Patient-centred haemorrhoidal disease management

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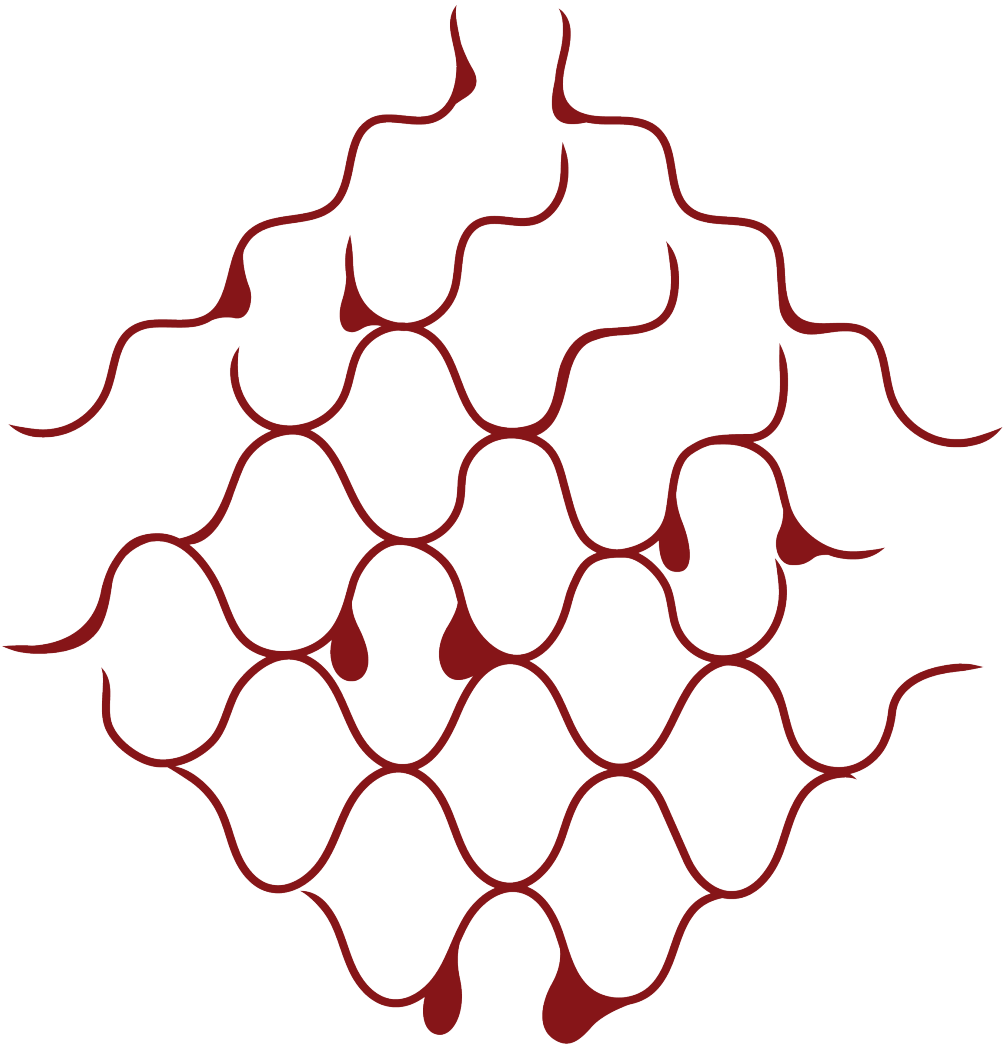
Sara Z. Kuiper



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Sara Zwier Kuiper

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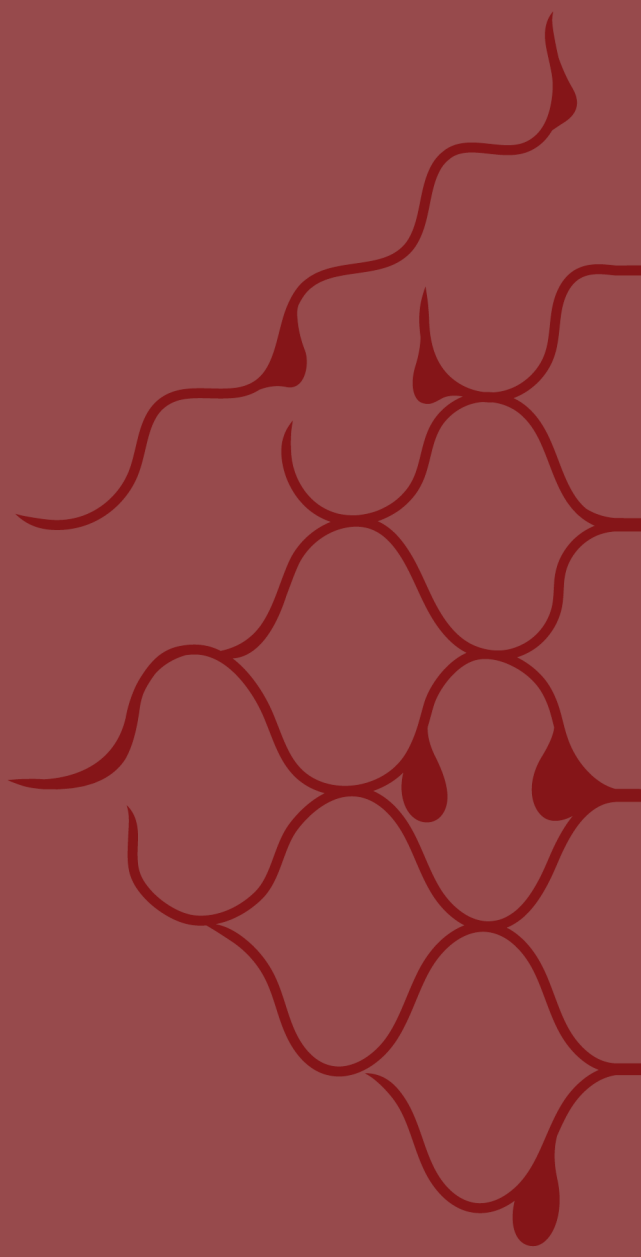
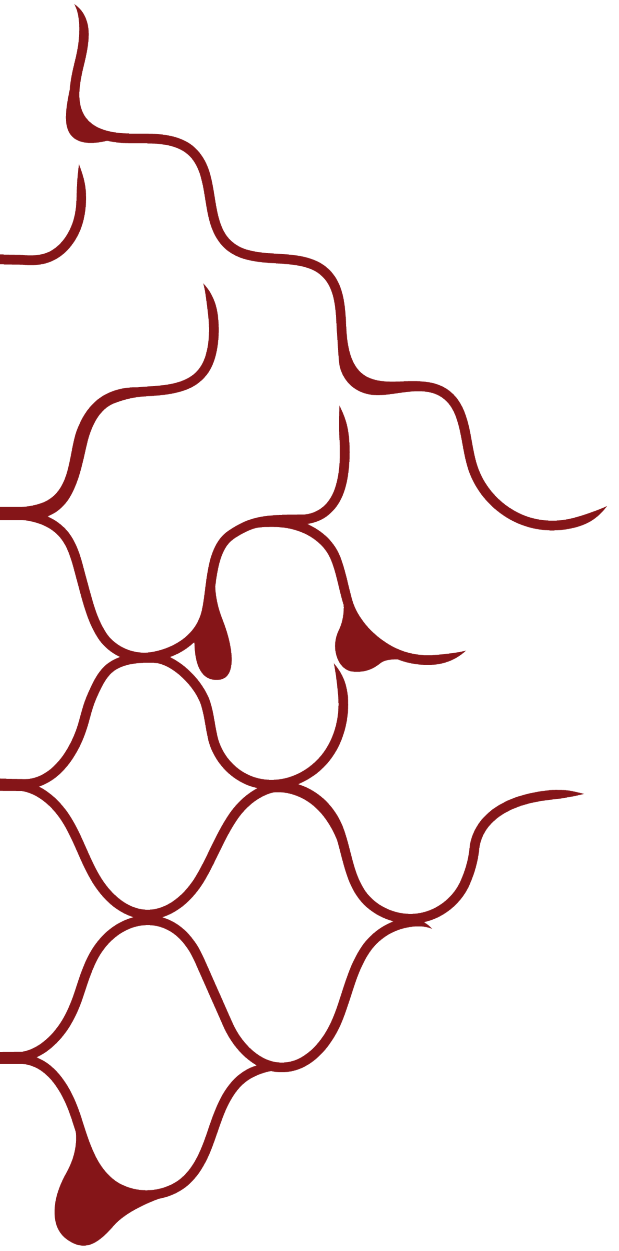




Chapter 1
General introduction

Background

Haemorrhoidal disease (HD) is the most common type of anorectal complaint in the Netherlands, with an annual prevalence of 10% in general practice[1]. Worldwide, the disease affects about one third of the population[2].

Haemorrhoids are normal vascular cushions filled with arterial-venous blood vessels and are located proximal to the dentate line in the submucosa of the anal canal[3]. The haemorrhoidal complex is surrounded by a strong web of connective tissue, composed of collagen, fibro-elastic tissue and muscle fibres[4,5]. The haemorrhoidal cushions are covered by columnar epithelium and tend to be in the left lateral, right anterior, and right posterior position of the anal canal. When looked at with the patient in the lithotomy position, these three preferred locations are ordered in a clockwise manner, indicating respectively at 3-, 7-, and 11- o-clock.

Whilst haemorrhoids are present in every person to ensure continence for stools, flatus and fluids/mucus, they become a disease when symptoms occur like prolapse, bleeding, soiling, itching and pain[6].

Prolapse can appear as a result of degenerative effects of ageing which weakens the supporting tissue around the haemorrhoidal complex. Furthermore, as a result of prolapse of the haemorrhoidal tissue, the mucosa will become vulnerable[7]. Risk factors like repeated passage of hard stool and straining can accelerate this process. The symptom of bleeding can be caused by localized mucosal trauma or inflammation of the haemorrhoid, which damages the underlying blood vessels[8]. The discharge of blood and mucus of the prolapsed haemorrhoid in combination with faecal remnants may lead to soiling and itching of the anus and perianal skin[9]. As a result of soiling, perianal eczema or perianal dermatitis can develop, which can cause pain[10]. The experience of severe pain from the haemorrhoidal complex is usually associated with thrombosis of perianal veins. The latter involves a separate treatment and is not part of this thesis.

HD is commonly reported according to the grading system of Goligher et al[11,12]. This system classifies HD in four grades: grade I are haemorrhoids that do not prolapse; grade II are haemorrhoids that prolapse but reduce spontaneously; grade III are haemorrhoids that prolapse and can be reduced manually; grade IV are haemorrhoids that prolapse and cannot be reduced manually.

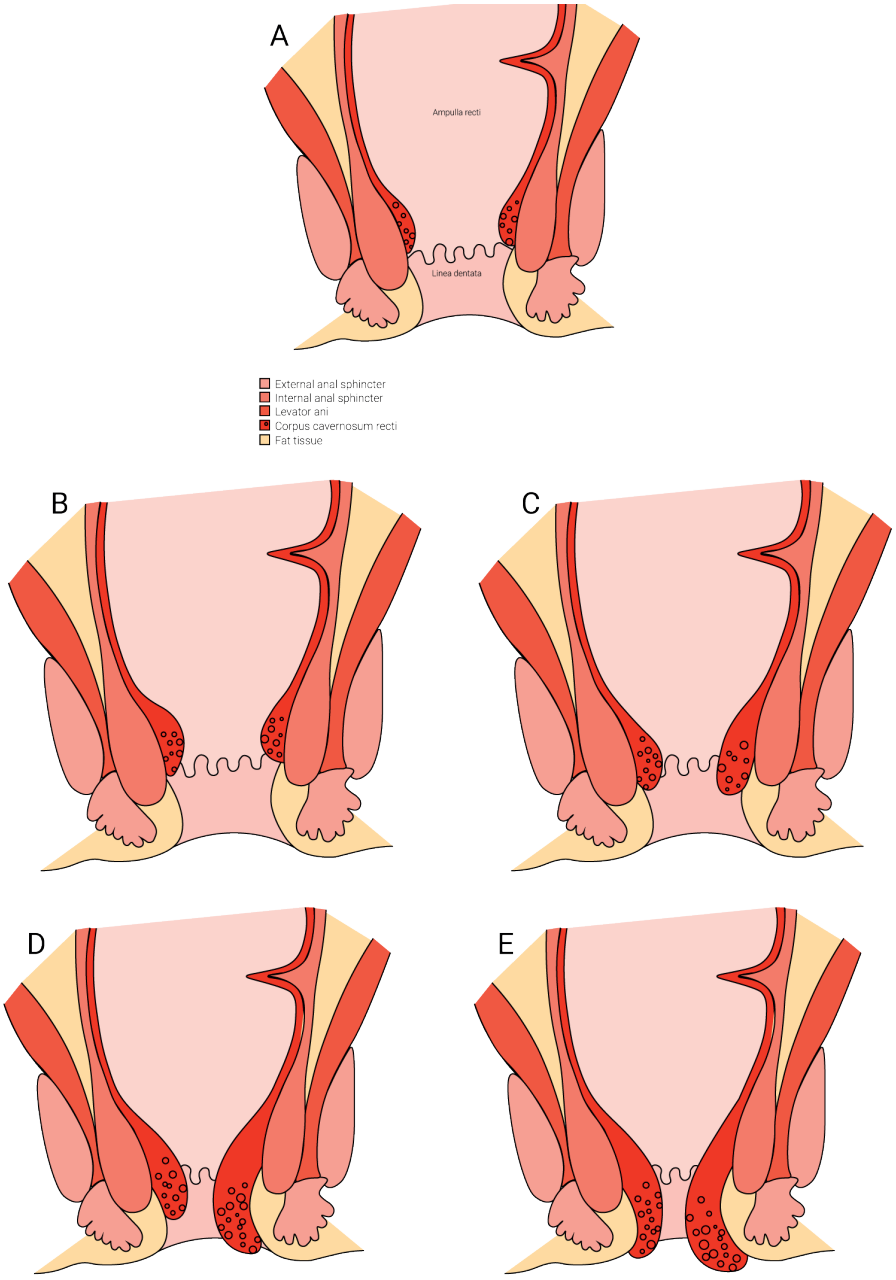


Figure 1 *(A) Healthy situation. (B) Haemorrhoidal disease Grade I. (C) Haemorrhoidal disease Grade II. (D) Haemorrhoidal disease Grade III. (E) Haemorrhoidal disease Grade IV.*

At the general practitioner

Despite the benign characteristics of HD, it has a high negative impact on quality of life. Qualitative research shows that patients with HD associate the symptoms of HD with emotional burden, daily adjustments and social impact. The symptom of blood loss resulted in feelings of fear, as it is seen in oncological pathologies, but also embarrassment and avoidance of social activities.

Furthermore, patients implement a variety of adjustments in their daily life to deal with HD, ranging from the use of sanitary pads to unorthodox pain treatments (anal ice sticks)[13]. Due to this significant influence on daily life, patients often seek advice for treatment. The first management step of HD is offered by the general practitioner (GP) and usually consists of lifestyle changes and dietary modifications like a high fibre diet[14,15]. In addition, topical and pharmacological treatments may soften the stool, ease anal pain and decrease sphincter tension.

At the hospital

If the conservative treatment of the GP is not successful, patients are referred to the surgery outpatient clinic at the hospital. In the Netherlands, about 50.000 patients are referred to hospital annually. Here, patients' refractory to basic treatment and/or grade I-II HD can be offered office-based procedures including Rubber Band Ligation (RBL), infrared coagulation or injection sclerotherapy. RBL is an easy, inexpensive and painless procedure, which can be repeated if necessary. However, thirty percent of the patients develop recurrent symptoms after basic treatment followed by repeated RBL[16].

Injection sclerotherapy is an alternative to banding and concerns a submucosal injection of 5% oily phenol in the haemorrhoidal complex. True value is questioned since this intervention may be as effective as conservative treatment with fibre supplementation[17].

With infrared coagulation, the haemorrhoidal tissue is coagulated through infrared light, resulting in local ischaemia and the formation of scar tissue. This treatment is indicated for low grades of HD and is characterised by an absence of serious complications and low costs[18,19]. Nevertheless, a longer learning curve of the surgeon is described for this intervention and the procedure is not widely used[15].

At the operating theatre

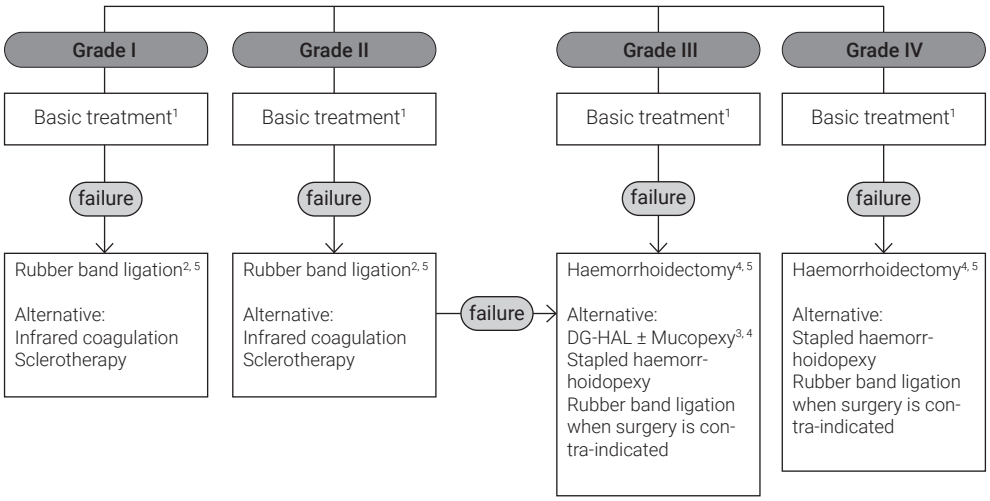
Patients who are refractory to office-based interventions or in case of grade III-IV HD a surgical intervention is usually the next step in the treatment algorithm. The options of surgical treatment include traditional haemorrhoidectomy, doppler-guided haemorrhoidal artery ligation (DG-HAL), and stapled or sutured haemorrhoidopexy.

Haemorrhoidectomy is perhaps one of the oldest operations performed and is reserved for grade III/IV symptomatic haemorrhoids and for patients having gr II haemorrhoids refractory to outpatient procedures. There are two types of the haemorrhoidectomy: the open technique (Milligan-Morgan) and the closed technique (Ferguson). The former entails an excision of both the dermal and the mucosal component of the haemorrhoid, while in the latter the mucosal component is removed, and the dermal tissue is preserved. Literature indicates that haemorrhoidectomy is the surgical treatment of choice based on outcomes like recurrence rate [14,15,20]. The major drawback of this technique is that it is very painful and long term complications like anal stricture and soiling can occur[21].

During a DG-HAL procedure, an ultrasound probe enables accurate detection and targeted suture ligation of the haemorrhoidal arteries (mucopexy or haemorrhoidopexy). Recently, the usage of an ultrasound device has been questioned since it has been stated that this not add significantly to the results achieved by a haemorrhoidopexy[22].

Stapled haemorrhoidopexy entails the excision of a complete circular strip of rectal mucosa approximately four centimetres proximal to the dentate line. This causes scar formation of the anal tissue. The procedure is performed using a trans anal circular stapler, which indicates the bottleneck of this intervention: the costs of the apparatus [20]. Besides, the initial high popularity of this technique tempered significantly after reporting of seldom but serious complications, like rectovaginal fistula[23-26].

In a sutured haemorrhoidopexy, there is no need for a separate device and the concept of scar formation is achieved by a simple surgical suture for one or more piles. The sutured haemorrhoidopexy is a relatively novel, but a regular surgical alternative[27]. However, long term outcome and high quality evidence of this technique is scarce.



[1]Toilet training, dietary changes (fiber) and topical treatment.
[2]Repeat banding.
[3]Doppler-Guided Haemorrhoidal Artery Ligation (DG-HAL).
[4]In grade III and IV there is a possibility to perform RBL when surgery is contra-indicated.
[5]Shared-decision making, taking into account patient preferences, availability of procedures and fitness for further procedures.

Figure 2 *Overview of the 'Evidence based treatment algorithm for haemorrhoids', curtesy of the European Society of Coloproctology Guidelines for haemorrhoidal disease (R.R. Van Tol et al., 2020).*

Optimal and evidence-based haemorrhoidal disease treatment

In spite of the high prevalence of HD, the level of evidence in this scientific field remains low. In PubMed, the term 'haemorrhoidal disease' displays not even 30,000 hits, in comparison with 118,000 hits on 'inflammatory bowel disease' which has a much lower prevalence rate of 0.3%[28]. The misbalance between the high societal burden and low scientific attention can be seen in all areas of proctology, not only in HD. Furthermore, proctology seems to have a low priority in surgical training. As proctological ailments affect a lot of people worldwide, the topic should not remain in its shadows. We believe that creating more awareness regarding proctology and HD in particular, shall lead to improved treatment options and high-quality healthcare.

Besides the disappointing quantitative numbers of HD research, the qualitative aspect is also piddling. Randomized controlled trials (RCT), considered as the golden standard of evidence-based medicine, are scarce in HD with only 44 results on PubMed. At the moment, the scientific evidence for HD management is inconclusive which makes it difficult to inform guidelines and daily practice. Undesirable practice variation can be a result of this situation[29]. One of the areas where consensus is absent regards the best treatment for patients suffering from HD, specifically in case of recurrent complaints of HD. Patients are offered different treatment modalities: continuing RBL or a surgical intervention. Another drawback of HD research is that it is difficult to compare results of studies with one another, seeing that study outcomes may be defined differently. Fortunately, the European Society of Coloproctology (ESCP), developed and published the Core Outcome Set (COS) for patients with HD in 2019. COS are developed with the purpose to gain more homogeneity in the selection of outcomes in clinical trials[30]. As a result, comparison of study results can be improved and this will facilitate evidence synthesis.

To enhance the implementation of the most (cost)effective treatment of recurrent HD, there is a need for a randomized trial assessing the (cost-)effectiveness of various treatment options in patients with recurrent HD on the basis of the COS for HD.

Patient-Reported Outcome Measures (PROM) in haemorrhoidal disease

Current guidelines and treatment options for HD are based on proven effectiveness of clinical assessment of parameters such as recurrence, prolapse and complications[16,21]. However, these parameters – mostly selected by healthcare professionals – may not include all relevant benefits and harms experienced by patients.

Until now generally accepted consensus on what constitutes treatment success for patients having HD is lacking. Luckily, the recently published COS for HD emphasized the importance of the patient's experience[31]. The COS for HD indicated patient-reported symptoms as the primary outcome for clinical trials. Patient-reported symptoms can be measured by a Patient-Reported Outcome Measure (PROM) that collects information directly from the patient without interpretation by healthcare professionals or others[32]. Existing PROMs for HD do not involve patient input in a sufficient way and their methodology is suboptimal; incompleteness of psychometric testing or a lack of adherence to established guidelines[33]. Therefore, we developed a PROM for HD using robust methodology that includes multiple stakeholders, particularly patients: The PROM-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS).

Thesis objective

The main research question of this thesis was *'How can we optimize the management of HD?'*. The management of HD can be optimized in several domains, i.e., treatment options and patient-involvement. These domains of interest can be translated into sub research questions, which are answered in three parts of this thesis.

The first part – *Introduction to the field of proctology and haemorrhoidal disease* – gives an introduction to the field of proctology, with a focus on HD, and addresses the misbalance between the high incidence of HD and the quality of research that is performed. Furthermore, this part elaborates on the sub-question: *'What is the underlying aetiology of HD?'* by comparing histopathology between patients having HD and healthy controls (Chapter 4).

The second part – *Effective treatment for haemorrhoidal disease* – is based on two sub-questions: *'Which treatment is most (cost)effective for the treatment of recurrent HD based on recurrence and patient-reported symptoms?'* and *'Is the sutured haemorrhoidopexy a safe and effective treatment option for HD?'*. The first sub-question emphases on the design of a RCT to examine the effectiveness and cost-effectiveness of alternative treatment strategies for (recurrent) HD grade II and III (Chapter 5). The second sub-question is elaborated on in a retrospective study regarding the safety and efficacy of the sutured haemorrhoidopexy (Chapter 6).

The third part – *Patient-reported outcomes in haemorrhoidal disease – explores the sub-question: 'How to develop and validate a PROM to measure the symptom-burden of HD and how to ensure that usability, comprehensibility, and acceptability of the tool itself meets the standards and requirements of professionals and patients?'* This sub-question is elaborated on by means of exploring the role of PROMs in the management of HD (Chapter 7) and, consequently, the development and validation of an (inter)national PROM for HD (PROM-HISS) (Chapter 8 and Chapter 9). To conclude, the sub-question: *'How to translate and validate the Dutch PROM-HISS to English and support the uptake and dissemination of this tool in the international HD community?'* is dwelled upon in a cross-cultural translation study (Chapter 10).

Aims and outline of the thesis

The thesis research question and sub research questions are translated in the following parts and chapters:

PART I Introduction to the field of proctology and haemorrhoidal disease

Chapter 2 *Proctological Oblivion (editorial)*
The research field of proctology is not popular. As a result, the level of evidence remains generally very low. Although the disease burden of coloproctological complaints on a patient level may be limited, the disease burden on a population level is huge seeing the high prevalence of anal symptoms. Hence, our aim is to create awareness in the colorectal society of these widespread proctological diseases and endorse conducting high-quality proctological studies.

Chapter 3 *Haemorrhoidal Disease: Old solutions and future perspectives (editorial)*
The most frequently occurring anal illness is HD. The field of research regarding HD is an ever-changing and dynamic topic. An overview is given ranging from historical viewpoints to technical HD solutions and patient involvement.

Chapter 4 *A morphometric analysis of pathological alterations in haemorrhoidal disease versus normal controls: A controlled trial*
One of the aspects of HD that has not yet been unravelled is the pathophysiology of this disease. More and more evidence guides us towards the hypothesis that reduced connective tissue stability is associated with a higher incidence of HD. Exploring the disordered physiological processes that cause this disease serves as a cornerstone in our quest of optimal HD management.

PART II Effective treatment for haemorrhoidal disease

Chapter 5 *Effectiveness and cost-effectiveness of rubber band ligation versus sutured mucopexy versus haemorrhoidectomy in patients with recurrent haemorrhoidal disease (Napoleon trial): Study protocol for a multicentre randomized controlled trial*
HD is a frequently occurring disorder with a significant negative impact on patient's quality of life. Various treatment modalities are available for the treatment of recurrent HD: continuing RBL, a sutured mucopexy, and a haemorrhoidectomy. The choice for treatment is left to the preference of the patient and the experience of the surgeon, creating room for undesirable practice variation. This implies a need for a high-quality study regarding the treatment of recurrent HD, which is being conducted at the moment.

Chapter 6 *Picking up the threads: Long-term follow-up of the sutured mucopexy*
One of the surgeries performed for HD and part of the design of the Napoleon Trial is the sutured mucopexy. Till now, long-term results on the safety and efficacy of this treatment are lacking. Hence, this procedure is evaluated in this chapter.

PART III Patient-reported outcomes in haemorrhoidal disease

Chapter 7 *Making use of patient-reported outcome measures for haemorrhoidal disease in clinical practice: a perspective*
Patient-Reported Outcome Measures (PROMs) can be included in clinical trials as primary or secondary endpoints and are increasingly recognised by regulators, clinicians, and patients as valuable tools to collect patient-centred data. In chapter 7, a perspective is given on how PROMs can be embedded to optimize HD management.

Chapter 8 *Patient-Reported Outcome Measurement-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS): Development, reliability and construct validity*
The primary outcomes of the COS for HD were symptoms of HD, including blood loss, pain, prolapse, soiling and itching. These symptoms should be assessed with a PROM. Until now, several PROMs for HD were introduced. However, none were developed according to the COS, using established guidelines, or including relevant stakeholders (patients). Hence, we developed the PROM-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS). In the development and validation of the PROM-HISS, a stepwise approach was undertaken following the COSMIN-methodology[34]. In chapter 8, the reliability and validity of the PROM-HISS is assessed.

Chapter 9 *Responsiveness of the Patient-Reported Outcome Measurement-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS)*
A PROM shows responsiveness when it can detect change over time, either positive change (improvement), negative change (deterioration), or no change (stable). This chapter describes the results on a study on the responsiveness of the PROM-HISS.

Chapter 10 *Translation and cross-cultural validation of a PROM for haemorrhoidal disease (PROM-HISS) in English*
To implement the PROM-HISS in an international clinical landscape and to enhance the uptake of the COS for HD, the PROM-HISS is translated to English. Furthermore, the cross-cultural validity of this questionnaire is evaluated in an English-speaking country.

Part IV Appendices

General discussion
This chapter contains a general discussion providing the overall implications and methodological considerations of this thesis.

Summary | Nederlandse samenvatting
An English and Dutch summary of the thesis are given in this chapter.

Impact
The impact chapter reflects on the scientific and societal impact of this thesis.

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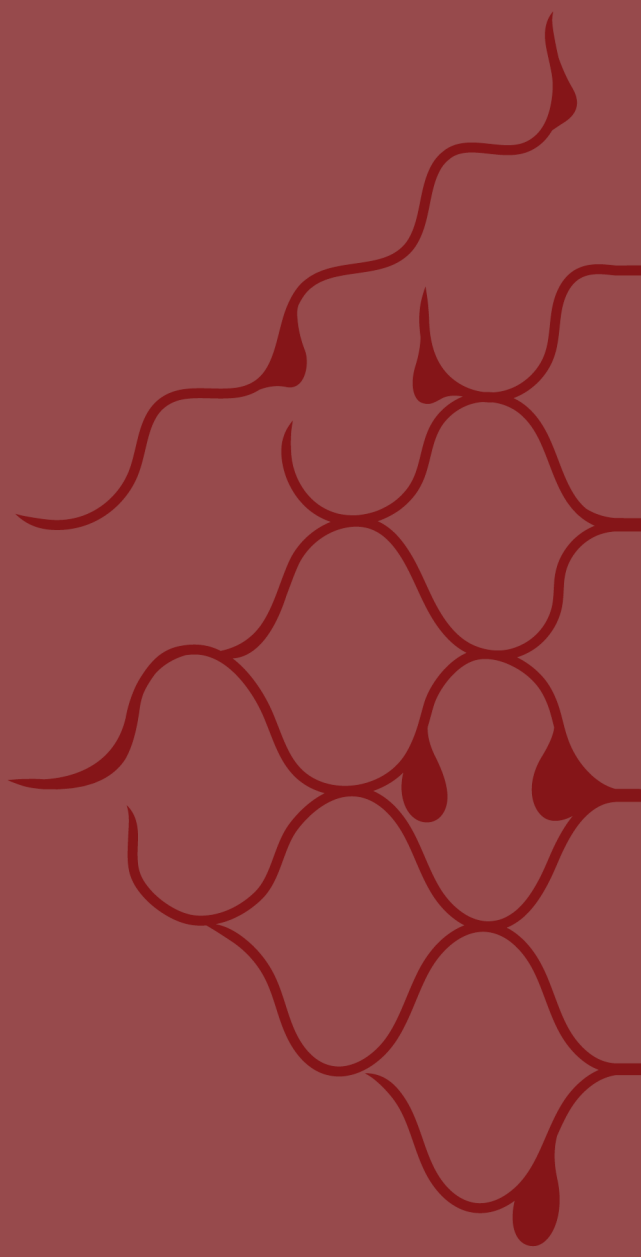

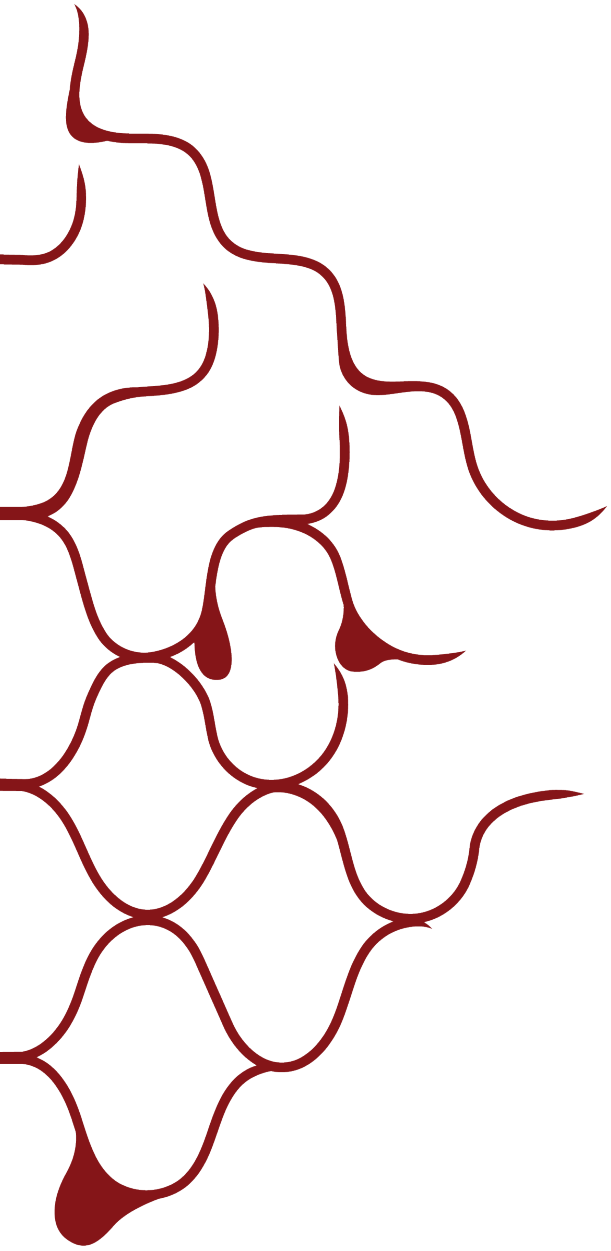

Chapter 2
Proctological oblivion

Sara Z. Kuiper, Carmen D. Dirksen,
Stephanie O. Breukink

Colorectal Dis. 2021

Editorial

Who could ever imagine that proctological complaints could be a true gamechanger? A striking example is the saga around the loss of Napoléon Bonaparte at the battle of Waterloo where his anal ailments may have hampered a military success.

However, not only emperors suffer from proctological diseases; the prevalence of anal symptoms ranges up to 15% in general practice[1]. If compared with the prevalence figures of patients having Inflammatory Bowel Disease (IBD), ranging around 0.3%, the former is a noticeably larger group[2].

Despite the high prevalence and noteworthy negative impact of proctological illnesses on quality of life, the level of evidence in this field remains generally very low. This observation was confirmed by the recently published European Society of ColoProctology (ESCP) guideline regarding the treatment of haemorrhoidal disease (HD)[3]. Moreover, the same pattern of robust research deficit is seen in other areas in the territory of proctology, i.e., faecal incontinence, perianal fistula and anal fissure. The term 'proctology' touches not even 80,000 hits on PubMed, compared to over 108,000 results for the much smaller population of IBD patients. Although the disease burden of coloproctological complaints on a patient level may be limited, the disease burden on a population level is huge; the same holds true regarding the economic burden[4].

Hence, the question rises why this imbalance in research exists and secondly how can we overcome this?

A solution may be to prioritise proctology on the research agendas of different (inter)national forums. As a result, more high-quality studies can be designed and conducted to raise the level of robust evidence.

In these trials we endorse the use of patient-centred outcomes as primary outcome measures, complemented by traditional clinical outcomes such as recurrence of disease, complications and duration of operation. Selecting only traditional clinical outcomes in proctology may not represent treatment success as experienced by patients. This venture was underwritten by the ESCP in the publication of a Core Outcome Set (COS) for HD; in this COS, 'patient-reported symptoms' was the item selected as the primary outcome[5]. Using a COS will also improve transparency between studies and facilitate the ability to compare and combine (future) studies. The development of a COS for other proctological diseases has also been set in motion. Furthermore, it is advised to perform cost-effectiveness studies alongside such trials to gain more insight in the costs and savings associated with effective treatment options. Considering the large numbers of patients involved in the management of proctological complaints, there is much to gain regarding efficient use of resources on a patient and population level.

Eventually these clinical trials in proctology, will allow proper evidence synthesis and improve evidence-based guidelines and clinical practice. This may seem like a small and obvious step, but it will mean a huge leap in reducing the human and economic burden of proctological disease.

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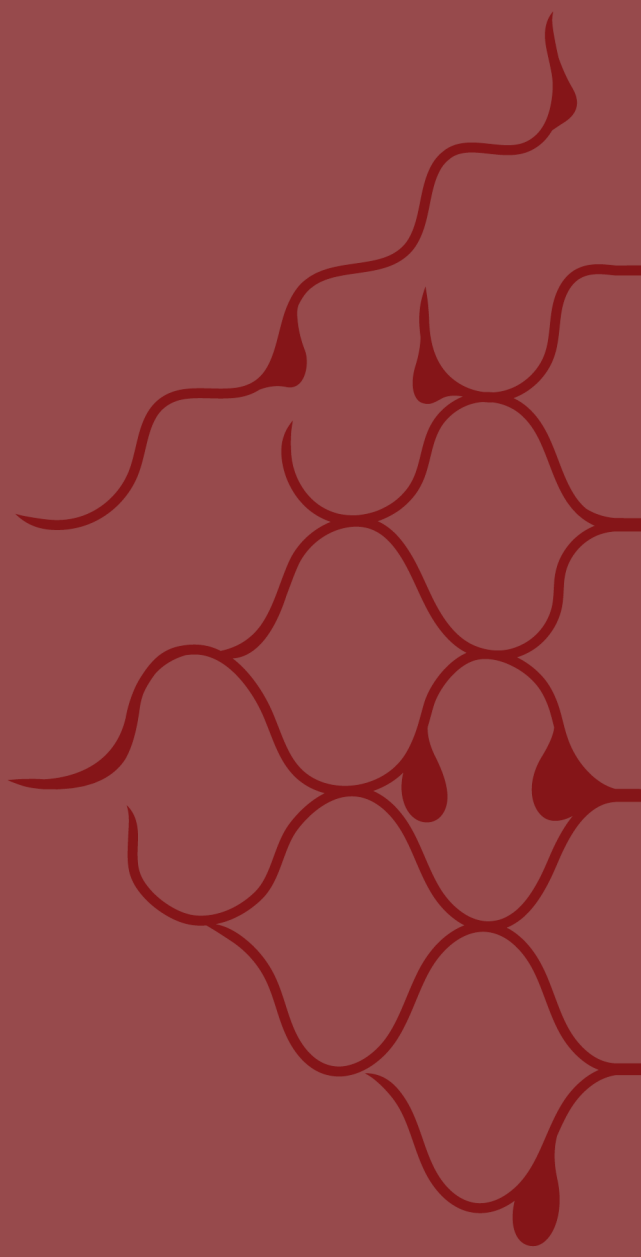

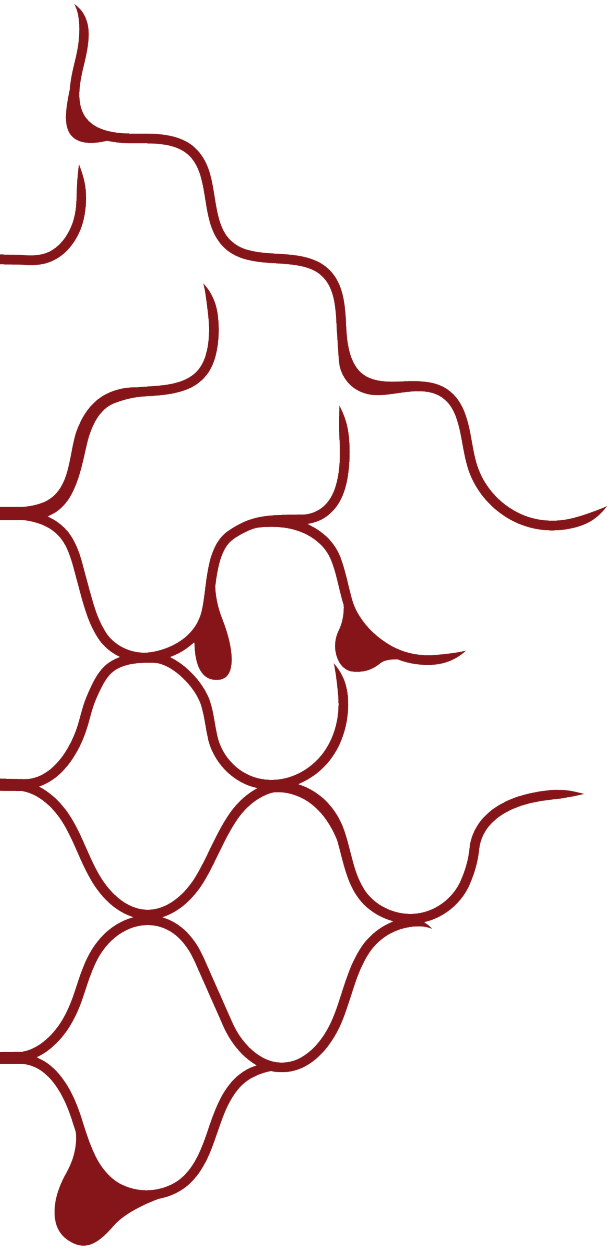

Chapter 3
Haemorrhoidal disease: Old solutions and future perspectives

Sara Z. Kuiper, Gaetano Gallo, Mario Trompetto, Arcangelo Picciariello, Stephanie O. Breukink

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Editorial

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

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

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

For higher grades of HD, Giordano and Schembari describe a modification of the mucopexy and haemorrhoidal dearterialization by adding an anolift to address the prolapsing component in HD. Pietroletti *et al*. studied the efficacy of a new formulation in rectal cream, containing Zn-L-Carnosine, in relieving acute symptoms of HD. Zinc-L-Carnosine is a cytoprotective compound stimulating mucosal repair in the gastrointestinal tract and shows to be a safe and effective treatment for bleeding or thrombosed haemorrhoids.

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

In line with the first treatment step for all grades of haemorrhoids, described in the European international guideline for HD[8], it is of paramount importance to optimize a patient's lifestyle and to

indicate risk factors. In the review by De Marco and Tiso, the authors stress the intake of adequate fluids, regular exercise, improving anal hygiene, and avoiding straining at stool.

Additionally, the authors mention the importance of good communication between the doctor and the patient, emphasizing on skilful listening. Understanding the disease-burden of a patient can assist in creating the best treatment approach. The usage of a patient-reported outcome (PROM) can be a valuable tool in this matter. Kuiper *et al.* evaluate the different PROMs available in the field of HD and endorse the use of such a tool in clinical practice to optimize personalized HD treatment[9,10].

This special issue of *Frontiers in Surgery* on haemorrhoids addresses several topics including non-surgical solutions, technical operative aspects, and the involvement of patient's experiences with HD. Despite the high incidence of this disabling disease, we know that the level of evidence of treatment remains low. To overcome this issue, a Core Outcome Set (COS) for HD can be utilized in clinical research[11,12].

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

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

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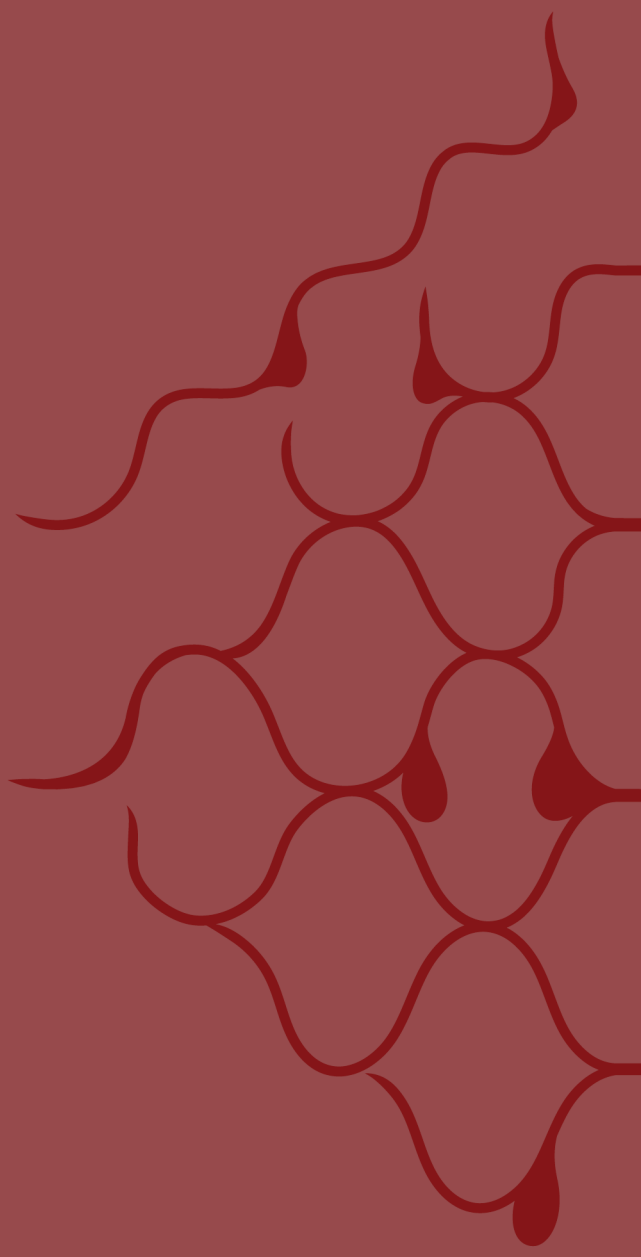

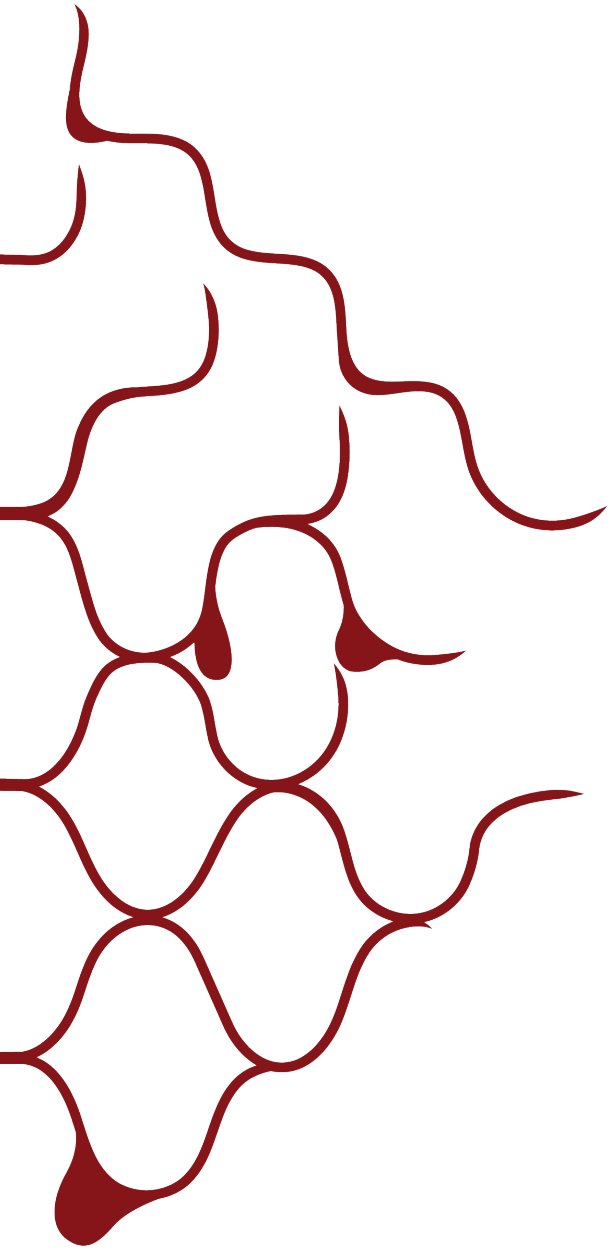

Chapter 4
A morphometric analysis of pathological alterations in haemorrhoidal disease versus normal controls: A controlled trial

Sara Z. Kuiper, Robin R. Van Tol, Arno Lataster, Jack P.M. Cleutjens, Jarno Melenhorst, Paul van Dijk, Sander M.J. Van Kuijk, Stephanie O. Breukink

J. Coloproctol. (Rio J.) 2021

Abstract

Introduction

Until today, the true pathophysiology of haemorrhoidal disease (HD) has not yet been unravelled. More and more evidence guides us towards the hypothesis that reduced connective tissue stability is associated with a higher incidence of haemorrhoids. This study aimed to compare the quantity and quality of collagen, and vessel morphometrics, in patients with symptomatic HD compared to normal controls.

Methods

Twenty-two samples of grade III and grade IV HD tissue from patients undergoing a haemorrhoidectomy between January 2004 and June 2015 were included in the study group. Samples of fifteen persons without symptomatic HD who donated their body to science and died a natural death served as controls. Quantity and quality of anal collagen, and anal vessel morphometrics were objectified. Quality of collagen was subdivided in young (immature) and old (mature) collagen.

Results

Patients with HD had an increased percentage of total anal collagen (62.1 ± 13.8 vs.18.7 ± 14.5 %; p = 0.0001), a decreased percentage of young collagen (0.00009 ± 0.00008 vs. 0.0008 ± 0.0008 %; p = 0.001), and a smaller surface area of the anal vessels (795.1 ± 1215.9 micrometre^2 vs. 1219.0 ± 1976.1; p = 0.003) compared with controls. The percentage old collagen did not differ between the control group and the study group (0.588 ± 0.286 % vs. 0.389 ± 0.242 %; p = 0.06).

Conclusion

The outcomes of this study suggest that alterations in anal collagen composition may play a role in the formation of haemorrhoids.

Introduction

Haemorrhoidal disease (HD) has a high prevalence in the Western world, affecting about one third of the population[1]. Despite the high prevalence and a large body of research, the aetiology and pathogenesis of HD has not yet been fully unravelled. Haemorrhoids are normal vascular cushions filled with arterial-venous blood vessels and are present in the submucosa of the anal canal. The expansion of the vascular cushions is important in providing a watertight seal to the anus and plays a paramount role in establishing faecal continence[2]. Haemorrhoids become a disease when the size of the haemorrhoidal complex enlarges in a pathological way and may result in symptoms like pain, blood loss, and/or prolapse[3]. Haemorrhoids are mostly classified by the severity of prolapse according to the grading system of Goligher *et al*[4-8].

Until now the exact pathophysiology of haemorrhoids remains unravelled and several theories are reported. The most widely accepted theory describes that the prolapse of the haemorrhoidal plexus is initiated by constipation and increased intra-abdominal pressure[9,10]. The increased intra-abdominal pressure may cause an enlargement and deterioration of the haemorrhoidal plexus, pushing the haemorrhoidal complex distally of the dentate line and thus resulting in a haemorrhoidal prolapse[11]. Besides, more and more evidence guides us towards the hypothesis that histological alterations, i.e. degeneration, of the haemorrhoidal plexus during aging play a role in the development of HD[1,12,13]. The haemorrhoidal plexus is surrounded by a web of connective tissue, composed of collagen, fibro-elastic tissue and muscle fibres[14,15]. The various fibres, sheets, and networks made of collagens are all extremely strong and resistant to normal shearing and tearing forces.[16] Degeneration of these fibrous elements and alterations in collagen metabolism may lead to destruction and loss of this supporting tissue.

Specific staining by Sirius Red (SR) is one of the most important stains to study collagen networks in different tissues. Under polarized light, stained collagen bundles appear green, red or yellow. Polarizing light microscopy produces an image only of material having repetitive, periodic macromolecular structure; features without such structure are not seen. Since collagen fibres fulfil these requirements, they are easily differentiated from the background, allowing for quantitative morphometric analysis[17]. The young collagen fibres colour yellow to green in comparison to the old fibres that appear orange to red by polarized light[18]. The difference between these histological characteristics is based on the amount of cross-links, which are abundant in mature collagen and lack in juvenile collagen. The thin young green collagen can be interpreted as type III collagen and the thick red collagen can be seen as the old type I collagen.

However, these interpretations should be made with precaution since we speak of spectra of colours which can overlap between the two types of collagen[19]. Therefore, in this article we chose to use the wording young collagen in case of yellow/green collagen that lacks cross-linking, and old collagen for orange/red collagen rich in cross-links.

In 2010, Willis *et al*. postulated that less connective tissue is associated with a higher incidence of haemorrhoids[13]. They found that disturbances in collagen I/III and collagen/protein ratios lead to reduced connective tissue stability. Furthermore, loss of connective tissue may result in dilation of supplying blood vessels, modifying the normal vascular anatomy.

Up to now, scarce reliable data exist on possible abnormalities in collagen composition in HD. Therefore, the aim of this morphometric study was to determine the quantity and quality of collagen in patients with HD versus healthy controls, and to reconsider the morphometrics of anal vascular structures in patients with HD.

Materials and Methods

Patients, donors and recruitment

Patients with internal symptomatic HD grade III or IV who underwent standard haemorrhoidectomies between January 2004 and June 2015 were included in the study group. During a haemorrhoidectomy, an elliptical incision was made in the haemorrhoidal tissue extending proximally through the dentate line to the upper limit of the haemorrhoid[20]. The surgeon excised the haemorrhoidal tissue including the mucosa and or part of the perianal skin[21,22]. Only patients older than 18 years with primary or recurrent HD were included. Patients who had undergone Longo procedures or any other major anorectal surgery were excluded from the study[23]. Further exclusion criteria were malignancies, aortic aneurysms, hernias, varicose or other connective tissue diseases, patients on corticosteroid-, cytostatic- or radiotherapy, and concomitant anorectal diseases (fistula, abscess, fissure, polyps. The resected haemorrhoidal specimens were fixed in 10% buffered formalin immediately after the operation and were processed to embed in paraffin for further investigation.

The control group was made up of persons who had donated their body to the department of Anatomy and Embryology of Maastricht University and who had died of a natural death between December 2016 and June 2018. Handwritten and signed codicils from the donors, as required by the Dutch law, are kept at the Department of Anatomy and Embryology. In review of the past medical histories of these cadavers, symptomatic HD as well as the above-mentioned exclusion criteria, was never listed as a condition they had. In these cadavers the pelvis was medially sawed through, leaving the halved recto-anal area. After trimming, the emerged specimens were fixed in 10% buffered formalin and processed to embed in paraffin.

Patients included in the study group all gave their written informed consent to participate in this study. Patients included in the control group gave pre-mortem permission to use bodily tissue in name of education and research.

Ethical clearance for this study and approval to use the resected specimens was obtained from the Maastricht University Medical Centre ethical review board (file number 2017-0065).

Collagen quantity and quality

Collagen quantity was analysed by collagen/total tissue ratio estimating the relative amount of collagen. The quality of the collagen was analysed by calculating the amount of new collagen and the amount of old collagen.

The paraffin blocks were cut with a microtome (Leica 2245, Nussloch, Germany) and the 5 µm thick sections were mounted on coated glass slides. After the paraffin was removed, serial sections of each specimen were stained with Haematoxylin Eosin (HE) and Sirius Red (SR) according to the local laboratory protocol. For HE this entailed staining for five minutes with HE stains (Mayer's

Hematoxylin/Eosin protocol) and for SR the stain was applied by staining for 30 minutes with SR (0.1% of SR in saturated aqueous picric acid).

Hematoxylin has a deep blue-purple colour which attach to nucleic acids and stains nucleic blue. Eosin stains cytoplasm and extracellular matrix with varying degrees of pink[24]. SR is a strong dye that identifies fibrillar collagen networks in tissue sections[25,26]. The SR-stained sections were observed with a microscope (Leica-DM4B, Nussloch, Germany) with 20 times objective. Pictures were made with normal and polarized light, creating images of the same areas under the same conditions (exposure time 17.8 milliseconds versus 300 milliseconds).

Using a designed computer program (Leica Qwin, Cambridge UK) the red stained collagen was detected on the bright field image. Within this mask the colour of the birefringence polarized collagen fibres was determined by the hue, saturation and intensity settings which determined the different colour aspects of the birefringence collagen fibres. The colours ranged from red, orange, yellow, green to teal. The same parameters defining threshold bands of hue, saturation, and brightness were applied to all the images[19]. Using the polarized light, a distinction can be made between relatively new collagen, which appears as green to yellow, and adult collagen, as orange to red.

Collagen quantity is expressed as percentage collagen relative to the total amount of tissue. The quality of the collagen is expressed as the percentage of new collagen and the percentage of adult collagen, relative to the total amount of tissue[12].

Structural vascular alterations

Structural vascular alterations were estimated by the dilatation of the anal vessels comparing HD patients with healthy controls. The perimeter of the anal vessel was calculated using CD31 endothelial antibody staining. Platelet-endothelial cell adhesion molecule 1, or CD31, is a transmembrane glycoprotein with various functions in multiple physiologic and pathologic pathways, and a very specific marker for endothelial cells[27]. The monoclonal anti-CD31 antibody recognizes a fixation-resistant epitope in endothelial cells[28].

Serial sections of each specimen were stained with CD31 endothelial antibody staining (DAKO-M0823, dilution 1:100). After incubation, only the sections with distinct membranous labelling for CD31 were taken into the analysis. Pictures of the sections with CD31 were uploaded on the computer and examined manually. The spaces surrounded by the CD31 staining were considered vessels. Both arteries and venules were taken into account. The demarcation of the vessel surface indicated by the CD31 stained endothelial cells was noted and integrated in a computer algorithm for analysis. Anal vascular morphometrics were specified into surface area, perimeter, and aspect of the vessel. The aspect of the vessel is a ratio and is calculated by dividing the length of the vessel by the width of the vessel. Surface area of the vessel is expressed in square micrometre (micrometre^2), perimeter of the vessel is expressed in micrometre and the aspect of the vessel has no dimension (ratio).

Statistics

All statistical analyses were performed using SPSS v25.0 (IBM Statistics). Normal distribution was assumed after performing the Shapiro-Wilk-test. Multiple linear regression analysis was used to adjust for baseline difference.

Data were expressed as means ± standard deviation (SD). Correlations between age and the percentage collagen were expressed as Pearson's correlation coefficient *r*. A *p* value of <0.05 was considered statistically significant.

Table 1 *A direct comparison of study versus control groups regarding collagen percentage, with an asterisk indicating statistical significance.*

	M:F ratio	Mean age in years (range)	Percentage collagen of total tissue	*P* value (percentage collagen)	Percentage young collagen	*P* value young collagen	Percentage old collagen	*P* value old collagen
Study (n = 22)	15:7	55.6 (31-78)	62.1 ± 13.8	*p* = 0.0001*	0.00009 ± 0.00008	*p* = 0.001*	0.389 ± 0.242	*p* = 0.06
Control (n = 15)	8:7	82.7 (60-95)	18.7 ± 14.5		0.0008 ± 0.0008		0.588 ± 0.286	

Results

Patients, donors and recruitment

The study group consisted of twenty-two patients who underwent a haemorrhoidectomy. The mean age of the study group was 55.6 (31-78) with a male:female ratio of 15:7. The control group entailed fifteen specimens with a significantly different mean age of 82.7 (60-95). The male:female ratio in the latter group was 8:7.

Collagen quantity and quality

The mean percentage of total collagen was higher in patients with haemorrhoidal disease (62.1 ± 13.8 %) than in the control group (18.7 ± 14.5 %; *p* = 0.0001). There was no difference in the mean percentage of collagen between men and women (50.3 ± 24.4 micrometre vs 34.9 ± 25.7 micrometre; *p* = 0.08).

Regression analysis showed that a higher age did not influence the percentage of collagen (*r* = 0.86). The percentage young collagen was higher in the control group (0.0008 ± 0.0008 %) than in the study group (0.00009 ± 0.00008 %; *p* = 0.001). The percentage old collagen did not differ significantly between the control group (0.588 ± 0.286 %) and the study group (0.389 ± 0.242 %; *p* = 0.06).

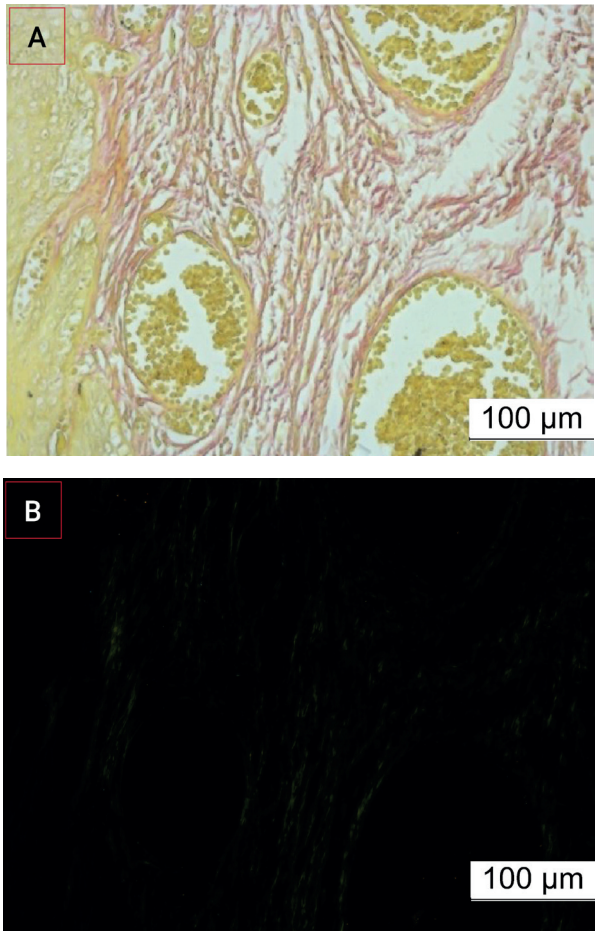

Figure 1 *A = Sirius Red staining under normal light, indicating the relation between young collagen (yellow to green) versus old collagen (orange to red) in a healthy control person. B = Sirius Red staining under polarized light, indicating the relation between young collagen (yellow to green) versus old collagen (orange to red) in a healthy control person.*

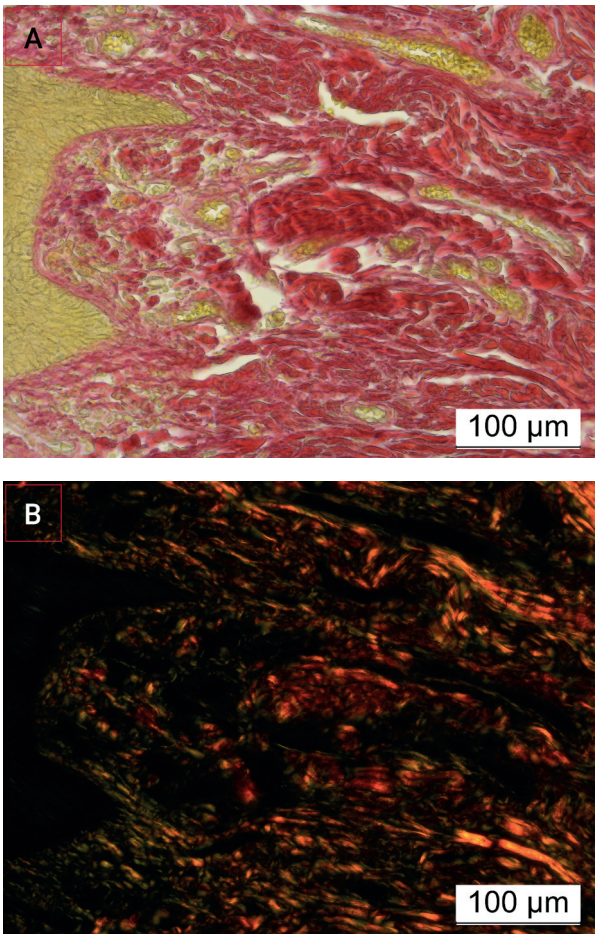

Figure 2 *A = Sirius Red staining under normal light, indicating the relation between young collagen (yellow to green) versus old collagen (orange to red) in a patient with haemorrhoidal disease. B = Sirius Red staining under polarized light, indicating the relation between young collagen (yellow to green) versus old collagen (orange to red) in a patient with haemorrhoidal disease.*

Structural vascular alteration

A direct comparison showed a difference in the surface area of the vessels between the study group (795.1 ± 1215.9 micrometre^2) and the control group (1219.0 ± 1976.1; $p = 0.003$). The perimeter of the vessel was not different between the study group (131.7 ± 110.8 micrometre^2) and the control group (149.0 ± 117.3; $p = 0.12$). The aspect of the vessel appeared larger in the study group compared to the control group (3.10 ± 7.5 vs. 2.16 ± 1.1, respectively; $p = 0.02$).

Table 2 *A direct comparison of study versus control groups regarding vessel data, with an asterisk indicating statistical significance.*

	Surface vessel in micrometre^2	*P* value (surface vessel)	Perimeter vessel in micrometre	*P* value (perimeter vessel)	Aspect vessel	*P* value (aspect vessel)
Study (n = 22)	795.1 ±1215.9	$p = 0.003$*	131.7 ±110.8	$p = 0.12$	3.10 ±7.5	$p = 0.02$*
Control (n = 15)	1219.0 ±1976.1		149.0 ±117.3		2.16 ±1.1	

Discussion and Conclusion

This study demonstrated that patients having haemorrhoids had increased total collagen, decreased young collagen and smaller surface area of the anal vessels compared to healthy controls.

In other studies examining the role of collagen in HD, an association was found between reduced connective tissue stability and an increase in the incidence of HD[12,13]. Yet, this study revealed a higher percentage of total collagen in patients with HD, suggesting ample connective tissue stability in this group. The mean age of the control group was significantly higher than the study group. Literature reports that the total amount of collagen reduces when you get older[29]. However, the higher mean age in the control group cannot function as an explanation for this outcome, as the regression analysis showed that age does not influence the percentage of collagen. Nonetheless, it has to be noted that the small sample size of this study could have affected the regression analysis.

In this study we found that patients with HD have an increased percentage of total collagen. Multiple studies have reported elevated resting pressure in patients with haemorrhoids, which could result in vascular stretching[30]. Mechanical vascular stretching has shown to stimulate collagen synthesis[31]. A possible hypothesis of the increased percentage of total collagen in HD could be a result of the expanded vessel walls.

Furthermore, this study showed that patients suffering from HD have a lower percentage of young collagen. This finding is in line with previous research by both Willes et al. and Nasseri et al. who demonstrated that patients suffering from HD have a decreased type I/III ratio. These studies made the direct interpretation of orange/red shades being the old collagen I and yellow/green tints as young collagen type III[12,13]. In this study, we made the distinction between young and old collagen. The young thin collagen fibres colour yellow to green in comparison to the old thick fibres that appear orange to red[18]. The significantly lower collagen I/III ratio in patients with HD can be based

on a diminished amount of cross-linking and hence, reduced mechanical stability of connective tissue. A decreased percentage of young collagen can cause the same cascade, leading to tissue destabilization. Nevertheless, the total amount of collagen was higher in HD patients and a statistical significant difference does not imply that the finding is clinically significant. Furthermore, a direct comparisons of collagen percentages cannot be made, since these studies only reported.

A closer look into alterations in anal vascular structures showed an increase in surface area and aspect of the vessel in healthy controls compared to patients with HD. Although the rise in abdominal pressure in HD can lead to distention of vessels, the effect of a lifelong erect posture of the healthy controls will possibly be greater[32]. Furthermore, it needs to be taken into account that the controls originate from post-mortem bodies which are spouted under pressure (0.2-0.3 Atm) with a formalin-mixture in the femoral artery. This process leads to a visible distension of the vessels.

One of the limitations of our study is the relatively small number of patients in both groups. Nevertheless, it is quite difficult to obtain specimens from haemorrhoidectomy operations while taking the various in- and exclusion criteria into consideration. The same accounts for the specimens from the control group, as also shown to be a difficulty in previous pathology studies[12,13]. Furthermore, the medical history of the control group does not mention HD, albeit people can suffer from HD without reporting this to their medical doctor.

Another aspect of our study which could diminish the power of the evidence is the difference between the study group and the control group. The groups differ both significantly in male:female ratio, as in mean age. However, making use of a regression analysis can give insight in possible confounders and help to correct for them.

The final limitation of this study is that both arteries as venules were taken into account when estimating the structural vascular alterations. The CD31 is a transmembrane glycoprotein which is present in the endothelium of arteries and veins. As a result, we were not able to make a distinction between these vessels. Yet, we were interested in a mean increase of diameter of the vessels overall. Since we calculated the diameter of arteries and veins in both groups, possible difference between the groups will be corrected.

The main strength of our study lies in the fact that it can assist in unravelling the true pathophysiology of HD, by further considering the involvement of alterations in collagen composition and anal vascular structure. Translating the findings of this study to clinical practice can contribute to optimize the care for patients with HD.

Although multiple options are available for the treatment of HD, the holy grail has not been found yet and many patients with HD are still seeking for their ideal cure. Therefore, it is important to have a better understanding of the pathophysiology of HD and the different mechanisms involved. The results of this study suggest that collagen can play a role in the formation of haemorrhoids, by facilitating constipation. The relationship between collagen and downregulation of protein synthesis demands further exploration. The reduced amount of young collagen in HD patients could be of interest for promising mechanisms in HD treatments. For example, the use of hyaluronic acid to improve remodelling of extracellular matrix is increasing in popularity[33]. Nevertheless, it needs to be kept in mind that the disease underlying haemorrhoids is multifactorial and that further research on this societal burden has to be performed.

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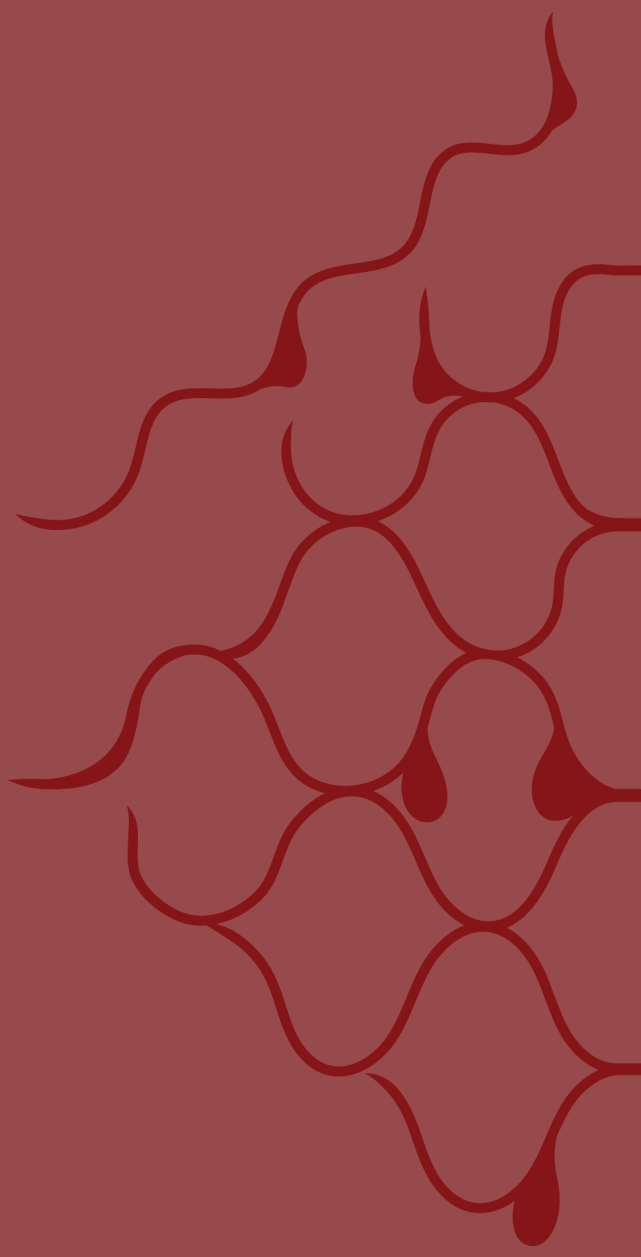

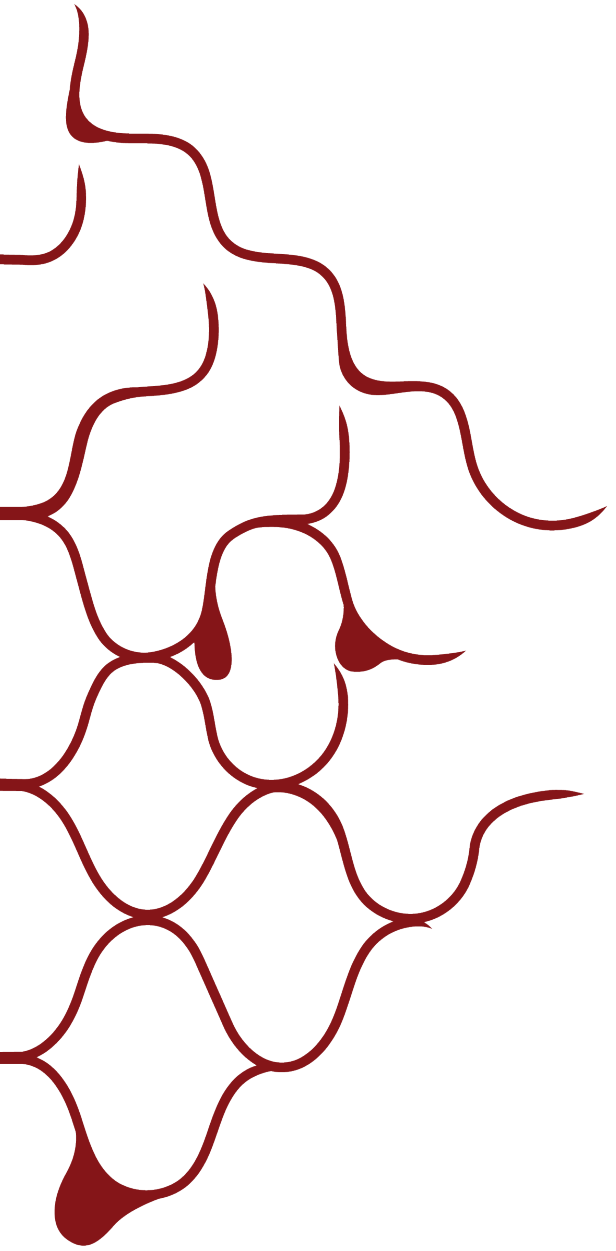

Chapter 5

Effectiveness and cost-effectiveness of rubber band ligation versus sutured mucopexy versus haemorrhoidectomy in patients with recurrent haemorrhoidal disease (Napoleon Trial): Study protocol for a multicentre randomized controlled trial

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On behalf of the Napoleon Trial Study Group

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Abstract

Background

Currently, there is no consensus regarding the best treatment option in recurrent HD, due to a lack of solid evidence. The Napoleon trial aims to provide high-level evidence on the comparative effectiveness and cost-effectiveness of repeat RBL versus sutured mucopexy versus haemorrhoidectomy in patients with recurrent HD.

Methods

This is a multicentre randomized controlled trial. Patients with recurrent HD grade II and III, ≥18 years of age and who had at least two RBL treatments in the last three years are eligible for inclusion. Exclusion criteria include previous rectal or anal surgery, rectal radiation, pre-existing sphincter injury or otherwise pathologies of the colon and rectum, pregnancy, presence of hypercoagulability disorders, oral anticoagulant therapy, with the exception of Carbasalate calcium (Ascal), and medically unfit for surgery (ASA>III).

Between June 2020 and May 2022, 558 patients will be randomized to receive either: (1) RBL, (2) sutured mucopexy, or (3) haemorrhoidectomy. The primary outcomes are recurrence after 52 weeks and patient-reported symptoms measured by the PROM-HISS. Secondary outcomes are impact on daily life, treatment satisfaction, early and late complication rates, health-related quality of life, costs and cost-effectiveness, and budget impact. Cost-effectiveness will be expressed in societal costs per QALY (based on EQ-5D-5L), and healthcare costs per recurrence avoided.

Discussion

The best treatment option for recurrent HD remains unknown. The comparison of three generally accepted treatment strategies in a randomized controlled trial will provide high-level evidence on the most (cost-) effective treatment.

Trial registration

ClinicalTrials.gov identifier: NCT04101773

Background

Haemorrhoidal disease (HD) is a very common anorectal disease with an incidence between 4.4 and 36.4% in the general population[1]. Haemorrhoids have troubled humankind since ancient times and might even have influenced world history. There is considerable indication that the emperor of France, Napoléon Bonaparte, suffered from HD. It has been said that on the day of the decisive battle at Waterloo, Napoleon was afflicted with thrombosed haemorrhoids which impaired his battlefield performance[2,3]. Whether or not the anal ailments of Napoléon cost him the victory on Europe's soil, this trial is forever crowned with his name.

HD is defined as the symptomatic enlargement and/or distal displacement of the superior haemorrhoidal plexus and the most used classification is according to Goligher[4]; grade I are haemorrhoids that do not prolapse; grade II are haemorrhoids that prolapse but reduce spontaneously; grade III are haemorrhoids that prolapse and have to be reduced manually; grade IV are haemorrhoids that prolapse and cannot be reduced manually. The main symptoms of HD are bleeding, itching, soiling, pain, and prolapse[5]. The first management step of HD is basic treatment that includes the use of laxatives and a high fibre diet[6,7]. If conservative treatment fails and in case of persistent symptoms, the next treatment modality is often rubber band ligation (RBL), which can be repeated multiple times. RBL is an easy, cheap and outpatient-based procedure[8]. However, 30% of the patients develop recurrent symptoms after basic treatment and repeat RBL[9].

Currently, haemorrhoidectomy is the surgical treatment of choice for persistent grade II HD reluctant to RBL and for grade III and IV HD. The major drawback of this technique is that it may be very painful and costly compared to RBL[10]. A relatively novel, but regularly performed surgical alternative is the sutured mucopexy. Although medical costs of sutured mucopexy are comparable to haemorrhoidectomy, the operation is less painful and requires less recuperation time[1,11].

A systematic review of the literature did not identify randomised controlled trials (RCT) comparing treatment modalities for patients with recurrent grade II or III HD (see Additional file 3 Search Strategy and Outcomes). The choice of the procedure for these patients is now left to the discretion of the healthcare professional, resulting in potentially undesirable practice variation[12].

The Napoleon trial is the first RCT, worldwide, comparing three generally accepted treatment strategies in recurrent grade II or III HD. It aims to provide high-level evidence on the comparative effectiveness and cost-effectiveness of repeat RBL versus sutured mucopexy versus haemorrhoidectomy in patients with recurrent HD after at least two previous RBL sessions.

Methods/Design

Objectives

The primary objective is to compare recurrence and patient-reported symptoms over a period of 52 weeks. The secondary objectives are to compare impact on daily life, treatment satisfaction, early and late complication rates, health-related quality of life, costs and cost-effectiveness, and budget impact.

Study design

The Napoleon trial is a nationwide multicentre, randomized controlled trial (RCT). Patients will be randomly assigned (1:1:1) to receive either RBL, sutured mucopexy, or haemorrhoidectomy (Figure 1). In total, 16 medical centres in the Netherlands will enrol patients.

Trial recruitment and allocation

Each medical centre participating in the Napoleon Trial will have a Local Investigator (LI), together forming the Napoleon Collaborative Study Group. All LI's are surgeons and will actively screen patients for eligibility at the outpatient clinic.

Study population

Patients can be included if they meet all of the following inclusion criteria:

1. Recurrent haemorrhoidal disease grade II or III according to the Goligher classification
2. At least two rubber band ligation treatments in the last three years
3. Able to complete online questionnaires
4. Sufficient understanding of the Dutch written language (reading and writing)
5. Written informed consent

Patients will be excluded if they meet any of the following exclusion criteria:

1. Previous rectal or anal surgery, with the exception of rubber band ligation
2. Previous surgery for haemorrhoidal disease (at any time)
3. Previous rectal radiation
4. Pre-existing sphincter injury
5. Pathologies of the colon and rectum
6. Medically unfit for surgery or for completion of the trial (ASA>III)
7. Pregnancy
8. Hypercoagulability disorders
9. Use of anticoagulant medication, with the exception of Carbasalate calcium (Ascal)

Recruitment procedure

Eligible patients will be recruited by the LI at the outpatient department of each participating medical centre. Following normal clinical practice, the LI will inform the patient about the different treatments available for their condition and explains the risks and benefits of all the treatment options. In case a patient is eligible for participation in the study, the LI will discuss the option of participating in the Napoleon Trial and will provide the potential participant with the Patient Information Folder (PIF) and the Informed Consent (IC) form.

The patient can take the PIF and IC home to have a chance to read this form extensively. During this time period, the patient has the option to get into contact with the study team to discuss possible participation. According to Good Clinical Practice, a patient is asked for formal consent prior to participation. Patients who decide to participate will send their signed IC form to the participating centre, after which they will be randomly assigned to one of the three treatment arms.

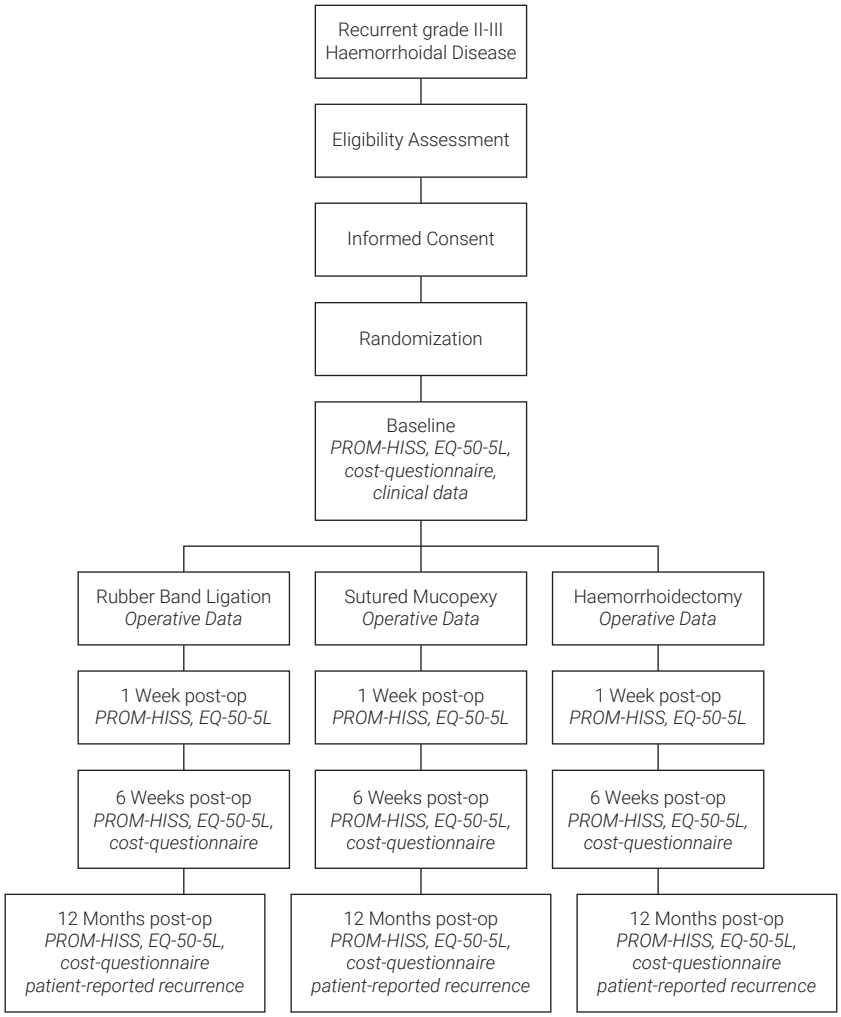

Figure 1: *Flowchart of the Napoleon Trial (PROM-HISS: Patient-Reported Outcome Measurement-Haemorrhoidal Impact and Satisfaction Score, EQ-5D-5L: EuroQol 5D)*

Table 1 *Schedule of enrolment, interventions, and assessments of the Napoleon Trial (PROM-HISS: Patient-Reported Outcome Measurement-Haemorrhoidal Impact and Satisfaction Score, EQ-5D-5L: Euroqol 5D)*

TIMEPOINT (state unit)	t_{-1}	t_0 = baseline	t_1 = intervention	t_2 = 1 week post-procedure	t_3 = 6 weeks' post-procedure	t_4 = 52 weeks' post-procedure
ENROLLMENT:						
Eligibility screening	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
Rubber Band Ligation			X			
Sutured mucopexy			X			
Haemorrhoidectomy			X			
ASSESSMENTS:						
Clinical evaluation		X			X	
Treatment details			X			
Recurrence				X	X	X
PROM-HISS		X		X	X	X
EQ-5D-5L		X		X	X	X
Cost-questionnaire		X			X	X
Early complications				X		
Late complications						X

Follow-up procedure

Follow-up will consist of clinical follow-up at six weeks and e-mail questionnaires at baseline, and 1, 6- and 52-weeks post-procedure. The treating physician will see all patients six weeks post-procedure, as part of standard care. During this clinical evaluation the recovery of the participant will be assessed. The assessment of recurrence will be completed at the end of follow-up, at 52-weeks post-procedure.

Participant withdrawal

The LI or CI can decide to withdraw a participant from the study for urgent medical reasons. Participants can leave the study at any time for any reason if they wish to do so, without any consequences. Withdrawal of participants will be recorded, including the reason.

Randomization and blinding

After written informed consent, participants will be randomized in a 1:1:1 ratio to RBL, sutured mucopexy or haemorrhoidectomy, using randomization stratified by centre, grade of HD (grade II or III HD) and sex, with random permuted block sizes of three and six. A unique record number will be generated and the allocation will be disclosed. Due to the comparison of outpatient-based and surgical treatment strategies in this study, blinding to the treatment allocation for participants and medical staff is not possible. The statistician will analyse the data blinded for treatment allocation.

Trial interventions

Rubber Band Ligation

Rubber Band Ligation (RBL) is a simple, inexpensive procedure. In RBL, a suction device applies a rubber band at the base of each haemorrhoidal cushion by using an anoscope[13-15]. The banding process causes necrosis of the banded tissue and as a result the haemorrhoid will shrink. The end result is a return of the haemorrhoidal cushions to a more normal size and configuration, with resolution of haemorrhoidal symptoms[16,17].

Sutured mucopexy

A sutured mucopexy is an operation performed under either general or spinal anaesthesia and was first described by Pakravan and colleagues[18]. The patient is placed in the lithotomy position. A proctoscope is used to give access to the anorectum. Proximal to the dentate line, a Z-shaped stitch is placed at the upper level of the haemorrhoidal complex, leaving ample space from the anocutaneous line. Before knotting this Z-shaped suture, a strip of mucosa between both stitches is excised. Then the Z-suture is tightened, pulling up the prolapsing haemorrhoid high into the anal canal. This procedure can be repeated in three to four quadrants of the anus as needed at the point of maximal prolapse[19,20].

Haemorrhoidectomy

Haemorrhoidectomy involves excision of the haemorrhoidal tissue. The procedure is performed under either general or spinal anaesthesia in a day-care setting. A retractor is placed into the anal canal for exposure. An elliptical incision is made in the external haemorrhoidal tissue extending

proximally through the dentate line to the upper limit of the haemorrhoids. It removes only the redundant anoderm and haemorrhoidal tissue, leaving the internal and external sphincter muscles intact[21]. There are two main excisional procedures currently carried out: open (Milligan and Morgan) and closed (Ferguson). In this trial both techniques are accepted, providing the flexibility for surgeons to undertake whichever procedure is part of their routine practice.

Harms

In accordance to section 10, subsection 4, of the Medical Research Involving Human Subjects Act (WMO), the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize a participant's health or safety. The sponsor will notify the accredited Medical Ethical Board without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited board. The CI will take care that all subjects are kept informed.

Adverse events (AE) are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the trial procedure. All AEs reported spontaneously by the subject or observed by the CI, LI, or his/her staff will be recorded. All Serious Adverse Events (SAE) will be reported in accordance with the guidance from the Central Committee on Research Involving Human Subjects (CCMO). A life threatening SAE, or SAE with death as a result, will be reported within 7 days after the local investigator has been informed. Other SAEs will be reported within 15 days.

Outcomes

Primary outcomes

The primary outcome is recurrence. The definition of recurrent HD is: "reappearance of initial symptoms as reported by the patient", this means "unchanged or worse symptoms of HD compared with before starting treatment". This is in accordance with recently conducted high level RCTs and the European Society of Coloproctology (ESCP) Core Outcome Set (COS) for HD[9,22,23]. Recurrence is assessed using patient's self-report of recurrence at 52 weeks' follow-up, in combination with a patient's report of unchanged or worse symptoms of HD post-procedure derived from the Electronic Patient File (EPF) over the course of 52 weeks.

Our second primary outcome is a patient-reported outcome focusing on symptoms of HD. Symptoms include blood loss, pain, prolapse, soiling and itching, and will be assessed using the Patient-Reported Outcome Measurement-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS). These 5 items are graded using a 5-point Likert scale, ranging from (1) 'none' to (5) 'very much'. The PROM-HISS, together with the other questionnaires, will be completed digitally at four moments during follow-up according to the COS: (1) at baseline; (2) at 1 week; (3) at 6 weeks; and (4) at 52 weeks post-procedure.

Secondary outcomes

Impact of symptoms on daily activities and patient satisfaction with treatment are assessed using the PROM-HISS. Each item is scored on a numeric rating scale from 0 to 10. Regarding impact on daily life, 0 denotes 'no impact at all' and 10 'severe impact on daily life'. For patient satisfaction with

treatment this ranges between 0 'not satisfied' and 10 'very satisfied'.

Early complications are complications manifested within 7 days post-procedure. Early complications include an 'abscess', assessed by physical examination, and 'urinary retention', assessed by ultrasonography. Complications are considered late complications when recorded at the 52 weeks' post-procedure follow-up. Late complications include 'incontinence', assessed by The Wexner Fecal Incontinence Score, 'anal stenosis', assessed by physical examination, and 'fistula', assessed by MR imaging in case of inconclusive physical examination. Health-related quality of life is assessed using the EQ-5D-5L[24]. It consists of a descriptive system comprising five (health) dimensions and a Visual Analogue Scale (VAS) that records the patient's self-rated overall health. By using an algorithm based on values obtained from the Dutch population index scores (i.e. utilities) for each patient can be calculated. These index scores are combined with length of life to calculate the Quality Adjusted Life Year (QALY).

Secondary economic outcomes are costs, cost-effectiveness and budget impact. Total societal costs over the course of 52 weeks will be calculated by multiplying individual-level resource use with the costs per unit. Resource use (e.g. treatment, control visits, visits to the GP, other diagnostic/medical procedures, medication) will be obtained from the Case Report Form (CRF) and from a recall health care resources questionnaire adapted from the Medical Consumption Quesionnaire [5] (e.g. over the-counter medication, and lost workdays), filled out at baseline, 6 weeks' and 52 weeks' follow-up.

Data collection and processing

Baseline characteristics will be obtained through the EPF by a member of the local clinical study team and stored in the CRF.

The EPF is screened to assess late complications, re-interventions, re-admissions, duration of medical centre stay and consultations at the medical centre. This will be reported in the CRF.

Role of the funding source

This study is funded by the Netherlands Organisation for Health Research and Development (ZonMw). The sponsor does not have any influence on study design, data collection, management, analysis, or interpretation of data.The funding source has no influence on the decision to submit for publication.

Statistical analysis

Baseline patient characteristics will be presented as means and standard deviations for continuous variables, and as absolute numbers and percentages for categorical variables, stratified by treatment arm. In case of incomplete records, missing data will be imputed using multiple imputation to accommodate intention to treat analysis. The number of imputations will be defined by the percentage of incomplete patients with respect to the variables of interest. Predictive mean matching will be used to draw values to be imputed. An interim analysis will not be performed for this study, due to the relatively short time span of the study.

Primary study parameters

Differences in the proportion of patients that have experienced a recurrence at 52 weeks after treatment between groups will be tested using Pearson's chi-square test and will be expressed by the percentage of recurrences per treatment arm. Differences between the three groups on the symptom score will be tested using analysis of variance (ANOVA) corrected for multiple testing using the Bonferroni correction. To compare PROM-HISS symptom score trajectories after 52 weeks' follow-up between groups, we will use linear mixed-effects regression with random intercept and slope. Covariates will include dummy-variables for the groups, time, and interactions between the groups and time.

Secondary study parameters

Differences between groups on the impact of symptoms on daily activities will be tested with ANOVA corrected for multiple testing using the Bonferroni correction. The occurrence of early and late complications (i.e., complications measured at 1 week or at 52-weeks post-procedure) will be compared between groups using Pearson's chi-squared test.

Total costs over the course of 52 weeks will be calculated by multiplying resource use with the costs per unit.

Economic evaluation

A trial-based economic evaluation will be performed from a societal and healthcare perspective with a time horizon of 52 weeks, and according to the Dutch guidelines for health economic evaluation [26]. Sources for evaluation of the costs will be cost prices of the Dutch costing manual and cost prices from the Pharmacotherapeutic compass (Farmaceutisch Kompas, 2016). Absence of work will be calculated by using the friction cost method, which is recommended by the Dutch manual for costing [27]. Cost-effectiveness will be expressed in societal cost per QALY (based on EQ-5D-5L) and healthcare cost per recurrence avoided. Standard bootstrap and sensitivity analysis will be performed to address uncertainty. Cost-effectiveness acceptability (net benefit) curves will be constructed to visualize the probability of either intervention being cost-effective for a range of threshold values.

In addition, a budget-impact analysis (BIA) will be performed in accordance with the Dutch guidelines for economic evaluations and the ISPOR guidelines[28]. The BIA will be performed using a simple decision analytic model. Different scenarios will be compared to investigate various levels of implementation or full substitution of any of the three interventions, as well as the swiftness of implementation (1-5 years). In order to test the robustness of the results, sensitivity analyses will be performed on data input and model assumptions.

Sample size and feasibility

Sample size

We assume an overall recurrence rate of approximately 30%[23]. We consider a between-group difference of 15% to be of clinical relevance. We need to include 158 patients per group, or 474 in total, to obtain 80% power to detect such a clinically meaningful difference, when using an alpha of 0.05/3, corrected for multiple testing. To accommodate a potential dropout rate of 15%, we will include 186 patients per group or a total of 558 patients. This sample size would provide ample

power (>95%) to detect a moderate effect size (defined as Cohen's d = 0.5) on differences in the co-primary outcome, the patient-reported symptom score.

Feasibility

About 50,000 patients are referred to a medical centre for HD in the Netherlands annually, of which roughly half suffer from a recurrence after the first RBL treatment. In most cases, these patients are offered a second RBL, which does not bring relief for one-in-three patients[9]. It is estimated that over 8,000 patients annually are eligible for our study. Bearing these numbers in mind, the aimed sample-size of 558 participants in two years will be feasible.

Data management

Each participant will receive a unique participant identification code. This code consists of a capital letter (A, B, etc.) indicating centre of inclusion and three numbers (001, 002, etc.) indicating order of inclusion. The study team, the Health Care Inspectorate, the monitors from the external clinical trial organisation and members of the medical ethical committee will have access to the participant data. Data will be stored in a password protected digital database. The CI safeguards the key to the participant identification code and the data. The data will be archived for 15 years after completion of the study. A full data management Plan can be obtained through the CI.

Data protection

All data concerning participants or their participation in this trial will be considered confidential and handled in compliance with all applicable regulations. Only members of the study team and LI have access to these data.

Data safety monitoring

Monitoring of the study will be performed by the Clinical Trial Centre Maastricht (CTCM) and is independent from the sponsor and competing interests. It will include checking informed consents, in- and exclusion criteria, reported serious adverse events, and completeness of the CRF. Monitoring includes one site initiation visit, three interim monitoring visits, and one close out visit per centre.

Auditing of the participating medical centres

Auditing will be performed by the CTCM and is independent from investigators and the sponsor.

Ethical approval

The study is conducted in accordance with the principles of the Declaration of Helsinki, the Medical Research Involving Human Subjects Act (WMO) and the General Data Protection Regulation. The protocol has been approved by the Medical Ethical Committee of the Maastricht University Medical Centre/Maastricht University (METC 19-076). Consent was also obtained from the participating centres.

Discussion

To our knowledge, the Napoleon Trial will be the first RCT worldwide comparing RBL, sutured mucopexy, and haemorrhoidectomy in recurrent grade II or III HD aimed at generating high-level evidence of (cost-) effectiveness. Currently, for recurrent grade II or III HD there is no standard treatment. Across the world, HD is a very common disorder, and numerous interventions exist for their management. The most commonly performed therapy is RBL. The literature concerning the efficacy and safety of RBL is substantial[29]. Although it is an easy to perform and relatively cheap option, recurrence rates are high and repetitive banding is often needed[9]. Based on solely the outcome "recurrence rate", the best results are secured with the haemorrhoidectomy. The surgical excision of haemorrhoids has been popular for centuries and has proven to be an effective treatment for merely the more advanced grades of HD[9,30]. The major drawback of this technique is that it is very painful and costlier compared to RBL. A relatively novel surgical alternative is the sutured mucopexy[1,11]. Although medical costs of sutured mucopexy are comparable to haemorrhoidectomy, the operation is less painful and requires less recuperation time. The recurrence rate of sutured mucopexy is ranked between that of RBL and haemorrhoidectomy.

To improve transparency between studies and facilitate the ability to compare and combine (future) studies, a ESCP COS for HD was recently published[22]. In the COS, patient-reported symptoms are selected as the primary outcome to be assessed in all clinical studies on HD. To assess symptoms, our study group recently developed a patient-reported symptom score for HD: The PROM-HISS. The PROM-HISS is based on most reported symptoms in literature and patient interviews[5]. Using this symptom questionnaire as a primary outcome will create awareness among clinicians to take patient's experiences and values into account when making HD treatment decisions. The implementation of the generated data from the Napoleon Trial can facilitate evidence-based treatment in the caretaking of patients with HD in the future and inform guidelines regarding HD.

Availability of the protocol

The full protocol can be obtained from the following link (https://zorgevaluatienederland.nl/evaluations/napoleon-trial). This protocol has been prepared in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT), a complete checklist is provided as Additional file 2.

Ancillary studies

Not applicable.

Indemnity

The sponsor/investigator has liability insurance, which is in accordance with article 7 of the WMO. This insurance provides cover for damage to research subjects through injury or death caused by the study.

Publication

The results of this study will be disseminated via publications in high-impact scientific journals and

presentations on conferences. Both negative and positive results will be published. Results found in this study can inform (inter)national guidelines for the treatment of HD.

Trial status

The start of the Napoleon Trial is currently on hold due to the outbreak of COVID-19.

Authorship

Contributors

All members of the study group have agreed that all study results will be published. With respects to this, no veto right exists. Before publication, all authors will have the opportunity to give comments on the manuscript. SZK, CDD, MLK and SOB drafted the manuscript. CDD, SMJK MLK, and SOB made substantial contributions to the conception and design of this study and CDD, SMJK, MLK, SOB and AJMW co-authored the writing of the manuscript. All other authors included in the Napoleon Trial Study Group (listed below) participated in the design of the study and are local investigators at the participating centres. All authors read and approved the final manuscript.

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Additional files

Additional file 1: Search Strategy and Outcomes Systematic Review
Additional file 2: SPIRIT checklist Napoleon Trial
Additional file 3: Study Participant Patient Information Form and Informed Consent Form (Dutch)

All additional files can be found at: https://www.sciencedirect.com/science/article/pii/S155171442030255X?via%3Dihub

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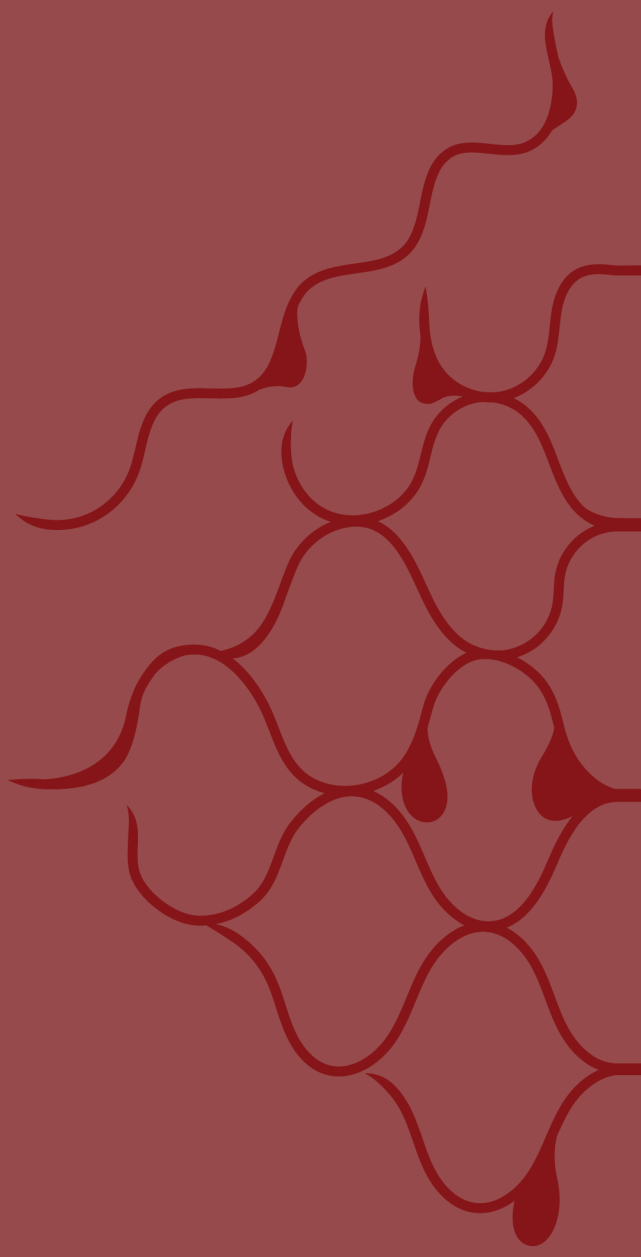

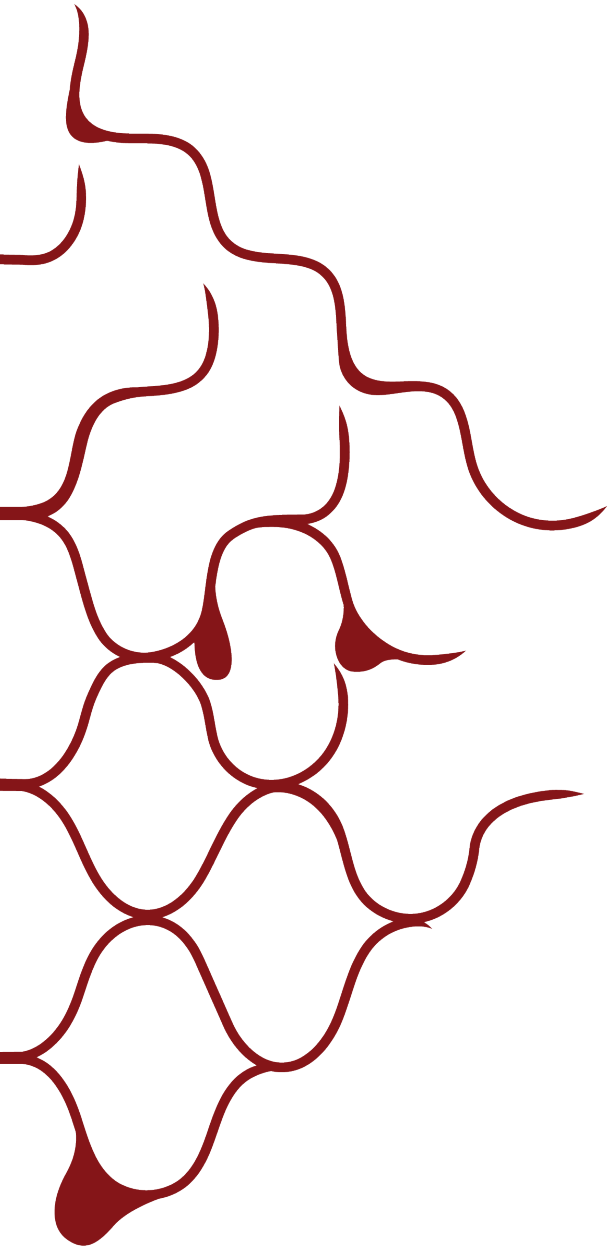

Chapter 6

Picking up the threads: Long term outcomes of the sutured haemorrhoidopexy: A retrospective single centre cohort study

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Abstract

Background

This study aimed to assess the short- and long-term safety and efficacy of the sutured haemorrhoidopexy (SH) in patients having haemorrhoidal disease (HD).

Methods

A retrospective study was performed assessing the following treatment characteristics: number of sutures needed; operation time; perioperative complications; postoperative pain; hospital stay. The short- and long-term postoperative complications, HD recurrence and data on current HD symptoms were assessed according to the Core Outcome Set for HD.

Results

Between January 2009 and December 2021 149 patients having HD underwent a SH. One-hundred and forty-five patients were included with a mean age of 61 years (±12.8), of which 70 women (48.3%). Patients were predominantly diagnosed with grade III (37.2%) HD and the median follow-up was nine years (5-11). Perioperative complications occurred in four cases (2.8%). In two patients (1.4%) short-term postoperative complications were reported and in seven patients (6.2%) long-term complications. The cumulative efficacy in terms of freedom of recurrence was 88.3% (95% CI, 83.1-93.5) at six months, 80.0% (95% CI, 73.5-86.5) at one year and 67.7% (95% CI, 59.7-75.7) at five years.

Conclusions

Sutured haemorrhoidopexy is a safe treatment for patients having HD and can be proposed as a minimally-invasive surgical treatment if basic and outpatient procedures fail.

Introduction

Haemorrhoidal disease (HD) is the most common proctologic disease in the Western world with prevalence rates up to almost 40% in the adult population[1]. Basic treatment, including lifestyle, dietary modification and the usage of laxatives, are the first steps in the management of all grades of HD[2]. In patients where basic treatment has not resulted in acceptable symptom reduction, outpatient-procedures like rubber band ligation (RBL), sclerotherapy and infrared coagulation should be considered as next treatment step[2,3]. For grade II-IV HD or if outpatient treatment is not sufficient, operative interventions can be proposed. Haemorrhoidectomy is still the gold standard and the most studied surgical treatment for HD[4]. The rationale of a haemorrhoidectomy is that the prolapsing haemorrhoidal tissue is excised and can no longer protrude from the anal canal. Though recurrence rates of HD after this procedure are low, around 14% at one-year post-procedure, the main drawback of the haemorrhoidectomy is the painful nature of this operation and the risk of loss of anal function over time[5,6].

Due to these disadvantages, new tissue sparing techniques were developed like the stapled haemorrhoidopexy. In comparison to the haemorrhoidectomy, less postoperative pain and a shorter recovery time are reported for this procedure[7]. However, the popularity of stapled haemorrhoidopexy declined over time due to the high costs of the stapler and rare but possible severe complications[8-11].

Another tissue sparing technique is the haemorrhoidal artery ligation (HAL), with or without Doppler-guidance. In this technique, no excision is performed, but instead, a pexy suture impedes the arterial inflow to the haemorrhoidal tissue[7]. Studies show that the addition of Doppler does not change the results achieved by the HAL[12,13]. As the HAL focusses mainly on the ligation of the arterial blood flow. A limitation of this technique is that the prolapse is not directly addressed. Since the sensation of tissue prolapse is one of the most frequent symptoms of HD, treatment should be targeted to alleviate this symptom[14]. In line with these tissue-sparing techniques, Pakravan *et al.* introduced the transanal open haemorrhoidopexy or sutured haemorrhoidopexy (SH), consisting of a suture through the haemorrhoidal complex to lift and fixate the haemorrhoidal complex higher in the anal canal[15]. In addition, a small excision of the anal mucosa is performed to maximise scar tissue. By using only one to three sutures, the SH is inexpensive in comparison to other surgical techniques. Two studies are known assessing the outcomes of the SH. One prospective study included 38 HD patients and reported that 84% of the patients was pain free immediately after surgery and no patients required additional surgery after six months[15]. The second study is a German retrospective study assessing SH in 110 patients with a follow-up of over eight years[16]. In 72.7% of the patients, HD symptoms were significantly improved or even vanished after treatment. The results of the latter study were not reported in the English language, diminishing the impact of the results in scientific society.

The question remains if SH could be a valuable surgical option in the treatment algorithm of HD once outpatient interventions fail. The present study evaluates both short- and long-term outcomes of the SH in patients with symptomatic grade I-IV haemorrhoids by means of a retrospective cohort study.

Materials and Methods

Patients

All consecutive patients, having symptomatic grade I-IV haemorrhoids, and operated in our centre between the first of January 2009 and the 31st of December 2021, were identified for this retrospective study. Patient numbers were retrieved from the electronic patient file (EPF) using the CTcue software package (CTcue b.v. – an IQVIA business, Amsterdam, The Netherlands) and were screened on eligibility. Men and women older than 18 years at the time of their operation, who underwent SH as a treatment for HD were eligible for inclusion. Eligible patients were subsequently asked written consent by their treating physician for accessing their EPF. Following consent, operative and follow-up data of all patients was retrieved from the EPF.

Additional written informed consent was obtained from patients participating in the telephone interview assessing the current symptoms of HD.

Surgical procedure

The procedure is displayed in Figure 1. No prophylactic antibiotics or bowel preparation were given. The procedure was performed under general anaesthesia with the patient in the lithotomy position. A proctoscope was used for exposure of the anorectum. The haemorrhoidal tissue was translocated distal in the anal canal with a small surgical clamp. A stitch was placed at the cranial side of the haemorrhoidal complex using 2-0 Vicryl. Distal to this stitch, a one centimetre strip of mucosa was excised or devitalized with a diathermic device to facilitate scar tissue formation. Subsequently, the original stitch was completed by performing a second piercing distal to the location of the mucosectomy. After tightening of this suture, the haemorrhoidal tissue was lifted proximally into the anal canal.

This procedure was performed in one to three haemorrhoidal columns depending on the severity of HD. An absorbable haemostatic gelatine tampon was inserted. No postoperative antibiotics were given.

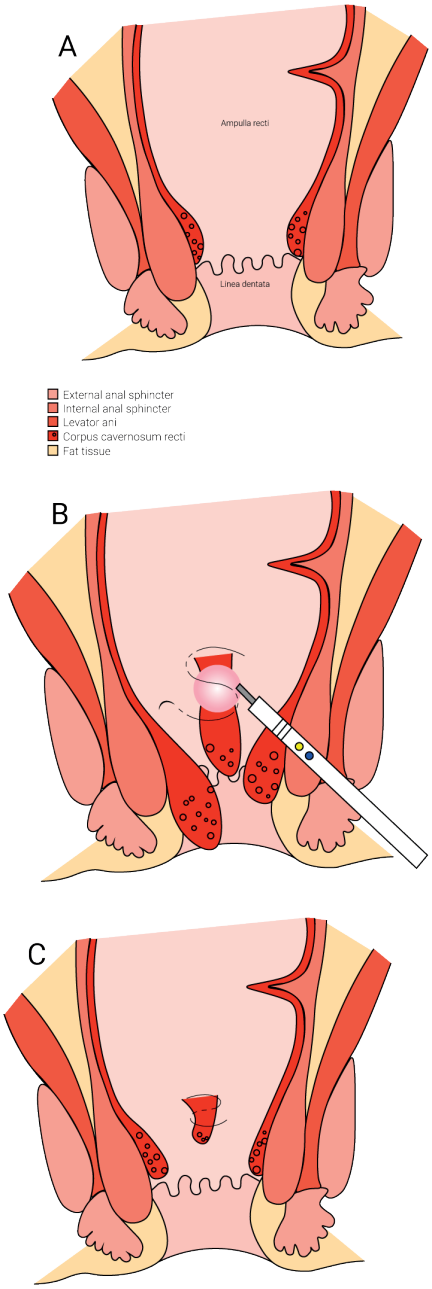


Figure 1 *The procedure of the sutured haemorrhoidopexy. (A) Healthy situation. (B) Haemorrhoidal disease. A stitch is placed at the cranial side of the haemorrhoidal tissue. A mucosectomy is performed with a diathermic device. (C) The stitch is tightened, lifting the haemorrhoidal tissue.*

Outcomes and instruments

Treatment characteristics and perioperative outcomes

Treatment characteristics were collected from the EPF consisting of the number of sutures needed, operation time (in minutes), perioperative complications, postoperative pain and analgesia use, and hospital stay (in days).

Outcomes according to the Core Outcome Set (COS) for Haemorrhoids

The short- and long-term postoperative complications were assessed according to the European Society of ColoProctology (ESCP) Core Outcome Set (COS) for HD[17].

Short-term postoperative complications consisted of urinary retention and the formation of an abscess, both assessed via physical examination (PE), occurring within or after seven days postoperatively. Long-term postoperative complications were defined as development of anal stenosis, incontinence or anal fistula over a period of one year postoperatively. Both anal stenosis and anal fistula were identified by means of a PE, and incontinence was classified according to the Wexner Incontinence Scale. The Wexner Incontinence Scale contains five questions regarding anal incontinence, describing the type and frequency of the complaint[18]. A higher the score on the scale correlates with an increase in anal incontinence complaints, with a cut-off value of ≥9 or higher indicating a degree of anal incontinence that affects quality of life[19].

All patients were invited for a telephone interview assessing their current symptoms of HD. During this interview, haemorrhoidal symptoms were assessed according to the Patient-Reported Outcome-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS)[20]. First, patients were asked to answer the symptom items of the PROM-HISS. Symptoms included blood loss, prolapse, pain, itching and soiling, and were scored on a Likert scale from 1 (no burden) to 5 (severe burden). Furthermore, the impact of these symptoms on daily activities was probed on a scale from 0 (no impact) to 10 (severe impact), and the satisfaction with treatment was scored on a scale from 0 (not satisfied) to 10 (very satisfied).

Recurrence and re-treatment

Next to the COS outcomes, we collected data regarding recurrence of HD complaints and re-intervention(s) from the EPF. Additional treatment(s) were scored if patients underwent further treatment after SH.

Data analysis

Patient characteristics were summarized using descriptive statistics. Categorical variables were presented as frequencies with percentages. Continuous variables were presented as mean ± standard deviation (SD) for a normal distribution or as median and first and third quartile for a skewed distribution (IQR). A one-way ANOVA was used to assess the difference between the amount of sutures needed and grade of HD. A Kaplan-Meier analysis was performed to analyse efficacy in terms of freedom of recurrence for the entire group, as well as for the subgroups based on HD grade. All statistical analyses were performed in SPSS (IBM SPSS Statistics version 25). Values of $p < 0.05$ were considered statistically significant.

Results

Patients

In total, 367 consecutive patients were retrieved from the EPF, of which 149 were deemed eligible as they were diagnosed with grade I-IV HD, underwent SH and were older than 18 years at the time of the operation. Four patients did not give consent for access to their EPF. Of the 145 patients, 50 patients gave additional written informed consent for a telephone interview to assess the current symptoms of HD. On average, patients were operated nine years ago (IQR 5-11) and were diagnosed with grade III (37.2%) or IV (29.7%) HD. As only one patient was diagnosed with grade I HD (0.7%), grade I and grade II HD were combined. Patient characteristics of the total cohort (n = 145) and the subgroup (n = 50) are summarized in Table 1. A study flowchart is shown in Figure 2.

Table 1 *Patient characteristics (n = number, y = years).*

Characteristics	Total (n = 145)	Subgroup[1] (n = 50)
Female, n (%)	70 (48.3%)	21 (42.0%)
Age, mean ±SD, y	61 ±12.8	62 ±11
Years between surgery and follow-up, median (IQR), y	9 [5-11]	7 [3-10]
Goligher's classification, n (%)		
Grade I + II	23 (15.9%)	5 (10.0%)
Grade III	54 (37.2%)	18 (36.0%)
Grade IV	43 (29.7%)	18 (36.0%)
Unknown	25 (17.2%)	9 (18.0%)

[1]*Subgroup with additional data on current symptoms and re-interventions.*

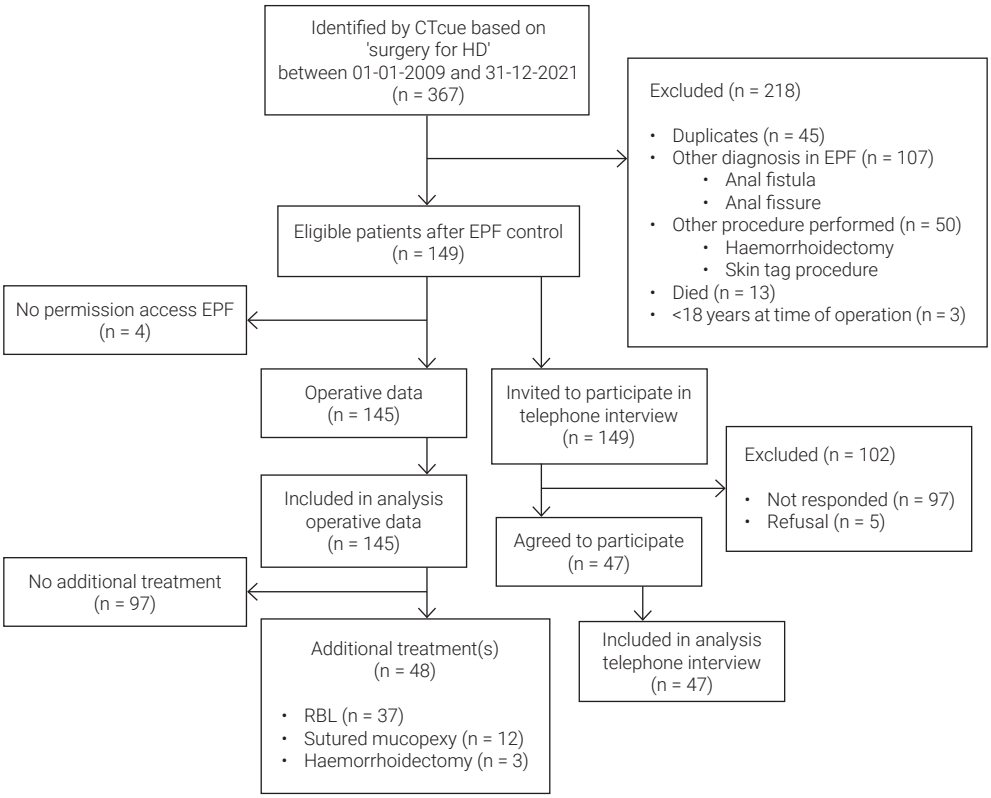


Figure 2 *Flowchart of the participating patients.*

Outcomes

Treatment characteristics and perioperative outcomes

The number of sutures varied between the interventions with a mean of three sutures per procedure. No statistically significant difference was seen in the number of sutures and grade of HD as determined by one-way ANOVA (p = 0.991), albeit grade I was excluded (p = 0.983). The mean operation time was 18.1 minutes (± 7.7). Perioperative complications occurred in four cases (2.8%); twice including a thrombosed haemorrhoid, once an anal fissure, and once the need for a perioperative subsequent haemorrhoidectomy.

Of the patients, 45 (31.0%) out of the 53 patients (36.6%) who reported pain needed analgesia for pain relief. In most cases, the analgesic of choice was oxycodone. Alternatives were combinations of acetaminophen, non-steroidal analgesics and/or oxycodone. The median duration of hospital stay was one day [1-3 days]. Outcomes are shown in Table 2.

Table 2 *Treatment characteristics and perioperative results (n = number, y = years).*

Characteristics	Outcome
Number of sutures	3 [1-8]
Operation time, min	18.1 ±7.7
Perioperative complications	4 (2.8%)
Analgesics needed	45 (31.0%)
Type of analgesic[1]	
Acetaminophen	25 (32.1%)
Non-steroidal analgesics	23 (29.5%)
Oxycodone	27 (34.6%)
Other	3 (3.8%)
Hospital admission, days	1 [1-3]

[1]*A combination of analgesics could be given.*

Outcomes according to the Core Outcome Set (COS) for Haemorrhoids

Short-term postoperative complications were recorded in two patients (1.4%). Both needed a urinary catheter. No abscesses were documented.

Long-term postoperative complications were seen in seven patients (6.2%); including four patients with faecal incontinence (2.8%), two patients with anal stenosis (1.4%) and one patient developed a fistula (0.7%). Faecal incontinence was expressed as the Wexner incontinence score, with a mean of 4.75 (±3).

Of the total of 145 patients, a subgroup of 50 patients (34.5%) gave informed consent for a telephone interview. Patients in this subgroup were operated seven years (median, IQR 3-10) before the telephone interview took place. More than half of the patients was still bothered by some feeling of a prolapse from the anus (56.0%), ranging from 'very little' to 'a lot'. Both blood loss and pain were reported in 19 cases (38.0%). About three-quarters of the patients did not experience 'itching' or 'fluid loss', with 'itching' being reported in 13 cases (26.0%) and fluid loss in 12 cases (24.0%). An overview of the responses on the PROM-HISS can be found in Table 3 and Figure 3.

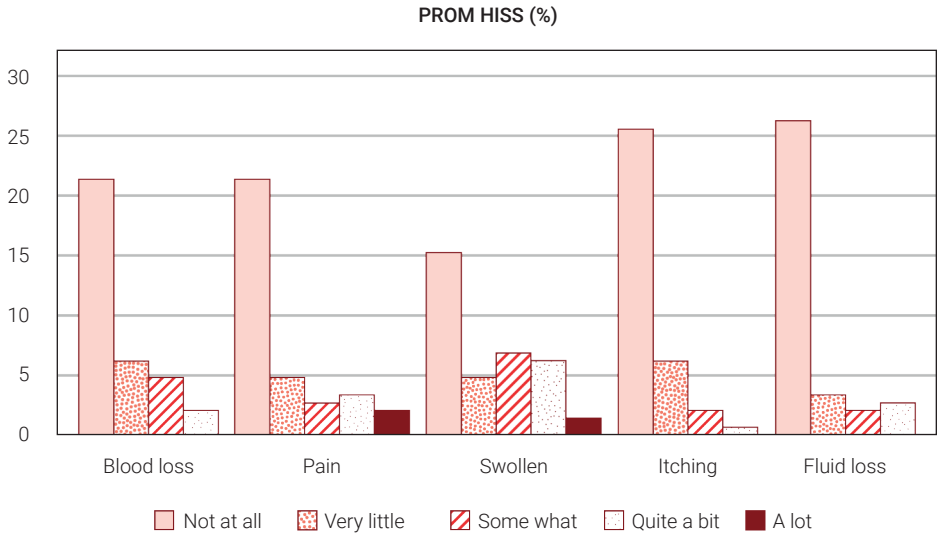


Figure 3 *Overview of the responses on the Patient-Reported Outcome Measure-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS).*

Table 3 *Overview of responses on the PROM-HISS, n (%) (PROM-HISS = patient-reported haemorrhoidal-disease-haemorrhoidal impact and satisfaction score, n = number).*

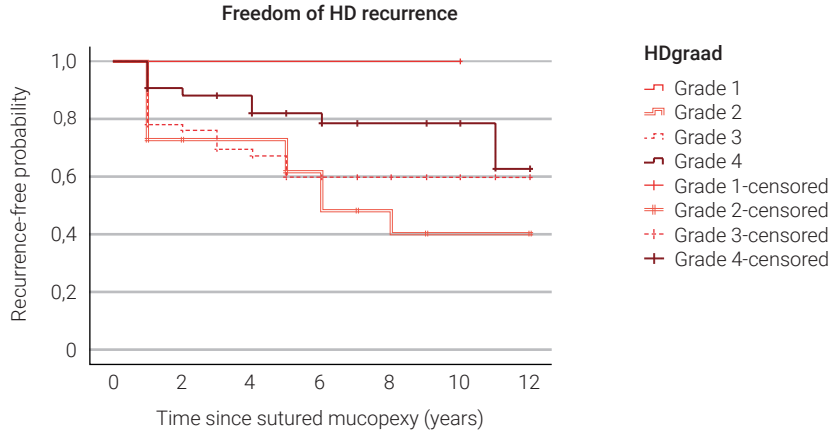
	Blood loss	Pain	Swelling	Itching	Fluid loss
Not at all	31 (62.0%)	31 (62.0%)	22 (44.0%)	37 (74%)	38 (76.0%)
Very little	9 (18.0%)	7 (14.0%)	7 (14.0%)	9 (18.0%)	5 (10.0%)
Somewhat	7 (14.0%)	4 (8.0%)	10 (20.0%)	3 (6.0%)	3 (6.0%)
Quite a bit	3 (6.0%)	5 (10.0%)	9 (18.0%)	1 (2.0%)	4 (8.0%)
A lot	0 (0.0%)	3 (6.0%)	2 (4.0%)	0 (0.0%)	0 (0.0%)

Recurrence and re-treatment

Recurrence of complaints after the SH was reported in 49 patients (33.8%), of which 48 patients underwent additional treatment(s). Most of these patients, 37 patients (77.1%), underwent additional RBL treatment(s), with a mean of 2.9 (±2). Fifteen patients underwent a subsequent operative intervention; 12 patients (25.0%) a SH and three patients (6.3%) a haemorrhoidectomy.

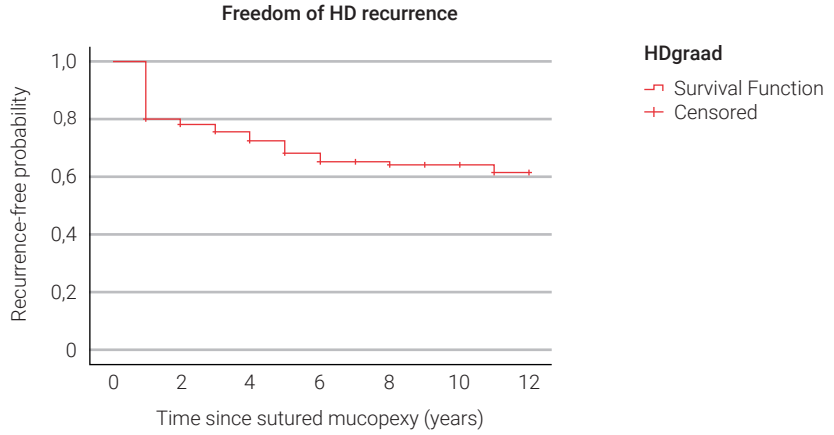
The efficacy in terms of cumulative freedom of recurrence was 88.3% (95% CI, 83.1-93.5) at six months, 80.0% (95% CI, 73.5-86.5) at one year and 67.7% (95% CI, 59.7-75.7) at five years, as can be seen in the Kaplan-Meier curve (Figure 4).

The distribution of recurrence according to HD grade can be found in Table 4. The probability of being free from recurrence was 39.9% (95% CI, 15.6-64.2) for grade II, 59.8% (95% CI, 45.9-73.7) for being free from recurrence was 39.9% (95% CI, 15.6-64.2) for grade II, 59.8% (95% CI, 45.9-73.7) for grade III, 62.7% (95% CI, 33.1-92.3) for grade IV after 12 years.



(a)

Number at risk	0	2	4	6	8	10	12
Grade 1	1	1	1	1	1	1	0
Grade 2	22	15	13	9	6	3	3
Grade 3	54	39	30	21	17	12	5
Grade 4	43	33	29	23	13	10	3



(b)

Number at risk	0	2	4	6	8	10	12
	145	106	90	70	51	37	15

Figure 4 *Kaplan-Meier curve of freedom of recurrence. (a) According to grade of haemorrhoidal disease. (b) According to follow-up time.*

Table 4 *Distribution of recurrence according to HD grade (HD = haemorrhoidal disease, n = number).*

Grade HD	n = 145	Recurrence
Grade I + II	23	11 (47.8%)
Grade III	54	20 (37.0%)
Grade IV	43	9 (20.9%)
Unkown	25	9 (36.0%)

Discussion

This retrospective cohort study assessing the short- and long-term efficacy and safety of the SH in 145 patients demonstrated a freedom from recurrence of 88.3% (95% CI, 83.1-93.5) at six months, 80.0% (95% CI, 73.5-86.5) at one year and 67.7% (95% CI, 59.7-75.7) at five years. Other studies reported lower recurrence rates for the SH than ours. Pakravan *et al.* included 38 patients of whom no one required additional surgery after the follow-up of six months[15]. Aigner *et al.* followed their 40 patients for one year and reported a recurrence rate of 5% in the SH group[12]. Only one randomized controlled trial has been conducted on the efficacy of SH, reporting 100 patients with a follow-up of two years[21]. In this trial, DG-HAL was compared with suture fixation alone. At two years' post-procedure, a low recurrence rate of 2.3% in the suture fixation group was seen. Our higher recurrence rate could be explained by our older population. The mean age of our study population was ten years higher than in the above-mentioned studies. It is known that the incidence of HD increases with age and the peak age for HD development is between 45 and 65 years[22,23].

In comparison with the haemorrhoidectomy, the probability of recurrent HD symptoms is higher after an SH. The recurrence rate after a haemorrhoidectomy ranges around 14 to 16% at one-year post-procedure[5,24]. This lower percentage could be related to the fact that more haemorrhoidal tissue is excised in comparison to the SH, attributing to its more invasive character. As a consequence, it is known that haemorrhoidectomy is associated with a higher complication rate of approximately 10% [25]. On the short term, urinary retention is seen in 2.1-16.4% of patients and local infection in 0.6-1.5% of patients[26-28]. Long term complications can include anal incontinence (15-21.1%), stenosis (2.9-4.7%), fistulas (0.2-1.2%) or otherwise anorectal loss of function[6,26-31].

Our study reported only two short-term postoperative complications (1.4%); both concerned a urinary retention, and seven long-term postoperative complications (6.2%), including four cases of incontinence; two cases of anal stenosis, and once an anal fistula. Our complication rates are comparable to the study by Gupta *et al.* who described the mucopexy technique in a large patient cohort (n = 616) with a follow-up of one year. In the study of Gupta *et al.*, complications were identified in 9% of the patients, which included retention of urine, pain needing readmission, bleeding needing readmission, external haemorrhoidal thrombosis, anal tags and pruritus[32].

Besides the higher overall complication rate of haemorrhoidectomy, up to 65% of patients report moderate to severe pain following this technique, resulting in increased analgesic use postoperatively

[33-35]. In our study, 53 patients (36.6%) reported postoperative anal pain and the majority of these patients needed analgesics. Pakravan *et al.* described the exact same technique and reported that most patients (89%) were free of pain after one-month follow-up[15].

Comparing results from previously published literature with our data is challenging due to the fact that inclusion criteria (i.e. source/target populations) and definitions and timing of the measurement of outcomes vary between different studies, i.e. our study only reported on postoperative pain directly after surgery. The heterogeneity in outcome reporting is one of the downsides of all the previously mentioned studies. For example, the outcome 'recurrence' was not defined in all studies, which hampers the possibility to reliable compare study results. In this study, we used the definition of recurrence as stated by the COS for HD[17]. Additionally, other study outcomes also followed the COS for HD, by assessing symptoms of HD via the PROM-HISS and recording predefined short- and long term postoperative complications. Subsequently, the outcomes of this study can be used to compare with future studies on HD treatment and contribute to (inter)national guidelines on HD[2].

This study has some limitations. The retrospective setting of our study should be taken into account when interpreting the results. As the data were collected from the EPF, which is not originally designed to collect data for research, some information is bound to be missing. Subsequently, selection and recall biases could be possible issues[36]. Moreover, if an outcome is not reported in the EPF, this does not mean that the event did not happen. Hence, under-reporting of outcomes could have ensued. Additionally, the relatively small sample-size of the subgroup results in estimates that are less precise compared to those of larger groups. Finally, the single centre set-up of this study could also be a limitation, by limiting generalizability.

Despite these limitations, to our knowledge, this is the first study reporting on the short- and long-term efficacy and safety on the SH. It provides real-world evidence that the SH has merit in the treatment algorithm of HD.

As stated in the European Society of ColoProctology guidelines for HD, the haemorrhoidectomy is still the mainstay operation for patients with grade II-III HD and/or in patients who are refractory to outpatient procedures, with the low recurrence rate as its principal selling point[2]. However, in terms of postoperative pain and long-term complications i.e. incontinence, the SH could serve as a worthy alternative for the haemorrhoidectomy. Possible benefits and harms of all treatments should be discussed by doctor and patient as part of shared decision making in the consultation room, allowing for a personalized treatment approach. Future work should include a prospective comparative study assessing the predefined outcomes, according to the COS for HD, to show the actual benefit and comparative value of SH.

Conclusions

This retrospective study based on real world data study shows that the SH is a safe treatment for HD and can be proposed as a minimally invasive treatment if basic and outpatient procedures are deemed ineffective. Comparative effectiveness to other treatments needs to be evaluated using prospective studies.

Author Contributions

Conceptualization, S.K. and S.B.; methodology, S.v.K.; formal analysis, K.D.; investigation, S.K., K.D. and P.K.; resources, L.M. and J.M.; data curation, S.K., K.D. and P.K.; writing—original draft preparation, S.K.; writing—review and editing, M.K., C.D. and S.B.; visualization, S.K.; supervision, S.B.; project administration, S.K.; funding acquisition, S.K. and S.B. All authors have read and agreed to the published version of the manuscript.

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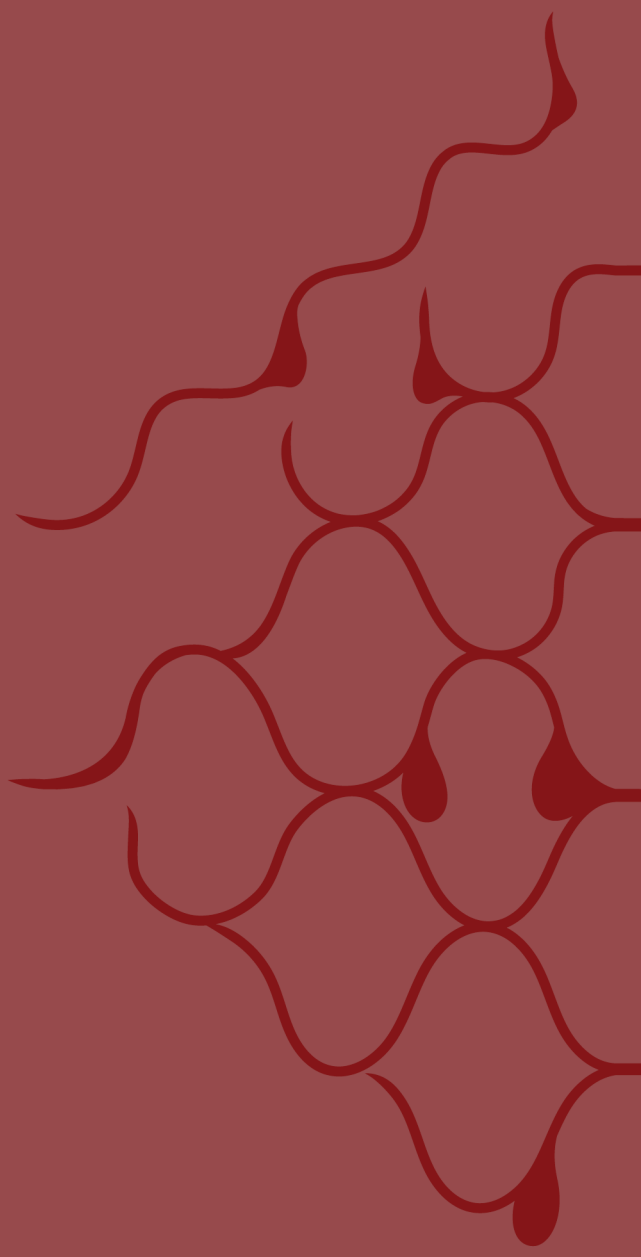

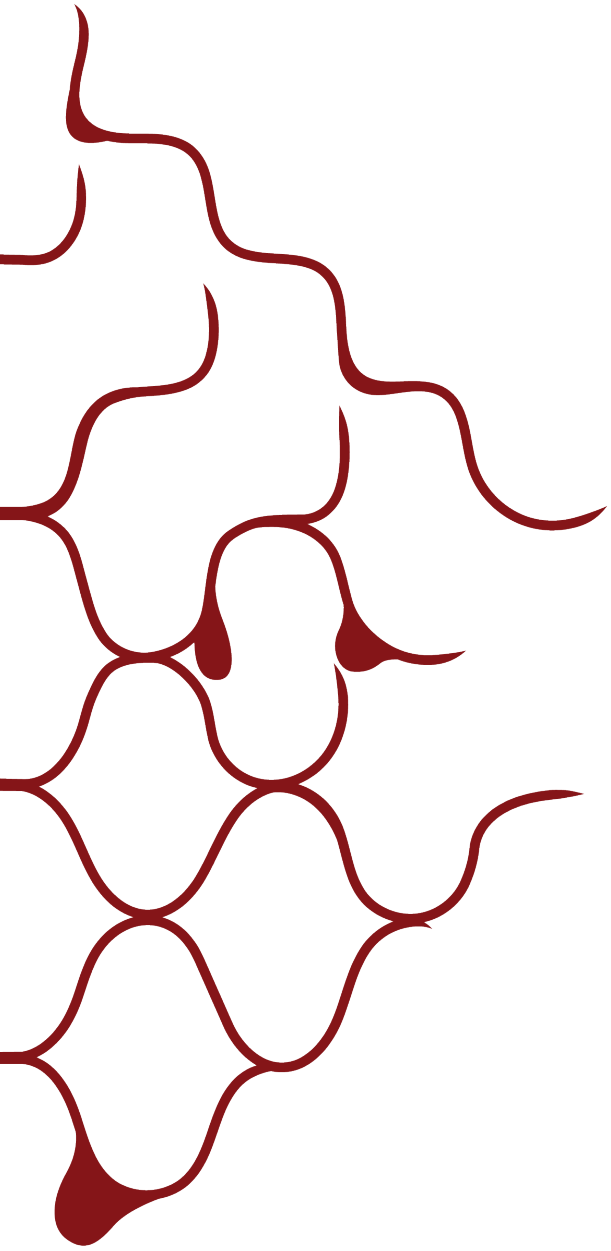

Chapter 7
Making use of patient-reported outcome measures for haemorrhoidal disease in clinical practice: A perspective

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Abstract

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

Introduction

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

In the past, traditional clinical outcomes such as "recurrence of disease" have been valued the most in clinical decision making and to denote treatment success. However, the emphasis is gradually shifting to the patients' perspective and patients' experience with symptoms of HD. This is also acknowledged in the recently developed European core outcome set (COS) for HD, by identifying patient-reported symptoms as the primary core outcome for clinical HD studies[6]. A COS is a consensus-based agreed minimum set of outcomes that should be measured and reported in all clinical trials of a specific disease[7]. A patient-reported outcome measure (PROM) captures a deeper understanding of the disease-burden by obtaining information directly from the patient about their experiences with the illness without interpretation by the healthcare professional or others[8]. PROMs can focus on symptoms, functional outcomes, or broader concepts such as health-related quality of life. They have initially been utilized in health research and are now increasingly being used in daily clinical practice to support treatment decision making and follow-up care[9,10].

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

The rise of PROMs in healthcare

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

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

Clinical decision making in haemorrhoidal disease

Many therapeutic options have been developed for the treatment of HD. The first management step for HD concerns basic treatment, including laxatives, a high fibre diet and topical treatments. If basic treatment fails, patients are usually referred to the hospital for surgical consultation. Besides outpatient procedures like rubber band ligation and sclerotherapy, surgical options can also be considered, i.e., sutured or stapled haemorrhoidopexy, or traditional excisional surgery[19]. The preferred procedure to treat HD mostly depends on the anal pathology of HD, categorized by the Goligher grade. The Goligher grading system categorizes HD into four grades: Grade I are haemorrhoids that do not prolapse; grade II are haemorrhoids that prolapse but reduce spontaneously; grade III are haemorrhoids that prolapse but have to be reduced manually; and grade IV are haemorrhoids that prolapse and cannot be reduced manually[20].

Yet, the classification has several limitations. Firstly, a validation study of the Goligher classification has never been performed and thus it is unclear whether this classification is the most appropriate way to categorize HD and guide treatment strategies. Secondly, in the classification, only the symptom 'prolapse' is included and is assessed by a clinician. Yet, patients with HD can suffer from other symptoms, i.e., blood loss, soiling, itching and pain[21]. The Goligher classification does not consider these associated symptoms of HD[22]. As a consequence, the broader impact of the disease on the patient may not be fully understood. While PROMs are ideally suited to assess this broader impact, they are not yet common practice in the treatment pathway for HD. There is indeed great potential in the usage of PROMs, not only to inform a treatment decision, but also to evaluate treatment success and the patient's satisfaction with the treatment[23]. It is known that consensus on treatment success can differ substantially between healthcare professionals and patients, given that the doctor observes the disease, yet the patient experiences the symptoms[3,24].

Current PROMs for haemorrhoidal disease

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

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

designing and reporting validation research were used[29]. The Haemorrhoid Severity Score (HSS) of Lee *et al.* uses the same symptomatology as Nyström and has assessed the psychometric aspect 'responsiveness' in two large multi-centre, randomised controlled trials (RCT)[30-32]. The fifth PROM described in the Jin review is the Haemorrhoidal Disease Symptom Score and Short Health Scale for Haemorrhoidal Disease (HDSS and SHS-HD) developed by Rørvik and colleagues[33]. Validation of the HDSS and SHS-HD was built on consensus-based standards for designing and reporting validation research. This score encompasses all five symptoms as introduced by Nyström barring a modification of the question on prolapse. The scoring system by Nyström assesses how frequently the patient needs to reduce the prolapse, restricting the question to patients with a Goligher grade III. In contrast, the HDSS asks how often the patient experiences a swelling or prolapse in the anus, making the question applicable to Goligher grades II-IV. A short health scale was added to probe the impact of the HD symptoms on daily life, as well as impact on mental and general well-being. A quality of life instrument complements the use of a HD-symptom score since it provides a more generic view on how the symptoms are perceived in a day-to-day setting. The HDSS SHS-HD by Rørvik *et al.* has shown satisfactory results when methodologically assessed and can be used in the consultation room.

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

Future directions in haemorrhoidal disease PROMs

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

Additionally, in our experience as clinicians, the conversation with the patient is facilitated when a PROM has been completed before the consultation since it can quickly identify issues of concern to the patient[37].

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

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

Conclusion

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

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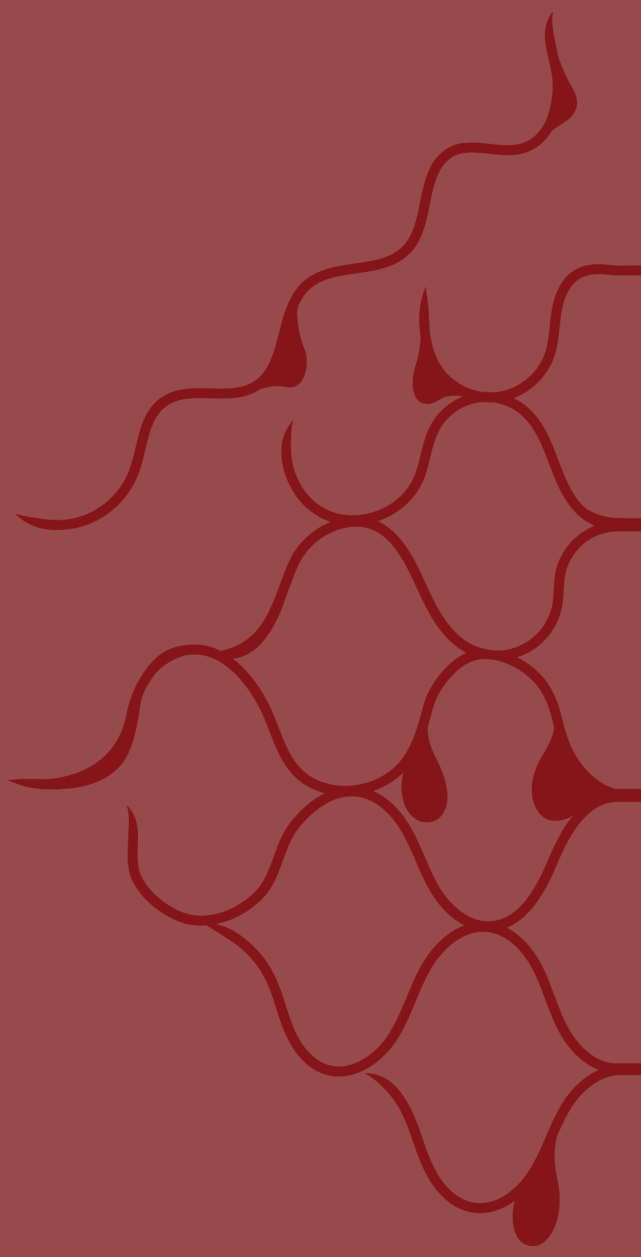

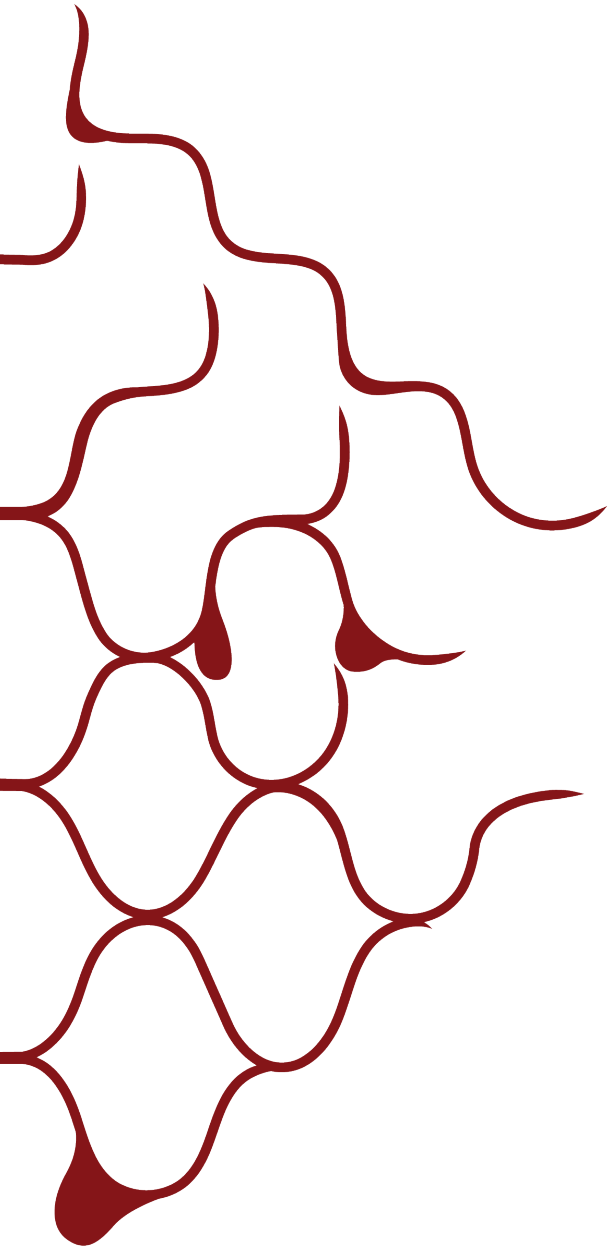

Chapter 8
Patient-Reported Outcome Measure-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS): Development, Reliability and Construct Validity

Sara Z. Kuiper, Merel L. Kimman, Robin R. Van Tol, Sophie F. Waardenburg, Sander M.J. Van Kuijk, Carmen D. Dirksen, Stephanie O. Breukink

Colorectal Dis. 2022

Abstract

Aim

Haemorrhoidal disease (HD) is a frequently occurring disorder with a significant negative impact on a patient's quality of life. We describe the development and validation of the Dutch Patient Reported Outcome Measure-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS).

Method

The development of the PROM-HISS followed recommended guidelines. Face and content validity, structural properties, reliability and construct validity were evaluated in a HD population. Reliability was tested by assessing the test-retest reliability, defined by the Intraclass Correlation Coefficient (ICC), and internal consistency measured with Cronbach's alpha. Construct validity was evaluated using confirmatory factor analysis (CFA) and hypotheses testing.

Results

The PROM-HISS consists of three domains: (1) HD symptoms (blood loss; pain; prolapse; soiling; itching), (2) impact of symptoms on daily activities, and (3) satisfaction with treatment. The PROM-HISS showed good face and content validity. The PROM-HISS was completed by 102 patients (65% male), with a mean age of 58 years (23-81 years). The ICCs of the different items in the domain HD symptoms ranged between 0.56 and 0.79 and were interpreted as good. The Cronbach's alpha value was 0.80 and considered satisfactory. The CFA provided further evidence for construct validity with a good model fit. A high score on the symptoms of HD correlated with a high impact of HD on daily activities (Pearson's $r = 0.632$, $p<0.01$) and a low degree of satisfaction (Pearson's $r = 0.378$, $p<0.01$).

Conclusion

The PROM-HISS is a reliable and valid instrument to evaluate symptoms of HD, impact on daily activities and satisfaction with treatment.

What does this paper add to the literature?

The Patient Reported Outcome Measure-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS) evaluates the symptom burden of haemorrhoidal disease, impact on daily activities and satisfaction with haemorrhoid treatment. It shows sound structural properties, internal consistency and construct validity. We endorse the use of the PROM-HISS in research settings and clinical practice.

Introduction

Haemorrhoidal disease (HD) is a frequently occurring disorder with a significant negative impact on a patient's quality of life[1]. HD affects a large number of people in the world, with prevalence rates ranging between 4.4 and 36.4% in the general population[2,3].

While there are ample clinical studies evaluating the effectiveness of varying HD treatment strategies, there is a lack of uniform outcome definition, measurement and reporting in the research data. This limits research quality and complicates evidence synthesis[4,5]. Hence, the European Society of Coloproctology (ESCP) has recently developed a Core Outcome Set (COS) to achieve standardization of outcomes and outcome measurement in HD studies. The primary outcomes of the COS were symptoms of HD and the secondary outcome was treatment satisfaction[6,7]. Symptoms and satisfaction should both be reported by patients and can be evaluated using a patient-reported outcome measure (PROM). A PROM collects information directly from the patient without interpretation by a healthcare professional or others[8-10]. A recently published systematic review aimed to determine the most appropriate instruments that classify the severity of HD disease according to symptoms, identified five studies describing the development and validity of PROMs and scoring systems based on core symptoms reported by patients[11]. Nevertheless, these measures have several drawbacks and an established PROM for haemorrhoids is missing. In some cases, several psychometric properties of the PROM were not tested, i.e. validation, responsiveness[12]. In others, the tools were not developed in our population of interest (patients with HD), and no input from this group was asked in the development process[13,14]. Lastly, consensus-based standards for designing and reporting validation research were not used[15,16].

Hence, we decided to develop a PROM that specifically addressed the primary outcomes of the ESCP COS in strong collaboration with HD patients. In taking on this endeavour, we closely followed the Consensus-Based Standards for the Selection of Health Measurement Instruments (COSMIN) guidelines development and testing[17]. The COS, which was dominated by a health care professional view, and the patient interviews, served as a fundament for the development of the Patient-Reported Outcome Measure-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS) for HD. This paper describes the development and validation of the Dutch PROM-HISS.

Materials & Methods

The development of the PROM-HISS consisted of several steps, following recommended guidelines for the development and validity of health status questionnaires[18,19]. A panel of experts included a health outcomes researcher, a colorectal surgeon, two clinical statisticians, a health technology assessment expert and two researchers in the field of coloproctology.

Step I. Development of the PROM-HISS

A first collection of items relevant for inclusion in the PROM-HISS, was generated by combining topics and symptoms derived from review of existing measures (e.g. the Sodergren score[12], the Haemorrhoidal Symptom Score[16]), individual patient interviews[20], and discussion with the panel of

experts. The initial relevant items were grouped in an overarching framework of domains and further evaluated in a face-to face meeting with the panel of experts. Several aspects of the PROM-HISS concept were further elaborated on; i.e. initial items and their instructions, minimum age, the variety of response options, and appropriate recall period. By combining the input from the panel of experts, a first version of the PROM-HISS was developed. The process of assessing the items in a face-to face meeting was repeated several times and alterations of the items were based on majority agreement of the panel of experts. Consensus on the first version of the PROM-HISS was reached when no other adjustments were made. This version was used in the consecutive testing steps.

Step II. Evaluation of face and content validity

Individual patient interviews were conducted to assess the face and content validity and the time needed to fill out the questionnaire.

Both male and female adult patients (18 years old) diagnosed with HD grade I-IV were invited by their treating physician to participate in the face and content validity test. Patients were interviewed at the outpatient clinic, face-to-face, by one of two trained interviewers (SK and RT). A cognitive verbal probing technique was used[21]. After initial completion of the questionnaire the participant was asked the following questions for each item individually: (1) 'did you understand the item?', (2) 'is the item relevant to you?' (3) 'were you able to retrieve the information required?', and (4) 'were you able to make a judgement?'. Finally, participants were asked whether they felt important items or domains were missing.

Step III. Evaluation of structural properties, reliability and construct validity

The COSMIN-methodology was used to assess the structural properties, reliability, and construct validity of the PROM-HISS[22]. Data were collected prospectively between April 2020 and February 2021 from Dutch patients older than 18 years with HD grade I-IV. Patients were recruited from one hospital and were identified using hospital records. Patients who had visited the outpatient clinic in the previous year because of complaints of HD were invited by their treating physician via email. Permission was asked electronically and after obtaining written informed consent the PROM-HISS and the EQ-5D-5L, a measure of health-related quality of life (HRQoL), were sent to the patients by mail[23]. Data on age, sex, and grade of HD of each participant were retrieved from the EPF.

Structural properties

A stacked bar chart graphically presents the distribution of scores and percentage of missing values. Floor and ceiling effects were considered present when at least 15% of respondents scored the lowest or highest possible score, respectively[24].

Reliability

Reliability includes test-retest reliability and internal consistency measures. For the test-retest reliability, all participants were asked to complete the PROM-HISS a second time, one week after initial completion. The Intraclass Correlation Coefficient (ICC) was used as a measure of the reliability of the questionnaire[25]. ICC estimates and their 95% confident intervals (CI) were calculated for each item based on absolute agreement and a 2-way mixed-effects model and positively rated when at least 0.70[18].

Internal consistency is the degree of the interrelatedness among items within a domain or construct. Internal consistency is relevant for the five items in the domain 'symptoms'. It assesses whether the symptoms are correlated (homogeneous), thus measuring the same concept. The internal consistency was estimated by calculating the Cronbach's alpha. A low Cronbach's alpha indicates a lack of correlation between the items. The internal consistency was considered good when Cronbach's alpha was between 0.70 and 0.95[18].

Construct validity

A confirmatory factor analysis (CFA) with robust maximum likelihood estimation was performed to test whether the data fit a premeditated factor structure[26]. The CFA test was used for the symptom domain consisting of five items. For the CFA test the Chi-square, the Root Mean Square Error of Approximation (RMSEA) and the Comparative Fit Index (CFI) were taken into account. The Chi-square index assesses the fit between the hypothesized model and data from a set of measurement items (the observed variables). The RMSEA is a measure for model fit. Furthermore, the CFI assesses the model fit by analysing the discrepancy between data and the hypothesized model. We hypothesize that all five symptoms form one model. Convergent validity was evaluated by means of the Average Variance Extracted (AVE), which provides information about the amount of variance that is captured by the construct and should exceed 0.50[27].

Upon findings of good internal consistency and model fit of the domain symptoms, a sum score can be calculated by coding responses for each item on a 1-5 scale and averaging responses. A higher sum score (range 1-5) represents a higher symptom burden. This sum score can then be used for additional assessment of the construct validity.

Construct validity was further evaluated by testing a set of hypotheses about expected relationships between the PROM-HISS and another high-quality comparator instrument, the EQ-5D-5L. The EQ-5D-5L examines a patient HRQoL and consists of a descriptive system and Visual Analogue Scale (VAS). The descriptive system comprises of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The VAS records the patient's self-rated health[23]. We hypothesize that a high score in the symptoms of HD correlates with a lower HRQoL score. Furthermore, we hypothesize that a high sum score on the symptoms of HD measured by the PROM-HISS correlates with a high impact of HD on daily activities and a low degree of satisfaction of treatment, as reported in literature[20].

Finally, we investigated whether scores on the domains of the PROM-HISS (e.g. symptoms, impact on daily activities, and treatment satisfaction) varied between pre-defined subgroups of patients in a manner that is consistent with a-priori hypotheses. We expect varying scores for two different HD groups; low HD grade group:grade I and II HD, and high HD grade group:grade III and IV HD. More specifically, we tested if the higher grade HD group is associated with higher symptom scores (i.e. more severe symptoms) and a higher (negative) impact on daily activities by using an independent student's T-test.

Statistical analyses were performed in SPSS statistical package version 25 (IBM SPSS Statistics 25) and R version 3.6.1.

Results

Step I. Development of the PROM-HISS

Based on the patient interviews reported earlier and the meetings with the panel experts, the first version of the PROM-HISS was drafted[20]. This version consisted of the following three domains: (1) HD symptoms, (2) impact of HD on daily activities, and (3) satisfaction with treatment. The first domain comprises of five symptom-items including blood loss, pain, prolapse, soiling and itching. Both the second and the third domain contain one item; impact of HD on daily activities, and patient's satisfaction with treatment, respectively. The five symptom-items of the first domain are graded using a 5-point Likert scale, ranging from (1) 'not at all', (2) 'a little', (3) 'reasonable, (4) 'a lot', and (5) 'very much'. The remaining two domains are each scored on a numeric rating scale from 0 to 10. Regarding the impact of symptoms, 0 correlates with 'no impact at all' and 10 with 'highly impacted on daily activities'. For patient satisfaction with treatment, this ranges between 0 'not at all satisfied' and 10 'very satisfied'. The recall period for the items in the PROM-HISS is 'in the past week'.

Step II. Evaluation of face and content validity

Ten patients, with a mean age of 56 years (37-73) and equal males and females were interviewed. Six patients (60%) were diagnosed with Goligher grade II HD; three (30%) with grade III; and one (10%) with grade IV. The majority (90%) had received a rubberband ligation treatment for HD. Items were generally well understood by patients and considered relevant. On average, the questionnaire was completed in three minutes (range 1-5 minutes).

Two respondents indicated that they missed a possibility to ventilate their feelings of shame and embarrassment about HD. Expert panel agreement was reached that this aspect is considered outside of the scope of the PROM-HISS that aimed to focus on HD specific symptoms and impact of symptoms on daily activities. Henceforth, the PROM-HISS was considered suitable to take forward into further validity testing.

The PROM-HISS was developed in Dutch (Appendix A). See Table 1 for an overview of the provisionally translated different domains and items of the PROM-HISS.

Step III. Evaluation of structural properties, reliability and construct validity

The PROM-HISS was sent out to 236 patients, of which 102 patients completed the questionnaire at least once. This group consisted of 66 males (65%) and 36 females (35%), with a mean age of 58 years (23-81 years) and diagnosed with HD grade II (55%) or III (39%). Of the 102 patients, 91 (89%) had recently received a treatment for their haemorrhoids, either once (26%), twice (24%) or three or more times (40%). In most cases the treatment concerned rubber band ligation (88%), and in some, an operation (10%).

Demographic characteristics of the cohort are summarized in Table 2. A study flowchart of this process is displayed in Figure 1.

Table 1 *Domains, items and response options of the PROM-HISS*

Domain	*Items*	*Response options*
Symptoms	Blood loss Pain Prolapse Itching Soiling	Likert scale – 1 (not at all) to 5 (very much)
Impact on daily activities	Impact on daily activities	Scale – 0 (no impact at all) to 10 (highly impacted on daily activities)
Satisfaction with treatment	Satisfaction with treatment	Scale – 0 (not at all satisfied) to 10 (very satisfied)

Table 2 *Demographic characteristics (n = number, y = years)*
**Patients could have received both RBL and an operation*

Characteristics	*n = 102*
Sex, n (%)	
Women	36 (35%)
Men	66 (65%)
Age, mean, [range], y	58.4 [23-81]
Goligher's classification, n (%)	
Grade I	2 (2%)
Grade II	56 (55%)
Grade III	40 (39%)
Grade IV	4 (4%)
Treatment, n (%)	
Treatment(s) received	91 (89%)
If yes, treatment specified*	
Rubber band ligation	90 (88%)
Operative treatment	10 (10%)

Structural properties

As the PROM-HISS was sent out digitally and participants could not proceed to a next question without having completed the former, there were no missing data.

The distribution of respons levels was satisfactory for all items of the domain 'symptoms', see Figure 2. All items showed responses across the full range of response options. The mean scores of the different items were 1.8 (SD 1.0) for blood loss, 2.0 (SD 1.1) for pain, 2.3 (SD 1.6) for prolapse, 1.9 (SD 1.0) for itching and 1.9 (SD 1.1) for soiling. Within the domain 'impact on daily activities' the range of response options was used with a mean score of 2.6 (SD 3.2). The same trend was seen in the domain 'satisfaction with treatment', which was rated with a mean of 6.5 (SD 2.8). However, floor effects were identified in all items of the domain 'symptoms'. Likewise, in the domain 'impact on daily activities' a floor effect was seen, with 50% of respondents reporting a score below 1. No ceiling effects were identified in the three domains.

Reliability

All patients received the PROM-HISS and EQ-5D-5L twice, and eighty-four patients (82%) completed the second questionnaire. The mean time between test and retest was 11 days [range 6-34]. The ICCs (95% CI) of the different items in the domain 'symptoms' were: blood loss 0.56 (0.39-0.69); pain 0.61 (0.46-0.73); prolapse 0.67 (0.53-0.77); itching 0.72 (0.60-0.81); and soiling 0.79 (0.69-0.86).

The Cronbach's alpha value was 0.80 and fell within the recommended range of 0.70–0.95, providing evidence for an internally consistent (homogeneous) scale for symptoms.[18]

Construct validity

To assess the construct validity, a CFA of the domain 'symptoms' was performed (see Figure 3). Chi-square indicated that the covariance matrix derived from the model represents the population covariance (p=0.67) and represents an acceptable model. The RMSEA was zero and the CFI value exceeded 0.95 (1.000), suggesting a model with satisfactory fit. Convergent validity was considered good, with moderate to large sizes of all factor loadings and an AVE above 0.50 (i.e. 0.54). Findings from the internal consistency testing and the CFA support the use of a sum score for the domain 'symptoms', in order to further assess construct validity.

As postulated, a high (sum) score on the symptoms of HD measured by the PROM-HISS correlates with a high impact of HD on daily activities (Spearman's *rho* = 0.668, p<0.01, 2-tailed), and a low degree of satisfaction (Pearson's r = 0.378, p<0.01, 2-tailed).

An overall high score of symptoms of HD on the PROM-HISS was linked to a lower score of HRQoL as measured by the EQ-5D (Pearson's r = 0.574, p<0.01, 2-tailed). Contrary to our expectations, we did not find a significant difference between low or high grade HD and the symptom score (2.0 ± 0.8 vs. 2.0 ± 0.8, respectively, p=0.79, 2-tailed) nor between low or high HD grade and impact on daily activities (2.5 ± 3.4 vs. 2.7 ± 3.1, respectively, p=0.81, 2-tailed).

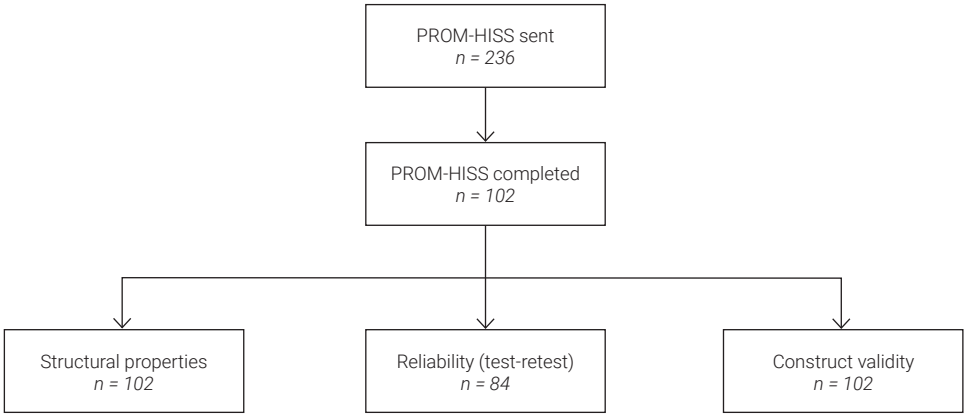

Figure 1 *Flowchart of the participating patients of the evaluation of structural properties, reliability and construct validity*

Discussion and Conclusion

The present study details the development of the PROM-HISS and reports on its psychometric properties. The PROM-HISS evaluates the severity of HD symptoms, impact on daily activities and satisfaction with treatment.

Structural properties of the PROM-HISS were satisfactory, with good response distribution. Overall, low categories were marked in the domain 'symptoms' with floor effects in all items. Similarly, floor effects were seen in the domain 'impact on daily activities'. This may be explained by the fact that our study population consisted of patients who had received a rubberband ligation treatment at the outpatient clinic in the last year. The timing in the treatment trajectory may have resulted in a reduced number and severity of HD symptoms and impact on daily activities. However, the PROM-HISS is specifically developed to evaluate symptom burden and treatment satisfaction throughout the patient journey.

Test-retest reliability measured by the ICC was high, exceeding the 0.70 bar in two out of five symptoms, indicating that the PROM-HISS can yield consistent results on different timepoints. However, for the symptoms 'blood loss', 'pain' and 'prolapse' this benchmark was not reached. A probable explanation is that these symptoms are more prone for day-to-day fluctuations than 'itching' and 'soiling'.

Good model fit of the CFA suggests that the data adequately represents the underlying framework of the domain 'symptoms'. Furthermore, high factor loadings support convergent validity of the measure. Overall, the measure has a good internal consistency and model fit. Its unidimensionallity allows for its items to be pooled into an summary score for the domain 'symptoms', facilitating comparisons between patients.

This study confirmed our hypothesis that if a patient suffers greatly from his or her symptoms of HD, this will translate in a high impact of HD on daily activities and low treatment satisfaction. Contrary to our expectations, we found that neither the score on the symtoms domain nor impact on daily activities differed significantly between a low or high grade of HD. This indicates that the experienced burden and severity of symptoms is not related to the grading of HD and therefore that the Goligher classification, that is used to assign the grades, may not include aspects of the disease relevant to the patient[28].

The strength of the PROM-HISS is that it has the potential to support an evidence-based approach to surgical data and that it provides an insight into patients' experiences with HD in a quantitative and systematic manner. Compared to generic measures (such as the SF-36), a condition-specific PROM, like the PROM-HISS, assesses a particular aspect of health or a condition, relevant to the patient, and is generally more sensitive to detect improvements (or deteriorations) in health or differences in effectiveness between treatments[29]. The PROM-HISS is not the first of its kind. However, it is the first PROM for HD to be developed in conjunction with the HD patient population and closely following the COSMIN guideline for the development of health outcome measurement instruments[22].

There are some limitations that need to be addressed. First, most participants were Caucasian, and it concerned a Dutch population. To establish cross-cultural validity, the PROM-HISS should be translated and tested in different cultural environments. Second, the participants were mostly diagnosed with grade II or III HD, and had attended the outpatient clinic for treatment in the last year. Patients with grade I and IV HD were underrepresented in this study. Furthermore, treatment consisted mainly of RBL suggesting a rather conservative treatment approach in our hospital. Third, the psychometric aspect of responsiveness has not been addressed in this study. Longitudinal data are needed to assess responsiveness. However, this aperture will be tackled in the near future using PROM-HISS data that are currently being collected in two large Dutch randomised controlled trials[30,31].

During the face and content validity testing, it was mentioned that the psychological burden related to HD was missed in the PROM-HISS. Yet, the focus of the PROM-HISS lies primarily in the physical aspects of HD and its impact on daily activities. Despite not adding the concept of psychological burden of HD to the PROM-HISS, we do recommend health care providers to take this aspect of HD into account during consultation.

The PROM-HISS is a unique PROM evaluating the HD symptom burden, impact on daily activities and satisfaction with HD treatment. The PROM-HISS shows sound structural properties, internal consistency and construct validity. We endorse the use of the PROM-HISS in research settings and clinical practice. Further research is encouraged to examine the responsiveness of the PROM-HISS and clinically relevant difference, and asses, next to its use in clinical trials, its merits to inform treatment decisions in clinical practice.

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Appendix A

Patient-Reported Outcome Measure-Haemorrhoidal Disease and Satisfaction Score (PROM-HISS)

Onderstaande vragen gaan over de klachten die u ervaart van uw aambeien. Er zijn geen goede of foute antwoorden.
In hoeverre heeft u de afgelopen week onderstaande klachten ervaren? (Kruis aan wat van toepassing is)

	Helemaal niet	Nauwelijks	Redelijk	Behoorlijk	Zeer hoge mate
Bloedverlies uit de anus	o	o	o	o	o
Pijn aan de anus	o	o	o	o	o
Uitstulping zwelling uit de anus	o	o	o	o	o
Jeuk aan de anus	o	o	o	o	o
Vochtverlies uit de anus	o	o	o	o	o

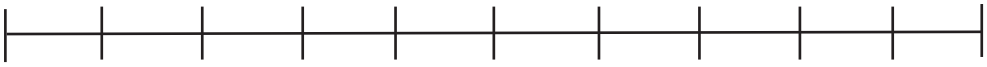
Hebben bovenstaande klachten u afgelopen week gehinderd in uw dagelijkse activiteiten (zoals verzorging van uzelf en anderen, huishouden, werk of sport)? (Zet een X op onderstaande lijn)

0 1 2 3 4 5 6 7 8 9 10

Helemaal niet gehinderd — Zeer veel gehinderd

Indien u recent een behandeling in het ziekenhuis heeft ondergaan (bijv. elastiekjes schieten of een operatie), hoe tevreden bent u met het resultaat wat betreft afname van de klachten? (Zet een X op onderstaande lijn)

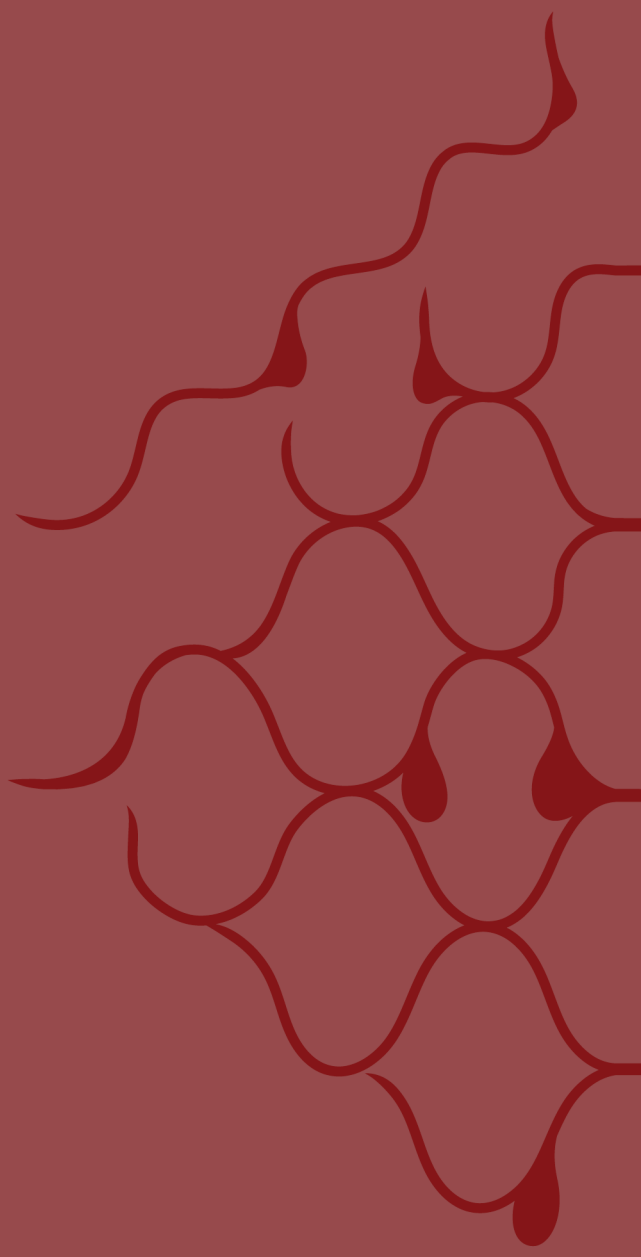
o N.v.t., ik ben (nog) niet in het ziekenhuis behandeld

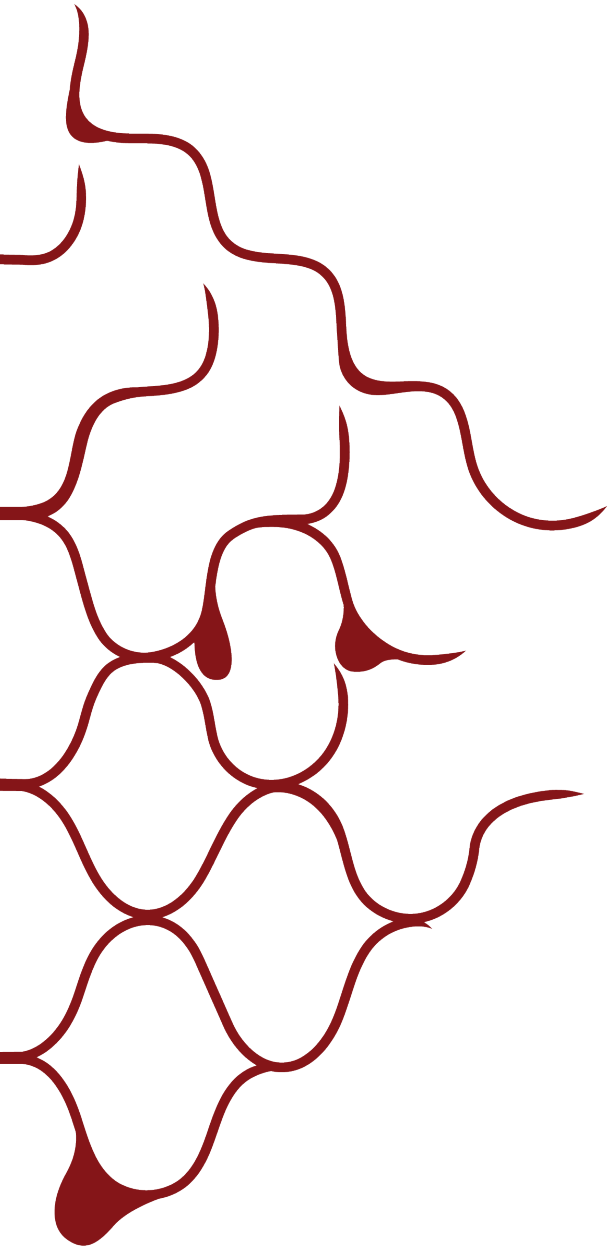


0 1 2 3 4 5 6 7 8 9 10

Helemaal niet tevreden — Zeer tevreden

Dank voor uw deelname!





Chapter 9
Responsiveness of the Patient-Reported Outcome Measure-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS) in patients with haemorrhoidal disease

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Abstract

Aim

In this study, we aimed to assess the responsiveness of the symptom score of the recently developed Patient-Reported Outcome Measure- Haemorrhoidal Impact and Satisfaction Score (PROM-HISS). Furthermore, the minimally relevant difference (MRD) was determined.

Methods

The PROM-HISS' responsiveness was tested using a criterion (i.e. anchor) and construct (i.e. hypotheses testing) based approach. Patients with HD completed the PROM-HISS before and one week after treatment in hospital. A global self-assessment of change question (SCQ) was administered one-week post treatment and functioned as the criterion. The following analyses were performed: 1) correlation between the PROM-HISS symptom score and the criterion (SCQ) and 2) hypotheses testing. The MRD was determined as change in symptoms of the subgroup reporting 'somewhat fewer complaints' on the SCQ.

Results

Between February and August 2022, 94 patients with grade II-IV HD from three hospitals were included. The correlation between the SCQ and a change on the PROM-HISS symptom score was 0.595 indicating that an improvement on the SCQ corresponds to an improvement on the PROM-HISS symptom score. As hypothesized, the mean change in PROM-HISS scores was significantly different between subgroups of patients based on their SCQ responses. Patients reporting a small change in HD symptoms on the SCQ corresponded to a mean change of 0.3 on the PROM-HISS symptom score.

Conclusion

The PROM-HISS symptom score is a responsive instrument as it identifies change in HD symptoms as a result of treatment. The estimated MRD of 0.3 can be used to inform clinical research and practice.

What does this paper add to the literature?

This study shows that the Patient-Reported Outcome Measure-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS) can detect changes in symptoms of haemorrhoidal disease. Furthermore, we identified that a change in symptoms of 0.3 points is a meaningful improvement to patients. Results of this study can inform clinical research and practice.

Introduction

The patient perspective is increasingly considered important in all levels of healthcare decision making and can be captured by a Patient Reported Outcome Measure (PROM)[1,2]. A PROM provides a more complete understanding of the impact of the disease on the patient's life[3,4]. The growing interest in a patient's perspective is also seen in the management of haemorrhoidal disease (HD)[5,6]. HD is the most common anorectal disease and symptoms patients experience include blood loss, pain, prolapse, itching and soiling[7]. The HD Core Outcome Set (COS) of the European Society of Coloproctology (ESCP) supports the emphasis on the patient's perspective and indicates that HD symptoms is the primary core outcome to be evaluated in clinical studies which should be assessed by a PROM[8].

Following the HD COS, the Patient-Reported Outcome Measure-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS) was developed and has shown to be a valid and reliable instrument to measure the burden of HD symptoms, its impact on daily activities and satisfaction with HD treatment[9]. Active patient involvement was present in all steps of the development of the PROM-HISS and both the development and the psychometric evaluation of the PROM-HISS closely followed the Consensus-Based Standards for the Selection of Health Measurement Instruments (COSMIN) guidelines[10]. The psychometric aspect 'responsiveness' of the PROM-HISS has not been assessed yet. Responsiveness is an aspect of validity and is defined as 'the ability of an instrument to detect change over time in the construct to be measured'[11]. The ability of the PROM-HISS to detect change over time is important in order to assess treatment effectiveness.

The aim of this study was to determine whether the PROM-HISS is able to detect a change in HD symptoms in patients undergoing treatment. Moreover, we aimed to determine the minimal change on the symptom score that is relevant from the patient's perspective to inform clinical research and daily practice.

Methods

Study population and design

Patients in three Dutch hospitals were identified by clinicians via the electronic patient file based on their appointment at the outpatient clinic. Before presenting at the outpatient clinic, they were digitally invited to participate in this study by their treating physician via the data management system Castor.

The invitation email contained the patient information file and if patients agreed to participate a follow-up email was sent with a link to the first survey. One-week after the treatment, the second survey was sent by email. Patients were considered eligible if they were 18 years or older, diagnosed with HD grade I-IV and would receive a treatment for HD in the upcoming weeks. Treatments included a minimally invasive procedure (rubber band ligation) and operative interventions such as a sutured haemorrhoidopexy or haemorrhoidectomy. Patient characteristics consisting of age, sex, HD grade, and received treatment were collected from the electronic patient file (EPF). Data on educational level was collected directly from the patient by the data management system Castor. Participants

were asked to complete the PROM-HISS at baseline (pre-treatment) (T_0) and at one week (T_1) after receiving their HD intervention, according to the follow-up scheme of the COS for HD (8). Furthermore, patients were asked to complete a global self-assessment of change question (SCQ) at T_1. Informed consent was obtained from all individual participants included in the study.

For an overview of the study measures, see the study flowchart in Figure 1.

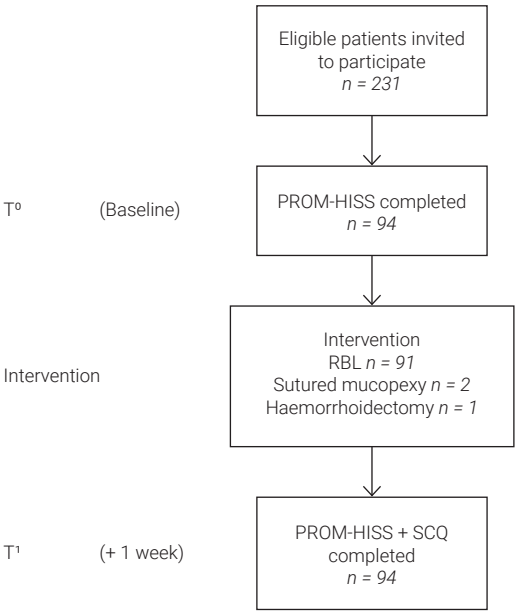

Figure 1 *Study flowchart*

PROM-HISS = Patient-Reported Outcome Measure-Haemorrhoidal Impact and Satisfaction Score

SCQ = Self-assessment of Change Question

RBL = Rubber Band Ligation

Patient-Reported Outcome Measure-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS)

The PROM-HISS is a short HD-specific health measure consisting of three domains: (1) HD symptoms, (2) impact of HD on daily activities, and (3) satisfaction with treatment effect. The first domain comprises of five symptom-items including blood loss, pain, prolapse, soiling and itching. Both the second and the third domain contain one item: impact of HD symptoms on daily activities, and patient's satisfaction with the effectiveness of the treatment regarding improvements in symptoms respectively. The five symptom-items are graded using a 5-point Likert scale, ranging from (1) 'not at all', (2) 'very little', (3) 'somewhat', (4) 'quite a bit', and (5) 'a lot'. A sum score is calculated by averaging the responses to the five items. A higher sum score (range 1–5) represents a higher symptom burden (9). The remaining two domains are each scored on a numeric rating scale from 0 to 10. Regarding the impact of symptoms on daily activities, 0 correlates with 'no impact at all' and 10 with 'highly impacted on daily activities'. For patient satisfaction with treatment, this ranges between 0 'not satisfied' and 10 'very satisfied'.

Global Self-assessment of Change question (SCQ)

A SCQ was used to indicate if patients had experienced? a change in their complaints of HD post-treatment compared to pre-treatment[12]. The SCQ was stated as follows: 'To what extent have your complaints of HD changed compared to before the HD treatment?' There were five response options: '(1) I have much fewer complaints'; '(2) I have somewhat fewer complaints'; '(3) The complaints have not changed'; '(4) I have somewhat more complaints'; and '(5) I have a lot more complaints'. Subgroups of patients with varying levels of change were established according to the responses to the SCQ.

Responsiveness

In the process of determining the responsiveness of the PROM-HISS we followed the COSMIN guidelines and recommendations by Terwee *et al*.[14,15]. A criterion (i.e. anchor) and construct (i.e. hypotheses testing) based approach was used.

Criterion based approach

The SCQ was used as the criterion, and its correlation (Spearman's r) with the change in the PROM-HISS symptom score was assessed. A correlation above 0.5 was considered as evidence of responsiveness[14,15].

Construct based approach

The following hypotheses were tested:

a. The mean PROM-HISS symptom score of the study population is lower (i.e. fewer symptoms) after treatment compared to baseline.

b. The mean changes in the PROM-HISS symptom score differ for the different patient subgroups as determined by the SCQ scores. A gradual increase in change scores is expected with the smallest (or no) change for the subgroup reporting 'the complaints have not changed' and larger changes for the 'somewhat fewer' and 'lot fewer' complaints categories and 'somewhat more' and 'a lot more' complaints categories.

c. The effect size of the subgroup of patients reporting 'much fewer complaints' is expected to be positive and moderate to large (i.e. > 0.50), while the effect size of the subgroup of patients reporting 'somewhat fewer complaints' is expected to be positive and small (i.e. between 0.20 and 0.49), and the effect sizes of the no change group is expected to be around 0, and patients reporting 'more complaints' are expected to have negative effect sizes.

d. The change in PROM-HISS symptom score will have a significant and positive correlation of at least 0.4, as the recommended cut-off by Terwee et al., with the change score in the PROM-HISS domain 'impact on daily activities'[9].

e. Similarly, the change in PROM-HISS symptom score will have a significant and positive correlation of at least 0.4 with the PROM-HISS domain 'satisfaction with treatment effect'[9].

f. We expect differences between the patients undergoing RBL versus the patients undergoing an operative treatment, with more patients in the RBL group indicating 'fewer complaints' at one-week post-procedure as a surgical intervention can give more post-operative pain[16].

For hypothesis a, a mean of HD symptom score at T_0 is calculated and compared with T_1. For b, analysis of variance, with Games Howell post-hoc procedures, was performed to assess whether the PROM-HISS could discriminate between the SCQ categories.

For hypothesis c, the standardized response mean (SRM) as a statistical indicator of change was calculated for each subgroup. The SRM is expressed as the ratio of the mean PROM-HISS change score to the standard deviation (SD) of the score change[17,18]. For hypotheses d and e, Spearman's r correlation coefficients were estimated. For hypothesis f, mean changes in the PROM-HISS symptom score between the RBL patients and the operative patients were compared with a T-test. As a rule of thumb, we use the criterion that 75% of the results should be in accordance with the hypotheses[19].

The PROM-HISS was sent out digitally and patients could not proceed without completing the full questionnaire. If patients did not complete the questionnaire within two weeks, a telephone consult was scheduled to obtain the results on the PROM-HISS and the SCQ.

Minimally relevant difference (MRD)

To determine the MRD, we used an anchor-based approach and identified the mean change scores on the PROM-HISS in the subgroups that reported experiencing 'somewhat more complaints' or 'somewhat fewer complaints' on the SCQ[20, 21].

Statistical analyses were performed in SPSS statistical package version 25 (IBM SPSS Statistics 25).

Results

Between February and August 2022, 231 eligible patients were invited to participate of whom 100 agreed to participate (response rate 43%). A total of 94 patients completed both measurement moments and were included in the analysis. This group consisted of 57 males (61%) and 37 females (39%), with a mean age of 56 years (23-83 years). Most of these patients were diagnosed with grade II (51%) or grade III (41%) HD. The majority of the patients, 65 patients (69%), had received one or

more treatments for their HD in the past; 20 patients (31%) had received a rubber band ligation (RBL), 13 (20%) an operative intervention and 32 (49%) had received a treatment but were uncertain about its nature. Overall, patients had graduated from high school or obtained an associate degree (48%) or a university degree (45%). During this study, 91 patients (97%) received a RBL, two patients a sutured mucopexy (2%) and one patient a haemorrhoidectomy (1%). Demographic characteristics of the study population are summarized in Table 1.

Table 1 *Demographic characteristics of the study population (n = number, y = years)*

Characteristics	N = 94
Sex, n (%)	
Men	57 (61%)
Women	37 (39%)
Age, mean, [range], y	56 [23-83]
Goligher's classification, n (%)	
Grade I	1 (1%)
Grade II	48 (51%)
Grade III	38 (41%)
Grade IV	6 (6%)
Unkown	1 (1%)
Previous treatment, n (%)	
No	29 (31%)
Yes	65 (69%)
Rubber band ligation	20 (31%)
Operative treatment	13 (20%)
Unkown	32 (49%)
Educational (highest degree completed) (%)	
No degree or elementary school	7 (7%)
Graduated high school or associate degree	45 (48%)
University degree (Bachelor, Master, PhD)	42 (45%)
Study treatment, n (%)	
Rubber band ligation	91 (97%)
Sutured mucopexy	2 (2%)
Haemorrhoidectomy	1 (1%)

Responsiveness

Criterion based approach

The SCQ on T_1 (one-week post-treatment) correlated to the change score of the PROM-HISS between T_0 and T_1 (r = 0.595) which indicates a 'good' responsiveness.

Subgroups were established using SCQ responses. As the number of patients in the 'somewhat more complaints' and 'a lot more complaints' were small (n = 6 and n = 7 respectively), these subgroups were combined to form one subgroup of patients who indicated 'more complaints' compared to pre-intervention. Mean change scores on the PROM-HISS symptom domain are presented for the full sample and subgroups (see Table 2).

Construct based approach

In accordance with our first hypothesis, the mean symptom score of the PROM-HISS of the total group is lower after receiving treatment (i.e. fewer symptoms).

As hypothesized, the mean change scores for patients reporting 'more complaints' were higher than the mean change scores for patients reporting 'fewer complaints' and 'no change in complaints'. As expected, the mean symptom score of the PROM-HISS between T_0 and T_1 increased in the 'more complaints' group, indicating a rise in HD symptoms. A decrease in the PROM-HISS symptom score can be seen in the subgroups indicating 'fewer complaints', with the largest decrease seen in the subgroup of patients reporting 'much fewer complaints' on the SCQ. Symptom scores in the 'no change in complaints' subgroup stay almost the same between T_0 and T_1. Scores were significantly different between groups, as can be seen in Table 2. Post-hoc procedures showed that the PROM-HISS could discriminate the 'somewhat fewer complaints' and the 'much fewer complaints' subgroup from the patients reporting 'no change in complaints'. But not between the subgroup indicating 'more complaints' and the 'no change in complaints' subgroup.

Effect sizes were in the expected direction and size (see Table 2), in agreement with our third hypothesis. In the subgroup of patients indicating 'no change in complaints', a small SRM was found (SRM 0.20-0.49). The other subgroups indicating 'more complaints' and 'fewer complaints' show effect sizes in the expected direction and size; ranging from a moderate effect size for the 'more complaints' subgroup and for the 'somewhat fewer complaints' subgroup (SRM 0.50-0.79), and a large effect size for the 'much fewer complaints' subgroup (SRM ≥ 0.80)[22].

Table 2 *Mean baseline scores (T_0), one week scores (T_1), related change scores and standardized response means (SRM) of the PROM-HISS, for the total group and based on the subgroups of the SCQ.*

	PROM-HISS[§]					
	T_0	T_1	$\Delta T_0 - T_1$ (SD)	SRM	Mean difference (SE)	*p*-value
Total group (n = 94)	1.5	1.2	-0.3 (0.8)	-0.397	-	-
Subgroups						
More complaints (n = 13)	1.4	1.8	0.4 (0.7)	0.598	-0.1 (0.3)	0.980
No change in complaints (n = 18)	1.6	1.7	0.2 (0.6)	0.278	-	-
Somewhat fewer complaints (n = 37)	1.4	1.1	-0.3 (0.5)	-0.702	0.6 (0.2)*	0.011
Much fewer complaints (n = 26)	1.6	0.6	-1.0 (0.7)	-1.292	1.1 (0.2)*	0.000

[§]A higher sum score on the domain 'symptoms' of the PROM-HISS correlates with a higher symptom burden
*Subgroups are significantly different at a 0.05 significance level

Testing our fourth hypothesis, we found that the change score between T_0 and T_1 on the domain 'impact on daily activities' on T_1 correlated significantly with the change in the symptom score of the PROM-HISS between T_0 and T_1 (r = 0.446).

Regarding our fifth hypothesis, we found that the change score between T_0 and T_1 on the domain 'satisfaction with treatment effect' on T_1 correlated significantly with the change in the symptom score of the PROM-HISS between T_0 and T_1 (r = 0.400).

Our final hypothesis could not be tested, since only three patients underwent a surgical intervention.

In sum, >75% of our hypotheses were met and we conclude that the responsiveness of the symptom score of the PROM-HISS is good.

Minimally relevant difference (MRD)

The difference in the mean score of the subgroup 'somewhat fewer complaints' and 'somewhat more complaints' was calculated and denoted the MRD for improvement and deterioration, respectively. This translated in a change score of 0.3 in the 'somewhat fewer complaints' subgroup. Hence, a change of at least 0.3 on the symptom score of the PROM-HISS represents a relevant change for patients.

Discussion

This study shows that the PROM-HISS symptom score can detect a change in HD symptoms over time (pre- and post-treatment) and can be considered a responsive measure. Furthermore, a change of 0.3 on the symptom score of the PROM-HISS indicates a minimally relevant change in symptoms according to patients and can be used to inform both research as clinical purposes.

In order to assess change over time as a result of a treatment, the ability of a measurement instrument to detect either improvement or deterioration is an essential psychometric property.

Following COSMIN recommendations, we combined a criterion- and construct-based approach. A gold standard or criterion measure for patient-reported outcomes is difficult to find. However, global rating scales, like the SCQ, can function as a gold standard provided that they assess the same construct as the instrument under study[14]. The SCQ specifically assessed the experienced change in symptoms compared to before treatment and showed a good correlation to the change scores of the HD symptoms of the PROM-HISS one week after HD treatment. Very high correlations are seldom seen because the change score is based on two measurements, both with some degree of measurement error included. Furthermore, mean change scores for subgroups of patients who reported varying levels of change in symptoms on the SCQ were significantly different and were in the expected direction and sizes. Hypothesized relationships of the change score on the PROM-HISS with change scores in other measures were also confirmed. Since our patient population consisted of mainly RBL treatment patients, we could not test our last hypothesis.

The MRD showed a value of 0.3, indicating that a change score of 0.3 on the symptom score of the PROM-HISS is perceived by patients as a relevant decrease in complaints. This value can be used to inform sample-size calculations for research practices and to give insight in whether a meaningful change in HD symptoms has occurred as a result of HD treatment from a patient's perspective. Although there may be differences in what is perceived relevant improvement or deterioration, we selected the MRD of the 'somewhat fewer complaints' subgroup, because the sample size of the subgroup indicating 'more complaints' was small (n = 13) and consisted of a mixture of patients indicating 'somewhat more complaints' and 'a lot more complaints'.

Some limitations need to be addressed. There were a limited number of patients who deteriorated. Consequently, this subgroup remained small and it is therefore uncertain whether the PROM-HISS can detect deterioration. Yet, our prospective design, including patients just before an intervention that is effective in reducing complaints of HD, made it impossible to include a large subgroup of patients with symptoms worsening. Next, we compared the symptom burden before and one-week after treatment. Further testing is necessary to ensure that the PROM-HISS is also able to detect more subtle changes between one and six weeks and longer term follow-up. Furthermore, our study group could be perceived as somewhat homogeneous, considering the majority of patients undergoing RBL and mostly diagnosed with grade II or III HD. The characteristics reflects daily practice, in which RBL procedures are performed more regularly than operative procedures for HD and most HD patients are diagnosed with grade II and III HD[23]. Also, the recent COVID-19 pandemic negatively influenced the number of operations for HD[24]. Hence, the responsiveness of the PROM-HISS in patients receiving a RBL procedure cannot be directly extrapolated to patients receiving an

operative intervention or diagnosed with grade I and IV HD. Lastly, the study group had a relatively mild complaints of HD, which is reflected in the low symptom score of the PROM-HISS.

Yet, this study is highly relevant for the use of the PROM-HISS in clinical research. The PROM-HISS was developed in response to the ESCP COS and this study was the essential last step in the assessment of psychometric properties of a (new) PROM[8]. With this study we have shown that its symptom score can adequately capture effects of a treatment. Moreover, the study has identified that a change in symptoms of at least 0.3 indicates a meaningful improvement to the patient. Since responsiveness and MRD are both related to patient population and timing, the outcomes may be different for other HD subpopulations (based on treatment or grade) or when looking at long-term effects. We thus recommend that both the responsiveness as the MRD of the PROM-HISS needs to be evaluated continuously. Furthermore, the change score of an individual patient can be higher or lower than the mean MRD reported in this study. The outcomes of the symptom score of the PROM-HISS should therefore function as a key to open the conversation with the patient about personal changes in or improvement of HD symptoms.

At the moment, the PROM-HISS is only available in Dutch. To disseminate the ESCP COS and the PROM-HISS in the international scientific community, our research group is in the process of translating and validating this questionnaire to English and French.

Conclusion

The PROM-HISS is able to pick up changes in HD symptoms post-treatment. In addition, by determining the MRD we identify meaningful changes from a patients' perspective which can support in interpreting results of clinical research and inform daily practice.

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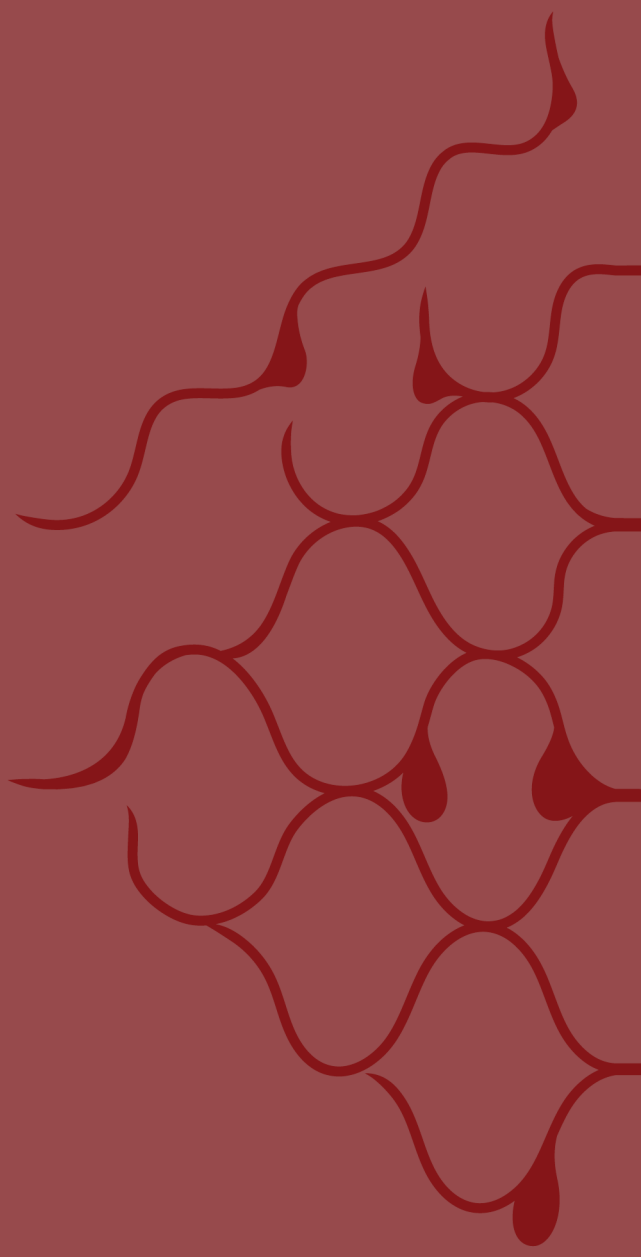

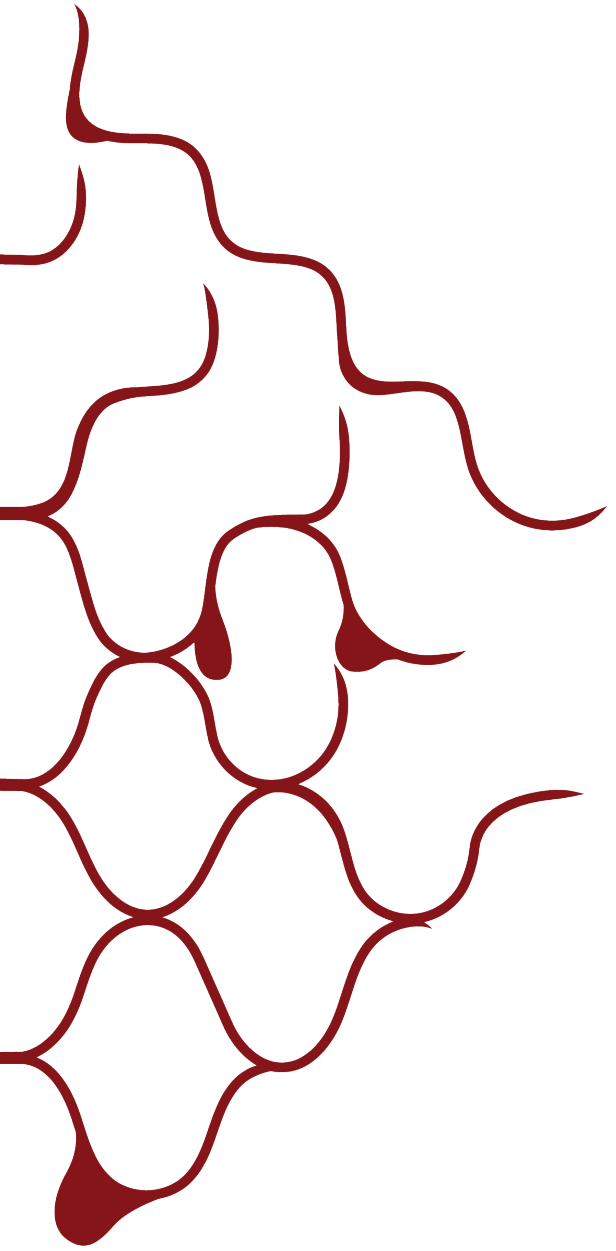

Chapter 10
English translation and cross-cultural validation of the Patient-Reported Outcome Measure-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS)

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Abstract

Aim

The aim of this study was to translate the Dutch Patient-Reported Outcome Measure-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS) to English and perform a cross-cultural validation.

Method

The ISPOR good practice guidelines for the cross-cultural validation of PROMs were followed and included two steps: (1) Two forward and two backward translations. The forward translation concerned the translation from the source language (Dutch) to the target language (English), performed by two independent English speakers, one medical doctor and one non-medical. Subsequently, a discussion about discrepancies in the reconciled version was performed by a stakeholder group. (2) Cognitive interviews were held with patients with haemorrhoidal disease (HD), probing the comprehensibility and comprehensiveness of the PROM-HISS.

Results

Discrepancies in the reconciled forward translation concerned the terminology of HD symptoms. Furthermore, special attention was paid to the response options, ranging from 'not at all', indicating minor symptoms, to 'a lot', implying many symptoms. Consensus among the stakeholder group about the final version of the translated PROM-HISS was reached.

Interviews were conducted with ten native English-speaking HD patients (30% female), with a mean age of 44 (24-83) and primarily diagnosed with grade II HD (80%). The mean time to complete the PROM-HISS was 1 min 43 seconds. Patients showed a good understanding of the questions and response options, found all items relevant and did not miss important symptoms or topics.

Conclusion

The translated English language PROM-HISS is a valid tool to assess symptoms of HD, its impact on daily activities and patient's satisfaction with HD treatment.

What does this paper add to the literature?

This study shows that the translated English Patient-Reported Outcome Measure-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS) is a valid tool to assess symptoms of haemorrhoidal disease, impact on daily activities and satisfaction with treatment. The PROM-HISS can be used in clinical research and practice.

Introduction

Haemorrhoidal disease (HD) is the most common type of anorectal complaint with prevalence rates up to 44% and it has a negative impact on patients' quality of life[1,2]. Symptoms of HD include blood loss, prolapse, pain, itching and soiling[3]. Qualitative research indicates that patients with HD suffer from these symptoms and the symptoms have an impact on their daily life[4]. Furthermore, a patient's perspective on treatment success might vary from the perspective of the physician. The European Society of Coloproctology (ESCP) Core Outcome Set (COS) for HD, published in 2019, emphasizes the importance of the patient's perspective in both daily practice and in research settings. The primary outcome of the COS are the symptoms of HD, and the secondary outcome is treatment satisfaction[5]. These outcomes are best measured by a Patient-Reported Outcome Measure (PROM), collecting the outcome directly from the patient without interpretation by healthcare professionals or others[6].

Recently, a PROM specifically for patients suffering from HD was developed and validated: The PROM-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS)[7]. The PROM-HISS was based on interviews with HD patients and its development and testing closely followed the COSMIN-guidelines[4,8]. The COSMIN-guidelines are a standardized tool used to guide the study design, or reporting of studies, on measurement properties[9]. The PROM-HISS was found to be a valid and reliable tool for evaluating the symptoms of HD, the disease's impact on daily activities and the patient's satisfaction with HD treatment[7].

Currently, the PROM-HISS is only available in Dutch. In order to ensure uptake of the primary outcome of the COS to as wide a geographical area as possible, the next step is the translation of the PROM-HISS into multiple languages. This paper describes the English language translation and cross-cultural validation process of the PROM-HISS.

Methods

The design of this study consists of two parts: (1) Translation of the PROM-HISS from Dutch to English; and (2) the cross-cultural validation of the English language PROM-HISS in the UK. In the process of translation and cross-cultural validation, the formal guidelines for translation of PROMs were followed[10].

Translation

Patient evaluation is recommended during the translation process because cultural nuances may differ between countries[10]. The translation of the PROM-HISS entailed a forward translation and a backward translation. The forward translation from source language (Dutch) to target language (English) was performed by two people, of which one had a medical background (medical doctor) and the other one did not (air traffic controller). Both were native English speakers who also had excellent understanding of the Dutch language. The translators were asked to file a report with their translation, highlighting challenging phrases or uncertainties.

The two translations were combined and if translations differed, consensus on the translation

was sought in the stakeholder team through discussion. The stakeholder team consisted of a Dutch (SB) and a Scottish (but fluent in English) colorectal surgeon (AW), a specialty research doctor (RC), a Scottish-based resident in colorectal surgery (HO), a Dutch professor in health technology assessment (HTA), a Dutch senior researcher in HTA (MK), and a Dutch clinical researcher (SK). The combination of the two forward translations including the adjustments from the stakeholder team was named FT1-2 (forward translation from translator 1 and translator 2).

Subsequently, version FT1-2 was used for the backward translation, in which the questionnaire was translated from the target language (English) to the source language (Dutch), by two native Dutch speakers. One had a master's degree in the English language and literature and the second one was a professional English translator. Both had no medical background, were not informed about the explored concepts and were blind to the original version of the PROM-HISS. The combined backward translation was discussed in the stakeholder team and after consensus was reached on all items, this version was named BT1-2 (backward translation from translator 1 and translator 2). A written report of the synthesis of the two forward- and backward translations was stored.

The English-speaking stakeholder team members were asked about the relevance and comprehensiveness of the items in FT1-2 from their perspective, ensuring equivalence between the source and target version of the questionnaire[11]. Comments and adjustments proposed by the stakeholder team were discussed and used to create a pre-final version of the translated PROM-HISS, FT3, to be used in the subsequent steps of the cross-cultural validation.

Cross-cultural validation

The acceptability of the translated version for the target population was tested to ensure that the intended meaning of the PROM-HISS was not compromised by the translation. Interviews with patients were performed according to the 'cognitive interview principle', in which the participant's comprehension of the questions and their response options is evaluated[12,13]. This formal research method makes thought processes more explicit as participants are prompted to think aloud as they complete the PROM-HISS. Patients were recruited from one hospital in the UK by their treating physician at the outpatient clinic. Patients were invited if they were older than 18 years old, diagnosed with HD grade I-IV and if they were equipped with sufficient understanding of the English language, both in writing and speaking. Eligible patients were only included if written informed consent was obtained. Participants were interviewed face-to-face by a native English-speaking specialty research doctor (RC).

Interviews were scheduled at the outpatient clinic and recorded with an audio recorder. Participants were asked to complete the questionnaire, after which they were interviewed about the comprehensiveness of the instructions, questions, and response options (face validity). Furthermore, patients were asked about item relevance and missing domains or items (content validity). Also, the time needed to fill out the questionnaire was recorded. Results of the cognitive interviews were summarized in a report and served as groundwork for the establishment of the final translated PROM-HISS (English).

Results

Translation

The two forward translations were discussed in the stakeholder group and minor adjustments were made in the final translation of the PROM-HISS, which was named FT3.

Identical to the Dutch version of the PROM-HISS, the English version consists of three domains: (1) HD symptoms, (2) impact of HD on daily activities, and (3) satisfaction with treatment. The first domain comprises of five symptom-items, the second and the third domain contain one item.

One of the topics discussed concerned the difference between 'affected' and 'experienced' to indicate the burden of the five symptoms asked in the first domain. Despite the fact that 'to affect' can be used to probe 'a reaction to a thought or an experience', the literal translation is 'to influence' which does not match the Dutch source word. Furthermore, the stakeholder team agreed that the term 'affected' could have negative implications and an emotional charge, which could steer the patient in its choices. Hence, the term 'experienced' was selected.

Next, the five items in the first domain were evaluated. Blood loss and pain were translated identically by the two forward translators and therefore did not require attention by the stakeholder team. The third item, prolapse, was translated once into swelling/protrusion and once into lumps/swelling from the anus. Bearing in mind that 'lumps' are usually associated with breast pathologies[14], the stakeholder team agreed on the alternative wording, 'swelling/protrusion from the anus'. For the fourth item, 'itching anus' was preferred over 'irritable anus', seeing that the latter can also be interpreted as pruritis ani[15]. The fifth item was translated as 'soiling' by the translator with a medical background, reflecting the medical term, while the native forward translator defined it as 'fluid loss from the anus'. In view of the fact that the PROM-HISS is for patients without a medical background or functional illiteracy, the lay man's wording was elected[16].

The response options for the first domain are scored using a 5-point Likert scale and were defined as (1) 'not at all', (2) 'very little', (3) 'somewhat, (4) 'quite a bit', and (5) 'a lot'. The wording 'somewhat' was preferred over 'reasonable' due to the greater comprehensibility in the English language.

Regarding the second domain, consensus was reached on the phrase 'hindered by daily activities' instead of 'influenced by daily activities'. The PROM-HISS aims to assess the burden of the symptoms of HD and 'to hinder' relates more to limitations experienced by the patient but caused by the disease. This domain is scored on a numeric rating scale from 0 to 10, where 0 was indicated as 'not hindered at all' and 10 as 'very hindered'.

The third domain, satisfaction with HD treatment, was identically translated by the two forward translators. This domain is scored on a numeric rating scale from 0 to 10, where 0 was indicated as 'not satisfied at all' and 10 as 'very satisfied'. The term 'very' was selected instead of 'extremely' in the last response option, considering that the latter could be interpreted as an exaggeration.

Cross-cultural validation

Individual interviews were conducted with ten native English-speaking HD patients (30% female), with a mean age of 44 (24-83) and primarily diagnosed with grade II HD (80%). The mean time to complete the PROM-HISS was 1min 43 seconds and instructions, items and response options were

generally well understood. Some patients had difficulty understanding the item 'fluid loss', because they had not experienced this complaint. Patient E described it as: "[Fluid loss is] not so much that it is not relevant to haemorrhoids, probably something that was not relevant to my personal experience (…)" (Patient E, male, 30 years old, grade II HD). As fluid loss is one of the five most prevalent HD symptoms, this item was not amended in the PROM-HISS[3].

Furthermore, one patient indicated that he had been trying to self-medicate for quite a long time before presenting at the hospital and was wondering if over-the-counter remedies should be part of the questionnaire (patient I, female, 54 years old, grade II HD). As the main interest of the PROM-HISS is satisfaction of in-hospital HD treatment, questions about previous HD medications were not included.

Lastly, sometimes it was not clear for patients which timeframe was used in the PROM-HISS to recall their complaints of HD. Patient F states the following about this: "(…) there's probably science or who knows the reasons for asking for a specific week, but if you had a lot of bleeding a few weeks ago (…) and then you haven't seen any for a few weeks, you might find the answer for that question, like am I supposed to answer the week in which I had a lot of bleeding or this week when I had very little." (Patient F, male, 27 years old, grade II HD)

The PROM-HISS uses a recall period of one week (i.e. the week preceding the completion of the PROM-HISS), which is in line with the COS for HD[5]. As perhaps the instructions could be misinterpreted, we choose to indicate the timeframe of one week in capital letters in the translated version of the PROM-HISS.

Overall, patients indicated all items to be relevant and no missing items. Demographic characteristics of the cohort are summarized in Table 1.

The interview guide used during the cognitive interviews can be found as Appendix A.

The final version of the English language PROM-HISS can be found as Appendix B.

Table 1 *Demographic characteristics (n = number, y = years)*

Characteristics	N = 10
Sex, n (%)	
Women	3 (30%)
Men	7 (70%)
Age, mean, [range], y	44 [24-83]
Native English	10 (100%)
Educational (highest degree completed) (%)	
12th Grade or less	1 (10%)
Graduated high school or equivalent	-
Some college, no degree	5 (50%)
Associate degree	-
Bachelor's degree	-
Post-graduate degree	1 (10%)
Unknown	3 (30%)
Goligher's classification, n (%)	
Grade I	0 (0%)
Grade II	8 (80%)
Grade III	2 (20%)
Grade IV	0 (0%)
Received treatment, n (%)	5 (50%)

Discussion

In the process of both the translation as the cross-cultural adaptation, the ISPOR guidelines for the cross-cultural validation of PROMs were followed.

While translating the Dutch PROM-HISS to English, we saw that some words can be interpreted differently, like 'to experience' or 'to be affected'. We discussed these wordings in the stakeholder group, in order for the PROM-HISS to be as similar as possible in both languages and to be easily comprehensible by patients.

Patient participation in the development and translation of PROMs is crucial and recommended as best practice[17,18]. Patient participation was integral to the development of concepts and items in the original and translated PROM-HISS[7]. In the process of the cross-cultural validation, patients were actively involved by means of cognitive interviews. The cognitive interviews did not lead to changes in the translated version of the PROM-HISS as instructions, questions, and response options were well understood and no missing or abundant items were identified.

The PROM-HISS is the first HD specific PROM designed by and for HD patients, which has followed established guidance. In the literature, only 50% of translated PROMs have followed recommended guidelines[19]. A recently published systematic review, aimed at determining the most appropriate instruments that classify the severity of HD disease according to symptoms, identified five studies describing the development and validity of PROMs and scoring systems based on core symptoms reported by patients[20]. Nevertheless, these measures have several drawbacks that limit their use in the HD population, related to psychometric assessments and lack of patient involvement in the development[21-25].

The Dutch PROM-HISS has already been tested on its psychometric properties (i.e. structural properties, reliability and construct validity) in a larger sample. Cross-cultural validation tries to ensure a consistency in the content and face validity between source and target versions of a questionnaire. As a result, it is expected that the translated version of the PROM-HISS would perform in a similar way[11]. Nevertheless, this is not necessarily the case as some wordings in the target language may have a different content to and/or conceptual basis from the source language[10,11]. It is therefore highly recommended to continuously assess for the retention of the psychometric properties of a PROM.

With the publication of our study results, the PROM-HISS is now available in English. This is a positive contribution to the research field of HD, considering that the uptake of both the COS and the PROM-HISS will be utilised by the international scientific community. Despite all efforts, the use of a COS is low in clinical trials that have been published in major medical journals[26]. The COS for HD was designed to minimize heterogeneity in study reporting and to maximize comparison of different HD study results[5]. As a result, evidence synthesis will be boosted and (inter)national HD treatment guidelines will reap the benefits of this development.

There are limitations to this work. Firstly, the cognitive interviews were solely performed in one hospital in the UK. Hence, possible geographical preferences or traits cannot be ruled out. Secondly, patients with HD grade II were overrepresented in our study sample. The latter is a logical consequence of the place of patient inclusion. Only patients who seek help for their HD symptoms

will present to primary care providers and seek onward referral to the out-patient clinic. The majority of these have a higher incidence of grade II haemorrhoids [1,27].

Thirdly, language is personal, and translation is a subjective process. It is possible that with a different stakeholder team or patient population, a different PROM-HISS would result[28]. We aimed to maximize the diversity within the study participants, based on age, gender, HD grading, and educational level. These criteria have been selected to ensure a wide variety of contrasting views and experiences within the study sample. Despite the fact that PROMs should be accessible and comprehensible for all s of society, patients with low literacy skills and learning disabilities are often excluded from the development process[16]. In the validation process of the English language PROM-HISS, we included all degrees of educational level.

Lastly, as with all disease-specific PROMs, the PROM-HISS is restricted to its domains of relevance, i.e. HD symptoms. Other important health-related quality of life domains are not measured. Thus, we strongly recommend health care providers use the PROM-HISS as a starting point to commence an open conversation with their patients.

With the translation of the PROM-HISS to English, we crossed a language border to implement the use of the PROM-HISS in international clinical settings and therefore help foster the communication between physician and patient. Future work will focus on multiple language iterations of the PROM-HISS to facilitate wide-spread utilization of this tool and to further test on the psychometric properties of the translated and validated questionnaires.

Conclusion

The translated PROM-HISS is a valid tool to assess symptoms of HD, impact on daily activities and satisfaction with treatment in English-speaking clinical HD practice and research settings.

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Appendix A

Interview guide Cross-cultural adaptation PROM-HISS 26th of July 2022

Participants

Participants will be identified in the outpatient clinic at Raigmore Hospital, Inverness. Eligible participants are adult patients (m/f) diagnosed with Haemorrhoidal Disease (HD) grade I-IV. A purposive approach to sampling is selected with the aim of maximizing diversity within the study participants. The selected criteria aim to ensure that subsets within the study population that may express contrasting views and experiences are represented. Key criteria are:

- Age
- Gender/sex
- Grading HD
- First language
- Level of education

Interview guide

A cognitive interview approach will be used to explore a patient's experience with the PROM-HISS. Interviews will be recorded and transcribed verbatim.

Introduction:

Thank you for participating in the study.

The aim of today's interview with you is to ensure that the questionnaire that I will ask you to fill out in a moment is clear to you. This questionnaire, we call it the PROM-HISS, is a questionnaire about the experienced burden of symptoms of HD. At the moment, this questionnaire is only available in Dutch. In order to make this questionnaire also available to English speaking patients, we have translated the PROM-HISS from Dutch to English. Now, it is important to make sure that English and Dutch speaking patients have the same understanding of the questions and the response options, so that we can compare or combine the outcomes of their questionnaires. Furthermore, we are interested to see if you may miss a particular issue related to HD complaints in the questionnaire.

We ask you to complete the PROM-HISS and to think out loud, so to express what you are feeling when you are answering the questions. If you encounter any difficulties during completion of this questionnaire, you can indicate this. After completion, you can make further comments about the questionnaire and we will also ask you a few things.

We would like to audio-record this interview, is that ok with you?

Completion of the PROM-HISS:

Audio-recording is started.

Patient completes the PROM-HISS in presence of Rowena Cooper at the outpatient clinic of Raigmore Hospital, Inverness.

The patient is asked to 'think aloud' as much as possible (i.e. express thoughts and feelings when

reading the questions and selecting the response option)
Patients may raise any questions or difficulties about completing the questionnaire.

After completing the PROM-HISS:
Were you able to complete the PROM-HISS? (Y/N)
Did you find it easy or difficult, or something in-between?
Did you read and understand the instructions in the questionnaire? (Y/N)
If no, which part or text component did you not understand and can you explain why? Do you have a suggestion what could be changed?
Did you read and understand the questions in the questionnaire? (Y/N)
If no, which question(s) or text component did you not understand and can you explain why? Do you have a suggestion what could be changed?
Did you understand the response options? (Y/N)
If no, which one(s) did you not understand and can you explain why? Do you have a suggestion what could be changed?
Did you miss any items or questions regarding your complaints of HD that are relevant for you?
If yes, which ones and could you try to explain why?
Where there any items or questions that you found irrelevant?
If yes, which ones and could you try to explain why?
These were our questions about the questionnaire. Is there anything else that you would like say about the questionnaire?
Thank you very much for your participation and time.

Appendix B

Patient-Reported Outcome Measure-Haemorrhoidal Disease and Satisfaction Score (PROM-HISS)

The questions below are about the symptoms you experience from haemorrhoids. There are no right or wrong answers. To what extent have you experienced the symptoms listed below in the PAST week? (Select the answer that applies)

	Not at all	Very little	Somewhat	Quite a bit	A lot
Blood loss from the anus	o	o	o	o	o
Pain around the anus	o	o	o	o	o
Swelling/ protrusion out of the anus	o	o	o	o	o
Itching anus	o	o	o	o	o
Fluid loss from the anus	o	o	o	o	o

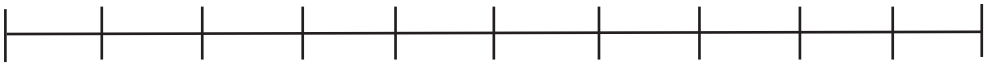
Have the above symptoms hindered your daily activities in the past week? (e.g. taking care of yourself and others, household activities, work or exercise) (place an X on the line below)

0 1 2 3 4 5 6 7 8 9 10

Not hindered at all Very hindered

If you have recently undergone treatment for haemorrhoids in a hospital (e.g. elastic banding or an operation), how satisfied are you with the results regarding symptom reduction? (Place an X on the line below)

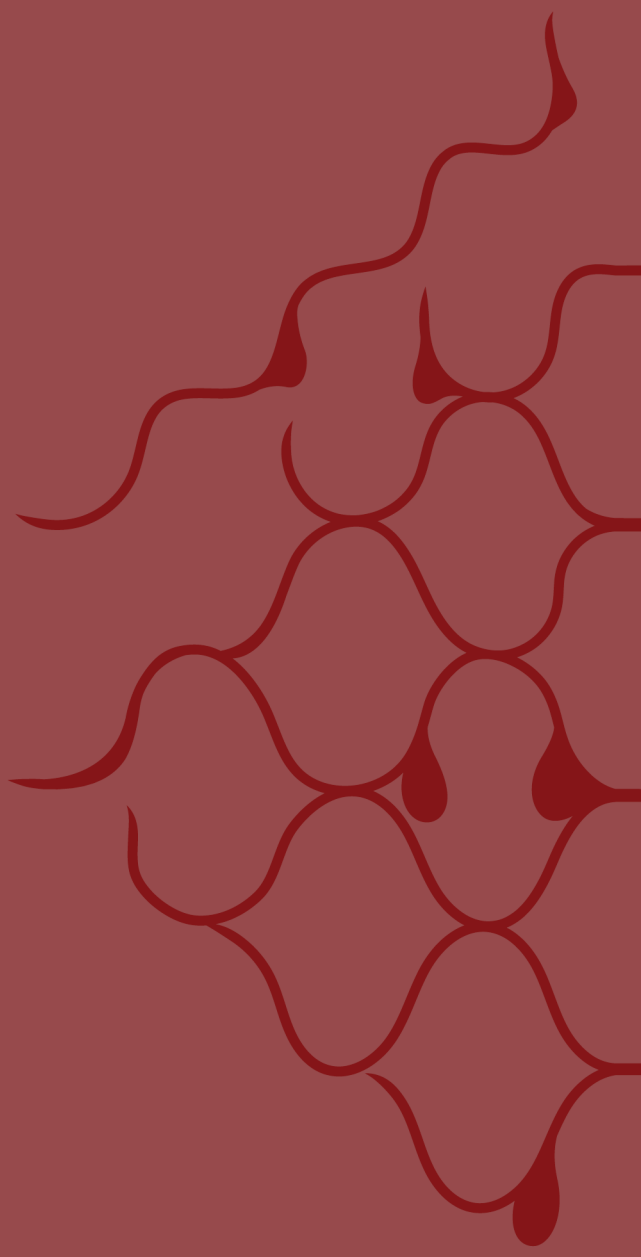
o Not applicable. I have not (yet) received hospital treatment.

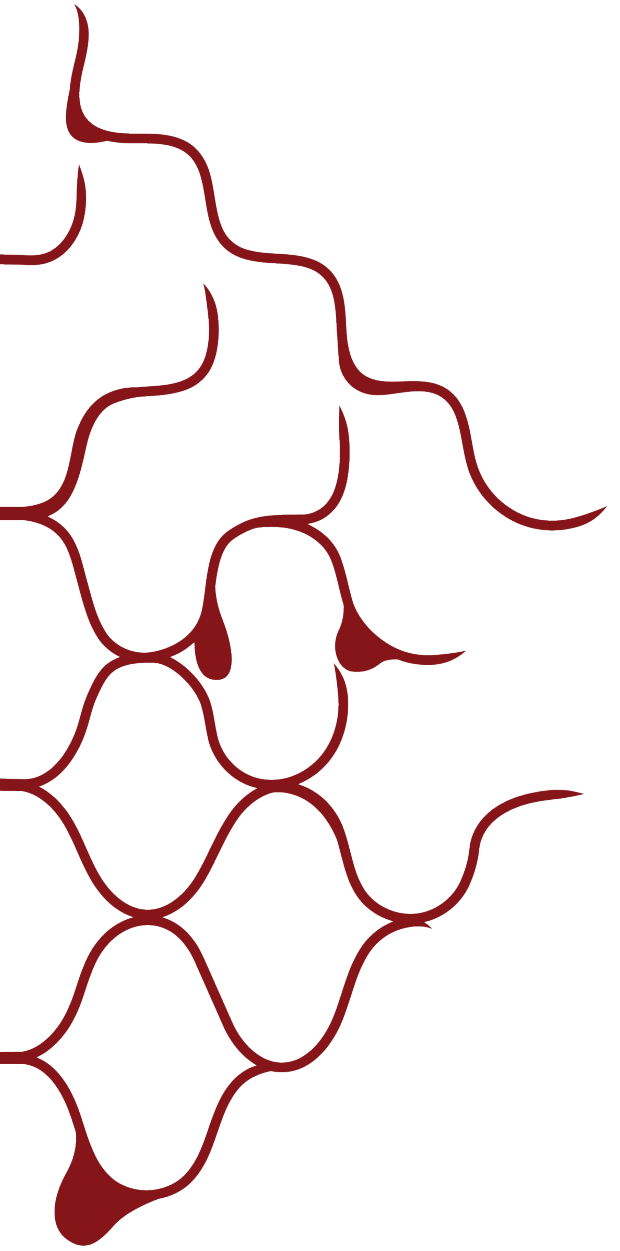


0 1 2 3 4 5 6 7 8 9 10

Not satisfied at all Very satisfied

Thank you for completing the questionnaire!





Appendices

General Discussion

Some parts of this chapter are published in Medisch Contact.

"All healthy bodies look like each other, but every unhealthy body is in its own way unhealthy" – Tolstoj in D. Liebermann

Haemorrhoidal disease (HD) is a prevalent disease with high yearly incidence rates. Various treatment modalities are available, but their place in the treatment algorithm of HD remains debatable, due to the lack of high-quality scientific evidence on (cost-)effective treatment, hampering optimal HD management. The studies described in this thesis evaluate the various (surgical) techniques available for (recurrent) HD. Furthermore, the use of patient-reported outcome measures (PROMs) in HD was studied and a HD specific PROM was developed.

In this chapter, the main findings of the studies are discussed, as well as methodological designs and implications for clinical practice and future research.

Main findings and comparison with literature

Introduction to the field of proctology and haemorrhoidal disease

Proctology, and in particular HD, is a generally overlooked area of scientific research, despite the fact that the prevalence of anal symptoms ranges up to 15% in general practice and HD related healthcare costs are rising[1,2]. Optimal therapeutic management of HD remains debatable as high level of evidence is still lacking[3]. Prioritizing HD research on scientific agendas and performing high-quality studies will allow proper evidence synthesis and improve evidence-based guidelines and clinical practice. In order to correctly combine and compare study results with one another, it is advised to adhere to the European Society of Coloproctology (ESCP) Core Outcome Set (COS) for HD (**Chapter 2** and **Chapter 3**)[4]. A COS is a consensus-based agreed minimum set of outcomes that should be measured and reported in all clinical trials of a specific disease[7]. Using a COS will improve the patient relevance of outcomes measured in clinical trials and enhance homogeneity in outcome reporting on HD[4]. The studies reported in **Chapter 5** and **Chapter 6** adhered to the COS in determining their study outcomes.

Haemorrhoids are present in every person to ensure faecal continence and only become a disease when the normal function of these vascular cushions can no longer be preserved[5,6]. Due to increased abdominal pressure, in case of prolonged straining or constipation, the anal cushions can become dilated and weakened[7]. Furthermore, degenerative alterations in the connective fibres may lead to destruction and loss of the supporting tissue[8]. Despite the numerous reported theories, the exact pathophysiology of HD remains unknown. In Chapter 4 we described a case control study assessing the pathological alterations of HD patients compared to healthy controls. Primarily, we looked at the quantity and the quality of anal collagen, in which quality of collagen was subdivided in young (immature) and old (mature) collagen. As a secondary outcome, we objectified the anal vessel morphometrics of these two groups. Patients with HD had an increased percentage of total anal collagen, a decreased percentage of young collagen, and a smaller surface area of the anal vessels compared with healthy controls. No difference was seen in the percentage old collagen between the

control group and the patient group. Conversely, two previous studies on HD pathology showed an association between reduced connective tissue stability and an increase in the incidence of HD[8,9].

However, these studies did not distinguish between young and old collagen, which hampered the ability of comparing the outcomes of these studies with our data.

One potential limitation of our study was the significantly higher mean age of the control group in comparison with the HD patients. The higher mean age in the control group was inevitable, considering that we made use of tissue of persons who were deceased

due to a natural cause. Yet, the difference in collagen cannot be explained by the higher mean age in the control group, as the regression analysis showed that age did not influence the percentage of collagen.

Next to collagen alterations, literature reported that HD was associated with a distention of haemorrhoidal arteries, which reflected a malfunctioning haemorrhoidal complex[10-12]. Nevertheless, in our study, we found a greater distention of vessels in healthy controls compared to HD patients. This could be attributed to the higher mean age and lifelong upright position of the healthy controls.

Overall, the outcomes of our study 'A morphometric analysis of pathological alterations in haemorrhoidal disease versus normal controls: a controlled trial' (Chapter 4) suggest that alterations in anal collagen composition may play a role in the formation of haemorrhoids. Further research on anal collagen metabolism needs to be performed to provide further insight on the aetiology of HD.

Effective treatment for haemorrhoidal disease

Annually, 50,000 patients in the Netherlands are referred to the hospital because of persistent symptoms of HD[13]. Thirty percent of these patients, proximally 15,000 patients a year, develop recurrent symptoms after the first two treatment steps; basic treatment and repeat rubber band ligation (RBL)[14,15]. There is high level of evidence justifying these first two treatment steps[3,16]. In case of recurrent HD, patients are offered different treatment modalities: continuing RBL or a surgical intervention. A Dutch national survey conducted by our research group evaluating the management practices of HD demonstrated considerable variation in the best (surgical) treatment option regarding recurrent HD, resulting in potentially undesirable practice variation[17]. Currently, the treatment of recurrent grade II and III HD depends on the preference and the experience of the surgeon and of the patient, without high level evidence substantiating this practice variation. This implies a need for a high quality study regarding the (cost-)effectiveness of treatments for recurrent grade II and III HD.

The *Napoleon Trial*, of which the protocol is presented in this thesis (**Chapter 5**), aimed to compare three interventions for recurrent HD: rubber band ligation versus sutured haemorrhoidopexy versus haemorrhoidectomy in patients with recurrent HD. This randomized controlled trial (RCT) was initiated to inform healthcare providers on the most effective and cost-effective option of recurrent HD, based on recurrence of HD and several patient-reported outcomes. Study interventions were selected based on the ESCP guidelines for the treatment of HD[3]. The haemorrhoidectomy was chosen as study intervention as this operation is the first choice of treatment in grade III HD according to the ESCP guidelines. Recent studies like the *eTHoS Trial* confirm the efficacy of this technique[15,18]. The second study intervention, repeat banding (RBL), was selected based on the results of the *Hubble Trial*. The *Hubble Trial* compared the RBL with the haemorrhoidal artery ligation (HAL) procedure in

patients with grade II and III HD and found repeat banding to be a more palatable option than having an operation, based on post-operative pain and complications. Furthermore, the *Hubble Trial* showed a recurrence rate of 49% after RBL and a second session of RBL was needed in 31% of the patients[19].

Napoleon's third study intervention was the sutured haemorrhoidopexy, which is a minimally invasive operative technique. The recurrence rate after the sutured haemorrhoidopexy is around 30% and is ranked between that of RBL and haemorrhoidectomy, with the lowest recurrence rate of 14% after the haemorrhoidectomy[12,15,20]. Doppler-guidance was not included in the sutured haemorrhoidopexy, as it is does not add significantly to the results achieved by the sutured haemorrhoidopexy alone[21,22].

The haemorrhoidectomy and the sutured haemorrhoidopexy are both more expensive procedures that RBL, resulting in initially higher hospital costs. However, as the recurrence rate after RBL is higher compared to both surgical options, repeat procedures following RBL will remain necessary in a subgroup of patients, resulting in possibly higher cumulative hospital and societal costs over a longer period of time. Repeat recurrence also means that patients continue to suffer from the symptoms (blood loss, prolapse, pain, itching, and soiling) associated with HD, which will have an impact on health-related quality of life and quality adjusted life years (QALYs). The aim of the *Napoleon Trial* was to assess how effects and costs compare between the three interventions.

One of the study interventions of the *Napoleon Trial* was the sutured haemorrhoidopexy. Long-term outcomes and large studies on this technique are lacking. In **Chapter 6** we described a single centre cohort study assessing the long-term efficacy and safety of this technique. The cumulative efficacy in terms of freedom of recurrence was almost 90% at six months, 80% at one year and almost 70% at five years. In comparison with previous studies, our recurrence rates are slightly lower[23,24]. However, our follow-up period was significantly longer (5-11 years), reporting on the cumulative recurrences over time, and we were equipped with a larger sample (n = 145). In our study, we reported two (1.4%) short- and seven (6.2%) long-term complications of the sutured haemorrhoidopexy. These complication rates are comparable with other studies reporting on the sutured haemorrhoidopexy[24,25].

As stated in the ESCP guidelines for HD, both the sutured haemorrhoidopexy and the haemorrhoidectomy can be offered to patients with grade III-IV HD and/or in patients who are refractory to outpatient procedures[3]. The probability of recurrent HD symptoms is higher after a sutured haemorrhoidopexy compared to a haemorrhoidectomy, with recurrence rates between 14 to 16% at one-year post-haemorrhoidectomy[15,26]. The lower recurrence rate could be attributed to the greater amount of tissue that is excised during a haemorrhoidectomy. As a result, it is known that haemorrhoidectomy is associated with more postoperative pain and a higher complication rate of approximately 10%, ranging from urinary retention and abscesses on the short term, to anal incontinence, stenosis, fistula, and anorectal loss of function on the long-term[10,27-31]. Hence, in terms of postoperative pain and long-term complications, the sutured haemorrhoidopexy could serve as a minimally invasive alternative to the haemorrhoidectomy.

Patient-reported outcomes in haemorrhoidal disease

According to the ESCP COS for HD, the primary outcome of clinical studies should be patient-reported symptoms of HD, measured by a Patient-Reported Outcome Measure (PROM)[4]. Patient-Reported Outcome Measures, or PROMs, capture a deeper understanding of the disease-burden by obtaining

information directly from the patient about their experiences with the illness, without interpretation by the healthcare professional or others[32]. The additional value of using PROMs in clinical practice has been demonstrated and their popularity in various healthcare settings, including HD, is rising[33].

Over the years, several PROMs for HD have been developed[34]. However, these were not suitable to assess HD complaints because of various reasons; some PROMs for HD were not specifically designed to assess solely complaints of HD. For example, the Haemorrhoid and Fissure Quality of Life Questionnaire (HEMO-FISS-QoL)[35] extents its population to patients with fissures, and both the Proctological Symptom Scale (PSS) and the Proctoprom take the full range of proctology patients into account instead of focussing on HD[36,37]. In other PROMs, no patients were involved in the development process, such as the Haemorrhoidal Disease Symptom Score and Short Health Scale for Haemorrhoidal Disease (HDSS and SHS-HD)[38]. Finally, other disease specific PROMS for HD, like the Sodergren score[39] and the Haemorrhoid Severity Score (HSS)[40], did not follow the COSMIN-guideline for designing and evaluating the measurement properties of a PROM (**Chapter 7**)[41]. The COSMIN-guideline represents the Consensus-based Standards for the selection of health Measurement INstruments and resulted as an initiative of an international multidisciplinary team of researchers with various backgrounds (medicine, epidemiology, etc.). The aim of the COSMIN is "(…) to improve the selection of outcome measurement instruments of health outcomes by developing and encouraging the use of transparent methodology and practical tools for selecting the most suitable outcome measurement instrument in research and clinical practice."[42] One of the goals of the COSMIN initiative is to call for standardization of outcomes and outcome measurement instruments by developing a COS, as our research group ensured for HD. As stated, the primary outcome of the COS for HD was patient-reported outcomes measured by a PROM.

As a disease specific PROM conducted according to the Cosmin guidelines was missing we developed, in close collaboration with patients, and validated the Patient-Reported Outcome Measure-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS) (**Chapter 8** and **Chapter 9**). The items in the PROM-HISS included the five mostly reported symptoms specified by the COS: blood loss, prolapse, pain, itching, and soiling and was conducted according to the COSMIN-guideline[43]. Furthermore, we added a question about satisfaction with treatment, considering that the COS advices 'satisfaction with treatment' as secondary outcome in HD research[4]. In developing this tool, we made use of a literature review, patient interviews and an expert panel. First, the face and content validity were evaluated by conducting individual cognitive interviews with ten patients. Second, structural properties, reliability and construct validity were measured in a cross-sectional HD population consisting of 102 patients (65% male) with a mean age of 58 years (23-81 years). The Intraclass Correlation Coefficient of the different items in the domain HD symptoms ranged between 0.56 and 0.79 and were interpreted as good. Furthermore, the PROM-HISS symptom domain was internally consistent with a Cronbach's alpha value of 0.80. The Confirmatory Factor Analysis provided further evidence for construct validity with a good model fit. A high score on the symptoms of HD correlated with a high impact of HD on daily activities (Pearson's $r = 0.632$, $p<0.01$) and a low degree of satisfaction (Pearson's $r = 0.378$, $p<0.01$). This study showed that the PROM-HISS is a reliable and valid instrument to evaluate symptoms of HD, impact on daily activities and satisfaction with treatment (**Chapter 8**).

Third, the PROM-HISS was tested on its responsiveness, which indicates whether a PROM can capture a change of symptoms over time. This requires a longitudinal study in which changes on the measure are expected to occur, for example due to the participants receiving a treatment[44]. The responsiveness study is described in **Chapter 9**. In this study, over 90 patients were asked to complete the PROM-HISS at baseline and one week after treatment (RBL or surgery). A global self-assessment of change question (SCQ) was posed to rate if improvement or deterioration had taken place, to be able to create subgroups of patients[44]. The SCQ and the PROM-HISS were both able to perceive variation in HD symptoms between baseline and one-week post-treatment (r = 0.595). Additionally, a priori formulated hypotheses can be used to assess responsiveness. As stated by De Vet et al. "(…) the hypotheses concern expected mean differences between changes in scores on the instrument in groups, or expected correlations between changes in scores on the two instruments (…)"[44]. For the PROM-HISS, most hypotheses were confirmed: the mean change scores were significantly different between the subgroups based on the SCQ, effect sizes ranged from small in the subgroup indicating 'no change' to a moderate effect size for the 'more complaints' subgroup and for the 'somewhat fewer complaints' subgroup, and a large effect size for the subgroup indicating 'much fewer complaints'. Furthermore, there were high correlations between a change in the PROM-HISS symptom score and the items 'impact on daily activities' and 'satisfaction with treatment'.

Lastly, a change of 0.3 on the symptom score of the PROM-HISS was identified to be clinically meaningful to patients, indicating the minimally relevant difference (MRD). In clinical practice, a MRD can support doctors and patients to understand the effects of a treatment[45]. Importantly, a MRD gives an indication of what is on average considered important by a group of patients. Therefore, an open discussion between the physician and the individual patient about the change in HD symptoms is essential to better understand what is perceived important by that individual patient[46].

We encountered some challenges while performing this study. First, the sample size of the subgroups indicating deterioration were relatively small, and therefore the ability of the PROM-HISS to detect deteriorations could not be assessed. Second, our study group could be perceived as somewhat homogeneous, considering the majority of patients undergoing RBL and mostly diagnosed with grade II or III HD. Yet, this is a reflection of daily practice[17].

The PROM-HISS was developed in a Dutch Caucasian population and is therefore not automatically generalizable to other languages. The study described in Chapter 10 concerns a translation and validation of the PROM-HISS in English in the United Kingdom. The translation of the PROM-HISS consisted of two forward and two backward translations. The forward translation concerned the translation from the source language (Dutch) to the target language (English), the backward translation is the translation from the target language to the source language. Ten interviews were performed to test if native English patients could understand and comprehend the instructions, questions, and response options of the translated PROM-HISS. Despite the fact that cultural groups vary in disease expression and patients from a different geological location could have denoted different items to be of importance in the PROM-HISS, English patients did not indicate to miss any item[47,48]. A few patients had difficulties with the symptom 'fluid loss', since they had not experienced this HD complaint. However, according to the COS for HD, 'fluid loss' is one of the most reported symptoms of HD and it was decided to maintain this symptom in the PROM-HISS.

Furthermore, the recall period of one week was sometimes found to be confusing as the complaints of HD can vary over time. We did not increase the time frame of the PROM-HISS, as we adhere to the time frame mentioned in the COS and as a larger recall time can lead to false responses[4,49].

Methodological design

This thesis includes studies with a diversity of designs. The original design of the *Napoleon Trial* was an RCT (**Chapter 5**). RCTs are seen as the gold standard to endorse or discard a new intervention and are alleged the cornerstone of evidence-based medicine[50]. One of the comments that nicely summarizes this, states '*observational studies propose, RCTs dispose*'[51]. However, there are drawbacks in the use of RCTs. RCTs demand several framework conditions and completion of a RCT can encounter various challenges[52]. Allocating a treatment to a patient, which happens in the process of randomization, can only work in specific circumstances. For example, when examining an experimental treatment that can only be offered in study context, or when patients do not have a treatment preference, randomization can be successful[53]. Nevertheless, it occurs quite often in (surgical) trials that the above-mentioned situations do not hold true. Research shows that not even half of the RCTs conducted in the Netherlands meet their required sample-sizes at the planned end date[54]. A recent document of The Netherlands Organisation for Health Research and Development (ZonMw) indicates that 56% of all Dutch healthcare evaluations -mostly RCTs- have a delay in their inclusion phase of over six months and 19% of even more than two years[55]. This delay can be partially explained by a comparison of interventions with (significantly) different characteristics. For example, when comparing an outpatient treatment (non-invasive) versus a surgical approach (invasive), as is the case in the *Napoleon Trial*[56]. Especially when interventions are already implemented in daily care, as is, again, the case in the *Napoleon Trial.* Furthermore, patients are more and more empowered to actively take part in the decision making regarding their treatment and express a treatment preference. Strong treatment preferences by patients hamper the recruiting process, causing an insufficient sample-size and a high drop-out rate. Hence, randomized study designs for these scenarios are difficult to conduct and therefore will not improve scientific evidence nor do they have the possibility to optimize daily clinical practice[57,58].

In the recruitment process of the Napoleon Trial, it showed that 71% of the eligible patients did not want to be included. The majority of these patients had difficulties with the randomization process or had a treatment preference (data in own management of the Napoleon Trial study group). Additionally, the COVID-19 pandemic had a significant influence on the performance of the study. At the same time as the inclusion phase of the Napoleon Trial commenced in March 2019, the world was struck by this pandemic. As a consequence, all elective surgeries were vastly diminished or cancelled, including proctologic surgical care like the sutured haemorrhoidopexy and the haemorrhoidectomy. The waiting list for a HD surgery lengthened, leading to a preference prompted by practicality for the RBL procedure, both by treating physicians as patients, as this treatment remained available for patients. For the process of the Napoleon Trial, this meant that these patients could not participate since they could not be randomized.

In order to overcome the problems with patient inclusion due to emerging patient preferences, we suggested to change the design from a RCT to a comprehensive cohort design. Such a design enables patients with a specific treatment preference to join in on scientific research, without having to be randomized to a treatment[58]. The comprehensive cohort design facilitates the willingness to participate and increases the chance to a successful study. Just as in a RCT, a comprehensive cohort design compares different interventions and is able to answer the research question. The comprehensive cohort is made up out of two cohorts: one randomization cohort, in which patients are allocated to a specific treatment by randomization, and an observational cohort, where patients can choose their preferred treatment[59]. A potential risk of a comprehensive cohort design is a misbalance between the randomization arms and the observational arms. Furthermore, statistical analyses in comparing the results between the two cohorts can be a challenge[60]. Although the subsidizing party endorsed the idea of applying an alternative design for answering the research question, the comprehensive cohort design was not approved and the RCT was prematurely stopped.

The studies reported in **Chapter 4** and **Chapter 6** involve a retrospective cohort study. Important flaws of the retrospective character are relatively high rates of missing data, and higher probability of selection- and recall bias[61]. However, retrospective studies have the ability to obtain a large quantity of data from medical databases rapidly[62]. **Chapter 6** is a retrospective study and is the first research on the sutured mucopexy with both a significant follow-up period (mean of 9 years) and a large sample-size (***n*** = 145). We encountered missing data due to medical record information being incomplete for some patients. For example, data on analgesics was particularly difficult to record as this aspect is poorly registered in the electronic patient file. Hence, under-reporting could have taken place which should be taken into account when interpreting the results of this study. **Chapter 4** is also a retrospective study, and the selection of the control group is a possible flaw. Since all patients in the control group died of a natural cause, consequently, the mean age of these patients was significantly higher than the age in our study group. It was not possible to avoid this aspect considering that obtaining anal tissue of living healthy controls is unethical and therefore not possible. All three final chapters (**Chapter 8-10**) encompass prospective observational cohort studies to assess psychometric properties of a newly developed PROM. In these three studies we adhered to the COSMIN-methodology[41], which is a state-of-the-art methodology to develop and validate PROMs[63]. Advantages of a prospective study are that it can be tailored to collect specific data. On the other hand, a disadvantage may be the long follow-up period and high costs[64]. **Chapter 8** and **9** were time-consuming as measurements were collected on different time points, which meant that the follow-up period lengthened. Furthermore, inclusion of sufficient patients was challenging due to a response rate of 43%. Low response rates are common, with e-mail response rates reported in the literature ranging between 25 and 30%[65]. Yet, the participating patients in both studies reflect the population seen in clinical practice as most HD patients are diagnosed with grade II and III HD. This reflection of daily practice can also be seen in the demographics of the included patients for **Chapter 10**.

Clinical implications and future perspectives

The findings of the studies described in this thesis have implications for both clinical practice and future research.

Currently, there is still no consensus on the most optimal management of recurrent HD. Pieces of the puzzle are being identified, but the effectiveness and cost-effectiveness of various treatment options need further study. A prospective comparative cohort study could be an option, overcoming some of the practical drawbacks of an RCT, and methodological drawbacks of a comprehensive cohort design. Future studies should adhere to the COS for HD in order to optimize comparison between study results and inform (inter)national guidelines as well as daily practice[4].

Furthermore, we advise to utilize the input of a patient advisory board (PAB) when performing studies. A PAB is a group of patients who have been diagnosed with the condition of interest and are able, in their role as hands-on experts, to translate the patients' voice when making study-related decisions. All members of the PAB fulfil the role of being a partner according to the participation matrix, meaning there is an equal collaboration with the researchers[66,67].

The PROM-HISS can be applied in both research settings as well as in clinical practices. The employment of the PROM-HISS in clinical practice is where the rubber meets the road. At the moment, we are implementing the PROM-HISS in the electronic patient system of our medical centre. The PROM-HISS is completed by the patient before presenting at the outpatient clinic and the treating physician can use the results of the PROM-HISS to identify important patient-specific subjects. Once implemented in clinical practice, a PROM can contribute to shared decision making (SDM) in the medical consultation room. This way of approaching patients enables an open conversation between patient and doctor discussing the possible benefits and harms of a treatment[68]. SDM has been defined as: "an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences"[69,70].

Every patient is unique and makes choices based on individual values, beliefs and preferences. In healthcare, this means that providing optimal care can mean something different for every patient. This translates to the concept of Value Based Healthcare (VBHC), which is defined as 'the creation and operation of a health system that explicitly prioritizes health outcomes which matter to patients relative to the costs of achieving this outcome'[71]. Several organisations in the Netherlands prioritize and stimulate VBHC[72-74]. VBHC is promoted by the use of PROMs[75]. Next to its use in daily practice, we stimulate the use of the PROM-HISS in research settings, according to the COS for HD[4].

Besides the translation of the PROM-HISS to English, our research team is in the process of translating this questionnaire to French. This project is a collaboration with the university hospital of Brussels, Belgium, and a proctology clinic in Beausoleil, France.

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Impact

To create value from knowledge, the data extracted from this thesis should be made suitable and/or available for social and economic use. This process is referred to as impact and should elaborate on the socio-economic relevance of the research. The findings of the studies described in this thesis aim to impact patients, health care professionals, the scientific community, and health insurance companies.

Patients

As patients become increasingly empowered and eager to take on an active role in the medical decision-treatment process, tools are needed to facilitate the conversation between doctor and patient[1]. One of these tools is a patient-reported outcome measure, or PROM in short. PROMs are questionnaires that measure the patient's experiences regarding health and well-being[2]. Several PROMs for haemorrhoidal disease (HD) exist, but generally lack a robust development and validation process. One of the deliverables of this thesis, is a PROM for HD, developed by and for patients with HD, following established guidelines: The PROM-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS). The PROM-HISS was found to be a valid, reliable and responsive measure and thus suitable for research. At the moment, we are employing the PROM-HISS in the electronic patient system of our medical centre to start using this tool in clinical practice. The PROM-HISS is completed by the patient before presenting at the outpatient clinic and the treating physician can discuss the results of the PROM-HISS with the patient to identify subjects that are important to that specific patient. This way, the patient's expectations and experiences function as the cornerstone of the treatment-decision and follow-up, resulting in a more patient-centred approach. Furthermore, for many patients haemorrhoidal symptoms still remain an embarrassing subject in the consultation room[3]. With the PROM-HISS, we aim to open the conversation about symptoms of HD and dwindle the taboo-image of this disease.

In research settings, the PROM-HISS can ensure that patient-relevant outcomes are included as evidence for the most (cost-)effective treatment for HD. By doing so, the patient himself or herself is at the helm of optimizing healthcare, both for him-, herself as for future HD patients.

All these PROM-related initiatives contribute to a more patient-centred approach in future healthcare. Informing patients and healthcare providers about PROMs and implementing them in daily practice contributes to a change in tomorrow's climate in healthcare, whilst simultaneously exerting a direct impact on the individual patient of today.

Health care professionals

Most studies described in this thesis were conducted in collaboration with various hospitals across the Netherlands. The most significant example of this is the *Napoleon Trial*, where over 20 medical centres were involved. The *Napoleon Trial* is a randomized controlled trial comparing the (cost)effectiveness of rubber band ligation, sutured haemorrhoidopexy and haemorrhoidectomy in

patients with recurrent HD. All three of the treatments are currently standard care and the protocol of the *Napoleon Trial* is presented in this thesis. Nevertheless, this study was prematurely ceased and high-quality evidence could not be distilled from the data. Various other study designs were explored, but were not deemed adequate or feasible at this stage. As a result, there is still no consensus on the most optimal management of HD. The Dutch Surgical Association (NVvH) still acquiesces the current knowledge gap regarding the most effective and cost-effective treatment for (recurrent) HD.

The nation-wide teamwork established for the *Napoleon Trial* has shown the ambition to resolve a research question and laid the base for future collaborations between colorectal surgeons in the Netherlands. Establishing partnerships all around the country facilitates conducting scientific research and contributes to evidence-based guidelines on the most (cost-)effective treatment in HD.

Results of this thesis regarding the sutured haemorrhoidopexy indicate that this procedure is safe and feasible to be used for patients suffering from mainly the prolapsing component of HD, as a worthy alternative to the traditional excisional surgery (haemorrhoidectomy). Furthermore, using the PROM-HISS in clinical practice facilitates the health care professional to discuss themes relevant for the patient. The involvement of numerous (colorectal) surgeons in the studies described in this thesis, enables the uptake and the implementation of the results.

Scientific community

The PROM-HISS which is presented in this thesis resulted from the primary outcome as stated by the Core Outcome Set (COS) for HD[4]. The COS has been developed to inform researchers as to which minimum set of outcomes should be included in future HD studies.

Broad use of the COS and PROM-HISS will decrease heterogeneity in study outcomes and enhance optimal evidence synthesis in the field of HD. We closely followed the statement of the COS in choosing the primary and secondary outcomes of the *Napoleon Trial*. One of the primary outcomes is symptoms as reported by the patient, making use of the PROM-HISS. We strongly recommend using the COS for HD in future studies to inform guidelines for the treatment of HD. Furthermore, the complete process of the development, validation and of a PROM is described in this thesis. These chapters can give guidance to scientific audience interested in performing such a process.

Lastly, the articles presented in this thesis were all published in peer reviewed international journals. Consequently, more attention from the scientific community is drawn to this prevalent and burdensome disease. With more attention comes more awareness to file for scientific grants regarding the treatment of HD. This will result in more high-quality research and an optimized management for patients with HD.

Health care organisations

Both the disease burden and the economic burden of HD are huge. In the United States of America, around 1.4 million individuals sought care for HD in 2014, with an estimated economic burden of about $800 million annually[5]. In the Netherlands, some 4,500 operations for HD are performed

annually and an unknown equivalent of RBL procedures[6]. With the increasing healthcare costs, health care systems (and organisations) need to fundamentally change and focus on true patient value for money. One of the solutions is to create 'a health system that explicitly prioritizes health outcomes which matter to patients, relative to the costs of achieving the outcome'[7]. This approach is called value-based healthcare (VBHC) and takes patient expectations and experiences as key concepts of care delivery[8]. Using a PROM, such as the PROM-HISS presented in this thesis, can determine the needs of patients, and can consequently attribute to VBHC.

Next to a function in patient-centred healthcare, PROMs such as the PROM-HISS can be used to measure and benchmark internal and external quality of care. Recently, the Zuyderland Medical Centre in collaboration with a health insurance company used aggregated data from a PROM to evaluate the internal quality of several departments within their hospital[9]. PROMs were integrated in the Quest Manager system (Philips VitalHealth) of the electronic patient system of the Zuyderland and digitally communicated with the patient[10,11].

In addition, also the use of PROMs in quality monitoring (e.g. benchmarking individual providers, teams, organisations), performance measurement (e.g. comparing healthcare systems) and policy (e.g. pay-for-performance, reimbursement decisions) is increasingly applied and advocated to capture what really matters to patients[12,13].

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Summary

Background

The main research question of this thesis was *'How can we optimize the management of haemorrhoidal disease (HD)?'*.

The first part – *Introduction to the field of proctology and haemorrhoidal disease* – gives an introduction into the field of proctology, with a focus on HD. Furthermore, this part elaborates on the pathophysiology of HD.

The second part – *Effective treatment for haemorrhoidal disease* – elaborates on successful interventions for the treatment of HD.

The third part – *Patient-reported outcomes in haemorrhoidal disease* – explores the role of PROMs in the management of HD and, consequently, the development and validation of an (inter) national PROM for HD (PROM-HISS).

Introduction to the field of proctology and haemorrhoidal disease

The prevalence of anal symptoms ranges from 11 to 15% in the adult population[1,2]. Despite the high prevalence and noteworthy negative impact of proctologic illnesses on quality of life, the level of evidence on effective and cost-effective treatments in this field remains very low. In **chapter 2** we emphasized the need to prioritize proctology on research agendas of different (inter)national forums to conduct more qualitative studies on proctologic ailments and to raise the level of robust evidence in this field. Haemorrhoids are one of the most common proctologic illnesses with an incidence of 8.3/1000 patients per year in the Netherlands and a prevalence of up to 39% in the general population[3,4]. **Chapter 3** aimed to highlight several dynamically evolving domains in current HD research, ranging from historical viewpoints to technical solutions and patient involvement.

The full picture of the aetiology of HD has not yet been grasped. Over the years, more and more studies investigating the correlation between connective tissue stability and the development of haemorrhoids have been published, but evidence is inconclusive. To contribute to this discussion, we compared the quantity and quality of anal collagen and vessel morphometrics in patients with symptomatic HD compared to normal controls. Quality of collagen was divided in young (immature) and old (mature) collagen, with old collagen being more cross-linked.

The study group consisted of twenty-two samples of grade III and grade IV HD tissue from patients who underwent a haemorrhoidectomy. The control group comprised of fifteen persons without symptomatic HD who donated their body to science and died a natural death. In **chapter 4** we described the results of this study, showing that patients with HD had an increased percentage of total collagen (62.1 ± 13.8 vs. 18.7 ± 14.5%; $p = 0.0001$), a decreased percentage of young collagen (0.00009 ± 0.00008 vs. 0.0008 ± 0.0008%; $p = 0.001$), and a smaller surface area of the anal vessels (795.1 ± 1215.9 micrometre^2 vs. 1219.0 ± 1976.1; $p = 0.003$) compared with normal controls. These outcomes suggest that alterations in anal collagen composition may play a role in the formation of haemorrhoids.

Effective treatment for haemorrhoidal disease

Prolapse of haemorrhoids is usually classified according to the Goligher grading; in which grade I defines a haemorrhoid that does not prolapse; grade II prolapses but reduces spontaneously; grade III is a prolapsing haemorrhoid that needs manual reduction; and grade IV is a prolapsing haemorrhoid that cannot be manually reduced [5]. Most common symptoms of HD include 'pain', 'prolapse', 'itching', 'soiling' and 'blood loss'[6]. The various available treatments focus on diminishing these symptoms and range from conservative to surgical procedures. The first treatment step is usually offered by the general practitioner and consists of laxatives and a high fibre diet[7]. If conservative treatment is not successful, the next treatment modality is often rubber band ligation (RBL), which can be repeated multiple times. RBL is an easy, relatively cheap, and outpatient-based procedure[8]. However, 30% of the patients develop recurrent symptoms after basic treatment and repeat RBL[9]. If symptoms reoccur after multiple bandings, no consensus exists regarding the best treatment option: continuing RBL or a surgical procedure. One of the first operations for HD is the haemorrhoidectomy[10]. However, this procedure can be painful and is costly compared to RBL. A relatively novel, but regularly performed surgical alternative is the sutured haemorrhoidopexy[11]. The costs of sutured haemorrhoidopexy are similar to the haemorrhoidectomy, but the procedure is less painful. High-level evidence on the most (cost-) effective treatment is lacking and thus the treatment of recurrent grade II and III HD currently depends on the preference of the surgeon and the patient.

Therefore, **chapter 5** entails the study protocol to conduct a multicentre randomized controlled trial comparing the effectiveness and cost-effectiveness of RBL versus sutured haemorrhoidopexy versus haemorrhoidectomy (*Napoleon Trial*). Over a timespan of two years, the *Napoleon Trial* was implemented in 20 medical centres across the Netherlands. Patients with recurrent HD grade II and III, ≥18 years of age and who had at least two RBL treatments in the last three years were eligible for inclusion. Exclusion criteria included previous rectal or anal surgery, rectal radiation, pre-existing sphincter injury or otherwise active pathologies of the colon and rectum, pregnancy, presence of hypercoagulability disorders, and/or medically unfit for surgery (ASA>III). The anticipated sample-size was 558 patients with a 1:1:1 randomization to either RBL, sutured haemorrhoidopexy, or haemorrhoidectomy. The primary outcomes were recurrence after 52 weeks and patient-reported symptoms measured by the PROM-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS), which is described in the next part – *Patient-reported outcomes in haemorrhoidal disease* –. Secondary outcomes were impact on daily life, treatment satisfaction, early and late complication rates, health-related quality of life, costs and cost-effectiveness, and budget impact.

One of the interventions assessed in the *Napoleon Trial* is the sutured haemorrhoidopexy. The technique of the sutured haemorrhoidopexy comprises of the resection of a small rectal mucosa flap (mucosectomy) followed by a suture, stitching the anal mucosa to the rectal wall. This prevents the prolapsing component of the haemorrhoidal tissue protruding through the anus, while preserving as much anal mucosal tissue as possible. **Chapter 6** assessed the long-term safety and efficacy of the sutured haemorrhoidopexy in the Maastricht University Medical Centre+ (MUMC+). Between January 2009 and December 2021, 145 patients of which 70 women (48.3%), with a mean age of 61 years (±12.8) who underwent a sutured haemorrhoidopexy in the last twelve years were included.

Perioperative and postoperative data were collected via the electronic patient file and the PROM-HISS was probed via telephone calls to get an in-depth understanding of the current HD status. Perioperative complications occurred in 4 cases (2.8%). The cumulative efficacy in terms of freedom of recurrence was 88.3% (95% CI, 83.1-93.5) at six months, 80.0% (95% CI, 73.5-86.5) at one year and 67.7% (95% CI, 59.7-75.7) at five years. A subgroup of 50 patients (34.5%) was interviewed via telephone according to the PROM-HISS. More than half of the patients still experienced some feeling of a prolapse from the anus (56.0%), ranging from 'very little' to 'a lot'. Both blood loss and pain were reported in 19 cases (38.0%). About one-quarter of the patients still experienced 'itching' or 'fluid loss', with 'itching' being reported in 13 cases (26.0%) and fluid loss in 12 cases (24.0%).

Patient-reported outcomes in haemorrhoidal disease

Literature research and patient interviews indicate that the most common symptoms of HD are blood loss, prolapse, pain, itching and soiling. These symptoms can have a noteworthy negative impact on quality of life[6,12,13]. The burden of these symptoms for a patient can be captured by a Patient-Reported Outcome Measure (PROM). A PROM is a tool which grasps a deeper understanding of a disease-burden for a patient, without the interference of a caregiver. The European Society of ColoProctology (ESCP) acknowledges the importance of symptoms and their impact on daily life as crucial outcomes of effectiveness in the Core Outcome Set (COS) for HD, by identifying patient-reported symptoms as the primary outcome for clinical HD studies[14]. A COS is a consensus-based agreed minimum set of outcomes that should be measured and reported in all clinical studies of a specific disease[15]. As no established PROM for HD was available, our objective was to develop a disease-specific PROM for HD, according to standardized guidelines and with the active involvement of patients[16].

In **chapter 7** we discussed the added value of a PROM in both clinical research as clinical practice, allowing the physician to obtain information directly from the patient about their experiences with the ailment. In the field of HD, there are two validated PROMs that followed specific guidelines. One of them is the PROM-HISS, developed by our research team.

Following the COSMIN-guideline for designing and evaluating the measurement properties of a PROM, the PROM-HISS was tested on several psychometric aspects. First, the face and content validity were evaluated by conducting individual cognitive interviews with ten patients. Second, structural properties, reliability and construct validity were measured in a cross-sectional HD population consisting of 102 patients (65% male) with a mean age of 58 years (23-81 years). Results reported in **chapter 8** indicate that the PROM-HISS is a valid and reliable tool to assess symptoms of HD, impact on daily activities and satisfaction with HD treatment.

Besides the reliability and validity of the PROM-HISS, a PROM should also be tested on the aspect 'responsiveness', i.e. the ability to assess improvement or deterioration of health or symptoms. **Chapter 9** shows that the PROM-HISS is a responsive instrument that can detect change in the patient's symptom burden over time. The clinically important difference was found to be 0.3 points on the symptom score of the PROM-HISS. This cut-off point can be used to give insight in whether a meaningful change in HD symptoms has occurred as a result of HD treatment from a patient's perspective.

To promote adoption of the COS and use of the PROM-HISS internationally, the PROM-HISS was translated to English, followed by cross-cultural validation. First, a forward translation of the PROM-HISS from Dutch to English was performed, followed by a backward translation from English to Dutch. Thereafter, ten patients from the United Kingdom completed the preliminary translated PROM-HISS and were subsequently interviewed to probe the comprehensives and comprehensibility of the questionnaire. Patients indicated that they understood the questions posed and that they could adequately reflect their disease experience in the PROM-HISS. As discussed in **chapter 10**, the translated PROM-HISS shows that it is a reliable and valid instrument in English to be used for research purposes. We propose the use of the PROM-HISS in clinical practice, but an implementation study needs to be performed to adequately put this tool into practice.

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Samenvatting

Achtergrond

Het doel van deze thesis betreft het optimaliseren van het behandelmanagement van patiënten met klachten van hemorroïden.

In het eerste deel van de thesis – *Introductie in het onderzoeksveld van de proctologie en hemorroïden* – wordt meer achtergrondinformatie over de proctologie en in het bijzonder over klachten van hemorroïden gegeven. Verder wordt er dieper ingezoomd op de pathofysiologie van hemorroïden.

In het tweede deel – *Effectieve behandeling van hemorroïden* – kijken we naar doeltreffende behandelmethoden voor klachten van hemorroïden.

In het derde deel – *Patiënt gerapporteerde uitkomstmaat voor hemorroïden* – bespreken we de toegevoegde waarde, de ontwikkeling en de validatie van een ziekte-specifieke patiënt-gerapporteerde uitkomstmaat om de symptoomlast van hemorroïden te meten en de acceptatie en disseminatie van dit instrument in de (inter)nationale hemorroïdengemeenschap te ondersteunen.

Introductie in het onderzoeksveld van de proctologie en hemorroïden

De prevalentie van anale symptomen varieert van 11 tot 15% in de volwassen bevolking[1,2]. Ondanks de hoge prevalentie en de aanzienlijke negatieve impact van proctologische ziekten op de levenskwaliteit blijft het niveau van bewijs voor effectieve en kosteneffectieve behandelingen op dit gebied over het algemeen zeer laag. In **hoofdstuk 2** benadrukken wij de noodzaak om proctologie op de onderzoeksagenda's van verschillende (inter)nationale gremia te plaatsen en meer studies van hoge kwaliteit naar proctologische aandoeningen uit te voeren om zodoende de kwaliteit van wetenschappelijk bewijs op dit gebied te verhogen. Van de proctologische ziektebeelden zijn klachten van hemorroïden een van de meest voorkomende, met een incidentie van 8.3 per 1000 patiënten per jaar in Nederland en een prevalentie tot 39% in de algemene populatie[3,4]. In **hoofdstuk 3** worden verschillende dynamisch evoluerende domeinen in het huidige onderzoek naar hemorroïden belicht, gaande van historische standpunten tot technische oplossingen en patiëntbetrokkenheid.

Momenteel bestaat er nog geen volledig beeld van de ontstaanswijze van hemorroïden. In de loop der jaren zijn verschillende studies gepubliceerd waarin de correlatie tussen bindweefselstabiliteit en de ontwikkeling van aambeien wordt onderzocht. Het bewijs is echter niet overtuigend. Om bij te dragen aan een vermoeden naar deze correlatie, vergelijken wij de kwantiteit en kwaliteit van anaal collageen en tevens de vaatmorfologie, bij patiënten met symptomatische hemorroïden in vergelijking met gezonde controles. De kwaliteit van het collageen wordt onderverdeeld in jong (onontwikkeld) en oud (ontwikkeld) collageen, waarbij oud collageen meer cross-linked is.

De onderzoeksgroep bestaat uit 22 coupes van graad III en graad IV HD-weefsel van patiënten die een hemorroïdectomie hadden ondergaan. De controlegroep bestaat uit weefsel van 15 personen zonder symptomatische hemorroïden die een natuurlijke dood zijn gestorven en hun lichaam aan de wetenschap hebben afgestaan. In **hoofdstuk 4** beschrijven we de resultaten van dit onderzoek,

waaruit blijkt dat patiënten met hemorroïden een verhoogd percentage totaal collageen hebben (62,1 ± 13,8 vs. 18,7 ± 14,5%; p = 0,0001), een verlaagd percentage jong collageen (0. 00009 ± 0,00008 vs. 0,0008 ± 0,0008%; p = 0,001), en een kleiner oppervlak van de anale vaten (795,1 ± 1215,9 micrometer^2 vs. 1219,0 ± 1976,1; p = 0,003) in vergelijking met gezonde controles. Deze uitkomsten suggereren dat veranderingen in de anale collageensamenstelling een rol kunnen spelen bij het ontstaan van hemorroïden.

Effectieve behandeling van hemorroïden

De mate van prolaps van hemorroïden wordt doorgaans geclassificeerd aan de hand van de Goligher gradering. Volgens deze classificatie wordt graad I gedefinieerd als hemorroïden die niet uitstulpen, graad II zijn hemorroiden die uitstulpen maar spontaan reduceren, graad III zijn uitstulpende hemorroïden die manueel gereduceerd kunnen worden, en graad IV zijn uitstulpende hemorroïden die niet manueel gereduceerd kunnen worden[5]. De meest voorkomende symptomen van hemorroïden zijn bloedverlies, verzakking, pijn, jeuk en vochtverlies[6]. De verschillende beschikbare behandelingen richten zich op het verminderen van deze symptomen en variëren van een conservatieve aanpak tot chirurgische ingrepen. De eerste behandelingsstap wordt meestal aangeboden door de huisarts en bestaat uit laxeermiddelen en een vezelrijk dieet[7]. Wanneer een conservatieve behandeling niet succesvol blijkt, is de volgende behandeloptie doorgaans rubberband ligatie (RBL), een behandeling die meerdere malen herhaald kan worden. RBL is een eenvoudige, relatief goedkope en poliklinische procedure[8]. Echter, 30% van de patiënten ontwikkelt na de eerste behandeling opnieuw hemorroïdensymptomen, waardoor RBL herhaald dient te worden[9]. Bij terugkerende symptomen van hemorroïden ondanks meermaals RBL-behandelingen, bestaat er geen consensus over de beste behandelingsoptie: voortzetting van RBL of een chirurgische ingreep. Een van de meest uitgevoerde operaties voor HD is de hemorroïdectomie[10]. Deze procedure kan echter pijnlijk zijn en de kosten zijn aanzienlijk hoger dan die van een behandeling met RBL. Een relatief nieuw, maar momenteel frequent uitgevoerd chirurgisch alternatief is de gehechte hemorroïdopexie[11]. De kosten van gehechte hemorroïdopexie zijn vergelijkbaar met die van de hemorroïdectomie; de ingreep is minder pijnlijk.

Hoogwaardig bewijs voor de meest (kosten)effectieve behandeling ontbreekt, waardoor de behandeling van recidiverende graad II en III hemorroïden momenteel afhangt van de voorkeur van de chirurg en de patiënt.

In **hoofdstuk 5** beschrijven we het studieprotocol voor een multicentrische gerandomiseerde gecontroleerde trial waarin onder meer de effectiviteit en kosteneffectiviteit van RBL versus gehechte hemorroïdopexie versus hemorroïdectomie wordt vergeleken (*Napoleon Trial*). Gedurende twee jaar is de *Napoleon Trial* uitgevoerd in 20 medische centra in heel Nederland. Patiënten met terugkerende hemorroïden graad II en III, ≥18 jaar oud en die ten minste twee RBL-behandelingen in de afgelopen drie jaar hebben ondergaan, komen in aanmerking voor inclusie. Exclusiecriteria zijn eerdere rectale of anale chirurgie, rectale bestraling, reeds bestaand sfincterletsel of anderszins actieve aandoeningen van het colon en rectum, zwangerschap, aanwezigheid van stollingsstoornissen, en/of medisch ongeschikt voor chirurgie (ASA>III). De verwachte steekproefgrootte is 558 patiënten met een 1:1:1 randomisatie naar ofwel RBL, gehechte hemorroïdopexie of hemorroïdectomie. De primaire

uitkomstmaten zijn (1) recidiefkans na 52 weken en (2) symptoomscore gemeten aan de hand van de PROM-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS), welke in het volgende deel – *Patiënt gerapporteerde uitkomstmaat voor hemorroïden* – wordt beschreven. Secundaire uitkomstmaten zijn impact op het dagelijks leven, tevredenheid over de behandeling, vroege en late complicaties, gezondheid gerelateerde kwaliteit van leven, kosten en kosteneffectiviteit, en budgetimpact.

Een van de interventies die in de *Napoleon Trial* wordt meegenomen, is de gehechte hemorroïdopexie. De techniek van de gehechte hemorroïdopexie bestaat uit het weghalen van een kleine hoeveelheid rectaal slijmvlies (mucosectomie) gevolgd door een hechting, waarbij het anale slijmvlies aan de rectumwand wordt gehecht. Op deze manier wordt voorkomen dat de uitpuilende component van het hemorroïdale weefsel de anus uitsteekt, terwijl zoveel mogelijk anaal slijmvlies behouden blijft. In **hoofdstuk 6** beschrijven we de veiligheid en werkzaamheid op lange termijn van de gehechte hemorroïdopexie in het Maastricht Universitair Medisch Centrum+ (MUMC+). Tussen januari 2009 en december 2021 zijn 145 patiënten geïncludeerd, 70 vrouwen (48,3%), met een gemiddelde leeftijd van 61 jaar (±12,8) die in de afgelopen twaalf jaar een gehechte hemorroïdopexie hebben ondergaan. Perioperatieve en postoperatieve gegevens zijn verzameld via het elektronisch patiëntendossier en de PROM-HISS is via telefoongesprekken afgenomen om inzicht te krijgen in de huidige hemorroïdenstatus van de patiënt. Perioperatieve complicaties traden op in vier gevallen (2,8%). De cumulatieve effectiviteit op basis van uitblijven van recidief is 88,3% (95% CI, 83,1-93,5) na zes maanden, 80,0% (95% CI, 73,5-86,5) na één jaar en 67,7% (95% CI, 59,7-75,7) na vijf jaar. Bij een subgroep van 50 patiënten (34,5%) is de PROM-HISS afgenomen. Meer dan de helft van de patiënten heeft nog steeds last van enig gevoel van een prolaps van de anus (56,0%), variërend van 'zeer weinig' tot 'veel'. Zowel bloedverlies als pijn zijn gemeld in 19 gevallen (38,0%). Rond een kwart van de patiënten heeft nog steeds last van 'jeuk' of 'vochtverlies', waarbij 'jeuk' is gemeld in 13 gevallen (26,0%) en vochtverlies in 12 gevallen (24,0%).

Patiënt gerapporteerde uitkomstmaat voor hemorroïden

Literatuuronderzoek en patiënteninterviews laten zien dat de meest voorkomende symptomen van hemorroïden bloedverlies, prolaps, pijn, jeuk en vochtverlies zijn. Deze symptomen kunnen een significant negatieve impact hebben op de kwaliteit van leven van patiënten[6,12,13]. De ernst van deze klachten en de belasting op het leven van een patiënt kan gemeten worden aan de hand van een Patient-Reported Outcome Measure (PROM). Een PROM is een instrument dat een breder inzicht geeft in de ziektelast van een patiënt, zonder tussenkomst van een zorgverlener. De European Society of ColoProctology (ESCP) erkent de belasting van hemorroïdensymptomen en hun impact op het dagelijks leven van patiënten als cruciaal bij het bepalen van effectiviteit van een behandeling. Dit is terug te zien in de recent opgestelde Core Outcome Set (COS) voor hemorroïden, waarin patiënt-gerapporteerde symptomen als primaire uitkomstmaat in klinische hemorroïdenstudies is vastgesteld[14]. Een COS is een overeengekomen minimum set van uitkomsten die gemeten en gerapporteerd dienen te worden in alle klinische studies naar een specifieke aandoening[15]. Deze patiënt-gerapporteerde symptomen dienen gemeten te worden aan de hand van een PROM.

Aangezien er indertijd geen goed gevalideerde PROM voor hemorroïden beschikbaar was, is het onze doelstelling geweest een aandoening-specifieke PROM te ontwikkelen aan de hand van de internationale richtlijnen voor PROM ontwikkeling en met actieve betrokkenheid van patiënten[16].

In **hoofdstuk 7** bespreken we de toegevoegde waarde van een PROM in zowel wetenschappelijk onderzoek als in de klinische praktijk, waarbij de arts rechtstreeks informatie krijgt van de patiënt over zijn ervaringen met de aandoening. In het vakgebied van hemorroïden zijn er twee gevalideerde PROMs beschikbaar die ontwikkeld zijn aan de hand van gedegen methodologie. Een daarvan is de PROM-HISS, ontwikkeld door ons onderzoeksteam.

De PROM-HISS testen we op verschillende psychometrische aspecten volgens de COSMIN-richtlijnen voor het ontwerpen en evalueren van de meeteigenschappen van een PROM. Ten eerste beoordelen we de indruks- en inhoudsvaliditeit middels individuele interviews met tien patiënten. Ten tweede meten we de structurele eigenschappen, betrouwbaarheid en constructvaliditeit in een cross-sectionele hemorroïdenpopulatie. Deze bestaat uit 102 patiënten (65% man) met een gemiddelde leeftijd van 58 jaar (23-81 jaar). Resultaten gerapporteerd in **hoofdstuk 8** geven aan dat de PROM-HISS een valide en betrouwbaar instrument is om symptomen van hemorroïden, impact op dagelijkse activiteiten en tevredenheid met hemorroïdenbehandeling te meten.

Naast de betrouwbaarheid en validiteit van de PROM-HISS moet een PROM worden getoetst op het aspect 'responsiviteit', dat wil zeggen het vermogen om verbetering of verslechtering van gezondheid of symptomen te beoordelen. **Hoofdstuk 9** laat zien dat de PROM-HISS een responsief instrument is dat verandering in de symptoomlast van de patiënt in de tijd kan detecteren. Patiënten geven aan dat een verandering van 0,3 op de symptoomscore van de PROM-HISS voor hen een relevante verandering betekent. Dit afkappunt kan gebruikt worden in onderzoek om een steekproefgrootte te berekenen en kan in de dagelijkse praktijk worden voorgesteld om verbetering of verslechtering van de ziekte vast te stellen.

Om de implementatie van de COS en het gebruik van de PROM-HISS internationaal te bevorderen, vertalen we de PROM-HISS naar het Engels en verrichten we een validatie. Allereerst vertalen we de Nederlandse PROM-HISS naar het Engels door twee personen met Engels als moedertaal. Daarna vertalen we deze Engelstalige versie naar het Nederlands door twee personen met als moedertaal Nederlands. Vervolgens vragen we tien patiënten uit het Verenigd Koninkrijk de vertaalde PROM-HISS in te vullen. Deze patiënten worden tevens geïnterviewd om de begrijpelijkheid van de vragenlijst te peilen. Patiënten geven aan dat zij de gestelde vragen en antwoordopties begrijpen en dat zij hun ziekte-ervaring adequaat kunnen weergeven in de PROM-HISS. In **hoofdstuk 10** wordt gesteld dat de vertaalde PROM-HISS een betrouwbaar en valide instrument is om te gebruiken voor Engelstalige onderzoeksdoeleinden. Als onderzoeksgroep introduceren we het gebruik van de PROM-HISS in de klinische praktijk. Er dient echter ook een implementatiestudie te worden uitgevoerd om te evalueren of het gebruik van de PROM-HISS van toegevoegde waarde is in de klinische praktijk.

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(Vrij naar: Piggeldy und Frederick, *'Liebe'*)

Curriculum Vitae

Sara Z. Kuiper was born on the 13th of July 1995 in Maastricht, the Netherlands. She attended secondary school at the Bernhard Lievegoed Vrije School in Maastricht after which she commenced her medical studies at the Faculty of Health, Medicine and Life Sciences (FHML) of Maastricht University in September 2013. During her second year of the Bachelor of Medicine, she started as a research-assistant in the field of faecal incontinence at the department of Surgery (Maastricht University Medical Centre, MUMC+). Her interest in surgical research sustained and in 2016 she made the transition to the area of haemorrhoidal disease. At the MUMC+, she completed her research internship on the quality of life of patients with haemorrhoidal disease under the supervision of dr. R.R. Van Tol and dr. S.O. Breukink. In her fifth year of Medicine, Sara was offered the chance to initiate and co-write a *ZonMw* research proposal regarding the most optimal treatment of recurrent haemorrhoidal disease. The research proposal was granted to the project team in June 2019 and in the same month, she graduated from medical school. Following the acceptance of the research proposal, Sara started as a PhD-student at Maastricht University under the supervision of prof. C.D. Dirksen, dr. S.O. Breukink and dr. M.L. Kimman. The *ZonMw* research proposal regarding the most optimal treatment of recurrent haemorrhoidal disease forms the outlines of this thesis.

Currently, Sara works as a resident not in training at the Urology department of Zuyderland Medical Centre in Sittard-Geleen and Heerlen.

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