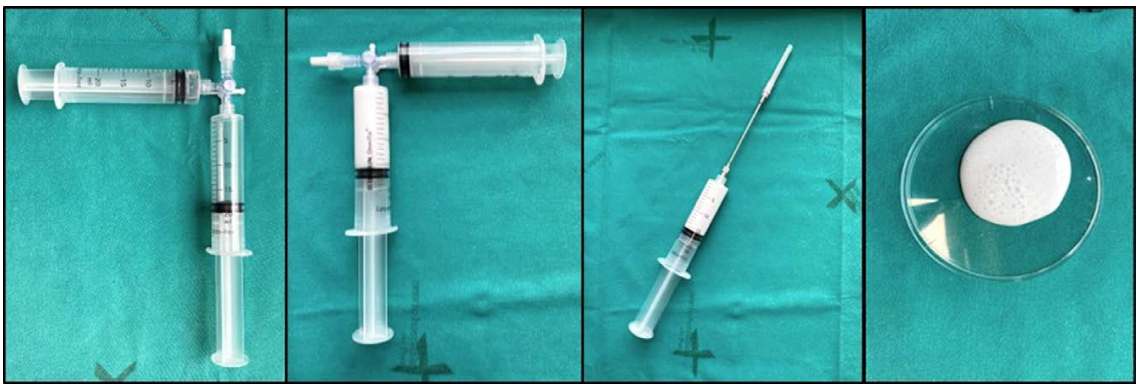


FIGURE 2. Polidocanol foam preparation according to the Tessari method.

During the intervention period, patients were observed at 3-week intervals. The required number of sessions was determined by the treatment success and the occurrence of complications: if there was complete therapeutic success 3 weeks after an office treatment (see below), or if the anoscopy did not reveal significant HD, no additional therapy was performed, and the patient entered the follow-up period. Patients who had only partial success (see below) would undergo another treatment session for up to a maximum of 3 procedures. If there was therapeutic failure (described in the following section) at the end of the third session or if there was a moderate or severe complication, the patient reached an end point of the study.

During the follow-up period, patients who achieved therapeutic success (partial or complete) at the end of the intervention period were observed every 3 months up to a maximum 1-year follow-up. Recurrence was evaluated during this period.

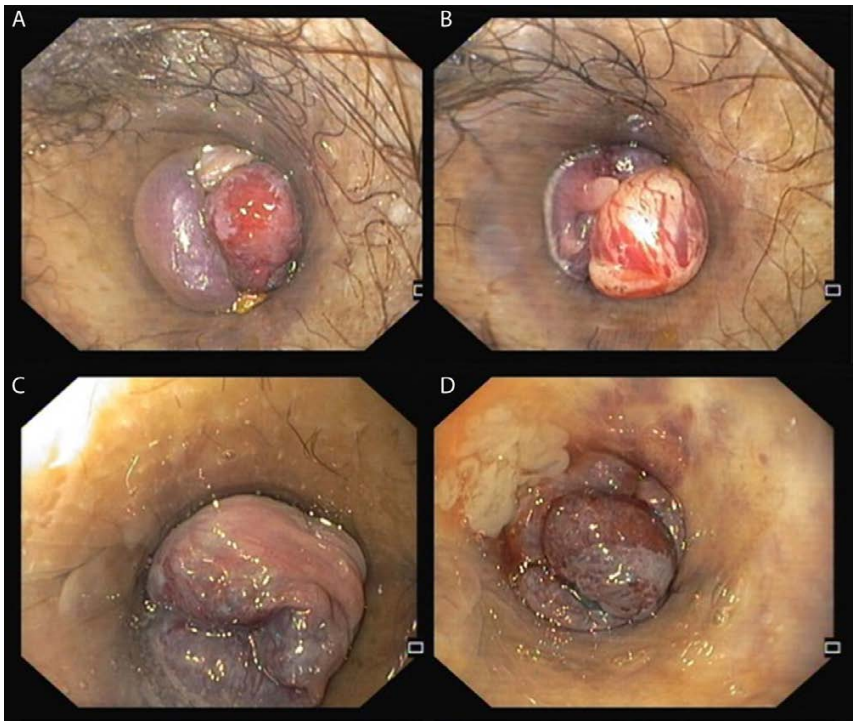


FIGURE 3. Anoscopy evaluation of internal hemorrhoidal disease grade II before (A) and after (B) polidocanol foam injection and before (C) and after (D) rubber band ligation

Efficacy Outcomes

Primary Outcomes Were Therapeutic Success and Recurrence

Therapeutic success, evaluated 3 weeks after each intervention, was defined as complete success (SHSS = 0 and HDBG ≤1), partial success (SHSS >0 and HDBG >1 but with improvement over initial scores), or therapeutic failure (patients who, at the end of 3 treatment sessions, maintained or worsened their initial SHSS and HDBG).

Recurrence during follow-up was classified as mild (SHSS and HDBG higher than at the beginning of follow-up but lower than at baseline, without need for intervention) or severe (SHSS and HDBG higher than before intervention).

Secondary efficacy outcomes included the required number of office-based treatment sessions and Goligher grade variation.

Safety Outcomes

Office-based procedure complications were recorded and classified as mild (eg, pain/discomfort, bright red blood on toilet paper, hemorrhoidal thrombosis requiring only medical treatment), moderate (eg, external hemorrhoidal thrombosis requiring surgical intervention, bright red blood that drips in the toilet not requiring blood transfusion or urgent surgery), or severe (eg, local/systemic infection; bleeding with hemodynamic instability, transfusion need, or urgent surgery; sexual impotence in men).

Sample Size and Statistical Analysis

Sample size calculation was based on therapeutic success. An estimated difference in therapeutic success of 29%[10,11] was assumed, and sample size was calculated considering a power of 80% (type II error β of 20%) and significance level α of 5% (type I error). A total of 88 patients (44 per group) was calculated. To safeguard against potential dropouts, a sample size of 120 (60 + 60) patients was considered.

Efficacy and safety outcomes were analyzed in an intention-to-treat analysis. Baseline characteristics and primary and secondary outcomes are presented as means with SD for normally distributed continuous variables and as medians with interquartile range for nonnormally distributed continuous variables. Categorical variables are described as frequency and percentages. Comparison of means was performed with the Student *t* test, and comparison of medians was performed with the Kruskal-Wallis test. Comparison of categorical variables was done using the χ^2 test or the Fisher exact test, where appropriate. Progression-free survival was compared using the log-rank (Mantel-Cox) test. Cox regression was used to determine risk factors for recurrence, and binary logistic regression was used to determine the risk factors for the occurrence of complications.

Statistical analysis software IBM SPSS Statistics 26.0 was used; p values <0.05 were regarded as statistically significant.

RESULTS

Baseline Characteristics

Two-hundred one patients were screened for participation between October 2018 and June 2019 (Fig. 4). Fifty-four patients did not meet inclusion criteria or had exclusion criteria and 27 declined to participate. One-hundred twenty patients were recruited and randomly assigned 1:1 to each arm (ie, 60 patients per study arm). No significant difference was found between the 2 therapeutic arms regarding baseline demographic characteristics and severity of HD (Table 1).

Efficacy Outcomes

Therapeutic success was observed in 93.3% of the patients in the PFS group compared with 85% in the RBL group (p = 0.14). Complete success was significantly higher in the PFS group (88.3% vs 66.7%, p = 0.009).

The RBL group needed more office-based sessions than the PFS group (1.6 ± 0.76 vs 1.3 ± 0.60, p = 0.02; Table 2). This difference was only significant for baseline Goligher grades II and III (Fig. 5). The number of interventions increased significantly with Goligher classification in the RBL group (p < 0.001) but not in the PFS group (Fig. 5).

In the PFS group, a mean total volume of 23.7 ± 10.8 mL of polidocanol foam was injected per patient (approximately 18 mL/session). The injected volume was higher with increasing Goligher classification (19.4 ± 6.5 mL, 22.9 ± 9.8 mL, and 28.5 ± 13.3 mL for grades I, II, and III; p = 0.01). In the RBL arm, a mean of 2.33 ± 1.09 elastic bands were required per patient (approximately 1.4 bands/session). The required number of elastic bands increased with the Goligher classification (1.44 ± 0.81, 2.20 ± 0.96, and 3.05 ± 0.91 for grades I, II, and III; p < 0.001).

Overall, only 13 patients (10.8%) did not achieve therapeutic success. Polidocanol foam sclerotherapy was unsuccessful in 4 patients, of whom 3 were successfully treated with RBL and 1 was referred for hemorrhoidal artery ligation. Rubber band ligation was unsuccessful in 9 patients, of whom 7 had therapeutic failure and 2 had moderate complications. From these, 7 were successfully treated with PFS and 2 were referred to surgery (Supplemental Digital Content 4 at http://links.lww.com/DCR/B817).

After excluding 13 patients who did not achieve therapeutic success, 107 patients (56 from the PFS group and 51 from the RBL group) were included in the follow-up period. Recurrence was observed in 1.87% (n = 2), 3.85% (n = 4), 11.0% (n = 11), and 14.8% (n = 13) of the patients at 3, 6, 9,

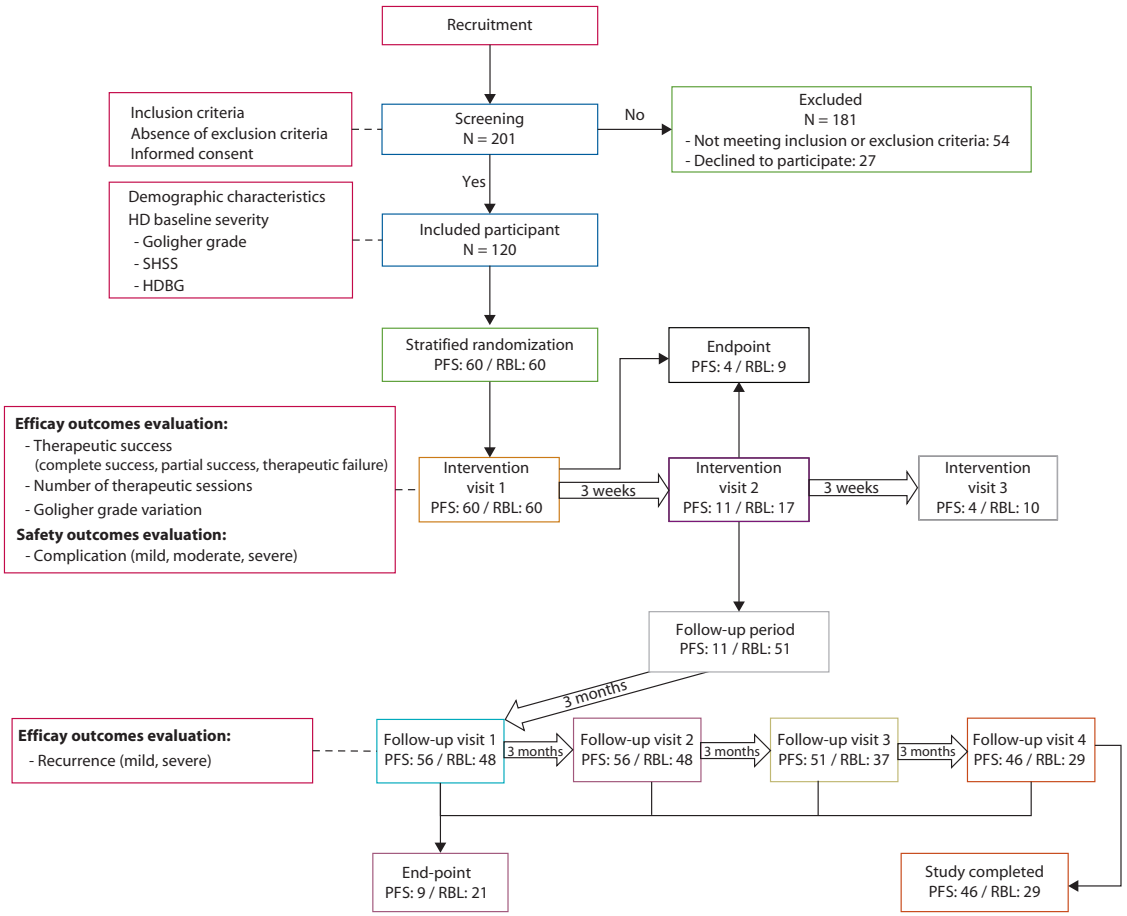


FIGURE 4. Trial flow chart diagram. Therapeutic success: complete success (SHSS = 0 and HDBG ≤1), partial success (SHSS >0 and HDBG >1 with improvement over baseline scores), and therapeutic failure (patients who, at the end of 3 treatment sessions, maintained or worsened their baseline SHSS and HDBG). Recurrence: mild (SHSS and HDBG higher than those at the beginning of the follow-up period but lower than at baseline, without the need for additional intervention); severe (SHSS and HDBG higher than the initial one requiring intervention). Follow-up; HD = hemorrhoidal disease; HDBG = hemorrhoidal disease bleeding grade; PFS = polidocanol foam sclerotherapy group; RBL = rubber band ligation group; SHSS = Sodergren hemorrhoid symptom severity score.

and 12 months. During follow-up, recurrence occurred in 9 patients (16.1%) from the PFS group and in 21 patients (41.2%) from the RBL group. Recurrence was severe in 5 patients (all from the RBL group). Two patients died of unrelated causes—one in each treatment group (Supplemental Digital Content 5 at http://links.lww.com/DCR/B817).

The mean recurrence-free survival was higher in the PFS group (11.78 months; 95% CI, 11.56–12.00) compared with the RBL group (10.74 months, 95% CI, 10.06–11.42; $p = 0.002$) (Fig. 6). In Cox regression analysis, the probability of recurrence was lower for the PFS group (HR, 0.335; 95% CI, 0.140–0.804; $p = 0.01$). No other variables had a detectable impact on recurrence risk (Table 3).

Safety Outcomes

The overall rate of complications was 20.0%, of which 91.7% were minor complications (pain/discomfort, 14; minor bleeding, 7; hemorrhoidal thrombosis requiring only medical treatment, 1). Two patients, both from the RBL group, were referred for surgical treatment due to moderate complications (hemorrhoidal thrombosis requiring drainage, 1; bleeding not requiring blood transfusion or urgent surgery, 1). No severe complications were observed (Table 4).

Complications were more frequent in the RBL group (30.0% vs 10.0%, $p = 0.01$). In binary logistic regression only PFS (OR, 0.282; 95% CI, 0.088–0.900; $p = 0.03$) was associated with a decreased risk of having complications (Table 5).

DISCUSSION

Our study is the first comparing PFS and RBL in the treatment of HD grades I to III. We found that PFS is more

TABLE 1. Baseline characteristics of the participants

Participant characteristics	*Total (n = 120)*	*PFT group (n = 60)*	*RBL group (n = 60)*	*p value*
Age, y, mean ± SD	53.7 ± 14.7	53.1 ± 15.5	54.3 ± 14.0	0.68
Sex, n (%)				0.86
Female	65 (54.2)	33 (55.0)	32 (53.3)	
Male	55 (45.8)	27 (45.0)	28 (46.7)	
BMI, mean ± SD	26.1 ± 4.5	25.9 ± 4.7	26.3 ± 4.3	0.63
Goligher grade,[a] n (%)				
I	32 (26.7)	16 (26.7)	16 (26.7)	
II	50 (41.7)	25 (41.7)	25 (41.7)	
III	38 (31.7)	19 (31.7)	19 (31.7)	
Hemorrhoidal disease bleeding grade, n (%)				0.70
1	42 (35.0)	20 (33.3)	22 (36.7)	
2	78 (65.0)	40 (66.7)	38 (63.3)	
Sodergren hemorrhoid symptom severity score, median (IQR)	7 (4.00)	7 (4.00)	7 (7.00)	0.07

Tests used to compare variables between groups: *t* test (age and BMI); χ^2 test (sex, Goligher grade, and bleeding grade); Mann-Whitney test (Sodergren Score).
IQR = interquartile range; PFS = polidocanol foam sclerotherapy; RBT = rubber band ligation.
[a]Randomization was stratified by the Goligher classification.

effective than RBL, with a significantly lower rate of recurrence and complications.

The interpretation of published studies comparing sclerotherapy with RBL or other HD therapies is not trivial. Sclerosing agents vary, as do the doses and injection methods used. On the other hand, subjective evaluation of prolapse reduction, intermittent blood loss, and recurrence of HD make comparative analyses difficult.

We used a combination of SHSS[22] (a validated symptom score) with HDBG[23] and the Goligher classification[21] to overcome the subjectivity typically associated with previously published clinical studies aimed at comparing different HD treatments. Stratified randomization made it possible to homogenize both therapeutic arms making them comparable in terms of baseline HD severity.

A meta-analysis of 18 randomized trials comparing various treatment methods for grade I to III HD concluded that RBL was more effective than sclerotherapy with liquid sclerosants and that patients who underwent ligation were less likely to need subsequent therapy.[10] Success rates of RBL range between 69% and 97%.[11] Concerning PFS efficacy, Fernandes and Fonseca[19] reported excellent results with 98% of 2000 patients (with HD grades II to IV) reporting subjective satisfaction with this therapy. Moser et al[18] compared the efficacy of liquid versus foam polidocanol in a trial of randomly assigned patients with HD grade I. Significantly better results were obtained with the foam formulation, with 88% of the patients treated successfully after only 1 sclerotherapy session. The participants in the group of polidocanol foam needed fewer sclerotherapy sessions than those treated with the liquid sclerosant (1.08 vs 1.42, $p = 0.001$).[18] More recently, Lobascio et al[20] evaluated the efficacy of polidocanol foam in 66 patients with HD grades II and III and reported a success rate of 86%. Participants were submitted to a mean of 1.21 office-based procedures.

TABLE 2. Efficacy outcomes

Outcomes	*PFS group (n = 60)*	*RBL group (n = 60)*	*p value*
Number of treatment sessions, mean ± SD	1.32 ± 0.60	1.62 ± 0.76	0.02
1, n (%)	45 (75.0)	33 (55.0)	
2, n (%)	11 (18.3)	17 (28.3)	
3, n (%)	4 (6.67)	10 (16.7)	
Goligher grade variation,[a] mean ± SD	−0.93 ± 0.80	−0.67 ± 0.82	0.07
HBDG variation,[a] mean ± SD	−1.28 ± 0.67	−1.02 ± 0.70	0.04
SHSS score variation,[a] mean ± SD	−7.18 ± 3.90	−4.43 ± 3.45	<0.001
Therapeutic success,[b] n (%)			0.14
Yes	56 (93.3)	51 (85.0)	
No	4 (6.67)	9 (15.0)	
Complete success, n (%)			0.009
Yes	53 (88.3)	40 (66.7)	
No	7 (11.7)	20 (33.3)	

Tests used to compare variables between groups: *t* test (average number of treatment sessions); Mann-Whitney test (bleeding grade variation, Goligher grade variation, Sodergren score variation); χ^2 test (treatment success).
HDBG = hemorrhoidal disease bleeding grade; PFS = polidocanol foam sclerotherapy; RBL = rubber band ligation; SHSS = Sodergren hemorrhoid symptom severity.
[a]Variable computed as measurement at the end of the intervention period minus baseline.
[b]Patients who achieved complete or partial success.

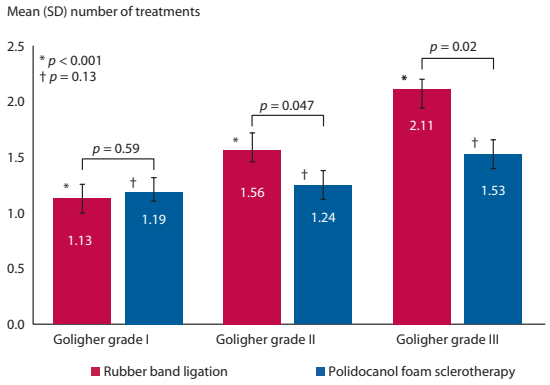
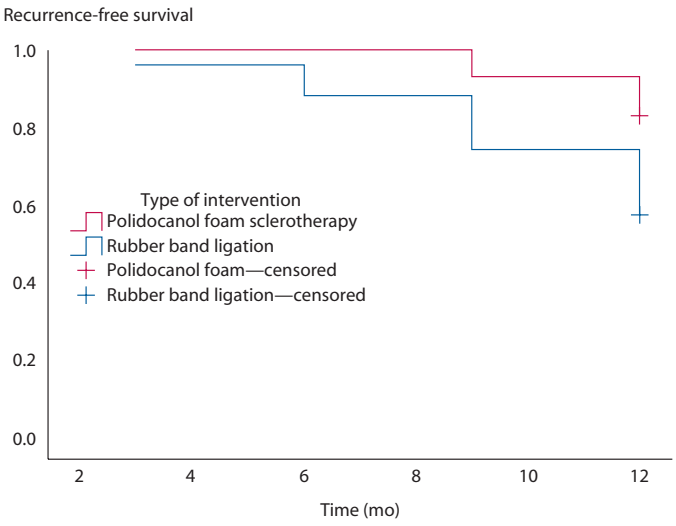


FIGURE 5. Comparison of mean number of treatments by treatment group and initial Goligher grades.

We achieved success rates comparable to those previously reported. Although there was a higher overall therapeutic success rate in the PFS group, the difference between the 2 techniques was not significant (93.3% vs 85%, $p = 0.14$). However, if we consider complete success rates, there was a significant difference favoring PFS over RBL (88.3% vs 66.7%, $p = 0.009$). Despite both techniques acting locally in the hemorrhoidal cushions, this difference in favor of PFS may be explained by a locally disseminated vascular sclerosis caused by the spreading of a considerable volume of foam along the hemorrhoidal plexus after the injection. The application of rubber bands exerts a much more localized and therefore perhaps less effective vascular disruption effect (Fig. 1). This mechanism may also explain our finding that, among more advanced hemorrhoidal grades (Goligher II and III), fewer therapeutic sessions were needed in the sclerotherapy group. In addition, we could observe that more RBL sessions were needed for increasing Goligher grades, which was contrary to PFS, where the injected polidocanol foam volume was higher with increasing Goligher grades but the number of treatment sessions did not increase significantly. These findings mean that, for more advanced hemorrhoidal grades, PFS allows more intensive hemorrhoidal treatment in each session by increasing the volume of the injected foam without increasing the number of treatment sessions. Another explanation of the higher number of treatment sessions in the RBL group is that, when a rubber band is applied in a hemorrhoid cushion, the access to the other cushions can be lost, making it necessary to perform additional sessions to treat all the hemorrhoidal cushions.

Thus, the higher effectiveness of PFS in more advanced HD resulted in fewer treatment sessions and medical visits, making this new office-based therapy very attractive in terms of the consumption of health resources.



Number at risk (events)

	0	3	6	9	12
Polidocanol foam sclerotherapy	55	55 (0)	55 (0)	51 (4)	46 (5)
Rubber band ligation	50	48 (2)	44 (4)	37 (7)	29 (8)

FIGURE 6. Kaplan-Meier curve for recurrence-free survival.

TABLE 3. Hazard ratios for the risk of recurrence

Characteristics	*HR (95% CI)*	*p value*
Age	1.007 (0.981–1.034)	0.613
BMI	0.922 (0.835–1.018)	0.109
Goligher grade, baseline		0.412
II	1.938 (0.658–5.705)	0.230
III	1.351 (0.368–4.962)	0.651
HDBG, baseline	1.788 (0.731–4.369)	0.203
SHSS score, baseline	1.096 (0.958–1.254)	0.183
Type of intervention (PFS)	0.335 (0.140–0.804)	0.014
Number of treatments	1.492 (0.734–3.036)	0.269
Success type (partial)	2.415 (0.930–6.271)	0.070

HDBG = hemorrhoidal disease bleeding grade; PFS = polidocanol foam sclerotherapy; SHSS = Sodergren hemorrhoid symptom severity.

Overall, both therapies were quite effective, with only 13 patients having therapeutic failure: 9 patients in the RBL group and 4 in the PFS group. However, most of the patients were successfully treated with other office-based treatments. Only 3 patients from our study were referred to surgery.

After office-based treatments, patients received systemic phlebotonic and topical medications for 2 weeks. As a venotropic agent, we used diosmin. A Cochrane review including 24 trials compared venotropics (mostly flavonoids) with placebo or no therapy and found a significant overall improvement in the intervention group.[25] For topical application, we used ruscogenin (venotropic) and trimebutine (spasmolytic). Although topical treatment is not supported by well-designed, robust studies, its use seems to be useful in the short-term treatment of HD.[8,9]

Recurrence of HD symptoms after office-based therapies, in general, is high across different studies. For RBL, recurrence of bleeding is reported to occur in 10% to 46% of the patients, and recurrence of prolapse is reported in up to 34% of the patients.[11] On the other hand, for injection (liquid) sclerotherapy, recurrence of bleeding is reported from 1.5% to 29.0% and recurrence of prolapse is reported in up to 16% of patients.[11]

In our study, we showed recurrence rates comparable to those previously described, and the probability of recurrence was lower for the PFS group. It is important to note that most of the recurrences were mild. We showed results slightly more favorable than those observed by Lobascio et al,[20] who reported recurrence rates of 21.1% for PFS in second- and third-degree HD. The follow-up period in that study was comparable to ours (1 year), yet 26.7% of our patients had first-degree HD, which may have contributed to our lower recurrence rates.

TABLE 4. Safety outcomes

Outcome	*All (n = 120)*	*PFS group (n = 60)*	*RBL group (n = 60)*	*p value*
Complications, n (%)	24 (20.0)	6 (10.0)	18 (30.0)	0.01
Mild	22 (18.3)	6 (10.0)	16 (26.7)	
Moderate	2 (1.67)	0 (0.00)	2 (3.33)	
Severe	0 (0.00)	0 (0.00)	0 (0.00)	

Tests used to compare variables between groups: Fisher exact test.
PFS = polidocanol foam sclerotherapy; RBL = rubber band ligation.

TABLE 5. Odds ratios for the risk of complications

	OR	*(95% CI)*	*p value*
Age	1.009	(0.974–31.046)	0.620
BMI	0.897	(0.781–31.029)	0.121
Goligher grade, baseline			0.226
II	0.515	(0.124–32.134)	0.360
III	1.830	(0.310–310.823)	0.505
HDBG, baseline	1.201	(0.372–33.882)	0.760
SHSS score, baseline	1.039	(0.845–31.277)	0.717
Type of intervention (PFS)	0.282	(0.088–30.900)	**0.032**
Number of interventions	4.484	(0.917–321.929)	0.064

HDBG = hemorrhoidal disease bleeding grade; PFS = polidocanol foam sclerotherapy; SHSS = Sodergren hemorrhoid symptom severity.

Bleeding and pain are among the most frequent complications associated with RBL. Postligation bleeding rates range from 3.5% to 50%, whereas postprocedure pain ranges from 8% to 80% in different series.[26] Bleeding is rare with hemorrhoidal sclerosis, making this technique a valid option for patients with bleeding disorders.

We observed complications in 24 patients (20.0%) that were more frequent in the RBL group (30.0% vs 10.0%, $p = 0.01$). These complications were mostly minor (91.7%) and did not imply any change in the therapeutic approach. Only 2 patients, both in the RBL group, experienced moderate complications.

Our study has limitations. First, it was performed in a single tertiary center, which may hinder generalization of our data to other populations. Second, both patients and the performers of the techniques were not blinded to treatment group, so ascertainment bias cannot be excluded. However, efficacy and safety outcomes obtained for both therapeutic arms are similar to those observed in previous studies, which argues against this. In addition, the use of patient-reported scores reduced the possible occurrence of bias associated with the lack of researcher blinding.

The strengths of this study include our randomization strategy, allowing for direct group comparison without significant differences concerning baseline HD severity. Also, patients were followed up for 1 year without losses of follow-up.

CONCLUSION

Both office-based procedures compared in this clinical trial proved to be effective in the treatment of HD grades I to III. Polidocanol foam sclerotherapy was more effective than RBL when considering complete success (symptom-free patients). Patients in the PFS group needed fewer office-based treatment sessions, had lower recurrence

rates, and were less likely to have complications than those undergoing RBL. These results show that PFS may offer clinical advantages compared with RBL, which is the current treatment standard. In addition, PFS is competitive compared with RBL in terms of health care resource use and costs.

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Supplemental Digital Content 1: GOLIGHER'S CLASSIFICATION

Grade	Degree of prolapse
I	No prolapse
II	Prolapse on defecation with spontaneous reduction
III	Prolapse on defecation requiring manual reduction
IV	Prolapse and irreducible

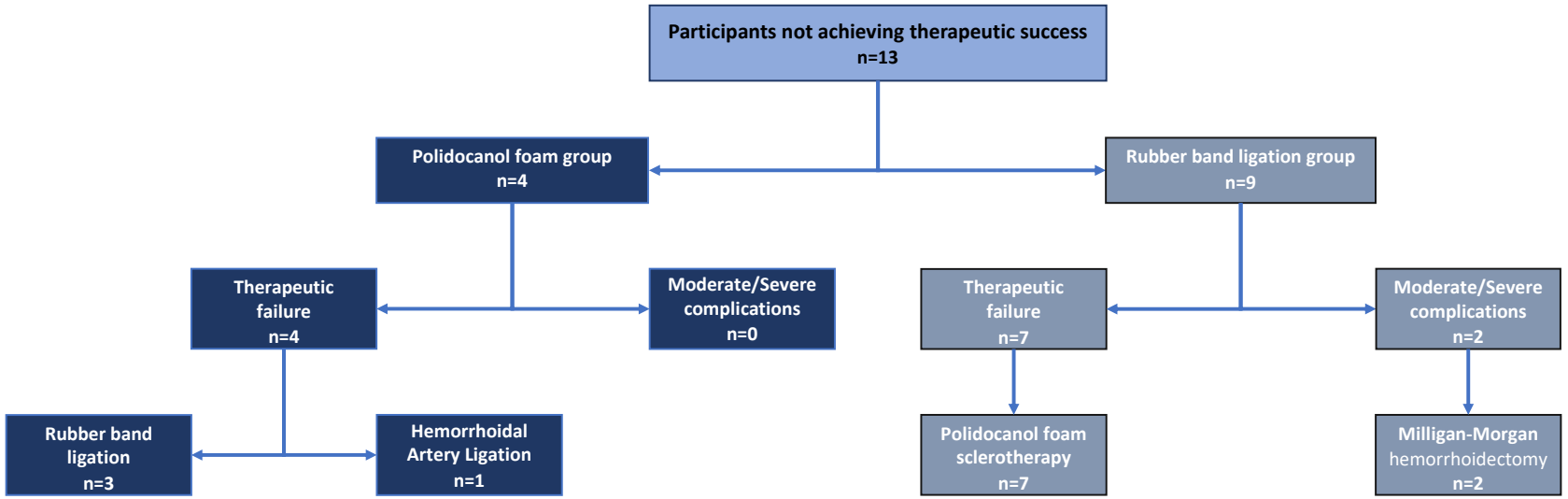
Supplemental Digital Content 2: SODERGREN HEMORRHOID SYMPTOM SEVERITY SCORING SYSTEM

1) have you considered or excluded another pathology? Yes/No 2) Does the patient suffer from rectal bleeding? Yes/No Only proceed with questionnaire if YES is the answer to both questions Please answer the following questions relating to symptoms, at or around your anus.		
Symptoms		**Points score**
How severe are your symptoms of itching or irritation? (circle number from 1-5)	0 No symptoms 1 Mild / do not really bother 2 me 3 4 Moderately bothersome 5 Severe	0 0 0 0 4 4
How severe are your symptoms of pain or discomfort at rest? (circle number from 1-5)	0 No symptoms 1 Mild / do not really bother m 2 3 Moderately bothersome 4 5 Severe	0 0 0 3 3 3
How severe are your symptoms of pain or discomfort on opening your bowels? (circle number from 1-5)	0 No symptoms 1 Mild / do not really bother 2 me 3 4 Moderately bothersome 5 Severe	0 0 0 0 3 3
How often do you feel that you might have a lump at your anus (prolapse)?	0 Never 1 Less than once a month 2 More than once a month 3 More than once a week 4 Every day	0 0 0 0 4
		Final score (0 – 14 points)

Supplemental Digital Content 3: HEMORRHOIDAL DISEASE BLEEDING GRADE

Type of bleeding	Grade
No rectal bleeding	0
Bleeding when passing stool less than once a week	1
Bleeding when passing stool 1–6 days per week	2
Bleeding when passing stool every day or with hemodynamic/laboratorial changes (anemia, with or without transfusion need, signs of hypovolemia)	3

Supplemental Digital Content 4: Participants not achieving therapeutic success flow chart diagram



SUPPLEMENTAL DIGITAL CONTENT 5: RECURRENCE COMPARISON BETWEEN TREATMENT GROUPS

	All	Polidocanol foam	Rubber band ligation	p
Recurrence 3 months	(n=107)	(n=56)	(n=51)	
				0.184
None: n (%)	104 (97.2)	56 (100.0)	48 (94.1)	
Severe: n (%)	2 (1.87)	0 (0.00)	2 (3.92)	
Deceased: n (%)	1 (0.93)	0 (0.00)	1 (1.96)	
Recurrence 6 months	(n=104)	(n=56)	(n=48)	
				0.088
None: n (%)	100 (96.2)	56 (100.0)	44 (91.7)	
Mild: n (%)	2 (1.92)	0 (0.00)	2 (4.17)	
Severe: n (%)	2 (1.92)	0 (0.00)	2 (4.17)	
Recurrence 9 months	(n=100)	(n=56)	(n=44)	
				0.357
None: n (%)	88 (88.0)	51 (91.1)	37 (84.1)	
Mild: n (%)	10 (10.0)	4 (7.14)	6 (13.6)	
Severe: n (%)	1 (1.00)	0 (0.00)	1 (2.27)	
Deceased: n (%)	1 (1.00)	1 (1.79)	0 (0.00)	
Recurrence 12 months	(n=88)	(n=51)	(n=37)	
				0.123
None: n (%)	75 (85.2)	46 (90.2)	29 (78.4)	
Mild: n (%)	13 (14.8)	5 (9.80)	8 (21.6)	

Tests used to compare variables between groups: Chi-square test (Recurrence).

CHAPTER V - “A NEW HOPE FOR A VULNERABLE POPULATION”

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Polidocanol foam sclerotherapy in the treatment of hemorrhoidal disease in patients with bleeding disorders: a multicenter, prospective, cohort study

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ORIGINAL ARTICLE

Polidocanol foam sclerotherapy in the treatment of hemorrhoidal disease in patients with bleeding disorders: a multicenter, prospective, cohort study

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Abstract

Background The management of hemorrhoidal disease (HD) in patients with bleeding disorders (BD) is challenging. Polidocanol foam sclerotherapy (PFS) is associated with a low rate of bleeding complications. The aim of this study was to compare the efficacy and safety of PFS in the treatment of HD in patients with and without BD.

Methods This prospective, multicenter, cohort study enrolled patients with (group B) and without (group A) BD, with symptomatic internal HD grades I–III over an 18-month period. All patients were treated with PFS. Patients with congenital BD did not undergo prior replacement therapy and those with acquired BD due to antithrombotic drugs, did not discontinue therapy. Efficacy outcomes included therapeutic success and HD recurrence during a 1-year follow-up period. To evaluate safety the complications related to PFS were recorded.

Results We included 228 patients (group A: 155, group B: 73; male/female: 114/114; mean age: 59.4 ± 15.9 years). The baseline hemorrhoidal disease bleeding grade ($p < 0.001$) and Sodergren hemorrhoidal symptom severity score ($p = 0.019$) were higher for group B. The overall therapeutic success rate was 93.4% with an average number of sessions of 1.51 ± 0.74, significantly higher for group B (1.68 ± 0.86 *vs* 1.43 ± 0.65, $p = 0.013$). Complications occurred in 11.4% of the patients, with bleeding reported in 4.8%. The majority of complications were mild (96.2%). No significant differences between the two groups were observed for therapeutic success, recurrence, or complication rate.

Conclusions Patients with BD may have more symptomatic HD at baseline. Even so, PSF showed similar effectiveness and safety in patients with BD compared to patients without BD.

Keywords Polidocanol foam · Hemorrhoidal disease · Sclerotherapy · Bleeding disorder

Introduction

Hemorrhoidal disease (HD) is one of the most common proctologic diseases [1–5]. The management of HD should be guided by patients' preference, comorbidities, disease grade, and treatment efficacy and safety [1, 6–14].

For symptomatic internal HD grades I to III refractory to conservative management, an office-based procedure should be offered as first line treatment [1, 7, 15–17]. Rubber band ligation (RBL) has been recommended as the gold standard treatment due to higher efficacy and lower recurrence rate [1, 11, 15, 18, 19]. However, high post-procedural bleeding rates (ranging from 3.5% to-50%), including late bleeding, have been reported [1, 15, 18, 20]. Sclerotherapy is associated with lower bleeding rates but is more recurrence-prone [1, 15, 21–24]. The innovative use of polidocanol as a foam has drawn attention in recent years because of its improved

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sclerosing capacity, superior efficacy, the need for fewer office-based sessions and less complications, including bleeding and pain [15, 21–23, 25, 26]. Polidocanol foam sclerotherapy (PFS) induces a local inflammatory reaction that leads to local sclerosis of submucosal tissue, and promotes fixation of the hemorrhoidal tissue and obliteration of the vascular bed with tissue fibrosis [27, 28]. This technique has been shown to be reproducible, cost effective, and associated with great patient satisfaction [15, 21–23, 26, 28–30].

Hemorrhoidal bleeding is both a major symptom and a treatment complication [1, 4, 5]. Patients with congenital or acquired (induced by antithrombotic therapy) bleeding disorders (BD) are vulnerable groups, with higher risk of bleeding. In these patients, HD management is more challenging as RBL and surgery might be contraindicated or require withholding of antithrombotic therapy, increasing the risk of thrombosis [1, 11, 31, 32].

With the increase in general life expectancy and high prevalence of cardiovascular disease, there is a growing use of antiplatelet and anticoagulant therapy, [33–36] which is associated with gastrointestinal bleeding risk ranging from 1.5 to 4.5% [37–42]. Patients with congenital BD, including hemophilia A and von Willebrand disease (VWD), are also predisposed to spontaneous, traumatic, and intervention-related bleeding. Gastrointestinal bleeding is at least two times more frequent and can account for half of all bleeding-related acute care admissions in these patients [43–45].

The management of HD in patients with congenital and acquired BD is far from optimally defined. Considering their higher bleeding risk and increased rate of surgical complications, they should benefit from less invasive office-based procedures for HD. Recently, Fernandes et al. [21] reported a promising triad of high efficacy, high tolerability, and high safety of PSF in a significantly large population that included patients with BD [15, 21]. More robust data on efficacy and safety of PFS treatment on these patients is required.

The aim of our study was to prospectively evaluate the efficacy and safety of PSF in the treatment of internal refractory HD grades I to III, comparing outcomes of patients with and without BD.

Materials and methods

Study design

We conducted a prospective, multicentre, cohort study enrolling patients with symptomatic HD grades I to III referred to the Proctology outpatient clinics of three tertiary hospitals.

The study was approved by the ethics committees of the intervening institutions and was registered at ClinicalTrials.gov with the identifier NCT04188171.

Participant selection

Inclusion criteria

Adult patients with HD grades I to III refractory to conservative therapy for at least 4 weeks (topical ruscogenin and trimebutine and oral diosmin), referred to the proctology outpatient clinics of three tertiary hospitals (Centro Hospitalar Universitário do Porto, Porto; Hospital da Senhora da Oliveira, Guimarães; and Hospital Professor Doutor Fernando Fonseca, Amadora), submitted to PFS from August 1st, 2018 until February 1st, 2020.

All participants had lower gastrointestinal endoscopy prior to inclusion.

Participants were assigned to one of two groups: group A, without BD (normal hemostasis laboratory tests and absent hemorrhagic symptoms) or group B, with BD (congenital BD or acquired due to antithrombotic therapy).

Exclusion criteria

The following patients were excluded: patients with known allergy to polidocanol, liver cirrhosis, inflammatory bowel disease, immunosuppression, other concomitant symptomatic perianal disease, pregnant and lactating women, history of HD office-based or surgical treatment in the previous 6 months.

Visits and outcomes

In the first visit, demographic data, HD baseline severity and presence and type of BD were collected. HD baseline severity was assessed using the Goligher classification (ESM Table 1) [12], the hemorrhoidal disease bleeding grade (HDBG) (ESM Table 2) and the Sodergren hemorrhoid symptom severity (SHSS) scoring system (ESM Table 3) [9, 10]. All patients received information about the enrollment and signed informed consent.

This cohort study included an intervention period (3 months) for evaluating efficacy and safety outcomes and a follow-up period (1 year) to assess for recurrence of disease.

Efficacy evaluation: intervention period and follow-up

The primary outcome for efficacy evaluation during the intervention period was therapeutic success, defined by an improvement in HDBG and SHSS score over baseline.

The required number of sessions (maximum of 3, at 1-month intervals) was decided by clinical and anoscopic evaluation: if after a month from the last intervention the patient had no significant HD on anoscopy, a HDBG

Table 1 Baseline characteristics and severity of hemorrhoidal disease of the participants (group A – without bleeding disorder; group B – with bleeding disorder)

	All ($n=228$)	Group A ($n=155$)	Group B ($n=73$)	p
Age (years): Mean ± SD	59.4 ± 15.9	54.3 ± 15.0	70.1 ± 12.0	***< 0.001***
Gender: *n* (%)				*0.118*
Female	114 (50.0)	83 (53.5)	31 (42.5)	
Male	114 (50.0)	72 (46.5)	42 (57.5)	
BMI: Mean ± SD	26.2 ± 4.5	26.0 ± 4.5	26.7 ± 4.5	*0.312*
Goligher grade: n (%)				*0.054*
I	45 (19.7)	36 (23.2)	9 (12.3)	
II or III	183 (80.3)	119 (76.8)	64 (87.7)	
Hemorrhoidal disease bleeding grade: *n* (%)				***< 0.001***
1	42 (18.4)	40 (25.8)	2 (2.7)	
2	166 (72.8)	111 (71.6)	55 (75.4)	
3	20 (8.8)	4 (2.6)	16 (21.9)	
Sodergren hemorrhoidal symptom severity score: median (IQR)	7 (4)	7 (4)	10 (3)	***0.019***

SD standard deviation, *IQR* interquartile range

Tests used to compare variables between groups: *T* test (Age and body mass index); Chi-square test (Gender, Goligher grade and initial bleeding grade); Mann–Whitney test (Sodergren score)

Table 2 Efficacy outcomes (intervention period)

	All ($n=228$)	Group A ($n=155$)	Group B ($n=73$)	p
Therapeutic success—*n* (%)				
Yes	213 (93.4)	144 (92.9)	69 (94.5)	*0.646*
No	15 (6.6)	11 (7.1)	4 (5.5)	
Number of treatment sessions—Mean ± SD	1.51 ± 0.74	1.43 ± 0.65	1.68 ± 0.86	
1 session—*n* (%)	145 (63.6)	103 (66.5)	42 (57.5)	*0.013*
2 sessions—*n* (%)	50 (21.9)	38 (24.5)	12 (16.4)	
3 sessions—*n* (%)	33 (14.5)	14 (9.0)	19 (26.0)	
Polidocanol dosage (total)—Mean ± SD	22.6 ± 10.9	22.5 ± 10.5	22.9 ± 11.7	*0.763*
Bleeding grade variation*—Mean ± SD	− 1.54 ± 0.71	−1.39 ± 0.70	− 1.85 ± 0.64	*< 0.001*
Sodergren score variation*—Mean ± SD	− 7.31 ± 3.70	−7.14 ± 3.70	− 7.67 ± 3.70	*< 0.001*

*SD*standard deviation

*Variable computed as measurement in the end of the intervention period minus baseline

Tests used to compare variables between groups: *T* test (Average number of treatment sessions; Polidocanol dosage, Sodergren score variation); Mann–Whitney test (Bleeding grade variation, Goligher grade variation); Chi-square test (Therapeutic success)

Table 3 Safety outcomes (complications)

	All ($n=228$)	Group A ($n=155$)	Group B ($n=73$)	P
Global complications—*n* (%)	26 (11.4)	19 (12.3)	7 (9.6)	*0.554*
Mild	25	19	6	
Severe	1	0	1	
Bleeding – *n* (%)	11 (4.8)	7 (4.5)	4 (5.5)	*0.751*
Mild	10	7	3	
Severe	1	0	1	

Tests used to compare variables between groups: Chi-square test

score ≤ 1 and a SHSS = 0, he would not be candidate to further therapy. Therapeutic failure was defined by maintenance or worsening of the initial HDBG and SHSS after 3 treatment sessions.

Number of office-based therapy sessions was defined as secondary efficacy outcome.

The efficacy outcome during the follow-up period was recurrence of disease (for those with therapeutic success), defined by a SHSS and HDBG score greater than at the end of the intervention period. Regardless of the number of treatment sessions, all participants were evaluated for recurrence at consecutive periods of 3 months for a 12-month period.

Safety evaluation

PFS-related complications were reported throughout the study. These were classified as mild if limited (e.g., pain/discomfort, minor bleeding, external hemorrhoidal thrombosis not requiring intervention), or severe if implying additional intervention, clinical risk and/or long-term effect (e.g., bleeding requiring blood transfusion, with hemodynamic instability or need of urgent surgery; external thrombosis requiring surgical intervention; urinary retention, prostatic infection, or sexual dysfunction in men; perineal abscess or sepsis).

Procedures and technical aspects

Procedures were performed on an outpatient basis, without use of sedation or local anesthesia, by three experienced proctologists. The patients with congenital BD did not have prior replacement therapy and those with acquired BD did not suspend antithrombotic therapy. A cleaning enema was prescribed before each session.

Polidocanol foam was prepared according to the *Tessari´s* technique, using 4 ml of liquid polidocanol 3% (Aethoxysklerol®) mixed with 16 ml of air in two disposable 20 mL syringes, through a three-way tap [25, 46] (Fig. 1). The sclerosant was applied shortly after preparation to preserve stability, according to the *Blanchard's* technique (Fig. 2), through a disposable transparent anoscope, with the patient in genupectoral position, using an intravenous 20G needle adapted to a 10 cm reusable extender. The procedure has a fast learning curve, comparable to RBL. It could be performed on > 1 hemorrhoidal pile (depending on the number of engorged hemorrhoidal cushions identified during anoscopy), with a maximum dose of 20 mL per session (each pile was injected until significant resistance was felt on the syringe plunger).

Statistical analysis

Differences in means were assessed with Student's *t* test and differences in medians with the Kruskal–Wallis test. Comparison of categorical variables was assessed using

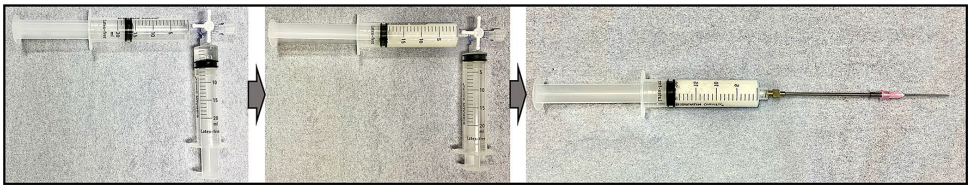

Fig. 1 Polidocanol foam preparation (Tessari´s technique)

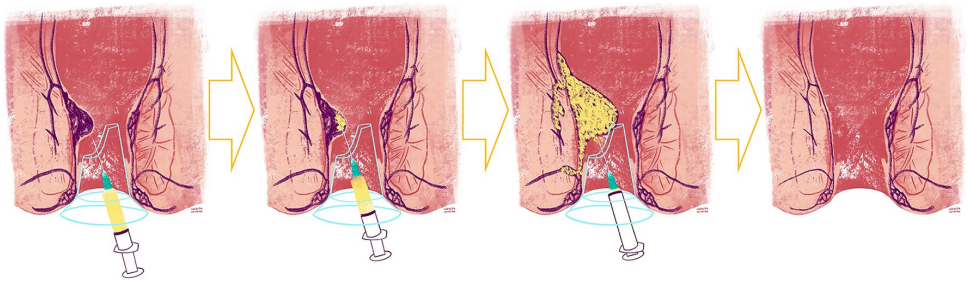

Fig. 2 Schematic representation of polidocanol foam sclerotherapy (according to Blanchard's technique)

the Chi-square test or Fisher's exact test, where appropriate. Progression free-survival was compared using the Log Rank (Mantel-Cox) test. Cox regression was used to assess risk factors for recurrence and binary logistic regression to assess the risk factors for the occurrence of complications. The IBM® SPSS® statistics software version 26.0 was used for all the statistical analysis. A p value < 0.05 was regarded as statistically significant.

Results

Baseline characteristics

From a total of 261 patients (24 patients did not meet inclusion criteria and 9 declined to participate), 228 were enrolled in the study (male/female: 114/114; mean age: 59.4 ± 15.9 years). One hundred and fifty-five patients were included in group A (without BD) and 73 patients in the group B (with BD) (Fig. 3). Group B was further divided into 7 subgroups according to type of BD (Fig. 4). Sixty-four patients were on antithrombotic therapy (including an antiplatelet or anticoagulant drug or both) and 9 patients had hereditary BD including VWD ($n = 3$), severe hemophilia A ($n = 2$), inherited macrothrombocytopaenia ($n = 1$) and hyperfibrinolysis syndrome ($n = 3$), with bleeding score by ISTH-BAT (international society of thrombosis and hemostasis – bleeding assessment tool) consistent with moderate hemorrhagic disease. [47]

Considering the baseline characteristics of the participants (Table 1), the mean age was significantly higher for Group B (70.1 ± 12.0 years *vs* 54.3 ± 15.0 years, $p < 0.001$). Regarding HD baseline severity, significantly more patients in the group B had HD with HDBG 2 or 3 (74.2% vs 97.3%, $p < 0.001$) and SHSS score was also significantly higher for this group (7 vs 10, $p = 0.019$).

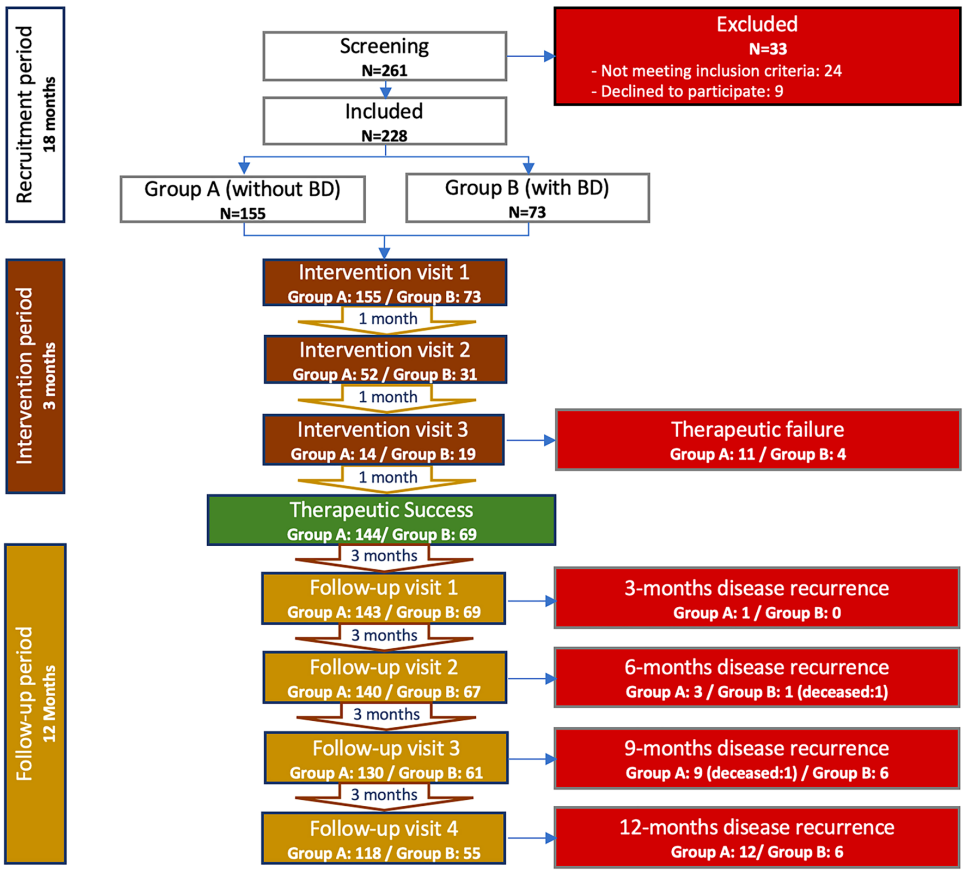

Fig. 3 Study flowchart. BD: bleeding disorders

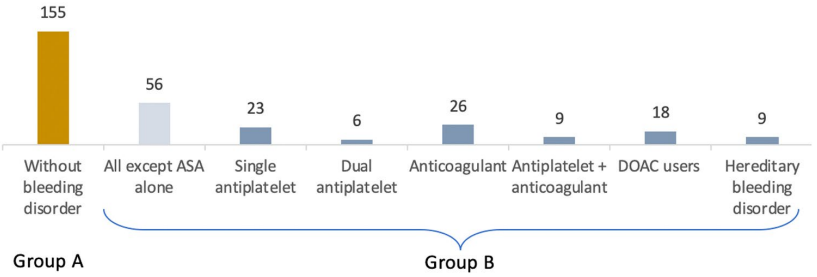

Fig. 4 Participants enrolled in the study (Group B subgroups). *ASA* aminosalicylic acid, *DOAC* Direct oral anticoagulants

Efficacy evaluation: Intervention period

The overall therapeutic success rate was 93.4% (n = 213), with no significant differences between groups (92.9% *vs* 94.5%, *p = 0.646*). Treatment was unsuccessful in 11 patients from group A and 4 patients from group B (Table 2).

The average number of sessions per patient was 1.51 ± 0.74 (min = 1, max = 3), significantly higher for group B (1.68 ± 0.86 *vs* 1.43 ± 0.65, *p = 0.013*).

The average volume of polidocanol injected was 22.6 ± 10.9 mL (group A: 22.5 ± 10.5 mL *vs* group B: 22.9 ± 11.7 mL; min. 8 mL, max. 60 mL), without significant differences between the two groups (p = 0.763).

Safety evaluation: type and rate of complications

Complications (Table 3) occurred in 11.4% (n = 25) of the patients (group A: 12.3% vs group B: 9.6%, *p = 0.554)*. Most were mild (96.2%): pain/discomfort (*n* = 14); minor bleeding (*n* = 10) and dyschezia (*n* = 1). Severe complications occurred in 1 patient group B (rectal bleeding requiring blood transfusion).

Bleeding complications were reported in 4.8% (*n* = 11) of the participants with no significant differences between the two groups (group A: 4.5%, *n* = 7 vs group B: 5.5%, *n* = 4; *p = 0.751*).

None of the baseline characteristics was a significant predictor for the occurrence of complications (Table 4).

In subgroup analysis, we found no significant differences in rate of complications from PFS between group B subgroups (Table 5).

Efficacy evaluation: Follow-up period

Two hundred and thirteen patients were included in the follow-up period (group A *n* = 144; Group B *n* = 69); 82.5% and 80.9% patients from groups A and B, respectively, showed no recurrence at 1-year of follow-up. Recurrence rates presented no significant differences between groups at any follow-up time point (Table 6; Fig. 5). Also, the mean time for recurrence at 12 months was not significantly different between the groups (group A: 11.7 ± 0.10 months *vs* group

Table 4 Hazard ratios for the risk of complications

	OR	(95% CI)	*P*
Age	1.002	(0.972, 1.032)	*0.919*
BMI	0.892	(0.793, 1.004)	*0.057*
Baseline Goligher grade			
II	0.376	(0.112, 1.264)	*0.114*
III	0.419	(0.106, 1.657)	*0.215*
Baseline hemorrhoidal disease bleeding grade			
2	0.572	(0.172, 1.900)	*0.361*
3	0.810	(0.116, 5.673)	*0.832*
Baseline Sodergren hemorrhoidal symptom severity score	1.109	(0.946, 1.301)	*0.202*
Group (B)	0.928	(0.263, 3.273)	*0.908*

OR odds ratio, *CI* confidence interval, *BMI* body mass index

Table 5 Safety outcomes (group B subgroups)

	Total—*n*	Complications—*n* (%)	*p*
Group A (without BD)	155	19 (12.3)	
Group B (All except ASA alone)	56	6 (10.7)	*0.533*
Group B (Anticoagulant only)	26	4 (15.4)	*0.211*
Group B (Antiplatelet single)	23	1 (4.3)	*0.302*
Group B (Anticoagulant + antiplatelet)	9	1 (11.1)	*0.868*
Group B (Dual antiplatelet)	6	0 (0.0)	*0.405*
Group B (DOAC users)	18	3 (16.7)	*0.240*
Group B (Hereditary BD only)	9	1 (11.1)	*0.868*

ASA aminosalicylic acid, *DOAC* direct oral anticoagulants, *BD* bleeding disorder

Tests used to compare variables between groups: Chi-square test

Table 6 Efficacy outcomes (disease recurrence)

	All ($n=213$)	Group A ($n=144$)	Group B ($n=69$)	*p value*
Recurrence at 3 months				*0.488*
No: *n* (%)	212 (99.5)	143 (99.3)	69 (100.0)	
Yes: *n* (%)	1 (0.5)	1 (0.7)	0 (0.0)	
Deceased: *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	
	($n=212$)	($n=143$)	($n=69$)	
Recurrence at 6 months				*0.366*
No: *n* (%)	207 (99.5)	140 (97.9)	67 (97.1)	
Yes: *n* (%)	4 (1.9)	3 (2.1)	1 (1.4)	
Deceased: *n* (%)	1 (0.5)	0 (0.0)	1 (1.4)	
	($n=207$)	($n=140$)	($n=67$)	
Recurrence at 9 months				*0.448*
No: *n* (%)	191 (92.3)	130 (92.9)	61 (91.0)	
Yes: *n* (%)	15 (7.2)	9 (6.4)	6 (9.0)	
Deceased: *n* (%)	1 (0.5)	1 (0.7)	0 (0.0)	
	($n=191$)	($n=130$)	($n=61$)	
Recurrence at 12 months				*0.894*
No: *n* (%)	173 (90.6)	118 (90.8)	55 (90.2)	
Yes: *n* (%)	18 (9.4)	12 (9.2)	6 (9.8)	
Deceased: *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	

Tests used to compare variables between groups: Chi-square test

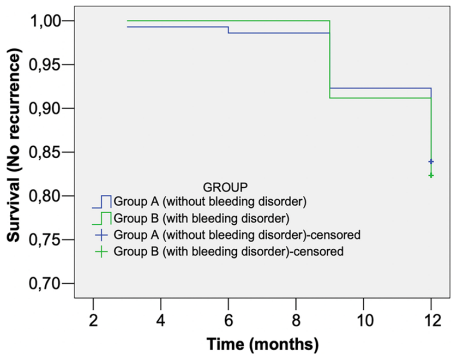

Fig. 5 Recurrence Probability (Cox regression)

Table 8 Hazard Ratios for the risk of recurrence

	OR	(95% CI)	*p*
Age	1.023	(0.996, 1.050)	*0.094*
BMI	0.994	(0.916, 1.077)	*0.875*
Baseline Goligher grade			*0.890*
II	0.841	(0.273, 2.591)	*0.763*
III	0.737	(0.208, 2.615)	*0.636*
Baseline hemorrhoidal disease bleeding grade			*0.311*
2	1.539	(0.471, 5.025)	*0.475*
3	3.194	(0.661, 15.428)	*0.148*
Baseline Sodergren hemorrhoidal symptom severity score	1.176	(1.045, 1.323)	***0.007***
Group (B)	0.394	(0.147, 1.059)	*0.065*

OR odds ratio, *CI* confidence interval, *BMI* body mass index

Table 7 Mean time for recurrence

Mean time for recurrence (months)	Mean ± SE	(95% CI)	*p*
Group A	11.71 ± 0.10	(11.52, 11.90)	*0.786*
Group B	11.74 ± 0.11	(11.52, 11.95)	

SE standard error, *CI* confidence interval

Tests used to compare variables between groups: Log Rank (Mantel Cox) tes

B: 11.7 ± 0.11 months, $p=0.786$) (Table 7). The probability of recurrence was higher for patients with higher baseline SHSS scores ($p=0.007$). No other characteristics were predictors of recurrence (Table 8).

Two patients, one in each group, died of unrelated causes (respiratory/pulmonary infections), at 6 and 9-month follow-up.

Discussion

The aim of our study was to prospectively evaluate the efficacy and safety of PFS in the treatment of symptomatic internal HD grades I to III in patients with a congenital or acquired bleeding disorder (group B), compared to patients without such disorders (group A). To the best of our knowledge, this is the first study to specifically evaluate clinical outcomes in this challenging population, known for having higher bleeding risk related to HD interventions. This prospective, multicentre, cohort study demonstrated that PFS was effective and safe in both groups of patients.

The mean age in our cohort was significantly higher for patients with BD which can be explained by the fact that older patients are more prone to cardiovascular comorbidities and, as such, need antithrombotic therapy more often. Also, at baseline, the patients with BD had more symptomatic HD with more severe bleeding grade.

We found a significant decrease in HDBG and SHSS scores after the PFS, in both groups of patients. Therapeutic success was reported in 94.5% and 92.9% of the patients with and without BD, respectively, without significant differences between the groups. These results are similar to those in the pioneer study of Moser et al. [22] that reported a success rate (assessed by the HDBG) of 88% and 98% after the first and the second PFS session, respectively. Our success rate is higher than that reported by Lobascio et al. [28] and our group [23] in a randomized controlled trial comparing PFS with RBL in the treatment of HD grades I-III. Also, Fernandes et al. [21] in a large cohort of patients with HD grades I-IV (including 210 patients under antithrombotic therapy), documented a 98% decrease in self-reported bleeding and reduction of prolapse in 86% (out of 1112 re-examined patients) with PFS, concluding that it was effective and safe even in patients on antithrombotic therapy. [15, 21] In a short-term report of PFS used as a bridge treatment in HD grades III-IV during the COVID-19 pandemic [29], all the patients had resolution of bleeding without complications while awaiting surgery. PFS treatment was considered effective, safe, repeatable, and associated with good patient satisfaction. The efficacy of PFS derives from its mechanism of action, which induces a local inflammatory reaction that anchors the hemorrhoidal tissue, leads to obliteration of the vascular bed and consequent fibrosis and tissue shrinkage [27, 28]. This might explain the clinical benefit as regards the major symptoms of hemorrhoidal disease, including bleeding, pain, prolapse, and relief of soiling and pruritus, due to reduction of vascular congestion.

Our number of PFS treatment sessions per patient was significantly higher for the group with BD which may be due to the higher baseline severity of HD in this group of patients. The number of therapy sessions in the group of patients without BD is in line with the previously reported by Moser et al. [22] and us [23]. The average polidocanol dose was similar to previous studies [23] and between the groups.

Concerning the safety of PFS treatment, our overall complications rate was similar to previous data published by our group [23], with pain being the most frequent post-procedure complication. However, the definition of pain, including its intensity and duration, varied in previous studies precluding an accurate comparison. Moser et al. [22] described the higher pain rates since they considered very short duration pain (resolving in less than 15 min). In that study 97% of the patients remained pain free between PFS sessions.

We did not find significant differences in the rate or type (mild or severe) of complications between patients with and without BD, and none of the baseline characteristics was a significant predictor for the occurrence of complications. Although none of the group B subgroups had a significantly higher incidence of complications, we noted a higher rate of complications in anticoagulated patients, particularly with DOACs. We should consider a possible small sample size bias that could attenuate potential significant differences.

There are reports of serious complications of HD sclerotherapy such as acute prostatitis [22], major bleeding, urinary retention and sepsis requiring surgery [21]. However, the incidence of major complications appears to be much more common with RBL [18]. The only severe complication in our cohort was bleeding requiring blood transfusion in a patient with BD (subgroup of anticoagulant + antiplatelet therapy).

Bleeding has been described as the most common complication of HD treatments. RBL is associated with bleeding rates ranging from 2.1% to 7% including minor and significant bleeding requiring medical evaluation or transfusion support [20]. There is also an increased risk of late (10–14 days after RBL) and potential life-threatening bleeding for patients on antithrombotic therapy [18]. The standard recommendation for minimizing bleeding risk is to withhold antithrombotic therapy for 7–10 days prior to, and after, hemorrhoidal procedures like RBL or excisional haemorrhoidectomy [11, 32]. Some studies on RBL [31] and surgical transanal hemorrhoidal dearterialization (TDH) [32] described a similar risk of bleeding with different suspension protocols and even under anticoagulation [32], without sufficient evidence, however, to modify current recommendations. Our overall bleeding rate of 4.8% was slightly lower than the 6% persistent bleeding described by Lobascio et al. [28]. We found a 5.5% bleeding rate after PFS for patients with BD, without significant differences comparing to patients without BD, while Fernandes et al. [21] reported 9% significant bleeding (referring to 22 patients under double antithrombotic therapy), in contrast to 0.05% bleeding in patients without antithrombotic therapy. In our study, none

of the patients discontinued antiplatelet or anticoagulation therapy prior to PFS treatment and no thrombotic or cardioembolic complications were reported. PFS treatment may thus provide a safer approach for these patients.

Recurrence rates were comparable in both groups with 82.5% and 80.9% (groups A and B, respectively) of the patients who had therapeutic success showing no HD recurrence at 1-year follow-up. Previous data showed similar recurrence rates for PFS [23, 28] and significantly higher ones with other techniques: recurrence of prolapse of up to 34% with liquid polidocanol [16] and a bleeding recurrence ranging from 10–46% for RBL [18].

There are several strengths in our study. First, the relevance of assessing clinical outcomes of PFS treatment in patients with HD and inherited or acquired BD. These patients are a vulnerable population, more prone to bleeding complications when undergoing invasive procedures, where HD management is much more challenging. We assessed clinical outcomes using validated severity scores, as an attempt to overcome subjective interpretations concerning efficacy of PFS in HD. Our study protocol was multicentric, which aimed to improve generalizability of data, and included a one-year follow-up period, which allowed for a more accurate evaluation of recurrence.

However, our study has some limitations. The heterogeneity of the antithrombotic therapy and the small sample size of the subgroups within the BD group precluded a more robust analysis. We did not account for the possible influence of distinct antiplatelet therapy dosage on rate of bleeding. Also, the 12-month follow-up is short considering the chronic and relapsing pathogenesis of HD.

Our results regarding the efficacy and safety of PFS for the treatment of internal HD grades I to III are aligned with other recent data which support the use of PFS as a first line procedure. PFS decreased hemorrhoidal bleeding and symptom severity, and was associated with a low incidence of complications even in patients with BD, with no need to carry out any bleeding prophylaxis or discontinue antithrombotic medications thus avoiding an eventual increase in the thrombotic risk.

Conclusions

Our results suggest that PFS is just as effective and safe for treatment of HD in patients with BD as in those without bleeding dyscrasia. Further larger scale studies are needed to determine whether PFS can become the established standard of care in the treatment of HD in patients with BD, as it may offer these patients a safe and effective office-based treatment, without the need to stop antithrombotic drugs or perform bleeding prophylaxis.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10151-022-02600-5.

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Availability of data and material (data transparency) The data that support the findings of this study are available on request from the corresponding author.

Code availability Not applicable.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

Ethics approval (include appropriate approvals or waivers) The study was approved by the Ethics Committee of the intervening institutions (243–18 (213-DEFI/212-CES)).

Consent to participate All participants provided written informed consent to participate in the study, as well as for the publication.

Consent for publication All authors had access to the study data and approved the final manuscript.

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ELECTRONIC SUPPLEMENTARY MATERIAL

ESM TABLE 1: Goligher classification

Grade	Degree of prolapse
I	No prolapse
II	Prolapse on defecation with spontaneous reduction
III	Prolapse on defecation requiring manual reduction
IV	Prolapse and irreducible

ESM TABLE 2: Hemorrhoidal disease bleeding grade

Type of bleeding	Grade
No rectal bleeding	0
Bleeding when passing stool less than once a week	1
Bleeding when passing stool 1–6 days per week	2
Bleeding when passing stool every day or with hemodynamic/laboratorial changes (anemia, with or without transfusion need, signs of hypovolemia)	3

ESM TABLE 3: Sodergren hemorrhoid symptom severity scoring system

1) Have you considered or excluded another pathology? Yes/No 2) Does the patient suffer from rectal bleeding? Yes/No Only proceed with questionnaire if YES is the answer to both questions Please answer the following questions relating to symptoms, at or around your anus.			
Symptoms			Points score
How severe are your symptoms of itching or irritation? (circle number from 1-5)	0 1 2 3 4 5	No symptoms Mild / do not really bother me Moderately bothersome Severe	0 0 0 0 4 4
How severe are your symptoms of pain or discomfort at rest? (circle number from 1-5)	0 1 2 3 4 5	No symptoms Mild / do not really bother m Moderately bothersome Severe	0 0 0 3 3 3
How severe are your symptoms of pain or discomfort on opening your bowels? (circle number from 1-5)	0 1 2 3 4 5	No symptoms Mild / do not really bother me Moderately bothersome Severe	0 0 0 0 3 3
How often do you feel that you might have a lump at your anus (prolapse)?	0 1 2 3 4	Never Less than once a month More than once a month More than once a week Every day	0 0 0 0 4
			Final score (0 – 14 points)

CHAPTER VI – DISCUSSION AND CONCLUSIONS

DISCUSSION

The first manuscripts presented in this thesis, namely "Portuguese Society of Gastroenterology Consensus on the Diagnosis and Management of Hemorrhoidal Disease" and "Office-Based Procedures in the Management of Hemorrhoidal Disease: Rubber Band Ligation versus Sclerotherapy – Systematic Review and Meta-Analysis", aimed to gather the scientific knowledge about the management of HD. They served as a starting point to understand how we could fit PFS into the armamentarium available for the treatment of this disease, as well as whether the specific group of patients with BD could benefit from this outpatient treatment. On the other hand, the manuscripts presented in chapter IV "Polidocanol Foam Sclerotherapy Versus Rubber Band Ligation in Hemorrhoidal Disease Grades I/II/III: Randomized Trial" and chapter V "Polidocanol Foam Sclerotherapy in the Treatment of Hemorrhoidal Disease in Patients With Bleeding Disorders: a Multicenter, Prospective, Cohort Study" studied, respectively, the performance of PFS when compared to RBL, and the clinical outcomes of hemorrhoidal sclerosis with the foam formulation in a group of patients with hemostasis disorders.

The standard of care for patients with hemorrhoidal disease

The current gold standard hemorrhoidal disease office-based treatment

HD treatment options include conservative measures, office-based procedures, and surgical treatments. Office-based procedures are, in HD grades I-III, useful and less invasive alternatives to hemorrhoidectomy/hemorrhoidopexy since the latter are more likely to have complications (Lohsiriwat, 2013; Sandler & Peery, 2019).

RBL, a simple and well-tolerated outpatient procedure that consists in the placement of elastic bands above the dentate line to strangulate the hemorrhoidal piles, resulting in ischemia, necrosis of the prolapsed mucosa and subsequent scarring (Davis et al., 2018), is usually the preferred office-based treatment for grades I to III HD because of its effectiveness when compared with other office-based procedures (Nastasa et al., 2015; Sun & Migaly, 2016). RBL is the most widely used outpatient treatment for HD grades II and III and, in previous publications, the overall improvement with RBL ranged from 73 to 84% (Cocorullo et al., 2017). HD recurrence is frequent with RBL, with a reported bleeding recurrence of 10% to 46% and a recurrence of prolapse in up to 34% (Cocorullo et al., 2017).

Bleeding and pain are the most frequent RBL complications (Albuquerque, 2016; Cocorullo et al., 2017; Iyer et al., 2004). Acknowledging the bleeding complications of outpatient techniques and the treatment of HD in patients with BD, it is recognized that antithrombotic drugs increase the risk of bleeding after RBL with reports of massive and even life-threatening bleeding after the banding procedure (Beattie et al., 2004; Odelowo et al., 2002; Parker, Gul, Bucknall, Bowley, & Karandikar, 2011; Patel et al., 2014). In a retrospective study of 805 patients undergoing RBL, higher bleeding rates were encountered in patients on warfarin (25%) and acetylsalicylic acid (7.5%) compared with patients not taking these medications (2.9%) (Iyer et al., 2004). The highest risk of bleeding seems to occur between 10 and 14 days after the procedure (Bat, Melzer, Koler, Dreznick, & Shemesh, 1993; Beattie et al., 2004; Odelowo et al., 2002) leading many authors to recommend antithrombotic withholding 7–10 days before and 7–10 days after RBL (Beattie et al., 2004; Nelson et al., 2008). In a retrospective study including 364 patients undergoing RBL, withholding antiplatelet medication 7–10 days after the procedure appeared to equalize the risk of bleeding to that of patients not taking this type of medication (Nelson et al., 2008).

Hemorrhoidal sclerotherapy is performed by injecting a sclerosing agent with the aim of decreasing blood flow and inducing scarring in the hemorrhoidal plexuses, thus preventing bleeding and prolapse (C. Blanchard, 1928; Siddiqui et al., 2014). Many sclerosants have been used over time. Sclerotherapy with older agents appears to have reduced effectiveness so it was recommended to be used in grade I and II HD (Acheson & Scholefield, 2008; Sneider & Maykel, 2010). Its effectiveness in HD grade III is inadequately studied but seems to be inferior than that seen in lower grades (Cocorullo et al., 2017; Iyer et al., 2004). As with RBL, recurrences are frequent after sclerotherapy, with bleeding recurrence reported in 1.5% to 29.0% and of prolapse in up to 16% of the patients (Cocorullo et al., 2017).

Mild anal pain and bleeding are the most common complications of sclerotherapy. However, bleeding risk is inferior to that observed with RBL (Moss & Bordeianou, 2013). In a case-matched series of 37 patients receiving sclerotherapy for symptomatic HD while on antiplatelet and/or anticoagulant therapy, there was no difference in procedure related bleeding rates (Yano et al., 2013).

A meta-analysis of 18 randomized trials comparing various treatment modalities for HD grades I to III concluded that RBL was more effective than sclerotherapy (not including studies with PFS) and that patients who underwent ligation were less likely to need subsequent therapy. Even so, RBL proved to be more painful than

other office-based techniques (MacRae & McLeod, 1995). In addition, a recent review, which included seven studies comparing sclerotherapy (but not PFS) and RBL concluded that RBL seems to be most effective in terms of symptom resolution for second-degree HD and equal or superior for treating grade III HD. However, sclerotherapy is associated with lower rates of severe post-operative pain and minor complications. The authors propose that sclerotherapy with 3% polidocanol or aluminum potassium sulfate and tannic acid should be offered first line, as it has less complications, followed by RBL in cases of HD relapse (Tutino et al., 2021). In recent years two sclerosants have attracted the attention of the scientific community for their effectiveness and safety: ALTA (not available for use in Portugal) and polidocanol foam.

ALTA demonstrated an improvement of bleeding in 69–100% of grades I to III HD (Porrett & Lunniss, 2001; Takano et al., 2006; Tsunoda, Nakagi, Kano, Mizutani, & Yamaguchi, 2014; Yano et al., 2013) and an over 90% resolution of prolapse in grade II HD (Miyamoto, Asanoma, Miyamoto, & Shimada, 2012; Takano et al., 2006; Tsunoda et al., 2014). A prospective study showed, with this procedure, an overall prolapse improvement in 100% of patients (Scaglia et al., 2001), while another reported only 52% of improvement of prolapse in grade III (Yano et al., 2014).

When the consensus paper (chapter II) was published, the evidence concerning PFS was scarce, with only 3 available publications. Namely, a RCT showing that polidocanol foam performed better than the liquid form in grade I HD (Moser et al., 2013), and 2 retrospective studies, one including 615 patients with HD grades I-IV reporting a rectal bleeding resolution in 83% of the participants with very low complications rates (pain and anal itching in 2.7% and 3.7%, respectively) (Ronconi M, 2019), and the other which included 2,000 patients (grades II-IV) concluding that polidocanol foam therapy was very successful (98% of the patients reporting bleeding control and prolapse reduction) and safe (complications were rare and usually minor even in patients under antithrombotic medication) (Fernandes & Fonseca, 2019).

Taking into consideration the low-quality evidence and that, despite HD high prevalence, most of the knowledge on its management is based on somehow outdated literature and/or individual clinical experience, we aimed to set the ground to the clinical question with chapter I. In addition, although there were several published guidelines and consensus addressing this issue (Davis et al., 2018; Trompetto et al., 2015), there were no national guidelines published to date. We recognize the importance of empirical knowledge acquired by clinicians who

treat the disease in daily practice, as well as the historic nature and, often, lack of quality of publications in this field. As such, we decided to conduct a guideline in the form of a consensus. In this way, we created the first Portuguese consensus on the diagnosis and management of HD in collaboration with a group of twelve gastroenterologists who are national experts in proctology. This document gathered the published evidence on the subject in the form of statements, achieving one of the first intended endpoints that was the uniformization of clinical practice on HD. The statements were revised, voted and classified according to the quality of evidence (Atkins et al., 2004).

We developed statements for various aspects of the clinical approach to HD such as clinical evaluation and diagnostic tests, HD grading, medical management, office-based treatment, treatment of HD in special groups of patients, and HD's complications. Among these, we highlight those that foresaw the need for more research on the role of the PFS and, in this way, impelled us to carry out the investigations discussed below:

1. Statement 12 ("Sclerotherapy with liquid sclerosants is safe but poorly effective and therefore should be used only for grade I internal HD (high-quality evidence). Since postprocedural bleeding is uncommon, it should be considered for patients who have higher bleeding risk (moderate-quality evidence).");
2. Statement 13 ("The use of other sclerosing techniques, such as polidocanol foam and aluminum sulfate and tannic acid (ALTA), seems to be safe and effective even in patients under anticoagulation and/or antiplatelet therapy. The efficacy and safety compared to other office-based procedures are yet to be defined (low-quality evidence).");
3. Statement 16 ("In patients taking antiplatelet and/or anticoagulant medication, the risk of bleeding is increased after RBL (low-quality evidence). In these patients, sclerotherapy appears to be safe (moderate-quality evidence).").

The publication of the first Portuguese consensus for the diagnosis and treatment of HD is a milestone in establishing the *standard of care* regarding the approach of this disease in the Portuguese panorama. We acknowledge, however, some limitations to this work. Firstly, since there is no validated curriculum for proctology as a subspecialty, the choice of participants/experts was made by selecting clinicians who are dedicated or responsible for organized proctology consultations at their institutions. Secondly, the discussion of the different surgical

approaches to HD was not included. The option to limit the discussion of HD treatments was premeditated and related to the fact that we wanted to create a short and concise document for practicing gastroenterologists. Thirdly, when preparing this guideline, we did not use the AGREE II instrument, which is a checklist that allows the assessment of the quality of guidelines (Brouwers et al., 2010). Finally, we are aware that an article of this nature will become outdated as new evidence on this subject is published. In fact, as mentioned above, after the date of publication of our guideline, some trials addressing PFS have already been published, including the studies presented in chapters IV and V. With this new evidence comes the need to revise some of the statements in future updates. Also, future guidelines should be expanded to include discussion of surgical approaches to HD.

The second study of this thesis is a systematic review and meta-analysis (chapter III) which compared efficacy and safety outcomes of the two most commonly performed office-based procedures for HD: RBL and sclerotherapy. In terms of effectiveness, we found that both RBL and sclerotherapy are equivalent in controlling overall HD symptoms and specifically pain relief. However, RBL performed better concerning the reduction of prolapse and hemorrhoidal bleeding control. Disease recurrence at 3 months did not differ significantly between the two procedures. Regarding safety, there was a higher incidence of pain after RBL procedure (except for patients with HD grade II). Despite this, patients undergoing RBL showed higher satisfaction rates.

As mentioned earlier in this discussion, an older but very relevant meta-analysis compared various HD treatment modalities evaluating outcomes such as response to therapy, need for further therapy, and complications. Like us, the authors found that RBL treated patients had a better response rate to therapy for HD grades I-III and were less likely to require further therapy than those treated with sclerotherapy. Pain was significantly more likely to occur following RBL (MacRae & McLeod, 1995).

In our meta-analyses, the comparison was restricted to RBL versus sclerotherapy, but we made a discrimination of the most relevant hemorrhoidal symptoms that should guide the response to therapy (prolapse reduction, bleeding control, pain relief). We also considered patient satisfaction as one of the efficacy outcomes. Since we included only randomized controlled trials and prospective cohort studies comparing RBL and sclerotherapy, the study profile included in our meta-analysis is different from that included in the previous meta-analyses.

Considering the evidence available when conducting our research, results reaffirm RBL as the gold-standard office-based procedure for patients with HD grades I-III.
It is important to mention that interpretation of published studies comparing sclerotherapy with RBL is not always easy since sclerosing and banding techniques vary across studies. Also, the intermittent character of hemorrhoidal symptoms and the use of different scores can make the analysis inaccurate so, caution should be taken when interpreting the results. These aspects induce some limitations to our meta-analysis. First, the lack of standardization of therapies (number of bands used in each session, type, and volume of the injected sclerosant, number of hemorrhoidal pyles treated per session, and adjuvant medical therapy) contributed to the heterogeneity of the results. Second, when we performed sub-group analyses, only a small number of studies addressed some of the outcomes, which limits our conclusions. Lastly, one of the studies included patients with HD grade IV (Lohsiriwat, 2013). In most centers, grade IV HD is usually treated surgically. It should be noted that patients with grade IV included in that study represent only 2.5% of the sample so, the impact on results is limited.
As in the case of the consensus (chapter II), our systematic review and meta-analyses have an ephemeral expiry date as new evidence regarding PFS can significantly change the results (at the time of our review there were no trials comparing polidocanol foam with RBL). Further updates will be regularly needed to make the medical community aware of developments in outpatient HD treatment.

The efficacy and safety of polidocanol foam sclerotherapy compared to rubber band ligation

Since the first 3 publications addressing PFS, mentioned earlier in this discussion, which are dated from 2013 (Moser et al., 2013) and 2019 (Fernandes & Fonseca, 2019; Ronconi M, 2019), We have counted 5 more publications between the years 2020 and 2022 (Figueiredo et al., 2022; Gallo et al., 2022; Lisi et al., 2021; Lobascio et al., 2019; Pata et al., 2021). Interestingly, except for the first publication in which a comparison was made with liquid polidocanol, none of the others were intended to compare PFS with other types of office-based treatments.
Consequently, after the first part of the thesis (chapters II and III) where we explored the standard of care and identified the gold standard outpatient treatment of HD, the time came for us to contribute to this area of knowledge. So, we conducted the first randomized, controlled trial (chapter IV) challenging the effectiveness and safety of PFS against what was known to be the best outpatient

treatment so far, the RBL. The results showed that PFS is more effective than RBL, with significant lower rates of recurrence and complications.

In order to make outcomes more objective, we used a combination of the validated symptom score SHSS (Pucher et al., 2015; Sha, Roslani, & Poh, 2020) with HDBG. Goligher classification (Goligher J, 1984) allowed for a stratified randomization making both therapeutic arms comparable in terms of baseline HD severity.

Our efficacy results generally resemble those described in the literature for each of the procedures (see above). The PFS group had a higher overall therapeutic success than the RBL group, although we did not reach statistical significance in this outcome (93.3% versus 85%, p=0.14). Regarding the outcome "complete success" (patients who were completely asymptomatic after the intervention) we observed a significant difference in favor of PFS (88.3% versus 66.7%, p=0.009). Only 13 participants (4 from de PFS group and 9 from the RBL group) had therapeutic failure (i.e., at the end of three treatment sessions maintained/worsened the initial SHSS and HDBG). Ten of them were treated with another office-based procedure and 3 were referred for surgical treatment. We hypothesized that, with PFS, foam dispersion along the hemorrhoidal plexus could be more effective than the very localized action of RBL. "Locally disseminated vascular sclerosis", as we called it, could also explain why we needed, in advanced hemorrhoidal grades (Goligher II and III), fewer therapeutic sessions of PSF than with RBL. In fact, it was found that, for more advanced HD grades, PFS allowed a more intensive treatment by increasing the injected volume without increasing the number of treatment sessions. Another hypothesis is that the application of an elastic band to pile can make the access to other hemorrhoids difficult, thus avoiding their treatment in the same session. This need for fewer therapeutic sessions makes PFS particularly attractive especially at a time when the consumption of medical resources is crucial.

The HD recurrence rate is high in all types of office-based treatments, and this is a limitation often pointed out to this type of procedures. We know, however, that in the event of a symptom relapse, the initial office-based treatment can be successfully repeated (Cocorullo et al., 2017).

In our RCT, during the 1-year follow-up, recurrence was lower in the PFS group (16.1% versus 41.2%, p=0.005). All the recurrences with PFS were mild (i.e., SHSS and HDBG higher than at the end of therapy but lower than at baseline, without need for additional intervention) and its incidence rate was comparable to those previously described.

As previously mentioned, complications are common with RBL, especially pain and bleeding after the procedure, while bleeding complications are rare with sclerotherapy.

Complications were reported in 20% of the patients of which 90.1% were mild and, as such, self-limiting. These were more frequent among patients treated with RBL (30.0% versus 10.0%, *p=0.01*) which, given the available literature, was not surprising. Two patients in the RBL group had moderate complications and, fortunately, there were no records of severe complications.

Our study had some limitations. First, it was carried out in a tertiary center, which may induce a generalization bias. Second, since the techniques performed have very different technical procedures, it was not possible to blind neither the performer nor the participant, thus, we cannot exclude the existence of performance bias. Nevertheless, the efficacy and safety results for both therapeutic arms are similar to those observed in previous studies, which argues against this. Also, the use of patient-reported scores makes this type of bias less likely.

Strengths of this work include the randomization strategy that allowed for direct group comparison without significant differences concerning baseline HD severity. Also, it is the first randomized comparison of PFS and RBL in the treatment of HD grades I to III.

Efficacy and safety of polidocanol foam sclerotherapy in patients with bleeding disorders

Hemorrhoidal bleeding represents a major complaint for seeking medical advice as well as a frequent treatment complication (Lohsiriwat, 2012; Sun & Migaly, 2016). Patients with a congenital or acquired (induced by antithrombotic therapy) BD belong to a vulnerable group since they are more prone to bleed from either the HD or its treatments. In these patients, HD management is challenging as some office-based procedures like RBL or surgery might be contraindicated or imply withhold of antithrombotic therapy for several days, increasing thrombotic risk (Atallah et al., 2016; Gallo et al., 2020; Nelson et al., 2008). Bearing in mind their higher bleeding risk and increased rate of surgical complications, these are the patients who should benefit most from less invasive office-based procedures. Among the published literature addressing the topic of PFS, only 2 retrospective, non-controlled, cohort studies included patients with acquired coagulation disorders and none of them included patients with congenital hemorrhagic dyscrasia. Fernandes et al. reported a promising triad of high efficacy, high

tolerability, and high safety of PSF in a significantly large sample including 210 patients under antithrombotic therapy (Fernandes & Fonseca, 2019). Figueiredo et al. retrospectively studied PFS success rates in a sample of 243 patients, 69 of whom were on antithrombotic medication. Therapeutic success was achieved in 90.1% of patients and was not influenced by antithrombotics (Figueiredo et al., 2022).

We realized that there was a need for more robust data on efficacy and safety of PFS on this special group of patients and, as such, we carried out a multicentric study (chapter V) with the aim of prospectively evaluate the efficacy and safety of PSF in the treatment HD grades I to III comparing clinical outcomes between patients with and without BD.

In this study, we found that PFS was effective and safe in both groups of patients (with and without BD).

The participants mean age was higher for patients with BD, which can be explained by the fact that older patients usually have cardiovascular comorbidities and, therefore, need antithrombotic therapy more often. In addition, at baseline, patients with BD had more HD symptoms with a more severe bleeding grade, thus confirming the epithet of “vulnerable group”.

In terms of efficacy, in line with the available literature (Fernandes & Fonseca, 2019; Lobascio et al., 2021; Moser et al., 2013), we achieved high rates of therapeutic success with no statistically significant differences between the groups (94.5% and 92.9% of the patients with and without BD, respectively). Recurrence rates were also comparable in both groups. These results lead us to believe that polidocanol foam sclerosing action (Lobascio et al., 2021; Zheng, 2018) is minimally or not at all influenced by the coagulation status.

Despite the group of patients with BD required more therapeutic sessions in our study (1.68±0.86 vs 1.43±0.65, p=0.013), probably due to more severe baseline HD, the number of therapeutic sessions was not significantly different from that described in other publications (Gallo et al., 2022; Lobascio et al., 2021; Moser et al., 2013).

Concerning safety, complication rate was 11.4% (resembling our previous trial) of which pain was the most frequent (6.1%), followed by post-procedure bleeding (4.8%). Indeed, pain is the most frequently reported complication in other studies with PFS, with bleeding being less frequent (Fernandes & Fonseca, 2019; Gallo et al., 2022; Lobascio et al., 2021; Moser et al., 2013). There were no significant differences in the rate of complications between patients with and without BD. In

the group of patients with BD we found a 5.5% bleeding rate after PFS without significant differences comparing to patients without BD, while Fernandes et al. (Fernandes & Fonseca, 2019) reported 9% significant bleeding among 22 patients under double antithrombotic therapy in contrast to 0.05% bleeding in patients without antithrombotic therapy. In our cohort the only severe complication occurred in one patient under anticoagulation plus antiplatelet therapy who bled after the procedure requiring blood transfusion. It is of the utmost importance to mention that none of our patients discontinued antiplatelet or anticoagulation therapy, nor was any bleeding prophylaxis performed in patients with congenital coagulopathies prior to PFS. No thrombotic or cardioembolic complications were reported. Although none of the baseline characteristics was a significant predictor for complications, we observed a trend towards a higher incidence of complications in patients under DOAC, which suggests that the small sample size may be causing a sampling bias. Within the group of patients with BD, the wide variety of antithrombotics used made the subgroups small, averting a more robust statistical analysis. Despite this, there are several strengths that should be highlighted. The outcomes used validated severity scores, which aimed to reduce the subjectivity of their assessment. The protocol was multicentric, which allowed to expand the sample size, ensured greater generalizability of the results and, to a certain extent, reduced the risk of observer bias. We emphasize the clinical relevance of evaluating the results of PFS in the vulnerable population of patients with BD, whether inherited or acquired. In this subgroup pf patients, the management of HD is specially challenging since, in addition to often having a more severe HD, they are also more prone to bleeding complications when undergoing invasive procedures.

CONCLUSIONS

As defined by Thomas Kuhn in his book "The structure of scientific revolutions", we demonstrated that RBL is the prevailing "*paradigm"*, that is *"universally recognized scientific achievements that, for a time, provide model problems and solutions for a community of practitioners"*, against which we need to provoke a "*crisis*", by investigating PFS, in order to try to operate a "*scientific revolution"*, i.e. *"Research under a paradigm must be a particularly effective way of inducing paradigm change. All crises begin with the blurring of a paradigm (…) a crisis may end with the emergence of a new candidate for paradigm and with the ensuing battle over its acceptance."* (Kuhn, 1970).

In the consensus paper we aimed to assess the patterns of knowledge and practice to meet the standards of published evidence by elaborating consensus statements and classifying them according to the evidence level. Also, when available, we have highlighted new information on the subject. In this way, we have gathered in a document the standard of care for HD.

In the systematic review and meta-analysis, we found that, between the two most used procedures, RBL and sclerotherapy with liquid sclerosants, RBL is associated with a better control of hemorrhoidal prolapse and bleeding, but at the expense of higher post-procedural pain. Despite the higher incidence of pain, patients undergoing RBL were more satisfied with this treatment than those treated with sclerotherapy. These findings reaffirm RBL as the gold standard among the office-based treatments for HD.

These first two publications laid the foundations for the subsequent investigations. On one hand, in the case of the consensus, some of the statements pointed the need for more investigation addressing PFS, particularly comparing this technique with RBL and investigating its role in the treatment of patients with higher bleeding risk. On the other hand, the meta-analysis showed that RBL was the paradigm against which PFS should be compared.

The project then proceeded with the RCT comparing the safety and efficacy of RBL and PFS in the treatment of HD. We showed that both techniques are effective in HD grades I to III. However, PFS was superior considering complete therapeutic success. Furthermore, patients in the PFS group needed fewer office-based treatment sessions, had lower recurrence rates and were less likely to have complications than those submitted to RBL. Our results are practice changing and unique in the field of treatment for HD, since PFS defied and somewhat defeated

the gold-standard office-based therapy which has been RBL, with potential impacts in health care resources utilization and, consequently, costs. In this way, we may be facing a new paradigm regarding the outpatient treatment for HD.

Finally, in our prospective, multicenter, cohort study we assessed efficacy and safety of PFS comparing outcomes in a group of patients with a congenital or acquired BD with a control group of patients without such disorders. As far as we know, this is the first study to evaluate clinical outcomes in this challenging and vulnerable population, known for having more severe HD and higher bleeding risk related to hemorrhoidal interventions. We demonstrated that PFS is equally effective and safe in both groups of patients (with and without BD). Our results suggest that PFS can become the established standard of care in the treatment of HD in patients with BD, as it may offer a safe and effective alternative, without the need to stop antithrombotic drugs or to perform bleeding prophylaxis, thus avoiding a possible increase in the thromboembolic risk.

CHAPTER VII – “UPCOMING”

CHAPTER VII – "UPCOMING"

A limitation of the present project is the lack of comparison of PFS with surgical therapies, especially less invasive techniques such as hemorrhoid artery ligation, that share with office-based procedures the characteristics of having low rate of complications and fast recovery after surgery.
We recently published a randomized, pilot trial comparing PFS with HAL-RAR in which our results showed that PFS can be superior in terms of safety, complete therapeutic success and return to normal day-to-day activity (appendix 1).
A larger, randomized, controlled trial using this pilot study protocol is feasible and necessary to ascertain our results. Future research should also focus on long-term results of both techniques.

Also, it will be of very high clinical relevance to evaluate the performance of this new sclerosing agent in the treatment of other special groups of patients. Patients with liver cirrhosis have unique pathophysiological features such as portal hypertension and BD that, not only increase the severity of HD, but can also contraindicate RBL. Likewise, the hypoalbuminemia and low immunoglobulin levels that often affect these patients make them poor surgical candidates due to impaired wound healing and increased risk of infections.
A study specifically targeting these patients is planned and approved by the ethics committee of Centro Hospitalar Universitário do Porto with the identifier 2021.051(041-DEFI/042-CE) (appendix 2).

APPENDIX 1

3% polidocanol foam sclerotherapy versus hemorrhoidal artery ligation with recto anal repair in hemorrhoidal disease grades II-III: a randomized, pilot trial

Sara Neves, Daniela Falcão, Ana Povo, Fernando Castro-Poças, Jorge Oliveira, Paulo Salgueiro

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3% polidocanol foam sclerotherapy versus hemorrhoidal artery ligation with recto anal repair in hemorrhoidal disease grades II-III: a randomized, pilot trial

Running title: POLIDOCANOL FOAM VS HAL-RAR IN HEMORRHOIDAL DISEASE

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Ethics approval: This study protocol was approved by the institute's committee on human research: [2019.292 (235-DEFI/252-CE)].

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Keywords: Hemorrhoidal disease. Polidocanol foam sclerotherapy. Doppler-guided hemorrhoidal artery ligation.

Abbreviations list

HD: hemorrhoidal disease
SP: polidocanol foam sclerotherapy
HAL-RAR: doppler-guided hemorrhoidal artery ligation with recto-anal repair
RAR: recto-anal repair
HAL: doppler-guided hemorrhoidal artery ligation
SHSS: Sodergren hemorrhoidal severity score
HDBG: Hemorrhoidal disease bleeding grade
OR: odds ratio
CI: confidence interval
SD: standard deviation

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ABSTRACT

Purpose: We aimed to compare polidocanol foam sclerotherapy (SP) versus doppler-guided hemorrhoidal artery ligation with recto-anal repair (HAL-RAR) in the treatment of hemorrhoidal disease (HD).

Methods: Prospective, randomized study including patients with HD grades II and III. Participants were randomly assigned (1:1) into SP or HAL-RAR, during a recruitment period between September 2019 and February 2020. Therapeutic success (Sodergren's and bleeding scores) was the primary outcome. Other outcomes evaluated complications and implication in professional life. Efficacy and safety outcomes were evaluated during the 8 weeks after the surgery or the final SP session.

Results: Forty-six patients were allocated either to SP (n=22) or HAL-RAR (n=24). Most patients achieved therapeutic success (SP 100% vs. HAL-RAR 90.9%, p=0.131). Complete success was higher in SP group (91.7% vs. 68.2%, p=0.045). SP patients had less complications (25% vs. 68.2%, p=0.003). HAL-RAR had a greater negative impact in patients' work activity.

Conclusion: SP was more effective and safer than HAL-RAR. SP patients had less impact on their work activity.

Clinicaltrials identifier NCT04675177.

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Introduction

Hemorrhoidal disease (HD) is an extremely frequent anal disorder. Although it is very difficult to accurately assess the exact prevalence, it can be as high as 38.9% in adult patients undergoing colonoscopy for colorectal cancer screening.(1, 2) The prevalence is similar in both sexes and it is peaked between the ages of 45 and 65, with a subsequent decrease after age 65 years.(3)

Treatments include medical therapies, office-based procedures, and surgery.(4, 5)

Hemorrhoidal sclerotherapy is indicated for HD grades I-III HD.(6) Polidocanol foam have better outcomes than its liquid formulation.(7) Polidocanol damages the endothelium causing the vessel occlusion and local fibrosis.(8) Polidocanol foam sclerotherapy (SP) can have complications such as local discomfort, bleeding and, less commonly, erectile dysfunction and urinary retention.(6)

Surgical hemorrhoidectomy is usually reserved for refractory cases or higher HD grades (9, 10) however, the less invasive hemorrhoidal artery ligation with/without recto-anal repair (HAL-RAR), is also used in HD grades II-III (6, 11).

Since there is an overlap in the treatment of grade II and III HD (office based versus surgical therapy) and there are no comparative studies between SP and HAL-RAR, we decided to include this subgroup of patients.

Therefore, we aimed to compare SP (3%) versus HAL-RAR in the treatment of grades II-III HD.

Methods

We included patients over 18 years of age with HD grades II-III unresponsive to conservative treatment (diosmin + topical analgesics for 4 weeks) referred to Centro Hospitalar Universitário do Porto.

Participants were randomly assigned to either SP or HAL-RAR between September 2019 and February 2020. Randomization was computer-generated (assignments were enclosed in sequentially numbered and sealed envelopes). Since the procedures have different techniques, it was not possible to blind the patient or the clinician who applied the treatment. Therapeutic arms were hidden from the investigators who processed the data. Patients with cirrhosis, pregnant/breast-feeding women, bleeding

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disorders, immunosuppression, allergy to polidocanol or another perineal disease were excluded. All the participants signed informed consent. The trial was approved by the institution's ethics committee and registered at ClinicalTrials.gov (NCT04675177).

Efficacy and Safety outcomes

Sodergren hemorrhoidal severity score (SHSS) (12) and HD bleeding grade (HDBG) (13) were used to assess HD severity (Table 1 and 2, respectively).

Primary efficacy outcome was therapeutic success (evaluated 8 weeks after the final procedure), classified as complete (SHSS=0 and HDBG≤1), partial (SHSS and HDBG improvement over baseline) or therapeutic failure (worsening/maintenance of SHSS and HDBG).

Primary safety outcome evaluated complications categorized into mild (pain/discomfort, minor bleeding), moderate (external hemorrhoidal thrombosis, bleeding without hemodynamic instability), severe (sepsis, perineal abscess, bleeding with hemodynamic instability). Patients' professional life implications (number of work-loss days) was a secondary outcome.

Intervention: technical aspects (**Figure 1**)

SP GROUP

i. Polidocanol (Aethoxysklerol 3%) foam was prepared using Tessari's technique(14);

ii. An intravenous needle was used for intra-hemorrhoidal injection (through an anoscope);

iii. The number of sessions (maximum of 3 sessions at 3 weeks intervals) depended on the clinical response (if 3 weeks after the treatment, the participant scored SHSS=0 and HDBG≤1, there would be no additional therapy);

iv. Maximum dose per session of 20mL (4mL of polidocanol with 16mL of air).

HAL-RAR GROUP

i. HAL-RAR was performed in the operating-room, under regional anesthesia. A doppler-transducer (A.M.I.® HAL / RAR System) was used to identify the superior rectal artery branches which were ligated above the dentate line;

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ii. The procedure was repeated 1-1.5cm below the first series of sutures;

iii. RAR procedure (continuous suture applied longitudinally over the hemorrhoid starting 2-3cm above the dentate line) was performed in HD grade III;

iv. Surgical treatment was performed only once.

Statistical analysis

SPSS® v.26 software was used. Significance was pre-set at p≤0.05. Pearson's chi-squared test was used for categorical data. Normality of continuous variables was evaluated using the Kolmogorov-Smirnov test. Wilcoxon-signed-rank and Kruskal-Wallis tests were used for continuous data. Univariate and multivariate binary logistic regression were used to identify predictors of treatment's complications.

Results

Forty-six patients were included (SP=24; HAL-RAR=22). The flowchart of the patient selection process is shown in Figure 2.

Preoperative characteristics were comparable between groups (**Table 3**).

Overall therapeutic success was similar between the two groups however, complete success was higher for SP (91.7% vs. 68.2%, p=0.045). (**Table 4**).

The HAL-RAR group had a higher incidence of minor complications (**Table 4**). In the HAL-RAR group, pain was significantly higher when RAR was performed (71.4% vs. 25%, p=0.035).

In multivariate analysis, only the type of treatment was a significant predictor of complications (**SDC Table 1**). HAL-RAR was approximately six-times more likely to develop complications (OR=6.05, 95% IC 1.07-34.33, p=0.042).

Patients undergoing HAL-RAR had more prolonged absence from work (9.5±10.1 days vs. 0.6±0.2 days, p≤0.001; **Table 4**).

Study flowchart is represented in **Figure 2**.

Discussion

This is the first randomized study comparing SP with HAL-RAR.

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Overall therapeutic success showed no significant differences between groups, however, SP had higher complete success, as observed in previous studies, where SP was successful in >90%.(14-17) Although, in previous studies, sclerotherapy with liquid sclerosants has shown little efficacy in grade III hemorrhoids (5), the more recent literature shows high and consistent success rates of the polidocanol foam formulation in the treatment of grade III HD.(16-18)

The HAL-RAR group had a higher rate of complications, especially pain. Our results agree with previous studies: in a study including 2000 patients treated with SP, only 2% reported mild pain (15); in another study including patients with HD grades II and III submitted to SP, 14% experienced post-procedure pain (18); concerning HAL-RAR, post-operative pain rate can reach 30%.(19) When RAR is performed, other authors, as in our study, report a significant increase in postoperative pain.(20)

Interventions for HD should also have minimal negative effects on patients' day-to-day activities. In our study, HAL-RAR had greater impact on absence from work. This might reflect not only its more invasive nature, but also the need for anesthesia.

Although an evaluation of procedures' cost-effectiveness was not an objective, it should be noted that HAL-RAR is more expensive since it requires more equipment/professional staff.(13) The advantages of SP in terms of logistic and human resources proved to be particularly valuable during all the COVID19 pandemic contingencies.(21)

We acknowledge that it's a small sample study with short follow-up period and that long-term recurrence would be an important outcome to assess.

To conclude, we showed that SP could be superior to HAL-RAR in terms of safety, complete therapeutic success and also return to normal day-to-day activity. A large, randomised controlled trial using this pilot study protocol is feasible and necessary to ascertain our results. Future research should also focus on long-term results of both techniques.

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Table 1: Sodergren Hemorrhoid symptom severity scoring system

Have you considered or excluded another pathology? Yes □ No □ Does the patient suffer from rectal bleeding? Yes □ No □

How severe are your symptoms of itching or irritation?	0: No symptoms	0
	1: Mild / do not really bother me	0
	2:	0
	3: Moderately bothersome	0
	4:	4
	5: Severe	4
How severe are your symptoms of pain or discomfort at rest?	0: No symptoms	0
	1: Mild / do not really bother me	0
	2:	0
	3: Moderately bothersome	3
	4:	3
	5: Severe	3
How severe are your symptoms of pain or discomfort on opening your bowels?	0: No symptoms	0
	1: Mild / do not really bother me	0
	2:	0
	3: Moderately bothersome	0
	4:	3
	5: Severe	3
How often do you feel that you might have a lump at your anus (prolapse)?	0: Never	0
	1: Less than once a month	0
	2: More than once a month	0
	3: More than once a week	0
	4: Every day	4

Table 2: Bleeding grade in Hemorrhoidal disease

Type of bleeding	Grade
No rectal bleeding	0
Bleeding when passing stool less than once a week	1
Bleeding when passing stool 1-6 days per week	2
Bleeding when passing stool every day or hemodynamic e/ou laboratorial changes (anemia, with or without transfusion, signs of hypovolemia)	3

Table 3: Baseline characteristics

	All patients (n=46)		Polidocanol Foam Sclerotherapy (n=24)		Hemorrhoidal Artery Ligation ±Recto Anal Repair (n=22)		P value
	n | Mean	% | SD	n | Mean	% | SD	n | Mean	% | SD	
Age, years-old	49.6	±14.6	50.8	±17.6	48.3	±10.8	0.077
Sex (Male/Female)	16/30	34.8/65.2	10/14	41.7/58.3	6/16	27.3/72.7	0.306
Professional status							
Employee/Student	32	69.6	16	66.7	16	72.7	0.092
Unemployed/Retired	14	30.4	8	33.3	6	27.2	
Goligher's classification							
II	19	41.3	12	50.0	7	31.8	0.211
III	27	58.7	12	50.0	15	68.2	
Sodergren score	8.5	±3.7	7.6	±3.4	9.5	±3.8	0.096
Bleeding grade							
1	11	23.9	6	25.0	5	22.7	0.857
2	35	76.1	18	75.0	17	77.3	

Table 4: Efficacy and safety outcomes

	All patients (n=46)		Sclerotherapy with polidocanol (n=24)		Hemorrhoidal Artery Ligation ±Recto Anal Repair (n=22)		P value
	n | Mean	% | SD	n | Mean	% | SD	n | Mean	% | SD	
Treatments´ efficacy							
Therapeutic success							0.131
Complete	37	80.4	22	91.7	15	68.2	**0.045**
Partial	7	15.2	2	8.3	5	22.7	0.175
Therapeutic failure	2	4.3	0	0.0	2	9.1	0.284
Treatments´ complications							
Complications (overall)	21	45.6	6	25.0	15	68.2	**0.003**
Mild Complications	18	39.1	5	20.8	13	59.1	**0.003**
Mild pain/discomfort	15	32.6	4	16.7	10	45.5	
Bleeding (minor)	3	6.5	1	4.1	3	13.6	
Moderate Complications	3	6.5	1	4.2	2	9.1	0.950
Thrombosed Hemorrhoid	1	2.2	1	4.2	0	0.0	
Bleeding	2	4.3	0	0.0	2	9.1	
Professional implications							
Nᵉʳ days off -work	4.9	±8.2	0.6	±0.2	9.5	±10.1	**≤0.001**

Figure 1: Schematic representation of Polidocanol Foam Sclerotherapy (A); Hemorrhoid Artery Ligation (B1) and Recto-Anal Repair (B2)

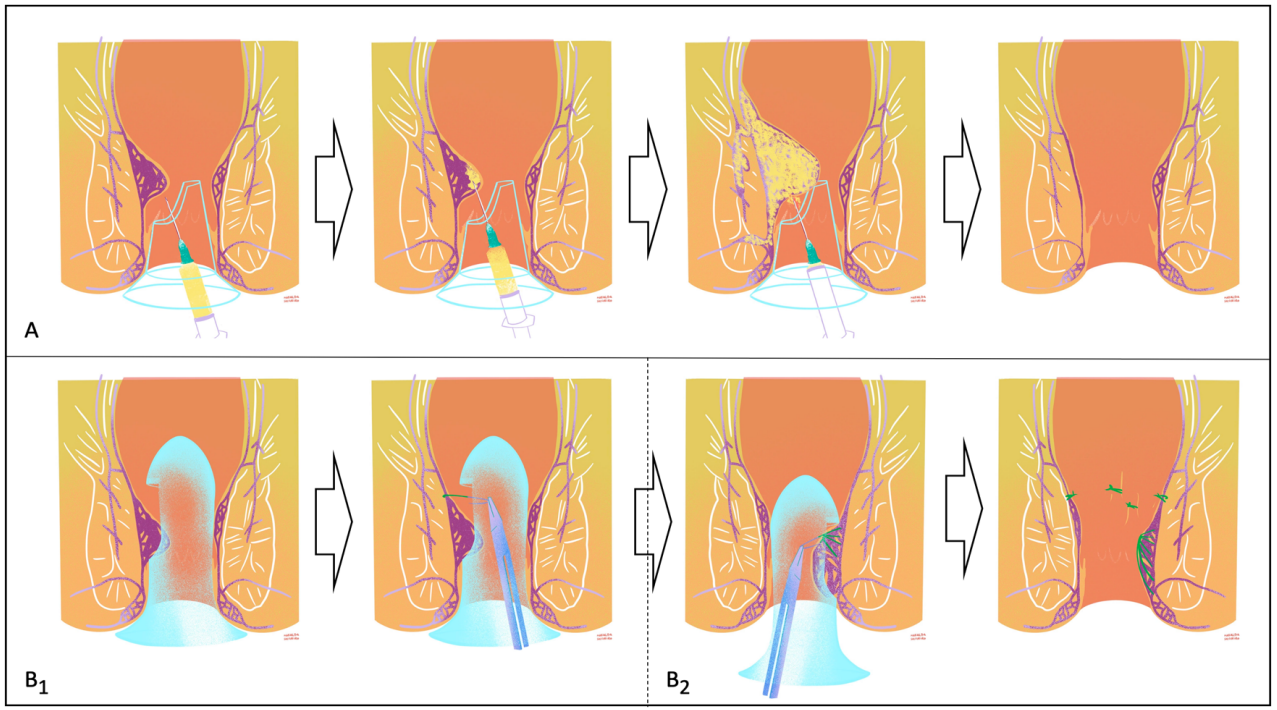
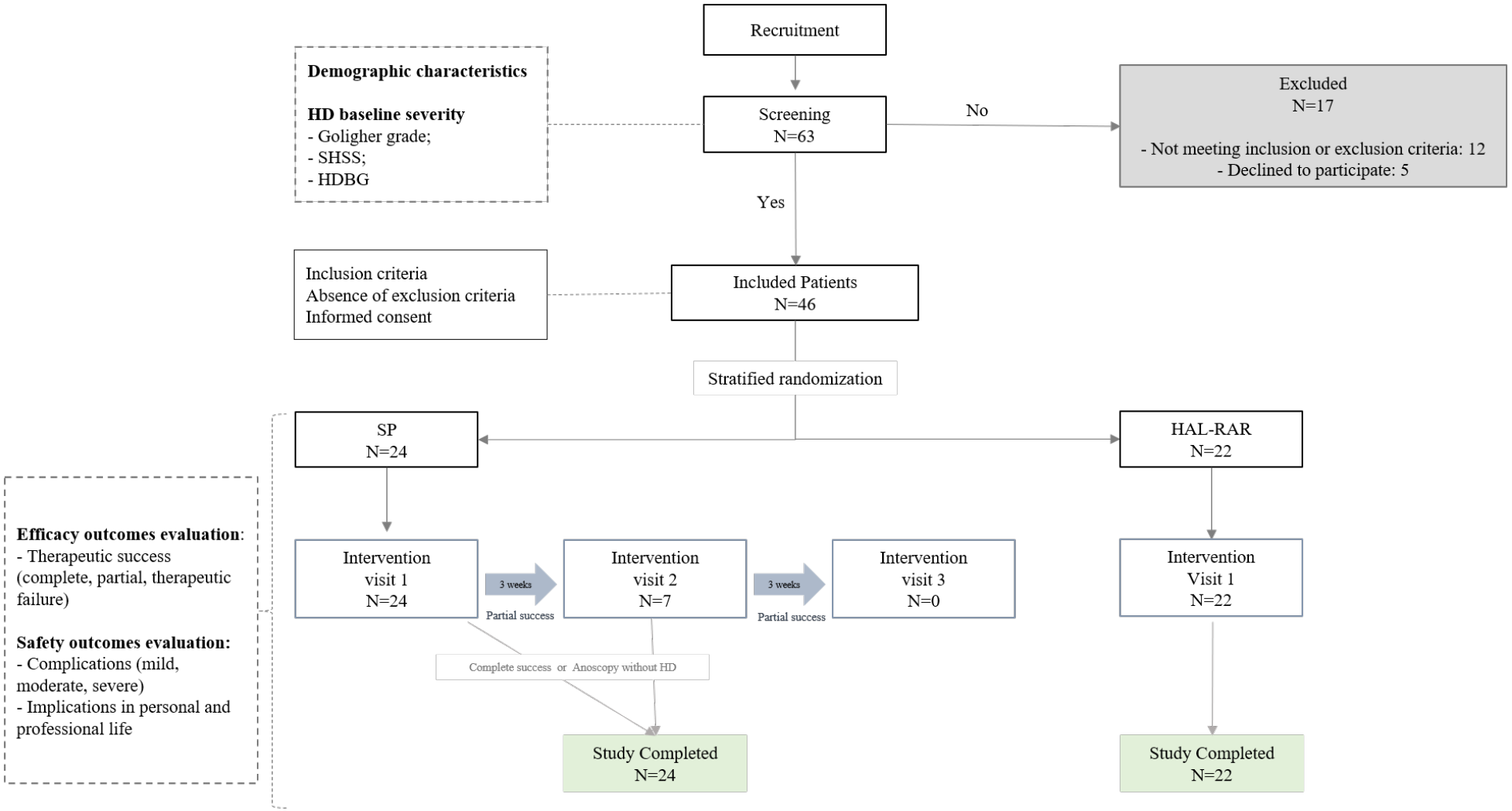


Figure 2: Study-design flow chart



Supplementary Digital Content

Table 1: Predictors of treatment's complications

	Univariable			Multivariable		
	OR	95% CI	P value	OR	95% CI	P value
Age, years	0.99	0.95-1.03	0.746	1.01	0.96-1.07	0.608
Goligher's classification (III vs. II)	1.28	0.39-4.17	0.686	0.49	0.09-2.87	0.432
Bleeding grade (3 vs. 2)	1.65	0.41-6.68	0.481	1.01	0.12-9.56	0.992
Sodergren score	1.18	0.99-1.41	0.066	1.23	0.96-1.56	0.100
Treatment (vs. Polidocanol foam Sclerotherapy)						
Hemorrhoidal Artery Ligation with Recto Anal Repair	6.43	1.77-23.30	**0.005**	6.05	1.07-34.33	**0.042**
Number of interventions	0.158	0.02-1.44	0.102	0.48	0.03-7.15	0.408

APPENDIX 2

TRIAL PROPOSAL: 2021.051(041-DEFI/042-CE)

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TITLE

"Sclerotherapy with Polidocanol Foam in the Treatment of First, Second and Third- Grade Hemorrhoidal Disease in Patients with Liver Cirrhosis: A Prospective, Cohort Trial"

INTRODUCTION

Hemorrhoidal disease (HD) is a common health problem, affecting up to 38,9% of adult population [1]. Despite being a benign condition, associated symptoms like bleeding, pain, prolapsing, swelling, itching, and mucus soiling impact considerably on patients' quality of life. HD is also a common finding in up to 36% of cirrhotic patients [2], as hemorrhoidal plexus is a possible site of portosystemic venous anastomosis. Despite portal hypertension does not increase the prevalence of hemorrhoids [3,4], elevated portal venous pressure, with a not so rare contribution of coagulopathy, may result in massive, life-threatening hemorrhoidal bleeding, unlike the normal population (4). Besides, internal HD bleeding is the most frequently identified cause of bleeding with origin on the lower gastrointestinal tract among cirrhotic patients with severe hematochezia [5].

HD treatment can be grouped into conservative (diet, lifestyle changes, laxatives, anti-inflammatory drugs, phlebotonics), office-based (sclerotherapy, ligation, photocoagulation, laser photocoagulation, among others) and surgical (hemorrhoidectomy, hemorrhoidopexy). The choice of therapy should be oriented by the Goligher's classification (**Table 1**) [6], or a symptom score such as Rørvik's Hemorrhoidal Disease Symptom Score (HDSS)(**Table 2**) [7].

Cirrhotic patients represent a group often neglected in clinical trials so, little is known about the optimal treatment for HD these patients. Surgical treatment with stapled hemorrhoidopexy has been described in cirrhotic patients as a feasible and safe approach, but with up to 46,7% of the procedures complicated with postoperative staple-line bleeding, although all of them managed with conservative treatment without reoperation or death [8,9]. Recently, Ashraf et al compared hemorrhoidectomy performed using rubber band ligation (RBL) with conventional hemorrhoidectomy in 40 randomized patients with liver

disease and diagnosed with grade I, II, or III hemorrhoids. Intraoperative blood loss was lower in RBL group (1.2 ± 1.6 ml vs 22.2 ± 6.58 ml, p=0,001), as well as operative time (9.00 ± 2.449 min vs 24.100 ± 3.669 min, p=0,001). Importantly, postoperative pain (35% vs 100%, p=0,001), bleeding (15% vs 45%, p=0,022) and urine retention (20% vs 55%, p=0,011) were lower in the RBL group, along with time of hospital stay (8.6 ± 2.54 h vs 60.65 ± 41.93, p=0,002) and time of wound healing (16.85 ± 1.87 days vs 31.00 ± 3.57 days, p=0,003) [10].
Bearing in mind the high rate of surgical complications in cirrhotic patients, these results suggest that office-based treatments, may be the preferred treatment for cirrhotic patients with HD grades I to III. Awad AE *et al* [11], compared the efficacy of endoscopic injection sclerotherapy (EIS) to RBL in the treatment of bleeding internal hemorrhoids in 120 adult patients with liver cirrhosis. Both techniques were highly effective in the control of bleeding with a low rebleeding [10% in the EBL group and 13.33% in the EIS group] and recurrence [20% in the EBL group and 20% in the EIS group] rates; also, EBL had significantly less pain and higher patient satisfaction than EIS. However, these authors have used liquid sclerosing agents (either ethanolamine oleate 5% or N-butyl cyanoacrylate). A recent portuguese study by Fernandes F *et al* [12] has evaluated the efficacy and safety of a sclerosing agent, polidocanol, foam injection in 2000 consecutive patients with prolapsed hemorrhoids (grades II/III/IV). This technique showed high efficacy (98%) and tolerability (92% with mild/no pain) with only 0,7% of serious complications (major bleeding n=3; urinary retention n=4; infection/suppuration requiring surgery n=2). Also, in this cohort, 210 patients (10,5%) were under anticoagulation or double antiplatelet therapy) and only 2 of these patients presented clinically significant bleeding. The authors conclude that polidocanol foam should be used as first-line treatment of most hemorrhoid patient, including those under anticoagulation and antiplatelet therapy. Nevertheless, no cirrhotic patients were included, so results cannot be generalized to this particular high-risk group.
The objective of this study is to prospectively evaluate the efficacy and safety of treatment of grade I, II and III internal hemorrhoidal disease with polidocanol foam in cirrhotic patients.

METHODS

Selection of participants:

Inclusion criteria: Adult patients with liver cirrhosis and symptomatic HD grades I to III refractory to conservative therapy (dietary modification, intestinal transit modifiers, topical and phlebotonics), during a period of 4 weeks, referred to the Gastroenterology consultations of Centro Hospitalar Universitário do Porto will be selected to hemorrhoidal sclerotherapy with polidocanol foam.

Exclusion criteria: known allergy to polidocanol, pregnant and lactating women, inflammatory bowel disease, other concomitant symptomatic perianal disease, history of office-based or surgical treatment of hemorrhoidal disease in the last 6 months, immunosuppression. All participants should have a recent endoscopic study (including upper endoscopy). Estimated inclusion period of 1 year.

Visits and data collection [Figure 1]:

Prior to the first intervention, demographic, clinical and laboratory data, as well as baseline severity of the HD and liver cirrhosis (Child-Pugh score, MELD, portal hypertension stigmata) are collected. During this visit all patients receive informed consent, behavioral care flyer and the date of the first intervention is scheduled. During the intervention period the participants are observed at 3-week intervals (maximum of 3 sessions). The required number of sessions (maximum of 3) is determined by clinical and anoscopic evaluation (if the participant is non-symptomatic and/or there is no significant hemorrhoidal disease on anoscopy, the patient will not be a candidate for additional instrumental therapy moving directly to the follow-up period). After each session all patients are instructed to adopt dietary measures and adequate hydration, maintaining therapy with topical and systemic phlebotonics and laxative if necessary. After the intervention period, a one-year follow-up is scheduled with medical appointments performed every 3 months. Direct contact is provided for any questions or notification of complications, in which case additional observation can be made.

Effectiveness evaluation [Figure 1]:

Intervention period

For efficacy evaluation during the intervention period the following outcomes will be assessed: 1) occurrence of therapeutic success (improvement of HDSS); the therapeutic success is subdivided in: complete (HDSS = 0), partial (HDSS > 0 but with improvement over the initial score) or unsuccess (participants that, after 3 sessions of office-based treatment worsened or maintained the initial HDSS; these patients are referred to other treatment options and they are excluded from further follow-up); 2) variation of Goligher classification [**Table 2**] before and after the intervention; 3) number of office-based therapy sessions; 4) polidocanol foam dose.

Follow-up period

Recurrence during the follow-up period (for patients who have had therapeutic success) will be defined as mild, if HDSS worsened compared to the previous visit but is still better than the initial visit; or severe if HDSS equals or worsens compared to the initial score, requiring instrumental or surgical treatment.

Safety evaluation:

Complications will be assessed and classified as: mild (e.g. pain/discomfort, minor bleeding, external hemorrhoidal thrombosis not requiring surgical intervention); moderate (e.g. external hemorrhoidal thrombosis requiring surgical intervention, moderate bleeding not requiring blood transfusion, urgent hemostasis or urgent surgery); and severe (e.g. sepsis, Fournier's gangrene, perineal abscess, bleeding with hemodynamic instability, transfusion need or urgent surgery, sexual impotence in man).

Technical aspects of the intervention:

The preparation of the foam is done according to the Tessari's technique using 2 disposable 20ml syringe, a three-way tap and a 10cm reusable extender adapted to intravenous needle **(Figure 2)**. The sclerosant is applied according to the Blanchard's technique through a disposable transparent anoscope with the patient in jack-knife (knee-chest) position. In each session treatment can be performed on more than one hemorrhoidal cushion. The maximum dose per treatment session is 20ml (mixture of 4ml of polidocanol 3% with 16ml of air).

Figure 1. Study design protocol

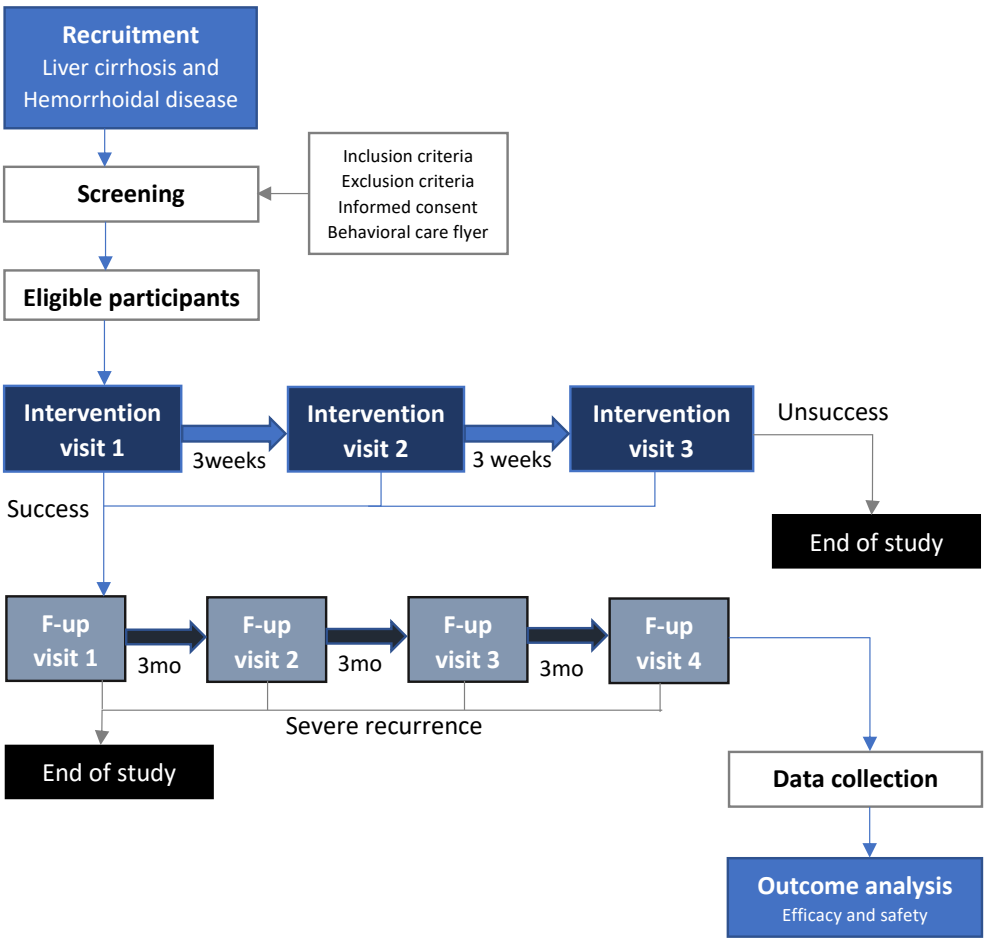

Figure 2. Polidocanol foam preparation according to Tessari technique

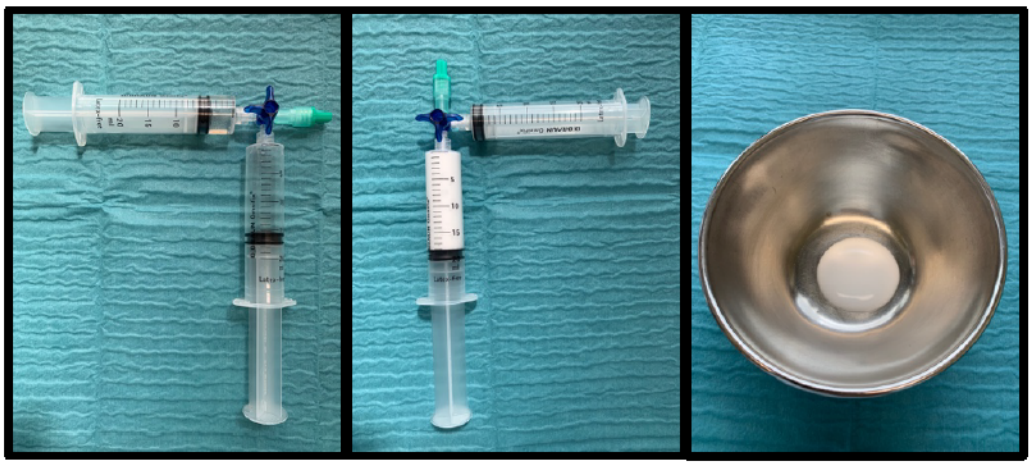

Table 1. Goligher's classification (Goligher JC *et al*, Surgery of the anus, rectum and colon. 5th ed. London: Billiere Tindall; 1984: 101p.)	
Grade 1	Hemorrhoids are visualized on anoscopy and may bulge into the lumen but do not prolapse below the dentate line.
Grade 2	Hemorrhoids prolapse out of the anal canal with defecation or straining but reduce spontaneously.
Grade 3	Hemorrhoids prolapse out of the anal canal with defecation or straining and require manual reduction.
Grade 4	Hemorrhoids are irreducible and may strangulate.

Table 2. Hemorrhoidal Disease Symptom Score (Rørvik *et al*, Dis Colon Rectum 2019; 62: 333–342)
The following questions deal with symptoms caused by hemorrhoids. Your answers should reflect your symptoms during the last 3 months (1 answer per question).

1. How often do you feel pain from your hemorrhoids?	☐ Never ☐ Less than once a month ☐ Less than once a week ☐ 1–6 days per week ☐ Every day (always)	0 1 2 3 4
2. How often do you feel itching or discomfort of the anus?	☐ Never ☐ Less than once a month ☐ Less than once a week ☐ 1–6 days per weekx ☐ Every day (always)	0 1 2 3 4
3. How often do you bleed when passing stool?	☐ Never ☐ Less than once a month ☐ Less than once a week ☐ 1–6 days per week ☐ Every day (always)	0 1 2 3 4
4. How often do you soil your underwear (soiling from the anus)?	☐ Never ☐ Less than once a month ☐ Less than once a week ☐ 1–6 days per week ☐ Every day (always)	0 1 2 3 4
5. **How often do you feel a swelling or a prolapsing hemorrhoid?**	☐ Never ☐ Less than once a month ☐ Less than once a week ☐ 1–6 days per week ☐ Every day (always)	0 1 2 3 4
		TOTAL:

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LIST OF ABBREVIATIONS

ALTA	Potassium aluminum sulfate and tannic acid
BD	Bleeding disorders
FDA	Food and Drugs Administration
HAL-RAR	Doppler guided hemorrhoid artery ligation with recto-anal repair
HD	Hemorrhoidal disease
HIV	Human immunodeficiency virus
IRC	Infrared photocoagulation
IBD	Inflammatory bowel disease
PFS	Polidocanol foam sclerotherapy
RCT	Randomized clinical trial
RBL	Rubber band ligation
SRA	Superior rectal arteries