

MESTRADO INTEGRADO EM MEDICINA

Sclerotherapy with polidocanol foam versus Rubber band ligation versus Hemorrhoidal Artery Ligation with Recto Anal Repair in the treatment of second and third-grade hemorrhoidal disease: a prospective study

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Abstract

Background: Hemorrhoidal disease is extremely frequent in the adult population and, as a benign pathology, the treatment should be guided by the patient's symptoms. Treatment of hemorrhoidal disease includes a conservative approach, office-based treatments and surgery. This study aimed to evaluate and compare the efficacy and safety of the treatment of hemorrhoidal disease with non-surgical office-based methods, namely sclerotherapy using polidocanol foam (SP) and rubber band ligation (RBL), and a surgical technique (doppler-guided hemorrhoidal artery ligation with recto-anal repair (HAL-RAR)).

Methods: Prospective, unicentric study including patients with symptomatic hemorrhoidal disease grade II and III refractory to conservative therapy, submitted either to SP (n=20), to RBL (n=19) or to HAL-RAR procedure (n=16), during a recruitment period of 6 months. Patients were evaluated for efficacy (Sodergren's scale of symptoms and severity of bleeding) and safety (complications and implication in personal and professional life), up to one month after treatment.

Results: Most patients achieved therapeutic success, either partial or complete (SP 100%, RBL 89.5%, HAL-RAR 87.5%) ($p=0.178$). Specifically concerning complete success, SP was significantly more successful recording a 100% rate, comparing to RBL (73.7%) and HAL-RAR (75.0%) ($p=0.046$). It was possible to obtain success with a similar number of interventions in the three treatment groups ($p=0.202$). Considering safety, SP was the less complicated procedure (25% reported complications in general), when compared to RBL (52.6%) and HAL-RAR (62.5%) ($p=0.041$). Additionally, HAL-RAR revealed a higher rate of mild complications ($p=0.033$). Also, in a multivariable analysis, HAL-RAR was the only significant predictor of complications (OR=7.11, 95% IC 1.07-55.65, $p=0.043$). HAL-RAR had a greater impact in patients' quality of personal life (62.5%), comparing to SP (15%) and RBL groups (36.8%) ($p=0.016$). This was also observed for professional life impact, measured in days of absence from work (HAL-RAR 8.56 ± 8.4 days, SP 0.6 ± 0.2 days, RBL 0.7 ± 0.3 days) ($p\leq 0.001$).

Conclusion: Office-based procedures gather all favorable conditions for being regarded as the first-line therapy for hemorrhoidal disease grade II and III.

Keywords: Hemorrhoids, Pathophysiology, Treatment, Sclerotherapy with polidocanol foam, Rubber-band ligation, Doppler-guided hemorrhoidal artery ligation, Outcome.

Resumo

Introdução: A doença hemorroidária é bastante frequente na população adulta e, por se tratar de uma patologia benigna, o tratamento deve ser orientado pela sintomatologia dos pacientes. O tratamento da doença hemorroidária engloba primariamente uma abordagem conservadora e, ainda, tratamento instrumental e cirurgia. O nosso objetivo foi comparar a eficácia e segurança de técnicas instrumentais, nomeadamente escleroterapia com polidocanol espumoso (SP) e laqueação elástica (RBL), e do procedimento cirúrgico (laqueação transanal das artérias hemorroidárias guiada por doppler (HAL-RAR)).

Métodos: Estudo prospectivo, unicêntrico, incluindo pacientes com doença hemorroidária sintomática grau II e III, refratária a medidas conservativas, foram alocados ao grupo de tratamento SP (n=20), RBL (n=19) ou HAL-RAR (n=16), durante um período de 6 meses. Os pacientes foram avaliados, um mês após o procedimento, para eficácia (escala de Sodergren e severidade da hemorragia) e segurança (complicações e implicações na vida pessoal e profissional).

Resultados: A vasta maioria dos pacientes obtiveram sucesso, parcial ou completo, sem diferença significativa nos três grupos (SP 100%, RBL 89.5%, HAL-RAR 87.5%) ($p=0.178$). Considerando especificamente sucesso completo, SP mostrou ser significativamente melhor, registando uma taxa de 100%, comparando com RBL (73.7%) and HAL-RAR (75.0%) ($p=0.046$). Foi possível obter eficácia terapêutica com o mesmo número de procedimentos nos três grupos de tratamento ($p=0.202$). No que diz respeito à segurança, SP foi o tratamento com menor taxa de complicações (25% reportaram complicações, em geral), quando comparado com RBL (52.6%) e HAL-RAR (62.5%) ($p=0.041$). Para além disso, HAL-RAR revelou uma maior taxa de complicações ligeiras ($p=0.033$). Na análise multivariável, HAL-RAR demonstrou ser o único preditor de complicações (OR=7.11, 95% IC 1.07-55.65, $p=0.043$). HAL-RAR demonstrou ter um maior impacto vida pessoal (62.5%), quando comparado com SP (15%) e RBL (36.8%) ($p=0.016$). O mesmo foi observado em relação ao impacto na vida profissional, avaliado em número de dias de absentismo laboral (HAL-RAR 8.56 ± 8.4 dias, SP 0.6 ± 0.2 dias, RBL 0.7 ± 0.3 dias) ($p\leq 0.001$).

Conclusões: Os tratamentos não cirúrgicos reúnem todas as condições favoráveis para serem considerados como terapia de primeira linha na abordagem à doença hemorroidária grau II e III.

Palavras-Chave: Hemorróidas, Patofisiologia, Tratamento, Escleroterapia com polidocanol espumoso, Laqueação elástica, Laqueação transanal das artérias hemorroidárias guiada por doppler.

List of abbreviations

CHUP | Centro Hospitalar Universitário do Porto

HAL | Doppler-guided hemorrhoidal artery ligation

HAL-RAR | Doppler-guided hemorrhoidal artery ligation with recto-anal repair

OR | Odds Ratio

RAR | Recto-anal-repair

RBL | Rubber band ligation

SP | Sclerotherapy with polidocanol foam

Table of contents

Agradecimentos	i
Abstract	ii
Keywords:	ii
Resumo	iii
Palavras-Chave:	iii
List of abbreviations	iv
List of Tables	vi
List of Figures	vii
Introduction	I
Methods	7
Sample selection	7
Visits and data collection	8
Intervention: technical aspects	9
Statistical analysis.....	11
Results	12
Discussion	14
Conclusion	17
Appendix	18
References	26

List of Tables

Table I: Characteristics of studied population	21
Table II: Treatments' efficacy.....	22
Table III: Complications' frequency.....	23
Table IV: Predictors of treatment's complications.....	24
Table V: Professional and personal life implications.....	25

List of Figures

Figure 1: Internal hemorrhoids: Goligher grading.....	18
Figure 2: Sodergren Hemorrhoid symptom severity scoring system (Pucher et al. 2015).....	19
Figure 3: Bleeding grade in Hemorrhoidal disease.....	20

Introduction

Hemorrhoids are normal vascular structures in the anal canal, arising from a cushion of dilated arteriovenous channels and connective tissues, that drains into the superior and inferior hemorrhoidal veins¹. They can also be described as arteriovenous communications between terminal branches of the superior rectal artery and the superior, middle, and inferior rectal veins².

Hemorrhoids contribute in about 15-20% to anal resting pressure, maintaining anal closure and continence. In addition to that, they have a protective function of the anal sphincters, during defecation, when engorged with blood and, also, a sensory function which is central to the differentiation between liquids, solids or gases as well as the subsequent decision to evacuate³. During the act of defecation, the fibroelastic component contracts and exsanguinates the hemorrhoidal pads, reducing their size. Consequently, the lumen diameter of the anal canal increases^{4,5}.

The pathophysiology of hemorrhoidal disease is not fully understood. For years, the theory of varicose veins, that describes hemorrhoids as varicose veins in the anal canal, had been accepted. But it is now obsolete because they are proven to be distinct entities. As a matter of fact, patients with portal hypertension and varices do not have an increased incidence of hemorrhoids^{2,6}.

Currently, it is common knowledge that hemorrhoids occur due to degeneration of the connective tissue causing abnormal downward displacement of the anal cushions, associated with venous dilatation and vascular distortion. In this way, the venous drainage is compromised and the hemorrhoids dilate. On histopathological examination, changes seen in the anal cushions include abnormal venous dilatation, vascular thrombosis, degenerative process in the collagen fibers and fibroelastic tissues, distortion and rupture of the anal subepithelial muscle. Apart from that, hemorrhoidal tissue contains inflammatory cells and newly formed microvessels^{7,8}.

Advancing age, genetic factors and absence of valves in the hemorrhoidal veins, but also behaviors such as inadequate dietary fiber, prolonged defecation effort and constipation as well as increased intra-abdominal pressure, are thought to contribute to this pathological process^{3,9}. Some studies have questioned the influence of constipation in the development of hemorrhoidal disease^{10,11}, however, the increase in defecation effort may precipitate the development of symptoms such as hemorrhage and prolapse⁶.

Hemorrhoidal disease is extremely frequent in the adult population, although it is very difficult to assess accurately the exact prevalence. Most studies have potential shortcomings resulting in

a wide range of rates¹². 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^{8,13}. Some authors suggest increased prevalence rates in caucasian and in higher socioeconomic status^{13,14}. There are few epidemiological studies of the prevalence of hemorrhoidal disease in Portugal, but in the United States it is known that ten million people suffer from hemorrhoidal disease, corresponding to a prevalence of 4,4%¹³.

A precise anamnesis and thorough physical examination are imperative for the diagnosis of hemorrhoidal disease¹⁵.

About 40% of individuals with hemorrhoidal disease are asymptomatic. However, when symptomatic, they may have a great variance of symptoms². Internal hemorrhoidal disease most commonly causes painless rectal bleeding, prolapse, mucous discharge or the feeling of incomplete evacuation. The typical symptoms of external hemorrhoidal disease are pruritus, anal discomfort and pain with thrombosis³.

Physical examination should include anal inspection, rectal examination and anoscopy⁸. Anal inspection may reveal any thrombosed external hemorrhoid, whereas digital examination include palpation for masses, tenderness and characterization of anal sphincter tone¹. Lastly, anoscopy and proctosigmoidoscopy should be performed routinely to identify internal hemorrhoids or fissures, and to rule out colorectal tumors or inflammatory bowel disease. If it remains uncertain after office examination, a total colonoscopy is often appropriate to exclude a proximal source of bleeding. Obviously, any patient older than 50 years requires a colonoscopy, unless recently performed. For younger patients, the decision for total colonoscopy must be based on risk factors, as family history of colorectal cancer and on alarm symptoms such as iron deficiency anemia, weight loss or a positive occult blood test^{2,16}.

Differential diagnosis of hemorrhoidal disease include all the conditions that may be concomitantly present or cause similar symptoms, namely anal fissure, perianal abscess, anal fistula, anal stenosis, neoplasia, inflammatory bowel disease, irritable bowel syndrome, pruritus ani, rectal prolapse, hypertrophied anal papilla, and skin tags^{3,6}.

Classification of a hemorrhoid corresponds to its position relative to the dentate line. External hemorrhoids are located below the dentate line and are covered by modified squamous epithelium, being richly innervated and therefore painful when there is associated thrombosis. On the contrary, internal hemorrhoids lie above the dentate line¹. Internal hemorrhoidal disease are often classified according to the degree of prolapse in the Goligher classification¹⁷ (Figure 1).

As a benign pathology, the treatment of hemorrhoidal disease should be guided by the patient's symptoms and their impact on quality of life. A prospective study by Pucher et al.¹⁸

presented the development and validation of the Sodergren score, which is a tool in the assessment of disease severity. Thus, it is possible to monitor the progression of disease. The lack of properly validated tools to evaluate disease-specific health-related quality of life in hemorrhoidal disease is recognized in the literature. Short Health Scale was proven, by a recent study, to be an useful and responsive measurement instrument of symptoms' impact on daily life and well-being, when adapted to hemorrhoidal disease¹⁹. This scale is a simplified instrument with four questions regarding symptom burden, functional status, disease-specific worries and general well-being²⁰.

Treatments of hemorrhoidal disease include medical therapies, office-based procedures and surgery. Specific choices of treatments mainly depend on the grade and severity of hemorrhoids, but also on the patients' age and comorbidities. The experience of healthcare professionals, hospitals and care centers are also determining factors.

Conservative measures are considered a first-line therapy and should be implemented in every grades of hemorrhoidal disease, even in patients undergoing instrumental or surgical treatment¹⁶. It typically includes lifestyle changes, dietary modification, with adequate fluid and fiber intake, laxative medication and topical treatment as local anesthetics, corticosteroids or anti-inflammatory drugs^{2,7}.

Instrumental office-based procedures are usually indicated for internal hemorrhoidal disease grade I and II which are refractory to conservative medical treatments and in selected cases of grade III hemorrhoidal disease^{2,7,21}. Despite being invasive, these techniques are more conservative than surgical treatments and are also effective⁸. The primary goals are to decrease the amount of redundant tissue, reduce vascularity, and affix the hemorrhoidal cushions to minimize prolapse²².

Office-based procedures include rubber band ligation (RBL), sclerotherapy (liquid and foam agents), infrared photocoagulation, cryotherapy, radiofrequency ablation among others.

RBL is widely acknowledged to be highly effective and the most commonly performed nonsurgical procedure in the treatment of II or III degree hemorrhoidal disease^{2,23}. Cumulatively, with subsequent treatments, a success rate of 80% is observed with rubber band ligation²⁴.

RBL works by positioning elastic bands above the dentate line to strangulate the piles, causing hemorrhoid tissue necrosis and its fixation to the rectal mucosa, preventing subsequent development of new hemorrhoidal tissue^{2,25}. Patients are placed in jackknife or left lateral position and the procedure is performed through an anoscope. The two most prevalent ligating devices are the McGivney forceps ligator and the McGown suction instrument, which uses suction to bring the redundant mucosa into the ligating barrel³.

Complications associated with this procedure include mild bleeding, pain, vagal symptoms,

slippage of bands and urinary symptoms, considered as minor complications. By contrast, major complications as massive bleeding, thrombosed hemorrhoids, severe pain, urinary retention, pelvic sepsis and death have been less commonly reported²⁶.

Hemorrhoidal sclerosis is a procedure indicated to treat grade I and II hemorrhoidal disease^{3,27}. It has also been used in the treatment of internal grade III hemorrhoidal disease, but there are limited data on its efficacy²⁸.

Performed through an anoscope and according to Blanchard technique, internal hemorrhoids are located and injected with a sclerosant material into the submucosa at the base of the hemorrhoid, above the anterolateral line²⁹. The sclerosant subsequently causes an inflammatory response and fibrosis that interrupts the vascular blood supply³⁰.

A variety of sclerosants have been used including ethanolamine, quinine, hypertonic saline, aluminum potassium sulfate and tannic acid (ALTA)^{31,32}, and 5% phenol in oil²¹.

Recently, a new sclerosing agent, polidocanol, started to be employed in the treatment of hemorrhoidal disease. It is a nonionic detergent and consists of a hydrophilic polyethylene oxide chain combined with hydrophobic aliphatic dodecyl alcohol. When injected into varicose veins, polidocanol damages the endothelium of blood vessels, allowing platelets to aggregate. Eventually, a dense network of platelets, cellular debris, and fibrin occludes the vessel, which is subsequently replaced with connective fibrous tissue³³. In addition to the treatment of hemorrhoidal disease, polidocanol is used for sclerotherapy of varicose veins of the lower extremities and for the treatment of esophageal varices³⁴.

The advantages of this sclerosing agent include a highly satisfactory efficiency, a low necrotic potential, and a good general tolerance³⁵. At the same time, it has a local anesthetic effect which permits almost painless sclerotherapy³⁶. Nevertheless, its use is contraindicated in patients with acute thromboembolic diseases and in those with allergy to the drug³³.

Polidocanol can be used in its liquid or foam form. It has been proved the foam formulation allows for greater efficacy, since it requires lower doses of sclerosant agent. This is because the sclerotic effect is maximized by increasing the contact surface area with varices walls³⁷. This foam is previously prepared according to the Tessari's method³⁸, in which two 10 mL syringes are connected by a 3-way stopcock. The syringes contain air and a sclerosing agent (3% polydocanole), with a ratio of 4:1, respectively, and twenty passages from one syringe to the other are made in order to obtain a sclerosing foam^{39,40}.

Several studies reported the efficacy of the use of sclerotherapy with liquid polidocanol in hemorrhoidal disease. Specifically for the treatment of grade I hemorrhoids, there is one study showing the superiority of polidocanol foam compared to its liquid formulation³⁴. However, there's a lack of research about its use in hemorrhoidal disease other than grade I.

The most common complications of sclerotherapy include minor discomfort or bleeding².

Although it is a very safe treatment option, some serious side effects, including erectile dysfunction and urinary retention, have been reported²¹. The proper injection technique of sclerosant is essential to avoid complications such as mucosal ulceration or necrosis, prostatic abscess and retroperitoneal sepsis²³.

Sclerotherapy is a valid alternative when conservative therapy has failed. Moreover, this procedure can also be used for the treatment of patients whose hemorrhage is the main symptom, for patients on antithrombotic medication, as well as cirrhotic and immunocompromised patients⁴¹.

Surgical treatment is reserved for refractory cases to nonsurgical approaches, grade IV or mixed hemorrhoidal disease (internal and external components)², symptomatic hemorrhoidal disease with concomitant anorectal pathology²³ and lastly if it's the patient's choice⁴².

Although surgical approach is apparently more effective than instrumental treatment, it is also associated with substantial postsurgical morbidity, particularly postoperative pain and limitation in day-life activities⁴³⁻⁴⁷. Several surgical methods have been described including open and closed hemorrhoidectomy, doppler guided hemorrhoidal artery ligation (HAL) and hemorrhoidectomy stapler. The choice of each method should consider the grade of hemorrhoidal disease and the predominant symptoms of the patient, together with the experience of the center⁴⁸.

HAL was first introduced in 1995 as an alternative to hemorrhoidectomy^{6,49}. This technique involves the use of Doppler ultrasound and a specialized anoscope⁴⁹. There are different nomenclatures, but the principles include the use of a Doppler probe to identify the six main feeding arteries within the anal canal and their ligation with absorbable suture above the dentate line, therefore associated with less pain. Finally, plication of redundant hemorrhoidal mucosa is performed (if there is hemorrhoidal or muco-hemorrhoidal prolapse), known as recto-anal-repair (RAR), mucopexy or hemorrhoidopexy^{2,50}. The aim of this recent surgical procedure is to treat patients' symptoms without tissue destruction⁵¹. Early results of HAL were promising, with lower pain scores than hemorrhoidectomy, and relief of bleeding and tissue prolapse in over 90% of patients⁵². Since then, several randomized clinical trials have been performed with mixed results⁵³⁻⁵⁵. Currently, HAL remains a viable approach to multicolumn internal hemorrhoids. However, the short-term benefits regarding postoperative pain have recently not been as remarkable as in the earlier studies². Also, there has been a progressive increase in long term recurrence rates, especially for grade III and IV hemorrhoids⁵⁶.

Some studies have been conducted with the purpose of comparing the efficacy of non-surgical office-based treatments with surgical ones. Brown et al.⁵⁷, in a multicentric, open-label and randomized controlled trial, compared RBL and HAL, revealing higher efficacy of the

surgical procedure. If, however, RBL is considered a course of treatment involving repeat banding, the procedures are equally effective. Besides, HAL was proved to be more painful than RBL.

In another study comparing infrared photocoagulation with HAL, Ahmad, et al.⁵⁸, showed that both procedures are minimally invasive and associated with minimal discomfort, but HAL is more effective than infrared photocoagulation in controlling symptoms of hemorrhoids.

There has been no comparative studies between polidocanol foam sclerotherapy (SP) and hemorrhoidal artery ligation, to date. Therefore, the purpose of the present study was to evaluate and compare the safety and efficacy of the treatment of hemorrhoidal disease with non-surgical office-based methods (SP and RBL) and a surgical method (doppler-guided hemorrhoidal artery ligation with recto-anal repair (HAL-RAR)).

Methods

Prospective, unicentric study (Centro Hospitalar Universitário do Porto (CHUP)) which aimed to compare the efficacy and safety of the treatment techniques in patients with hemorrhoidal disease grade II and III.

Patients referred to gastroenterology consultations were allocated to one of the two instrumental treatments considered in this study (RBL and SP). Meanwhile, patients referred to surgery consultations were submitted to surgical procedure (HAL-RAR).

Sample selection

The inclusion criteria were as follows: patients older than 18 years with symptomatic hemorrhoidal disease grade II and III (Goligher's classification) refractory to conservative therapy (dietary modification, intestinal transit modifiers, topical and phlebotonic medications) for a period of not less than 4 weeks, which were referred to CHUP proctologic and surgery consultation.

Exclusion criteria were: cirrhosis, pregnant or breast-feeding women, known allergy to polidocanol, another perianal disease that can cause symptoms similar to hemorrhoidal disease, colorectal malignancy, concomitant presence of external hemorrhoidal disease and/or hemorrhoidal thrombosis, office or surgical treatment for hemorrhoids within 6 months prior to inclusion, antiplatelet or hypocoagulant medication, hematological disorders, immunosuppressive states and inflammatory bowel disease. Patients unable to have general or spinal anesthetic were also excluded. Grade I hemorrhoidal disease patients were excluded since they should not be treated with surgical techniques. In the same way, instrumental techniques should not be used in grade IV of hemorrhoidal disease.

All participants should have had prior endoscopic study, at least sigmoidoscopy, or total colonoscopy if they were older than 50 years or younger, with a family history of colorectal cancer, colon adenomas, or suspected inflammatory bowel disease.

Only patients who agreed to informed consent were included, after a clear explanation of the type of study and the intervention that was going to be made. Patients could withdraw at any time if they wished or if there was a severe complication.

The study was approved by the Local Ethics Committee of CHUP [2019.292 (235-DEFI/252-CE)].

Patients were recruited for a period of 6 months (between September 2019 and February 2020).

A stratified randomization sequence was generated (ratio 1:1) to ensure balance of the non-surgical treatment groups (RBL and SP) with respect to the hemorrhoidal disease grade (II and III). Regarding the patients referred to surgery consultation, they were submitted to HAL-RAR procedure.

Visits and data collection

In screening visits, demographic and anthropometric data (such as age, sex, weight and height, education and employment status) were collected, as well as grade of hemorrhoidal disease. Baseline questionnaires were used to assess Sodergren's scale of symptoms (Figure 2) and the severity of bleeding (Figure 3).

Informed consent and an information brochure, explaining the study and adequate dietary and behavioral care, were provided. Additionally, all participants were given a direct contact for any doubts and notification of complications, in which case additional observation should be made.

When office-based treatments were performed, an intervention period was considered, in which patients were observed at 3-week intervals (minimum of 3 weeks and maximum of 9 weeks, depending on the number of instrumental treatments performed). On the contrary, surgical treatment were only performed once.

One month after this intervention period, Sodergren's scale of symptoms and severity of bleeding were reevaluated. In addition, complications registry, and implication in personal and professional life, measured in number of work-loss days, if applied, were also assessed (see below).

Efficacy evaluation

Treatments' efficacy was based on the following outcomes:

1. Therapeutic success (efficacy indicator composed by Sodergren score and bleeding grade):
 - Complete (Sodergren score = 0 and bleeding grade \leq 1);
 - Partial (Sodergren score >0 and bleeding grade >1 but, at least, one of them with improvement, regarding the initial score, and none of them worse);
 - Therapeutic failure (participants that, one month after the last instrumental treatment or one month after surgery, worsened or maintained the initial Sodergren score and bleeding grade);
2. Number of instrumental treatment sessions required;

Safety evaluation

Treatments' safety was based on the following outcomes:

I. Record of complications resulting from the therapy:

- Mild (e.g. pain/discomfort, pruritus, bleeding grade I)
- Moderate (e.g., external hemorrhoidal thrombosis, bleeding without hemodynamic instability, no blood transfusion, no need for haemostasis or urgent surgery): do not endanger the patient's life or leave long term sequelae;
- Severe (e.g. sepsis, Fournier's gangrene, perineal abscess, bleeding with hemodynamic instability, transfusional need or urgent surgery, sexual impotence in man): they put the patient's life at risk.

2. Implications in professional life were measured in number of work-loss days, if applied;

3. Implications in personal life were assessed with some simple yes-no questions (eg: personal and family relationships, sexual activity, physical exercise, social and civic activities), and if at least one of them was answered affirmatively, we considered treatment had significant impact in patient's personal life.

It should be noted that the presence of discomfort or occurrence of bleeding during the first 24 hours after each therapeutic intervention were not considered a complication, since it can be related to the procedure itself.

Intervention: technical aspects

The required number of sessions of any of the office-based treatments (maximum of 3 sessions) depended on the clinical response. Thus, if 3 weeks after the previous treatment, the participant scored zero points in the Sodergren scale and had a hemorrhage grade ≤ 1 , he was not a candidate for additional instrumental therapy.

As mentioned above, surgical treatment were only performed once.

After the treatment session, regardless of the treatment group, patients were instructed to take dietary measures: avoid spicy foods, take a high fiber diet and adequate hydration, while maintaining therapy with systemic and/or topic phlebotonics, and laxatives if necessary.

Foam polidocanol group

- i. Patients underwent preparation, two hours before the intervention, with cleaning enema (Disodium phosphate). No antibiotic prophylaxis was prescribed.
- ii. Preparation of the polidocanol (Aethoxysklerol 3%) foam according to Tessari technique³⁸ immediately before application, so that the "microbubbles" of the foam did not disintegrate;

- iii. The procedure was performed in the medical office. Application according to the Blanchard technique through a disposable transparent anoscope, in jackknife position, using a 20mL disposable syringe of the mixture (polidocanol + air) and a reusable 10 cm syringe extender adapted to an intravenous needle;
- iv. Patients were treated in a maximum of 3 sessions, at 3 weeks intervals;
- v. Maximum dose per treatment session of 20mL of mixture of 4mL of polidocanol 3% with 16mL of air;
 - i. In each session, the sclerosant was injected in one or more hemorrhoidary cushion;

Rubber band ligation group

- i. Patients underwent preparation, two hours before the intervention, with cleaning enema (Disodium phosphate). No antibiotic prophylaxis was prescribed.
- ii. The procedure was performed in the medical office. Reusable metal ligators connected to a vacuum system (McGown suction method) were used to apply the rubber bands through a disposable transparent anoscope, in jackknife position;
- iii. Performing a maximum of 3 sessions of ligation at 3-week intervals;
- iv. More than 1 band per session could be applied up to a maximum of 2 rubber bands.

HAL-RAR group

- i. Patients underwent preparation the night before the intervention with cleaning enema (Disodium phosphate). No antibiotic prophylaxis was prescribed.
- ii. The procedure was performed in the operating room of an outpatient surgery unit, under regional anesthesia, administrated by an anesthesiologist.
- iii. The operation was performed with patients in the jackknife position. A special proctoscope with a Doppler transducer in its tip was introduced inside the anal canal and distal rectum to search for final branches of the superior rectal artery, identifying the blood flow.
- iv. Once located, each branch was ligated with 2-0 absorbable polyglycolic-acid suture approximately 3/4 cm above the dentate line. The device was rotated slowly in clockwise direction to locate further arteries at that level. Once a full rotation had been made, the procedure was repeated 1/1.5 cm below the first series of sutures.
- v. Subsequently, RAR procedure was performed using the same proctoscope. A continuous running suture was applied longitudinally just over every prolapsed hemorrhoid. This suture started approximately 2/3 cm above the dentate line to lift the prolapsing hemorrhoid.
- vi. After the procedure, patients remained in postoperative recovery for a minimum of 4 hours.

Statistical analysis

The data collected were subject to statistical treatment through SPSS software v. 26 and significance was pre-set at $p \leq 0.05$. Pearson's chi-squared test was used for categorical data. Normality of continuous variables was performed by Kolmogorov-Smirnov. Nonparametrical statistics were assessed for continuous data (Wilcoxon signed rank test and Kruskal-Wallis test). Univariate and multivariate binary logistic regression were used to identify predictors of treatment's complications.

Results

Participants characteristics

A total of 55 patients with symptomatic hemorrhoidal disease grade II (41.8%) and grade III (58.2%) were included. Sixteen (29.1%) of these patients were allocated to surgical treatment, HAL-RAR, and the rest of them were randomly assigned to either SP (36.4%) or RBL (34.5%).

Patients demographic and preoperative characteristics, namely Goligher's classification, bleeding grade and Sodergren score, are comparable in the three groups, as shown in Table I, with the exception of mean age, that only showed a significant difference between SP (56.3 ± 13.4 years-old) and HAL-RAR group (46.3 ± 9.2 years-old) ($p=0.049$).

Efficacy

Overall, most patients achieved any kind of success, either partial or complete, being similar in the three therapeutic groups (SP 100%, RBL 89.5%, HAL-RAR 87.5%) ($p=0.178$), as shown in Table II. Specifically concerning complete success, SP recorded a 100% rate, comparing to 73.7% with RBL and 75.0% with HAL-RAR ($p=0.046$), with no evidence of a difference between RBL and HAL-RAR ($p=0.929$). Therapeutic failure was only registered in four patients (7.3%), two in the RBL group and the other two treated with HAL-RAR.

In the SP group, on average, only 1.3 (± 0.1) therapeutic sessions were necessary, using a mean polidocanol dose of 19.0 (± 2.0) mL. Whereas patients in the RBL group attended a mean of 1.3 (± 0.2) treatment sessions, using approximately 2.1 (± 2.0) of rubber bands (Table II). HAL-RAR was only performed once (1.0 ± 0.0). No statistical difference was obtained between treatments regarding the number of interventions ($p=0.114$).

When analyzing individually the evolution of Sodergren's score and bleeding grade, before and after the intervention, a favorable improvement, with significant decrease, in the three treatment groups was observed ($p \leq 0.001$). There was no significant difference between treatment groups, as shown in Table II.

Safety

Overall, twenty-one patients reported mild complications (SP 4, RBL 7, HAL-RAR 10), such as self-limiting hemorrhage and pain. Whereas, 4 patients presented a thrombosed hemorrhoid, therefore developing moderate complications (SP 1, RBL 3). Severe complications were not registered.

As shown in table III, there was a significant difference in the incidence of complications, between the three treatment groups ($p=0.041$). Less patients underwent complicated treatment in the SP group (only 25% reported complications), followed by a 52.6% rate of complications in the RBL

group. The surgical procedure, HAL RAR, has shown the highest prevalence of complications (62.5%), all of them being classified as mild ones.

Furthermore, specifically considering mild complications, HAL-RAR has also shown to be significantly more complicated than office-based procedures ($p=0.033$). As shown in table III, pain was the most frequently reported symptom, in the three treatment groups (SP 15%, RBL 31.6%, HAL-RAR 43.8%). In which concerns moderate complication, no statistical significant difference was found ($p=0.178$).

Predictors of treatments' complications

In a multivariable analysis, as shown in Table IV, and based on a new grouping variable (complication and no complications), none of the variables analyzed were significant predictors of any postprocedural complications (mild or moderate), except for the type of treatment chosen. The surgical technique, HAL-RAR, was found to be approximately 7 times more likely to develop complications (OR=7.11, 95% IC 1.07-55.65, $p=0.043$), when comparing to SP.

Personal and Professional Implications

Personal and professional implications were significantly different in the three treatment groups, as shown in Table V. Concerning personal life, 15.0% of the SP group reported impact on daily life, compared to 36.8% and 62.5% of the RBL and HAL-RAR groups, respectively ($p=0.016$). Regarding implications in professional life, HAL-RAR has demonstrated to have more prolonged absence from work (8.56 ± 8.4 days), when comparing to SP (0.6 ± 0.2 days) or RBL (0.7 ± 0.3 days) ($p\leq 0.001$).

Discussion

Treatments' efficacy was assessed through therapeutic success, number of interventions and evolution of hemorrhoidal disease, before and after treatment. The vast majority of patients achieved therapeutic success, in the three groups, without significant difference between them. Thus, determining a favorable evolution of hemorrhoidal disease, namely in Sodergren's score and bleeding grade.

Therefore, it was possible to obtain success with a similar number of interventions in the three treatment groups (approximately 1 for all, $p=0.202$), even though office-based treatments could be performed up to a maximum of 3 sessions, contrarily to a single surgical intervention.

The excellent results of SP in this study, being this technique significantly more effective than the others (regarding complete success), are consistent with previous studies, in which SP has shown to be successful in more than 90% of patients^{38,59}.

Intervention for hemorrhoidal disease is essentially aimed at improving quality of life of the patients⁵⁷. Wherefore, it is important for the treatment used to have, itself, the minimal negative impact in personal and professional life as possible. In order to assess treatment's impact in the patients' quality of life, the investigators evaluated personal and professional implications of each treatment modality. The results suggest that HAL-RAR had a greater impact on both patients' quality of personal and professional life. This might reflect not only the invasive nature of the procedure itself, but also the side effects of regional anesthesia. On the contrary, patients of the SP group showed a minimal personal (15.8%) and professional life implications (0.6 ± 0.2 days), which is consistent with Tessari et al.³⁸ results, revealing an 85% of patients very satisfied with their SP treatment.

Complications, such as pain or discomfort, bleeding and, less frequently, external hemorrhoidal thrombosis, were also considered for treatments' safety evaluation. This study revealed a significant difference between treatment groups, with SP being the therapeutic with less adverse events, reporting only 25% of post procedure complications. These results are in agreement with those of Fernandes and Fonseca⁵⁹ who have presented a high safety of SP, without clinically significant symptoms in the large majority of patients. Actually, in this prospective study, which included 2000 patients treated with SP, only 2% reported mild pain.

HAL-RAR group registered the highest rate of complications, all of them mild. Considering mild complications, this procedure has shown to be significantly worse than office-based procedures. All moderate complications were external hemorrhoidal thrombosis, with 3 out of 4 patients belonging to the RBL group. This finding relies within the spectrum of postoperative complications of RBL reported in other studies. Fernandes and Camacho⁶⁰ concluded that more

significant complications, which included external hemorrhoidal thrombosis, can occur in 1-5% of the patients.

Pain was the most common complication in all procedures, affecting almost 30% of the patients (SP 15%, RBL 31.6%, HAL-RAR 43.8%). Similarly, regarding SP, a recent study by Lobascio P. et al⁶¹ including 66 patients with hemorrhoidal disease grade II and III, reported 14% of postoperative pain. The prevalence of pain in RBL group is within the recently documented incidences in literature with variable rates (1-51%)^{24,62,63}, probably due to an operator-dependent factor, since it is frequently suggested that pain after RBL may be more severe if the band is applied below dentate line⁶⁴. Rates of significant pain following HAL-RAR ranged from 0 to 30% in previous studies⁶⁵, which is in agreement with the results of the present study.

Although pain intensity was not evaluated in this study, Brown et al.⁵⁷ reported that in HAL-RAR group it was significantly more intense and long lasting, comparing to a lower intensity and rapidly resolved pain in RBL group. Nevertheless, a prospective study including 30 patients submitted to HAL-RAR, stated that complications disappear progressively, achieving complete success in 92% after one-year follow-up⁵¹. These results are confirmed in other long-term reports^{66,67}.

Furthermore, multivariable analysis showed that the type of treatment chosen was the only predictor of complications identified. HAL-RAR patients were seven times more likely to develop complications in general, comparing to SP patients. Which reflects the invasiveness of this surgical procedure, comparing to office-based treatments.

Although evaluation of cost-effectiveness of the procedures was not a purpose of this study, it should be noted that HAL-RAR is notoriously more expensive than non-surgical procedures since it requires more equipment, more professional staff, a longer learning curve and a postoperative recovery period^{57,68}.

Limitations

An important limitation of the present study was the lack of data on long-term effectiveness, given the fact that recurrences may be a problem after therapy of hemorrhoidal disease, particularly with non-surgical methods. Anyhow, the investigators are willing to continue this study and evaluate our patients for, at least, one year.

Another limitation of this study was the small sample size, which may yield for less conclusive results with missed statistical significance.

The outcomes were mainly patient-reported which may contribute to subjectivity.

Furthermore, the process of allocation used is also a determining factor, given that only patients referred to gastroenterology consultation were randomized either to RBL or SP and the patients referred to surgical consultations were submitted to HAL-RAR.

Conclusion

Office-based procedures revealed as effective as HAL-RAR when considering global therapeutic success. Regarding specifically complete success, results are better for SP.

The surgical technique, HAL-RAR, revealed a significantly higher rate of complications than office-based procedures, along with more negative implications in patients' quality of life and, also, a longer absence from work.

In addition, office-based procedures are less expensive and less cumbersome in terms of logistic and human resources, as they are performed in a medical office, without anesthesia or recovery period. Therefore, these factors might be considered a disadvantage to HAL-RAR in terms of cost-effectiveness ratio.

Concluding, office-based procedures, especially SP, should be the first-line therapy for hemorrhoidal disease grade II and III, considering surgery as a possible alternative for refractory cases.

Appendix

Goligher Classification	Grade
No prolapse	I
Prolapsed with defecation, but reduced spontaneously	II
Prolapse with defecation requiring manual reduction	III
prolapsed and non-reducible	IV

Figure 1: Internal hemorrhoids: Goligher grading

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

SCORE FINAL	
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Figure 2: Sodergren Hemorrhoid symptom severity scoring system (Pucher et al. 2015)

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

Figure 3: Bleeding grade in Hemorrhoidal disease

Table 1: Characteristics of studied population

	All patients (n=55)		Sclerotherapy with polidocanol (n=20)		Rubber band ligation (n=19)		Hemorrhoidal Artery Ligation with Recto Anal Repair (n=16)		P value ¹
	n Mean	% SD	n Mean	% SD	n Mean	% SD	n Mean	% SD	
Age, years-old	52.5	±12.3	56.3 ^b	±13.4	53.7 ^{ab}	±11.9	46.3 ^a	±9.2	0.049
BMI, kg/m²	26.6	±4.9	26.8	±5.2	26.3	±5.3	26.7	±4.4	0.992
Sex									
Male	19	34.5	8	40.0	6	31.6	5	31.3	0.813
Female	36	65.5	12	60.0	13	68.4	11	68.8	
Academic qualifications									
Primary	14	25.5	6	30.0	6	31.6	2	12.5	0.195
Middle (2 ^o)	5	9.1	1	5.0	0	0.0	4	25.0	
Secondary (3 ^o)	10	18.2	4	20.0	5	26.3	1	6.3	
Higher secondary	13	23.6	4	20.0	5	26.3	4	25.0	
Bachelor	13	23.6	5	25.0	3	15.8	5	31.3	
Professional status									
Student/ Employee	38	69.1	12	60.0	13	68.4	13	81.3	0.157
Unemployed	6	10.9	2	10.0	1	5.3	3	18.8	
Retired	11	20.0	6	30.0	5	26.3	0	0.0	
Goligher's classification									
II	23	41.8	10	50.0	10	52.6	3	18.8	0.084
III	32	58.2	10	50.0	9	47.4	13	81.3	
Sodergren score initial	8.2	±3.9	7.4	±0.8	8.0	±0.9	9.2	±1.0	0.372
Bleeding grade initial									
Grade 1	16	29.1	6	30.0	6	31.6	4	25.0	0.907
Grade 2	39	70.9	14	70.0	13	68.4	12	75.0	

^{ab} Different superscripts in the same line indicate significant difference between treatments.

¹ Statistical analysis comparing the three treatment groups.

Table II: Treatments' efficacy

	All patients (n=55)		Sclerotherapy with polidocanol (n=20)		Rubber band ligation (n=19)		Hemorrhoidal Artery Ligation with Recto Anal Repair (n=16)		P value ¹
	n Mean	% SD	n Mean	% SD	n Mean	% SD	n Mean	% SD	
Sodergren score after treatment	1.4	±3.5	0.2	±0.2	2.4	±1.1	1.9	±1.0	0.142
Bleeding grade after treatment									
Grade 0	40	72.7	15	75.0	13	68.4	12	75.0	0.421
Grade 1	10	18.2	5	25.0	3	15.8	2	12.5	
Grade 2	5	9.1	0	0.0	3	15.8	2	12.5	
Therapeutic success									0.178
Complete	46	83.6	20	100.0	14	73.7	12	75.0	0.046
Partial	5	9.1	0	0.0	3	15.8	2	12.5	0.196
Therapeutic failure	4	7.3	0	0.0	2	10.5	2	12.5	0.284
Number of interventions	1.2	±0.5	1.3	±0.1	1.3	±0.2	1.0	±0.0	0.114
Polidocanol dose (mL)	-	-	19.0	±2.0	-	-	-	-	-
Number of rubber bands	-	-	-	-	2.1	±0.2	-	-	-

¹ Statistical analysis comparing the three treatment groups

Table III: Complications' frequency

	All patients (n=55)		Sclerotherapy with polidocanol foam (n=20)		Rubber band ligation (n=19)		Hemorrhoidal Artery Ligation with Recto Anal Repair (n=16)		P value ¹
	n	%	n	%	n	%	n	%	
Complications (overall)	25	45.5	5	25.0	10	52.6	10	62.5	0.041
Mild Complications	21	38.2	4	20.0	7	36.8	10	62.5	0.033
Mild pain or discomfort	16	29.1	3	15.0	6	31.6	7	43.8	
Bleeding grade I	5	9.1	1	5.0	1	5.2	3	18.7	
Moderate Complications	4	7.3	1	5.0	3	15.8	0	0.0	0.178
Thrombosed Hemorrhoid	4	7.3	1	5.0	3	15.8	0	0.0	

¹ Statistical analysis comparing the three treatment groups

Table IV: Predictors of treatment's complications

	Univariable			Multivariable		
	OR	95% CI	P value	OR	95% CI	P value
Age, years	0.98	0.94-1.03	0.373	0.99	0.93-1.06	0.731
Women vs. Men	2.42	0.75-7.79	0.138	4.70	0.96-22.97	0.056
Body mass index, kg/m²	0.96	0.85-1.07	0.460	0.93	0.81-1.09	0.371
Goligher's classification (III vs. II)	1.56	0.53-4.61	0.426	0.71	0.11-4.48	0.714
Bleeding grade (3 vs. 2)	2.32	0.68-7.92	0.181	3.71	0.60-22.78	0.157
Sodergren score	1.12	0.97-1.29	0.120	1.16	0.92-1.45	0.207
Treatment (vs. Polidocanol foam Sclerotherapy)						
Rubber band ligation	3.33	0.86-12.92	0.082	3.19	0.64-15.84	0.156
Hemorrhoidal Artery Ligation with Recto Anal Repair	5.00	1.20-20.92	0.028	7.11	1.07-55.65	0.043
Number of interventions	1.37	0.45-4.15	0.577	2.78	0.57-13.39	0.202

Table V: Professional and personal life implications

	All patients (n=55)		Sclerotherapy with polidocanol foam (n=20)		Rubber band ligation (n=19)		Hemorrhoidal Artery Ligation with Recto Anal Repair (n=16)		P value [†]
	n Mean	% SD	n Mean	% SD	n Mean	% SD	n Mean	% SD	
Personal life implication									
Yes	20	36.4	3	15.0	7	36.8	10	62.5	0.016
No	35	63.3	17	85.0	12	63.2	6	37.5	
Professional implication,									
Number of days off from work	2.9	±5.7	0.6 ^a	±0.2	0.7 ^a	±0.3	8.56 ^b	±8.4	≤0.001

^{a,b} Different superscripts in the same line indicate significant difference between treatments.

[†] Statistical analysis comparing the three treatment groups

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