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NEW INSIGHTS IN BENIGN ANORECTAL DISEASE

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GENERAL INTRODUCTION

Anorectal disorders are very common in surgical clinical practice. Since complaints are associated with social embarrassment, prevalence in the general population can be difficult to ascertain as many will never consult a medical practitioner. Despite national and several international guidelines, determining optimal therapy for anorectal disorders is often difficult. Therapy is aimed at symptom relief whilst preventing and minimizing functional impairment. For numerous benign anorectal disorders the initial conservative management comprises lifestyle advice, diet and toilet behavior. The next step in treatment is often one of the various surgical options. This might involve that the surgeon needs to choose the lesser of two evils. Contrary to decades ago, surgeons have broadened their focus on the patient's experience and expectation rather than on healing the benign disorder.

Anatomy

The rectum is situated in the pelvic cavity and consists of the distal 12 to 15 cm of the large bowel. The definition of the rectum is recently changed in order to enable greater consistency in tumour localization [1]. Frequently used definitions in daily practice were '< 15 cm from the anal verge', 'the level of the sacral promontory' and the 'anterior peritoneal reflection'. 'The sigmoid take-off' that was conducted with a Delphi study, can be identified as the mesocolon elongates as the ventral and horizontal course of the sigmoid on axial and sagittal views respectively on cross-sectional imaging. The rectum is partially enclosed by peritoneum, namely the upper two-third anteriorly and the upper third laterally. The pelvic cavity consist of several internal organ structures. Anterior in the pelvic cavity the urinary bladder and the urethra are located, in females there is a middle part that consists of the vagina and uterus, and the posterior part covers the rectum. The pelvic cavity is mainly vascularized by the superior rectal artery whereas the inferior rectal artery mainly supplies the anal canal [2].

The anal canal is located distal to the rectum. Anatomically, it starts at the dentate line and ends at the anal verge. Functionally, however, the accepted boundaries extend from the proximal aspect of the internal anal sphincter, which is longer than the anatomical length [2]. The dentate line is where the mucosa of the rectum becomes the epithelium of the anal canal. This epithelium is also called anoderm and is devoid of accessory skin structures as hair and sweat glands. Only at the anal verge does the epithelium and subcutaneous tissue resemble those of normal skin [3]. Distal to the dentate line, the anal canal has somatic innervation whereas proximal it is innervated by the autonomic nervous system, with no somatic pain fibers. Therefore, the location of an anorectal disease

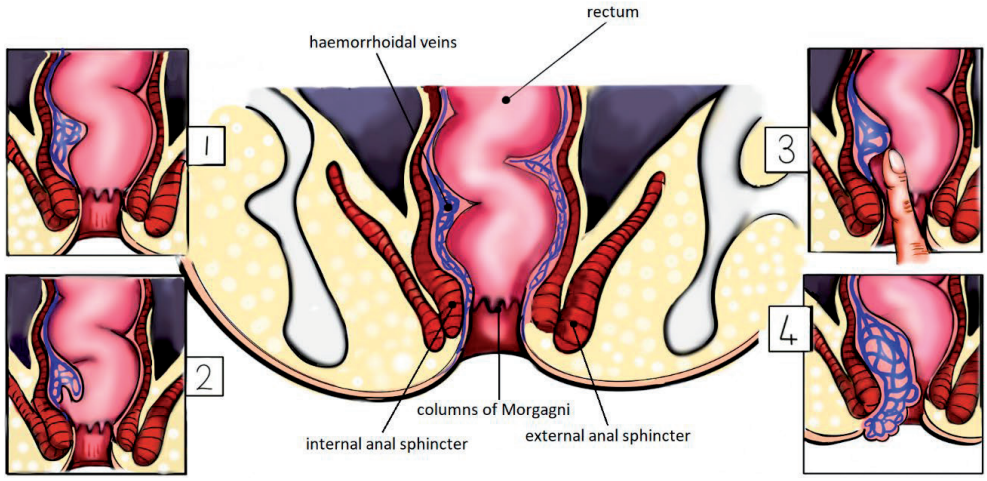

Figure 1. Anatomy of the rectum with the four grades of haemorrhoidal disease.

partly determines whether the therapy can be performed with or without anesthesia. Folds in the mucosa above the dentate line are called the columns of Morgagni (fig. 1). In the columns of Morgagni are the anal crypts into which drain several anal glands. The anal canal is surrounded by the internal anal sphincter and external anal sphincter. The internal anal sphincter is a thickened extension of the smooth muscle layer of the rectum. The external sphincter on the other hand, is skeletal muscle and wrapped around the internal anal sphincter where it merges proximally into the levator ani muscle – also known as the pelvic floor muscle. This is a broad and thin muscle representing three muscles, namely; pubococcygeus, iliococcygeus and the puborectalis muscle. The puborectalis is a sling-like muscle around the anal canal that forms the anal angle. It displays some resting tone, but contracts rapidly in response to any immediate increase in intra-abdominal pressure to prevent faecal incontinence [4].

Pathophysiology

The anus is normally collapsed by the resting tone of the internal anal sphincter along with the three anal vascular cushions and thereby continence is generally maintained. The internal anal sphincter has sympathetic as well as parasympathetic innervation of which the sympathetic nerves ensures contraction and relaxation of the internal anal sphincter, and the external anal sphincter is innervated by the pudendal nerve. The puborectal muscle that forms the anal angle is approximately 90 degrees at rest. When voluntary squeezing, this angle will be around 70 degrees. By attempted defecation this angle will be bigger – 110 to 130 degrees – due to relaxation of the puborectal muscle [5]. A desire to defecate is associated with a unique, consistent, and reproducible anal contractile response; the sensorimotor response (SMR). This response is considered to play an integral role in the brain-gut interactions that regulates anorectal sensation and

function [6]. Two other important anal reflexes are the recto-anal inhibitory reflex (RAIR) and the recto-anal contractile reflex (RACR). RAIR is a transient involuntary relaxation of the internal sphincter in response to distention of the rectum and RACR prevents accidental release of rectal contents and is innervated by the splanchnic and pudendal nerves [7, 8].

Diagnostics

To objectify the anorectal function, several diagnostic tests can be performed. Generally, digital rectal examination is the first diagnostic tool in patients that present with anorectal symptoms. It can be easily done by the physician and is less invasive. Imaging techniques as the endo-anal ultrasound or transperineal ultrasound are often performed to visualize the anorectal and pelvic anatomy but also to objectify the anorectal function. The endo-anal ultrasound is a rapid technique that shows the anal-sphincter anatomy. Sphincter abnormalities are shown in up to 90% of women whose sole risk factor for faecal incontinent is obstetric trauma [9]. The transperineal ultrasound can also be performed when introducing echo lucent gel in the rectum. If the patient is asked to squeeze or bear down, real time movement of the anorectal function can be observed. High-resolution anorectal manometry (HR-ARM) and the balloon expulsion test (BET) are considered the best established investigations for objective assessment of anorectal sensorimotor function. It is a comprehensive assessment with a probe that involves a series of measurements that describes the evacuatory function, involuntary and voluntary coordination and rectal sensation. This is often performed by a specialized nurse. The patient lies in left lateral position and anorectal pressures are measured with an anorectal probe at rest, during squeeze and during straining. Anal manometry was performed by a variety of methods between centres untill recently. Since this resulted in difficulties in interpretation of results, a working group introduced the 'London protocol' with standard operating procedures and a consensus classification system that was designed to bring standardization to several techniques [10].

An alternative anorectal function test is the surface electromyography which also consists a probe but with electrodes that enables measuring EMG signals from different sides and layers of the pelvic floor muscles. This is commonly utilized by the pelvic floor physical therapist to objectivize DRE and evaluate therapy. The oldest test is the classic defecography which examines emptying soft barium paste under fluoroscopy. Which of the anorectal function tests is most suitable in addition to DRE, is not always clear.

Haemorrhoidal disease

Haemorrhoids are cushions of vascular tissue located within the anal canal and are normal anatomical structures that are part of the human body [11]. They are believed to provide the fine continence for air and liquid stool. In popular parlance, the term 'haemorrhoid' is often used when complaints appear. The word 'haemorrhoid' is derived from the Greek

Table 1. Definitions of the four grades of Goligher Classification.

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

haemorrhoides, meaning flowing of blood (*haem*=blood, *rhoos*=flowing). In the authorized translation of the Bible this is written as 'emerods' [12].

Internal haemorrhoids emerge from above the dentate line while external haemorrhoids emerge from below and are often confluent with the anal verge. Patients suffering from haemorrhoidal disease complain of varying degrees of blood loss, soiling, prolapse, pruritus and anal pain. There are three major vascular cushions in the anal canal; one on the left, and an anterior and a posterior one on the right. Anal continence is ensured by the interaction between the vascular cushions and the internal anal sphincter. The internal anal sphincter is responsible for 60 to 80% of normal anal pressure while the vascular cushions contribute with 15-20%. Chronic intraabdominal pressure, in combination with the absence of valves within rectal veins, may result in dilatation of the internal haemorrhoidal plexus. Important factors in the etiology of haemorroidal disease are prolonged straining during defecation, diet and defecation habits [12]. Haemorroidal disease is usually classified by the Goligher classification, which ranks presence and severity of prolapse in four grades [13](table 1 and figure 1).

'The hand of the Lord was against the city with a great destruction: and he smote the men of the city, both small and great, and they had emerods in their secret parts' (1 Sam 5:9, King James Bible). Ancient references to haemorroidal disease date back thousands of years and can be found in the writings of the Hebrews, the ancient Egyptians and the ancient Greek. According to Papyrus (1700 BC) the Egyptians appeared to have used the infusion of acacia leaves or of alum as an astringent in the management of anal disorders, although whether these were used primarily for pruritus, condylomata or haemorroids is not clear [11]. Hippocrates (460-370 BC) was probably the first who described surgical treatment which described how to ligate the pile; 'and haemorrhoids in like manner you may treat by transfixing them with a needle and tying them with very think and woolen thread.' [14]. In the 19th century Frederick Salmon, founder of St Marks' Hospital, was the first who treated haemorrhoids by anal stretching, sclerotherapy and excision, and actually little has been added to the operation of haemorrhoidectomy since then. Surgeons have modified the operation since – most in the twentieth century – of which the modification described by Milligan and Morgen et al. and the closed version described by Ferguson et al. are the best known [15, 16]. The diathermy haemorrhoidectomy and the stapled haemorrhoidectomy were added as two new techniques in the late twentieth century.

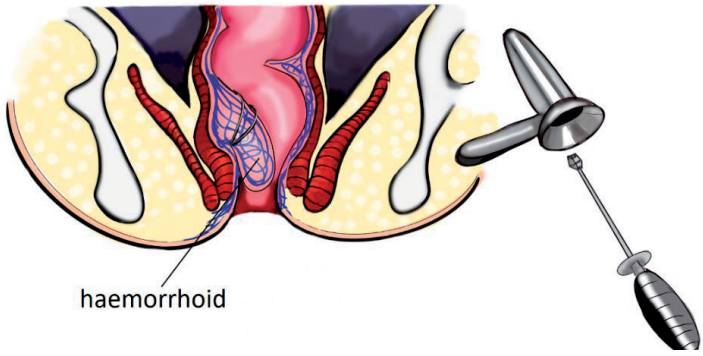

Figure 2. Rubber band ligation via proctoscopy.

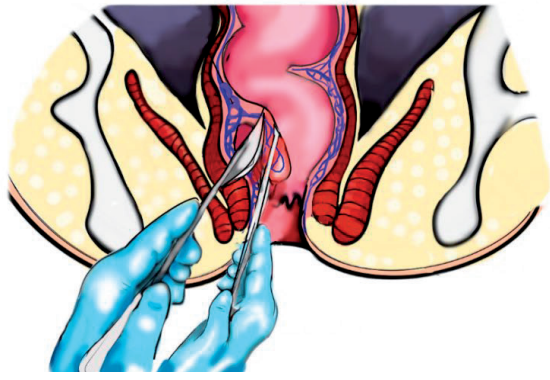

Figure 3. Haemorrhoidectomy.

Advice on diet and bowel habits modifications are the first conservative measures in treatment. The efficacy of local applications has rarely been assessed critically, but casual observations suggests that they do produce some symptomatic relief [12]. The most commonly used procedure for lower grade haemorrhoids is the rubber band ligation (RBL). The original Barron ligator was the instrument most frequently used until the suction band equipment became available (Barron, 1963). It produces fixation of the mucosa by applying rubber bands just above the upper limit of the cushion (figure 2). In current literature, the success rate of RBL, as a single procedure varies between 49-88% [17-20]. Although complications are rare, recurrence is common and repeated banding may be required [17].

Various techniques are currently practiced but yet, not one technique has adopted as the perfect gold standard. The haemorrhoidectomy (figure 3) is considered the gold standard in two recent British trials [17, 21]. A systematic review regarding operative procedures for haemorrhoidal disease, by Simillis et al., concluded that all procedures have their own advantages and disadvantages [22]. This suggests that patient expectations, priorities

and costs should be taken into account when deciding which procedure to advice and perform.

Perianal fistula-in-ano

A fistula-in-ano is a granulating track between the anorectum and the perianal skin. Fistula literally translated from the Latin defines a pipe or a reed [12]. In the absence of an underlying condition such as malignancy or Crohn's disease, more than 90% of crypto-glandular fistulas originate from an anorectal abscess [23]. An abscesses originates from an infected anal crypt gland at the level of the dentate line. The anal crypt gland becomes obstructed with debris and turns into and abscess. Despite adequate drainage of anorectal abscess up to 83% recurs or results in an anal fistula, the majority developing within 12 months [24]. Fistulas are generally classified according to Parks classification which is based on the anatomical correlation with the anal sphincters; intersphincteric, transsphincteric, extrasphincteric and suprasphincteric [25]. The Hippocratic Treatises provide some of the earliest details of the surgical management of fistula's with cutting setons [14]. In 1936 Lockhart-Mummery et al. described how difficult treatment for fistula-in-ano is; 'more surgeons' reputations are damaged by unsuccessful operation for fistula than by laparotomies. The bad results of laparotomy are generally buried with flowers, while the fistulae go about the world exhibiting the unsuccessful results of the treatment [26]. Functionality was mostly of secondary importance to healing of a fistula, nowadays it is considered unacceptable to cause irreversible disability for a benign disorder such as a fistula-in-ano.

The majority of the fistulas are low-lying, submucosal, and consist of a single straight track that merely traversing the lower fibres of the internal anal sphincter. Those fistulas can be managed by simply laying open the track via a fistulotomy [12]. The complex and higher ones are more challenging given the risk of potential impairment of continence and recurrence [27, 28]. A gold standard has not yet been considered and for this reason more sphincter-preserving techniques have been developed in the past decades which results in a plethora of surgical techniques available. Current surgical techniques include mucosal advancement flap (MAF), ligation of the intersphincteric fistula tract (LIFT) with reported healing rates between 70-80% and 69% respectively [29-33]. Other, newer, but often less performed sphincter-sparing procedures are the fistula laser closure (FiLaC™), video-assisted anal fistula treatment (VAAFT) and over-the-scope clip (OTSC®). Which procedure leads to optimal outcome for the individual patient suffering from fistula-in-ano is still not clear. Data of studies concerning treatment of fistula-in-ano are often difficult to compare due to heterogeneity between studies. Recently a core outcome set (COS) is published to establish consistency in future fistula research, with a substantial focus on patient priorities for treatment [34].

Anal fissure

Anal fissure is defined as an ulcer in the squamous epithelium of the anal canal, mainly seen in the posterior midline [35]. It is a very common disorder and the patient usually presents with an intense burning anal pain made worse by attempted defecation. Bright red blood is often present on wiping. A fissure is usually called chronic if the complaints present for longer than 4 to 6 weeks. Pathophysiology of the anal fissure is not yet fully understood but hard stool or sudden evacuation of liquid stool and a hypertonia of the internal anal sphincter are both suggested as the root cause. Hypertonia of the sphincter lead to reduced blood flow and consequently to ischemia which prevents the anal fissure from healing [36, 37].

Most anal fissures respond to a conservative approach. Treatment is aimed at reducing the pain and healing the anal fissure by regulation of soft stool and reducing hypertonia. This includes lifestyle advice, fiber intake, laxatives and topical ointments that reduce elevated internal sphincter tone such as isosorbide dinitrate and calcium channel blockers as diltiazem. In patients who are also diagnosed with pelvic floor dysfunction, pelvic floor physical therapy can be of added value [38]. When conservative treatment fails surgical procedures may be needed. Although Dutch and international guidelines are largely based on high-quality evidence, recommendations are ambiguous .The internal lateral sphincerotomy (LIS) has been widely accepted as the golden standard with high healing rates but with a risk of permanent incontinence. Also fissurectomy is often performed. A chemical sphincterotomy by injection of botulinum toxin can be a step up approach before performing LIS or fissurectomy. A systematic review and meta-analysis of RCT's showed a recurrence rate of 35% for botulinum toxin and 6% for lateral internal sphincterotomy [39] but with a higher rate of minor anal incontinence (incontinence to flatus) as compared to botulinum toxin.

Faecal incontinence

Faecal incontinence is the involuntary loss of rectal contents through the anal canal. The disorder is surprisingly common but the true prevalence is unknown, owing to the lack of standard definitions and under-reporting of symptoms by patients [9]. A US study from 1996 found an overall prevalence of 18% of which 2.7%, 4.5% and 7.1% of the population admitted to incontinence daily, weekly, or once per month or less, respectively [40]. A more recent publication in 2002 described that approximately 2% of the adult population suffers from involuntary loss on a frequent basis [41]. Patients are embarrassed, finding the disorder socially unacceptable and consequently many avoid activities outside of the home. Faecal incontinence can have multiple causes; functional, neurological, anatomical or congenital. Sphincter damage following surgery is the most common cause of incontinence preceded by obstetric trauma. Structural damage is the commonest cause of weakness [42] and isolated degeneration of the smooth muscle of the internal anal sphincter is the commonest cause of soiling [43].

Initial treatment of patients suffering from faecal incontinence is conservative with dietary advices, additional bulking agents and bowel habit training. If medical treatment fails, biofeedback under guidance of a pelvic floor physical therapist is generally the first-line treatment for faecal incontinence as well. In general, if biofeedback does not suffice, the next step in treatment is transanal irrigation. During this, routine water is introduced into the anus via a balloon or cone catheter to empty the distal part of the sigmoid colon and rectum, thereby leading to a state of pseudo-continence. When starting the treatment, patients are instructed by a conservative management nurse on how to use the device and to adjust frequency and volume of the water inserted. With regular irrigations, control of bowel function can be re-gained. Two systematic reviews and meta-analysis showed that transanal irrigation is successful in 45% till 59% of patients with chronic constipation, faecal incontinence or coexistent symptoms [44, 45]. This makes transanal irrigation an important treatment modality before introducing more invasive, surgical, methods such as sphincteroplasty, sacral neuromodulation or stoma formation. Sacral neuromodulation is an established treatment option since several years. It involves electrical stimulation to a sacral nerve root to modulate a neural pathway. Reported success rates vary but two recent large studies reported great clinical effectiveness; one showed 53% success rate in 325 patients with a follow-up of 7 years and a prospective multicenter French study reported reduction in leakage of more than 50% in 80% of the 221 patients [46, 47].

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OUTLINE OF THE THESIS

The aim of this thesis was to evaluate current management and current practice in anorectal benign disease. In **Part I** treatment of symptomatic haemorrhoids is studied. **Part II** evaluates current management of cryptoglandular perianal fistula-in-ano and chronic anal fissure. In **Part III** treatment of faecal incontinence and diagnostic tools are evaluated.

PART I

In **chapter one** a systematic review and meta-analysis is conducted to review clinical outcome of haemorrhoidectomy and rubber band ligation in grade II-III haemorrhoids. The primary outcome is control of symptoms and secondary outcomes are postoperative pain, postoperative complications, anal continence, patient satisfaction, quality of life and healthcare costs. **Chapter two** describes the protocol of a multicenter, randomized controlled, non-inferiority trial with cost-utility analysis that compares haemorrhoidectomy with rubber band ligation in grade III haemorrhoids. Primary outcome measure is quality of life at 24 months measured with the EQ-5D-5L, in-hospital (in)direct costs and out-of-hospital postoperative costs. The key secondary outcome is recurrence at 1-year post procedure. In **chapter three** a retrospective analysis is performed of all patients who were treated with rubber band ligation or haemorrhoidectomy in a tertiary referral center for proctology. Medical history, symptoms, reinterventions, complications and patient-reported outcome measurements (PROM) are analysed. In **chapter four** the interobserver variability of the most widely used classification for haemorrhoids is determined. A single-choice survey is used with 25 photographs of patients with haemorrhoidal disease, each with a description of timing of the photo and the complaints the patient suffers.

PART II

Chapter five describes current management of cryptoglandular fistula-in-ano among gastrointestinal surgeons and residents in the Netherlands. Dutch surgeons and residents who treat fistula-in-ano regularly are sent a survey invitation by email. Than a questionnaire that consists of 28 questions concerning diagnostic and surgical techniques in the treatment of intersphincteric and transsphincteric fistula-in-ano could be filled in. In **chapter six** a comparable study is done for the management of chronic anal fissure. Dutch gastrointestinal surgeons and residents are invited to participate in a questionnaire

that consists of 21 questions concerning their physical examination, diagnostic and surgical techniques and follow-up in the management of chronic anal fissure.

PART III

In **chapter seven** the correlation of commonly performed anorectal function tests is compared. Anal pressures and diagnosing pelvic floor dyssynergia between digital rectal examination and several anorectal function tests are examined. Anorectal function tests included 3D High resolution anal manometry (3D-HRAM), balloon expulsion test (BET), transperineal ultrasound (TPUS) and surface electromyography (s-EMG). **Chapter eight** includes an addendum of this thesis were the interim results of transanal irrigation in patients with constipation and faecal incontinence is shown. The main aims of the interim analysis are to evaluate the continuation rate of transanal irrigation in these patients and to evaluate effects of transanal irrigation on symptom severity and quality of life using validates questionnaires.

PART I

SYMPTOMATIC HAEMORRHOIDAL DISEASE

CHAPTER 1

RUBBER BAND LIGATION VERSUS HAEMORRHOIDECTOMY FOR THE TREATMENT OF GRADE II–III HAEMORRHOIDS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS

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Techniques in Coloproctology 2021

ABSTRACT

1

Background

The aim of this study was to review clinical outcome of haemorrhoidectomy and rubber band ligation in gradeII–III haemorrhoids.

Methods

A systematic review was conducted. Medline, Embase, Cochrane Library, Clinicaltrials.gov, and the WHO International Trial Registry Platform were searched, from inception until May 2018, to identify randomised clinical trials comparing rubber band ligation with haemorrhoidectomy for grade II–III haemorrhoids. The primary outcome was control of symptoms. Secondary outcomes included postoperative pain, postoperative complications, anal continence, patient satisfaction, quality of life and healthcare costs were assessed. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed.

Results

Three hundred and twenty-four studies were identified. Eight trials met the inclusion criteria. All trials were of moderate methodological quality. Outcome measures were diverse and not clearly defined. Control of symptoms was better following haemorrhoidectomy. Patients had less pain after rubber band ligation. There were more complications (bleeding, urinary retention, anal incontinence/stenosis) in the haemorrhoidectomy group. Patient satisfaction was equal in both groups. There were no data on quality of life and healthcare costs except that in one study patients resumed work more early after rubber band ligation.

Conclusions

Haemorrhoidectomy seems to provide better symptom control but at the cost of more pain and complications. However, due to the poor quality of the studies analysed, it is not possible to determine which of the two procedures provides the best treatment for grade II–III haemorrhoids. Further studies focusing on clearly defined outcome measurements taking patients perspective and economic impact into consideration are required.

INTRODUCTION

Haemorrhoids are one of the most common proctological disorders with an incidence of about 9 per 1,000 patients per year in the Netherlands [1] and a prevalence up to 39% in the general population [2]. Treatment consists initially of conservative measures such as lifestyle advice, diet and toilet behavior. In addition, there are various surgical options, Haemorrhoidectomy is considered the gold standard and this was recently confirmed in a British trial and systematic review [3, 4]. The most common minimally invasive procedure is rubber band ligation (RBL). Other minimally invasive procedures are sclerotherapy and laser treatment. These treatments are usually reserved for grade I and II haemorrhoids, although RBL is also used for grade III [5, 6]. Grade III and IV haemorrhoids can be treated with open haemorrhoidectomy, semi-closed haemorrhoidectomy, and stapled haemorrhoidectomy with possibly mucopexia or haemorrhoidal artery ligation (HAL).

Many studies and meta-analyses have been published on the subject of haemorrhoid treatment. All these studies focus on groups of comparable surgical procedures. It is common to distinguish between minimally invasive treatment for grade II and III disease (sclerotherapy and RBL) and surgical procedures for grade III and IV haemorrhoids (haemorrhoidectomy and stapled haemorrhoidectomy). However, the criteria for selecting a minimally invasive treatment versus an operation are not always that evident. There is obviously an overlap in indication, as has become clear from several surveys amongst treating surgeons [7, 8]. There are few trials comparing the clinical outcome of the two most common treatments RBL and haemorrhoidectomy. A systematic review from 2005, updated in 2016**,** of 3 small heterogeneous trials concluded that RBL leads to a higher recurrence rate, but on the other hand less pain, fewer complications, and a less stressful experience for the patient [9][10].

It remains unclear which of the two most common procedures is preferable as regards healthcare costs. There are hardly any studies investigating the cost effectiveness of the various treatments. Only 1 study compared costs of stapled haemorrhoidopexy with RBL in grade II haemorrhoids with results in favor of RBL [11]. A recent study from 2016 compared HAL with RBL, with HAL clearly entailing higher costs, even though the analysis includes the possibility of repeated RBL treatments [12]. Because haemorrhoidal disease is a benign condition, the main goal of treatment is the resolution of symptoms and improvement of patient wellbeing. It is therefore important to include patient related outcomes when determining the best treatment.

The aim of this systematic review was to assess the literature on the clinical effectiveness (including patient related outcomes) and cost effectiveness of RBL versus haemorrhoidectomy in patients with symptomatic grade II and III haemorrhoids.

METHODS

1

This systematic review was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. To reduce the risk of bias, a study protocol was made at an early stage and stated precise eligibility criteria. The protocol was registered in PROSPERO (registration number CRD42018102000) [14].

Search strategy

A comprehensive literature search was carried out from inception until May 2018,using a combination of free-text terms and controlled vocabulary. Medline, Embase, Cochrane Library, Clinicaltrials.gov, and the WHO International Trial Registery Platform were searched to identify randomized clinical trials comparing RBL with haemorrhoidectomy. The references of the identified trials were also searched to find additional trials for inclusion. Only studies written in English were included. There were no restrictions on publication year or publication status.

Search terms

The following search terms were used: ("Hemorrhoids"[Mesh] OR hemorrhoid*[tiab] OR haemorrhoid*[tiab] OR piles[tiab]) AND ("Ligation"[Mesh] OR ligature*[tiab] OR ligation*[tiab] OR band*[tiab]) AND ("Surgical Procedures, Operative"[Mesh:NoExp] OR "Hemorrhoidectomy"[Mesh] OR "Diathermy"[Mesh] OR "Electrocoagulation"[Mesh] OR "Lasers"[Mesh] OR hemorroidectom*[tiab] OR haemorroidectom*[tiab] OR hemorrhoidectom*[tiab] OR haemorrhoidectom*[tiab] OR hemorrhoid excison*[tiab] OR haemorrhoid excison*[tiab] OR Milligan-Morgan[tiab] OR ferguson[tiab] OR ligasure[tiab] OR diathermy[tiab] OR harmonic scapel[tiab] OR electrocauter*[tiab] OR laser*[tiab] OR thermocoagulation[tiab])

Inclusion and exclusion criteria

Randomised controlled trials (RCTs) comparing RBL to/with haemorrhoidectomy in grade II-III haemorrhoids according to Goligher's classification were included in this systematic review. Only studies considering non-emergency procedures in adult patients and reporting of the required outcomes were included. Adult patients (18 years or older) were included and all techniques (open, semi-closed, closed) or instruments (scissors, knife, diathermy, LigaSure, harmonic scapel) used for haemorrhoid excision were included. Non-randomised studies and studies not in English language were excluded.

Quality assessment

The methodological quality of the included studies was assessed using the following Cochrane Risk of Bias assessment tool: sequence generation, allocation concealment,

blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias [15]. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [16] was used to assess the quality (certainty) of evidence. It grades evidence as high, moderate, low or very low quality. Judgements included risk of bias, inconsistency, indirectness, imprecision and other considerations.

Outcomes of interest

The primary outcome was control of haemorrhoidal disease defined by need for retreatment within 1 year or by self-reported residual complaints. The secondary outcomes were postoperative pain, postoperative complications (bleeding requiring admission and/or reoperation, sepsis, anal stenosis, anal incontinence), anal continence (if measured by a validated patient-reported outcome measure), patient satisfaction, quality of life (if measured by a validated patient-reported outcome measure), and health-costs. All complications reported (by studies) were added and reported individually.

Data collection

Literature search results were uploaded to Covidence Software. This is a Cochrane supported software program that can import citations, screen titles, abstracts and full text. Data selection and extraction was conducted in accordance with Population, Interventions, Comparison, Outcome (PICOs). Identified trials were screened by two independent investigators. Titles, abstracts and full text were screened by both reviewers against inclusion and exclusion criteria. Trials that were excluded were documented with reasons for exclusion recorded. Efforts were made to contact trial investigators to resolve questions about eligibility or missing data but did not lead to additional data. The reviewers were not blinded to the journal titles or to study authors or institutions.

Statistical analysis

Binary data indicating number of patients with an event were analyzed using a binomial model calculating risk ratio (RR) and 95 % confidence interval (CI.). The estimates from individual RCTs were pooled using the random-effects model. Statistical heterogeneity was explored by X^2 test and expressed as I^2 and p value (considered significant if $p < 0.05$). The potential effect of predictors on the outcomes was investigated using a random-effects meta-regression model. Analyses were made using RevMan 5.3.5 (The Cochrane Collaboration) and RStudio.

A total of 324 references were identified from the relevant electronic searches. Two duplicates were removed. Two hundred ninety-five studies were excluded after screening titles and abstracts. **Twenty-seven** full-text studies were assessed for eligibility. Of these, 19 were excluded after full-text review. Eight RCTs were identified and included in the analyses (figure 1) [17–24]. The risk of bias in the included trials is summarized in

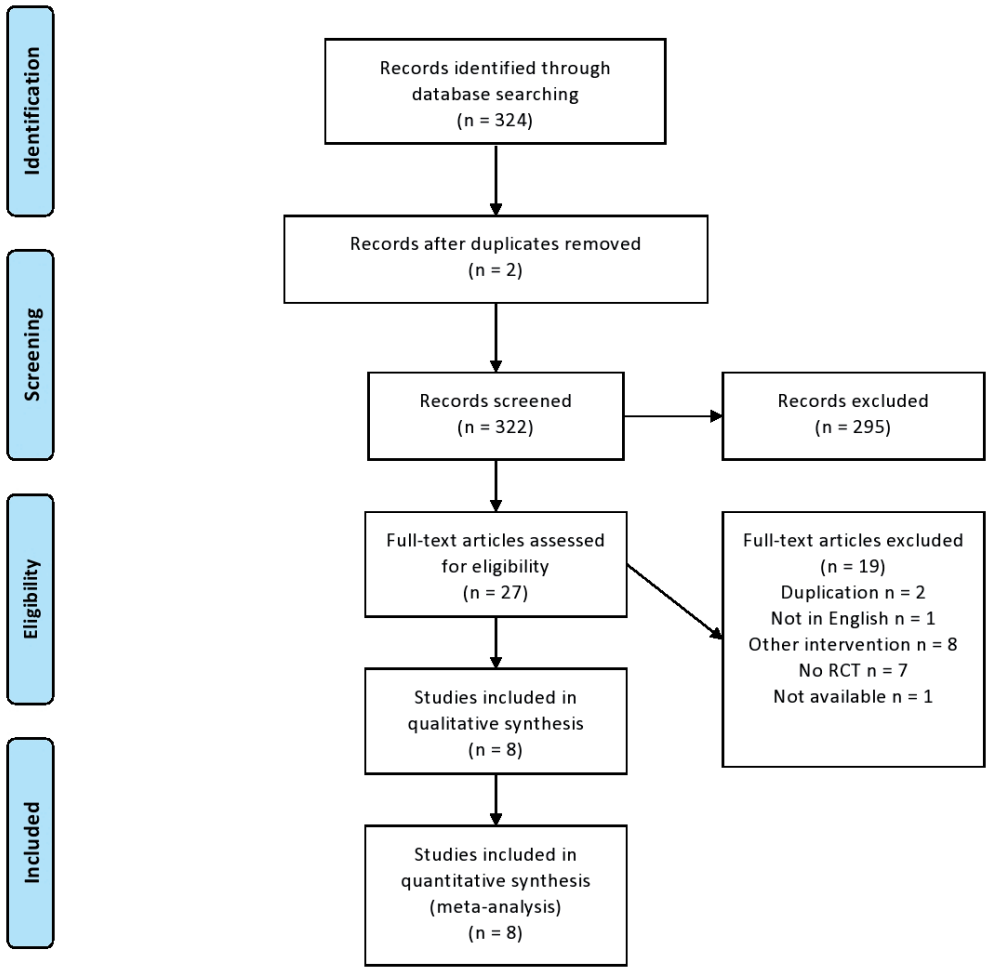


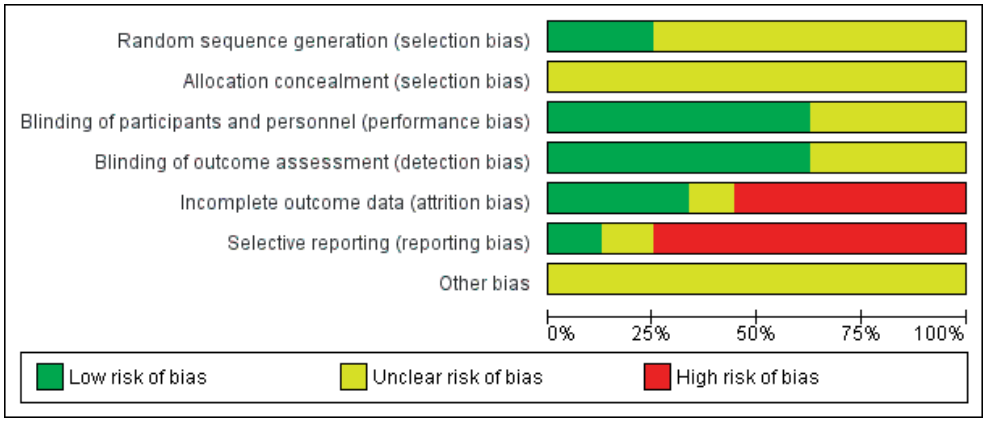
Figure 1. PRISMA flowchart of literature.

Figure 2a and 2b. The overall methodological quality of these studies was determined to be moderate. The 8 trials contained a total of 1208 patients with second and third degree haemorrhoids, who underwent RBL or haemorrhoidectomy (608 versus 600, respectively). The characteristics of the studies are shown in Table 1.

Recurrence and need for retreatment

Recurrence was identified as outcome in 4 of the 8 trials. RBL led to more recurrence than haemorrhoidectomy (4 studies, 322 patients, random effects; RR 4.77 (95% CI 2.60-8.76); $p<0.001$) as shown in Fig. 3). The index of heterogeneity between studies was assessed (I^2) for a fixed effects model, and was low (0%). Recurrence of disease was established in different ways: need of reintervention [22]; diminishment of bleeding and prolapse [23]

A



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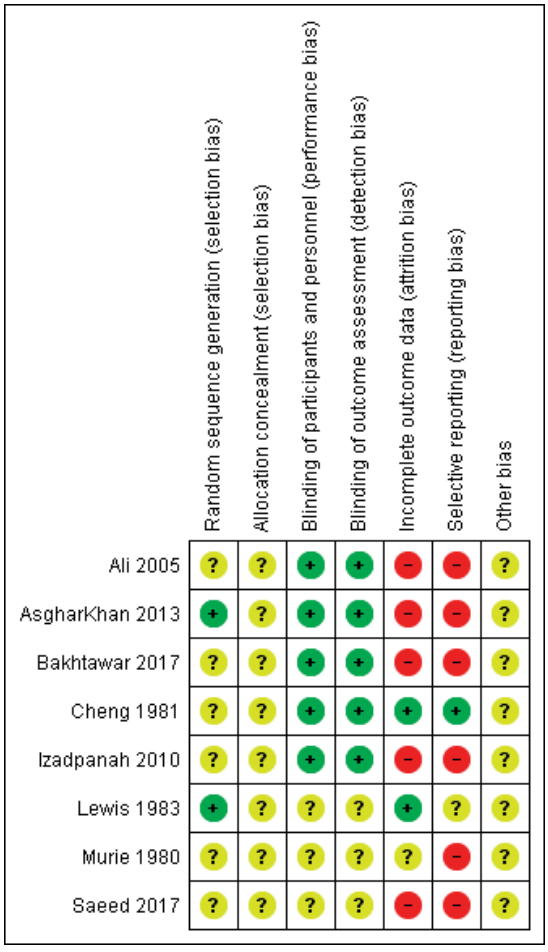

Figure 2. A Summary of risk of bias across included studies. **B** Summary of risk of bias for each included study.

and recurrence of complaints [18, 20]. GRADE evidence for recurrence within all included studies very low (Table 2).

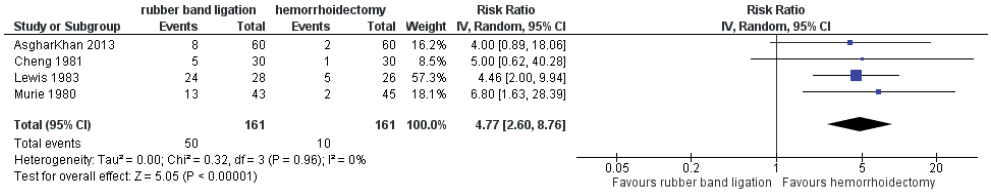

Figure 3. Recurrence rate. Relative risk values are shown with 95 per cent confidence intervals.

Postoperative pain

Patients experienced less post procedural pain after RBL as demonstrated in Fig. 4 (7 studies, 1110 patients, RR 0.17 (95% CI. 0.11-0.28); p<0.001). Heterogeneity between studies was moderate (I^2=76%,p<0.001). This statistical heterogeneity between the studies may be explained by variations in the method used to measure the postoperative pain or the moment it was scored. Often it was not even mentioned [17, 19, 20, 24]. Only Izadpanah et al used the visual analog scale to measure the pain score which was in favor of RBL (5 versus 8) [21]. The GRADE-rated evaluation showed low quality of evidence due to downgrading on risk of bias, indirectness and imprecision.

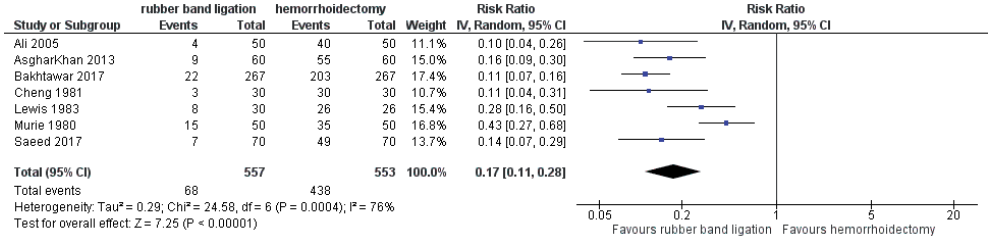

Figure 4. Postoperative pain. Relative risk values are shown with 95 per cent confidence intervals.

Postoperative bleeding

Seven studies including 1110 patients and 84 events described postoperative bleeding as an outcome. This was less common following RBL (random effects; RR 0.31 (95% CI 0.15-0.66); p=0.002). Heterogeneity between studies was moderate (I^2=48%)(Fig 5). None of the included studies describe how this outcome was defined. Following haemorrhoidectomy bleeding required reintervention in 15 patients [17, 18, 20, 22–24], Only Murie et al reported that transfusion was the intervention used for their only patient with bleeding after haemorrhoidectomy. In the RBL arm 1 patient needed readmission, no reintervention was described [22]. Quality of evidence was graded as very low for postoperative bleeding due to downgrading on risk of bias, indirectness and imprecision.

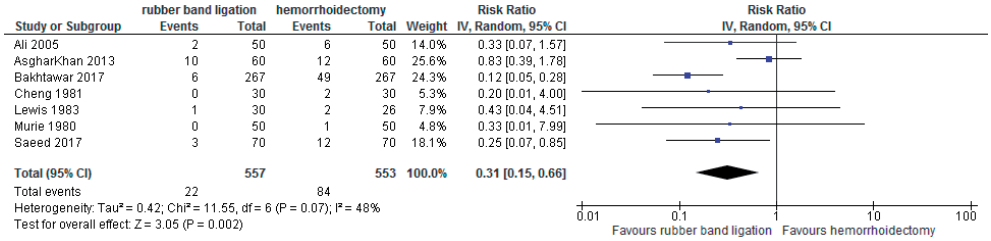

Figure 5. Postoperative bleeding. Relative risk values are shown with 95 per cent confidence intervals.

Urinary retention

Six studies reported data on urinary retention. All of them concluded that urinary retention requiring a urinary catheter is more common after haemorrhoidectomy than after RBL (6 studies, 1054 patients, random effects; RR 0.15 [95% CI. 0.09-0.25]; p<0.001) (Fig 6). The rate of urinary retention was 0-4% after RBL versus 6.7-56% after haemorrhoidectomy. Due to downgrading on risk of bias and indirectness quality of evidence was assessed low.

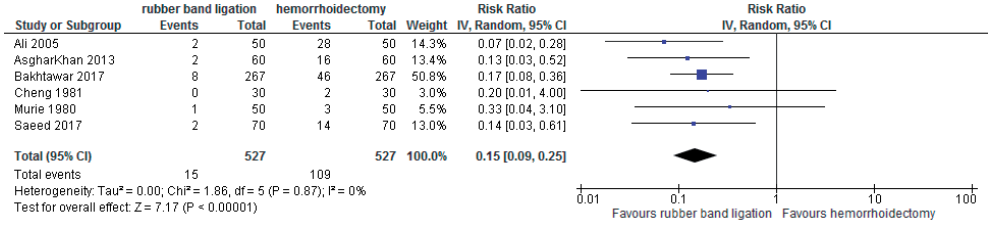

Figure 6. Urinary retention. Relative risk values are shown with 95 per cent confidence intervals.

ANAL CONTINENCE AND ANAL STENOSIS

Anal incontinence was scored in 3 studies [17, 19, 21] and none of them found incontinence after RBL(236 patients, random effects; RR 0.16 [95%CI. 0.02-1.28] p=0.080) (Fig 7)). Ashghar et al described incontinence in the haemorrhoidectomy group in respectively 5% and 7.7% of patients [19]. GRADE evidence for anal incontinence in all 3 studies was very low due to downgrading on risk of bias, indirectness and imprecision.

Five studies reported on anal stenosis (total of 942 patients, random effects; RR 0.11 [95% CI. 0.03-0.38] p<0.001) (Fig 8) . After haemorrhoidectomy 1-8.3% of patients developed anal stenosisd. Stenosis following RBL only occurred in 1 patient [19]. Quality of evidence was stated to be low for this outcome.

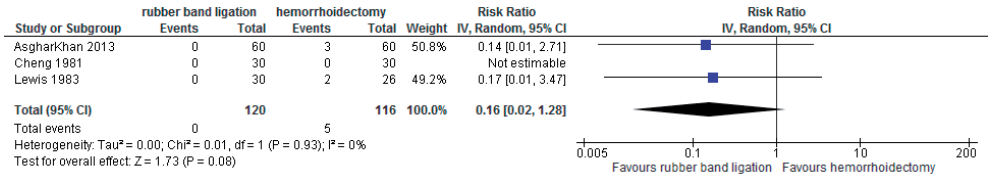

Figure 7. Anal incontinence. Relative risk values are shown with 95 per cent confidence intervals.

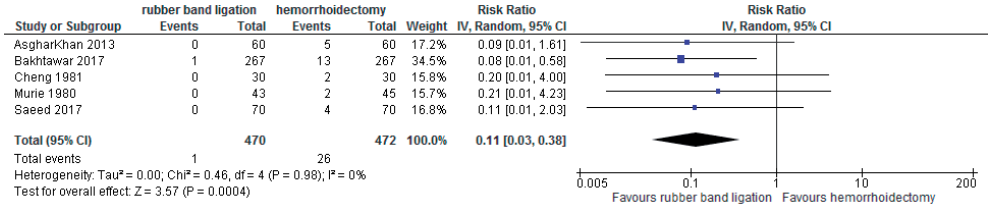

Figure 8. Anal stenosis. Relative risk values are shown with 95 per cent confidence intervals.

Patient satisfaction

Murie et al performed a patient assessment in which 93% of patients undergoing haemorrhoidectomy had an excellent to moderately successful result versus 88% of patients undergoing rubber band ligation [22]. Ashgar et al reported a patient satisfaction rate of 93% in the haemorrhoidectomy arm compared to 86% in the RBL arm [19]. This was due to the necessity of a repeat procedure in the RBL group. Regarding patient load Saeed et al reported a hospital stay of 2.5 days after haemorrhoidectomy versus 1 day after RBL [23]. Loss of working days following treatment was reported by Murie et al favoring RBL (32 versus 3 days): this difference was statistically significant.

Predictors for postoperative pain after RBL and haemorrhoidectomy

The variable significantly associated with more post procedural pain was age, which explained part of the heterogeneity. A meta-regression showed an age corrected RR of 0.23 for RBL compared to haemorrhoidectomy (95% CI 0.13-0.43, $p<0.001$). Only 5 trials were analyzed, as Cheng et al did not mention the standard deviation [17]. A meta-regression on sex was not associated with postoperative pain and did not explain the heterogeneity ($p=0.560$).

DISCUSSION

The present study gives an update of the results of the two most commonly used strategies in treatment of grade II and III haemorrhoids. The results of this review suggest that haemorrhoidectomy is superior to RBL in reducing symptoms but is associated with more

postoperative pain and adverse events. The review included only RCTs. Studies otherwise designed would result in an increase of bias. The overall quality of the included studies based on the Cochrane Collaboration's risk of bias tool was questionable. Incomplete outcome data (attrition bias) and selective reporting (reporting bias) were the major drawbacks. Furthermore, an important limitation was the lack of or poor definition of outcome measurements. The overall methodological quality of the included studies is moderate. Unfortunately none of the included studies described the randomisation process and 3 of the 8 studies compared more procedures than the two we were interested in. The included studies did not all use the same techniques of haemorrhoidectomy and RBL applications and only 3 studies reported the length of follow up which was respectively 3, 6 and 12 months [17, 21, 23]. The overall certainty of the evidence using the GRADE system was therefore low to very low (table2). It should be noted that 3 studies [18, 22, 23] are not of recent date but we still consider these relevant since the surgical procedures discussed have not changed since.

We defined control of haemorrhoidal disease by need for retreatment within 1 year or by self-reported residual complaints. Four studies report on effect of treatment and/or recurrence but a definition or follow up is not given making results hard to interpret. Three studies only mention effect of treatment on bleeding, prolapse [18, 23] or pruritus [22] while other symptoms of haemorrhoidal disease are not mentioned. This makes it difficult to comment on efficacy of treatment. Other trials reporting on the outcomes of these procedures also demonstrate a lower recurrence rate after haemorrhoidectomy with the same limitations [4, 9, 25]. Besides, should repeated banding be considered as recurrence or part of the treatment? For re-banding for instance two or three sessions is common and patients may find this a more agreeable than one operation if the results are comparable in the long run. Except for two trials [17, 24], which reported performing on session of RBL, none of the included trials describe the exact number of RBL sessions.

Overall, postoperative complications were more common after haemorrhoidectomy. Postoperative bleeding and pain were mentioned in all studies and was more common following haemorrhoidectomy. However, none of the studies defined bleeding and only one used a visual analog scale to assess postoperative pain [21]. In addition, the timing of these outcome assessments was not specified in most studies. Pain after RBL has been analyzed in other studies comparing RBL with more invasive procedures and was found to be less severe after RBL [12]. In a study by Watson et al [26] 183 patients were asked to rate their pain on a scale of 1-5 at different time points after RBL. The most severe pain was experienced at four hours following RBL and after one week 75% of the patients did not experience any pain at all. In the HubBle trial pain was less after RBL compared to a surgical procedure (HAL) at one day (3.4 versus 4.6) and one week (1.6 versus 3.1) following the procedure [12]. After 3 and 6 weeks pain scores were similar in both groups.

Urinary retention occurred far more often after haemorrhoidectomy. Rates of urinary retention are reported in the literature: 2-34% after haemorrhoidectomy and 0-0,4% after

RBL. [3, 27, 28] The mechanism responsible for urinary retention is thought to be the triggering of a reflex leading to inhibition of the detrusor muscle. Pain and stretching of the anal canal may induce this reflex. The extent of surgical resection is related to the risk of developing urinary retention, probably due to more postoperative edema and pain [29].

Anal incontinence following haemorrhoidectomy was reported in 3 studies [18, 20, 22] ranging from 0 to 7.7%. Anal incontinence after RBL was not reported. This is in concordance with the recent literature[30]. However, none of the studies used a validated scoring system for anal incontinence. Other literature using the Vaizey or Cleveland incontinence score mention similar scores for RBL and HAL[12]. Anal stenosis was found in one patient after RBL and was not common after haemorrhoidectomy either (26/472) but this difference was significant. This stresses the importance of a careful surgical technique in performing haemorroidectomy which is sometimes is considered simple surgery.

Treatment patients complaining of haemorrhoids aims to improve these symptoms, making quality of life an essential marker of success. Patient satisfaction was similar between groups but no validated questionnaires were used [20, 23, 24]. Literature on patient satisfaction following haemorrhoidal treatment is scarce. Brown et al found in a study comparing RBL with HAL found that patient satisfaction after RBL did not differ from HAL in the long term [31].

Murie et al reported 32 lost days of work after haemorrhoidectomy compared to three days after RBL[22]. Time until return to work and normal activities after haemorrhoidectomy has been reported to vary between 9 and 54 days [32]. This wide range can be due to the number of (one-, two-, three-) piles operated or the policyregarding postoperative pain management.

There are numerous studies on treatment of haemorrhoids with various techniques. This illustrates a lack of consensus about when to apply which technique for which symptoms. Treatment for a benign disease like haemorrhoids has to be safe and should be aimed at relieving symptoms. More conservative methods like RBL are reserved for grade II (but also III) haemorrhoids and more invasive surgical methods for grade III (but also II). That leaves a grey area in which the choice of treatment is not so evident. The gold standard for conservative methods is RBL and the gold standard for surgical procedures is haemorrhoidectomy [33]. Studies comparing these two methods are scarce and only 1 systematic review comparing 3 trials on this subject has been published [9].

Reliable outcome measurements relate to the definition of haemorrhoids. The choice of treatment is mostly based on gradation of haemorrhoids usually based on Goligher's classification [34]. However, symptoms do not reliably relate to Goligher's classification [35]. Clinical evaluation using only the Goligher scale could cause confusion regarding true symptomatic recurrence or symptom persistence. A more solid definition of failure or recurrence together with a validated score of symptoms is indispensable in evaluating treatment [36].

Van Tol et al recently analyzed outcome measurements used in trials on haemorrhoids [37]. Fifty-nine largely varying outcomes were identified. Based on these the authors developed four different core areas: symptoms, complications, recurrence and resource use/economical impact. When we consider these core areas in the analyzed trials symptoms are only rarely described. None of the studies used a validated symptom score. Recurrence was reported in 4 studies and was more common following RBL. Complications (postoperative pain, anal stenosis/incontinence, bleeding and urinary retention) were mentioned in 6 studies. Resource use/economical impact was not addressed in any of the studies.

It is also important to realize that haemorrhoidal disease is currently one of the most common disabilities. The condition often leads to disruption in an individual's personal and working life. Management has considerable cost implications and therefore economic consequences. None of the included trials mentions costs. Future studies should focus not only on and patient satisfaction with treatment but also on the economic impact of treatment.

CONCLUSION

The results of this review suggest that haemorrhoidectomy offers better symptom control compared with rubber band ligation in patients with grade II-III haemorrhoids, but is accompanied by more postoperative pain and complications. The main conclusion however must be that the studies analyzed are of poor quality and therefore no advice about treatment protocol can be given. Good quality trials with an emphasis on economic and patient related outcomes are needed. A multicentre randomised trial comparing RBL with haemorrhoidectomy has recently been initiated in the Netherlands.

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Table 1. Characteristics of studies included in the meta-analysis (haem=haemorrhoidectomy)

	Year	Country	Quality Assessment Score Risk of bias	Duration	II/III degree ratio	Total nr of patients	M/F ratio	Mean age (years)	Arms	Intervention	RBL	Haem	Technique RBL	Technique haem	Symptoms Bleeding	Symptoms Soiling	Mean follow up	Lost to follow up
Ali	2005	Pakistan	Unclear	7 months	20/80	100	1.3:1	50	2	RBL vs haem	50	50	2 bands per pile, 1 session	Milligan-Morgan	90	42	Till discharge	N/A
Asghar Khan	2013	Pakistan	Low	18 months	55/65	120	1:0.2	39	2	RBL vs haem	60	60	2 bands per pile	Milligan-Morgan	N/A	N/A	6 months	N/A
Bakhtawar	2017	Pakistan	Unclear	5 months	255/279	534	1:0.2	43	2	RBL vs haem	267	267	2 bands per pile	Milligan-Morgan	455	66	N/A	N/A
Cheng	1981	China	Low	14 months	120/0	120	1:0.9	42	4	RBL vs haem vs sclerotherapy vs anal dilatation	30	30	2 bands per pile	Milligan-Morgan	82	N/A	N/A	N/A
Izadpanah	2010	Iran	Unclear	20 months	72/78	150	1:1.5	40	3	RBL vs haem vs electrotherapy	51	47	N/A	Ferguson	120	N/A	3 months	N/A
Lewis	1983	England	Unclear	35 months	23/33	56	1:0.8	48	3	RBL vs haem vs cryotherapy vs anal dilatation	30	26	Max 3 bands, max 3 sessions	Milligan-Morgan	N/A	N/A	N/A	4
Murie	1980	Scotland	Unclear	24 months	32/56	88	1:0.5	52	2	RBL vs haem	43	45	2 bands per pile	Milligan-Morgan	84	-	12 months	4
Saeed	2017	Pakistan	Unclear	39 months	60/80	140	1:0.2	41	2	RBL vs haem	70	70	Max 2 bands per pile, 1 session	Milligan-Morgan	115	16	N/A	N/A

Table 2. GRADE evidence profile; Quality assessment per outcome.

Certainty assessment							№ of patients		Effect			
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**rubber band ligation**	**hemorrhoidectomy**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	**Importance**
Urinary retention												
6	randomised trials	serious [a,b]	not serious	serious [c]	not serious	none	15/527 (2.8%)	107/527 (20.3%)	**RR 0.15** (0.09 to 0.25)	**173 fewer per 1.000** (from 185 fewer to 152 fewer)	⨁⨁◯◯ LOW	CRITICAL
Postoperative pain												
7	randomised trials	serious [a,b,d,e]	not serious	serious [c]	not serious	none	68/557 (12.2%)	438/553 (79.2%)	**RR 0.17** (0.11 to 0.28)	**657 fewer per 1.000** (from 705 fewer to 570 fewer)	⨁⨁◯◯ LOW	CRITICAL
Postoperative bleeding												
7	randomised trials	serious [a,b,d]	not serious	serious [c]	serious [f]	none	22/557 (3.9%)	84/553 (15.2%)	**RR 0.31** (0.15 to 0.66)	**105 fewer per 1.000** (from 129 fewer to 52 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Anal stenosis												
5	randomised trials	serious [a,b,d]	not serious	serious [c]	not serious	none	1/470 (0.2%)	26/472 (5.5%)	**RR 0.11** (0.03 to 0.38)	**49 fewer per 1.000** (from 53 fewer to 34 fewer)	⨁⨁◯◯ LOW	CRITICAL
Recurrence												
4	randomised trials	serious [a,b,d,g]	serious [h]	serious [c]	serious [f]	none	50/161 (31.1%)	10/161 (6.2%)	**RR 4.77** (2.60 to 8.76)	**234 more per 1.000** (from 99 more to 482 more)	⨁◯◯◯ VERY LOW	CRITICAL
Anal incontinence												
3	randomised trials	serious [a,b,d]	not serious	serious [c]	serious [f]	none	0/120 (0.0%)	5/116 (4.3%)	**RR 0.16** (0.02 to 1.28)	**36 fewer per 1.000** (from 42 fewer to 12 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. Lack of allocation concealment and lack of blinding in all studies. This however, is unavoidable in most surgical RCTs.

b. Incomplete accounting of patients and outcome events. Of all studies, only three mentioned the loss to follow up.

c. Saeed, Murie, Bakhtawar, Khan, Ali not mentioned prespecified primary and secondary outcomes

d. No information on how the randomization sequence was generated

e. Unclear how postoperative pain was scored

f. Several outcomes were reported in few studies and few patients and few events.

g. Unclear how patient satisfaction was defined

h. Unclear how recurrence was defined

CHAPTER 2

HOLLAND TRIAL: COMPARISON OF RUBBER BAND LIGATION AND HAEMORRHOIDECTOMY IN PATIENTS WITH SYMPTOMATIC HAEMORRHOIDS GRADE III: STUDY PROTOCOL FOR A MULTICENTRE, RANDOMIZED CONTROLLED TRIAL AND COST-UTILITY ANALYSIS

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ABSTRACT

Introduction

Haemorrhoidal disease is one of the most common anorectal disorders which affects nearly half of the general population. Treatment of grade III haemorrhoids consists initially of conservative measures followed by rubber band ligation and haemorrhoidectomy when unsuccessful. Given the current guidelines and numerous modalities the obvious question which needs to be answered is which treatment is the best for grade III haemorrhoids. There is a need for evaluating treatment from the patient's point of view and transparency in surgical and non-surgical treatment outcome.

Methods and analysis

This multicentre, randomized controlled, non-inferiority trial with cost-utility analysis compares haemorrhoidectomy with rubber band ligation. Patients aged 18 years and older with symptomatic haemorrhoids grade III are recruited. Primary outcome measure is quality of life at 24 months measured with the EQ-5D-5L and in-hospital (in)direct costs and out-of-hospital postoperative costs. A key secondary outcome is recurrence at one year post procedure. Secondary outcomes are complaint reduction with proctology specific patient-reported outcome measurements (Haemorrhoid Severity Score, Procto-PROM, PROM-HISS, vaizey score), resumption of work, pain and complication rates. Data are collected at seven different time points. Standard post procedural care is followed.
A sample size has been calculated using a one sided alpha of 0.025 and a power of 80% with a standard deviation of 0.15 and a non-inferiority limit of 0.05. With stratification by centre and to adjust for 10% loss to follow up the total sample size will be 360 patients in total (180 per group).
Data will be analyzed according to the intention-to-treat and the per-protocol principle.

Ethics and Dissemination

The protocol has been approved by the Medical Ethics Review Committee of the Amsterdam University Medical Centres, location AMC. Findings will be disseminated in peer-reviewed journals and presented at conferences, whether they are positive, negative or inconclusive.

Trial registration number

NCT04621695, NTR8020

Strengths and limitations of this study

- This study addresses a knowledge gap regarding the optimal treatment of grade III haemorrhoids.
- Outcomes are not only based on clinical outcomes but also proctology specific patient-reported outcome measurements and cost-utility.
- As it is an evaluation of existing standard care, both Milligan-Morgan and Ferguson technique as well as RBL are not further standardized.
- It will prove to be challenging counselling patients to participate in a RCT, given the choice between invasive and non-invasive treatment.

INTRODUCTION AND RATIONALE

Haemorrhoidal disease is one of the most common anorectal disorders which affects nearly half of the general population[1]. In the Dutch population the prevalence is 13 per 1,000 patients per year [2]. Symptoms vary from blood loss, itching, soiling and prolapse and can be having a substantial impact on patients activities. Haemorrhoids are described most often by the Goligher classification: a universally used classification focusing on the degree of prolapse [3]. However in a large colonoscopy-based study no significant association could be demonstrated between haemorrhoid grade and haemorrhoid symptoms [1]. Treatment consists initially of conservative measures such as lifestyle advice, diet and toilet behavior [4]. In addition, various surgical procedures are possible, of which haemorrhoidectomy is considered the gold standard, an assumption recently confirmed in a British trial [5]. The most commonly used, low-invasive procedure is the rubber band ligation (RBL). With better understanding of origin and pathogenesis of haemorrhoids new surgical techniques were developed. In haemorrhoids III the current national guideline advised to treat either by haemorrhoidectomy or by rubber band ligation. If symptoms persist after four sessions of rubber band ligation than haemorrhoidectomy should be considered. Evidence for this policy is however low grade. The guideline is also not specific on residual complaints and doesn't adequately address the patients related aspects. Given the current numerous modalities the obvious question which needs to be answered is which treatment is the best. A systematic review of three small heterogeneous trials concludes that RBL leads to recurrence more often, but on the other hand is accompanied by less pain and with fewer complications and a lesser burden for the patient [6]. It is also unclear which of the two most common procedures, namely the open haemorrhoidectomy and the RBL, is preferable from a health economic point of view. There are hardly any studies that have looked at the cost effectiveness of the various treatments. Only study compared stapled haemorrhoidopexy with RBL, favoring RBL [7]. Another recent trial, published in 2016, compares haemorrhoidal artery ligation (HAL) with RBL, with HAL clearly entailing the most costs, even though the analysis includes the chance of repeated RBL treatments

[8]. Results from recent trials suggest that haemorrhoidectomy and repeated rubber band ligation are effective in treatment of grade II and III haemorrhoids [5,8]. An interesting conclusion from a recent systematic review regarding operative procedures for haemorrhoidal disease is that all procedures have their own advantages and disadvantages [9]. Therefore items like patient expectations and priorities and costs should be taken into account when deciding which procedure to advice and perform. There is a need for evaluating treatment from the patient's point of view and transparency in surgical and non-surgical treatment outcome. So far there is no sufficiently large trial that meets that demand. A recent national survey amongst Dutch surgeons with expertise in haemorrhoidal disease demonstrated varying practices in treatment of haemorrhoids [10]. A similar survey was conducted in Italy including more than 32000 patients [11]. Although (and maybe because of) the most frequently used treatment modalities differed from the ones in the Dutch study the conclusion is the same: necessity of developing practical (Dutch and European) guidelines for treatment of haemorrhoidal disease. Therefore, a well-designed study is essential to compare efficacy and safety of repeated rubber band ligation and haemorrhoidectomy for grade III haemorrhoids in a multicentre randomized setting.

Hypothesis

Because rubber band ligation is a lesser burden on patients, the hypothesis is that rubber band ligation performed in two sessions is not inferior compared to haemorrhoidectomy on quality of life (QOL) in patients with grade III haemorrhoids.

METHODS AND ANALYSIS

Study design

The HollAND trial concerns a randomized, controlled, multicentre non-inferiority trial comparing rubber band ligation with haemorrhoidectomy for treatment of grade III haemorrhoids. This trial was registered at the Dutch Trial Registry (NL8020) and at ClinicalTrials.gov (NCT04621695) prior to the start of inclusion. The protocol was drafted in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statements [12]. Patients will be accrued by all ten participating clinics. The design involves allocation of all appropriate consecutive patients with symptomatic grade III haemorrhoids to either rubber band ligation or haemorrhoidectomy. After eligibility has been established and patient details noted patients will be randomized to either one of the treatment groups. Assignment to one of the two groups is not blinded. Data will be analysed on 'intention to treat' basis in case patients are not subjected to the randomised treatment modality.

Import changes to methods after trial commencement

Recruitment commenced on 8 October 2019, and, following this, in response to early observations, changes were made to the protocol and trial methods.

In August 2020 (substantial amendment 8, protocol version 8.0), a change was made to the eligibility criteria to not exclude patients using oral anticoagulants. This following a site set-up visit where the principal investigator mentioned the amount of excluded patients as a result of this exclusion criterion.

Eligibility criteria

Inclusion criteria

- Haemorrhoids grade III (Goligher classification)
- Age 18 years and older
- Sufficient understanding of the Dutch written language (reading and writing)

Exclusion criteria

- Previous rectal or anal surgery with the exception of rubber band ligation
- Previous surgery for haemorrhoids (at any time)
- More than one injection treatment for haemorrhoids in the past 3 years
- More than one rubber band ligation procedure in the past 3 years
- Previous rectal radiation
- Pre-existing sphincter injury
- Inflammatory bowel disease
- Medically unfit for surgery or for completion of the trial (ASA>III)
- Pregnancy
- Hyper-coagulability disorders
- Patients previously randomised to this trial
- Not able or willing to provide written informed consent

Sample size calculation

The sample size calculation is based on a non-inferiority design. The primary outcome of the study is Quality-adjusted Life Years (QALYs). We have used the result from an earlier study in which rubber band ligation was compared to haemorrhoidal artery ligation, which is similar to haemorrhoidectomy [13]. For the sample size calculation we hypothesized an equal QALY between the two groups. Using a one sided alpha of 0.025 and a power of 80% with a standard deviation of 0.15 and a non-inferiority limit of 0.05 a total amount of 142 patients are needed in each treatment arm. To account for the stratification by centre, by using an intraclass correlation of 0.01 and 15 patients per centre, this number was increased to 162 patients per treatment arm. To adjust for 10% loss to follow up the total sample size will be 360 patients in total.

Investigational treatment

Rubber band ligation

Rubber band ligation, first described by Barron, is performed by a suction device that allows a rubber band to be applied at the base of the haemorrhoid via a proctoscope. Maximal suction force used is 40 mmHg. A maximum of 3-4 bands are used per session. This rubber band constricts the blood supply causing it to become ischaemic before being sloughed approximately 1–2 weeks later. The resultant fibrosis reduces any element of haemorrhoidal prolapse that may have been present. No sedation is required for this day-care procedure. Patients are asked to administer an enema 2 hours prior to the procedure. This is a very commonly performed procedure in all participating clinics.

Haemorrhoidectomy

There are two main excisional procedures currently carried out: open (Milligan and Morgan) and closed (Ferguson). Both have the intention of excising the haemorrhoidal cushions. The procedure is performed under either general or spinal anaesthesia in a day-care setting. Patients were asked to administer an enema 2 hours prior to the procedure.

Main study endpoint

Primary outcome measure is QOL at 24 months measured with the EQ-5D-5L with Dutch rating; in-hospital direct and indirect costs and out-of-hospital postoperative costs (measured with EQ-5D-5L and cost incremental analysis).

Secondary study endpoints

Key secondary outcome

This is recurrence at one year post procedure. Recurrence will be defined the same as in a systematic review and recent clinical trial [6,13]. A patient's self-reported assessment with a dichotomous question will be asked at 6 weeks and at 6, 12 and 24 months: "At the moment, do you feel your symptoms from your haemorrhoids are: (1) cured or improved compared with before treatment; or (2) unchanged or worse compared with before treatment?"

Any patient who answers '1' but has required further treatment since the initial procedure will be reclassified as '2', identified via hospital records, their consultant and patient questioning.

Patient-reported outcomes (PRO)

To measure QOL (at 12 months) and functional outcomes, several questionnaires will be used (table 1); the EQ-5D-5L and the Vaizey faecal continence score [14] to assess severity of faecal incontinence. Complaint reduction is assessed by the Hemorroid Symptom Score

Table 1. Trial scheme with planning QoL and PRO questionnaires.

	Baseline	Day 1	1 wk	6 wks	6 mths	12 mths	24 mths
EQ-5D-5L	●	●	●	●	●	●	●
ProctoPROM	●		●	●	●	●	●
PROM-HISS	●		●	●	●	●	●
Rome IV criteria	●						
HSS	●			●	●	●	●
Vaizey	●			●	●	●	●
iMCQ				●	●	●	●
iPCQ				●	●	●	●
Analgesia		●	●	●			
Patient reported recurrence				●	●	●	●
VAS pain		●	●	●			
Return to work			●	●			

(HSS) [15], the proctoPROM [16] and PROM-HISS which are proctology specific patient-reported outcome measurements. The proctoPROM is a validated questionnaire consisting of five questions concerning patients well-being. The PROM-HISS is recently developed in Maastricht (the Netherlands) and relates the symptoms [17]. Post procedural pain was also scored by a visual analog scale.

Participants are asked to complete the questionnaires at baseline, day 1, 1 and 6 weeks and 6, 12 and 24 months (table 1). These will be send to them by email and access to a web tool (Castor) will be provided. If the patient does not have an email account, the questionnaires will be send to the patients' home addresses, accompanied by a return envelope provided with postage stamps and the address of the hospital. They are given the opportunity to fill out the forms on a secure participant portal within the trial website. In case of unreturned forms, participants will be contacted by email or telephone to obtain the missing data.

Clinical outcomes

Complications, need for further treatment, absence from work.

Randomisation

After fully signed written informed consent, patients will be randomly assigned to be treated by either RBL or haemorrhoidectomy. Following full written consent, baseline data will be collected and patients will be randomly allocated in a 1:1 ratio to either treatment. Neither the recruiters nor the trial project group will be able to access the randomisation sequence. Randomization will be done web based using Castor. The randomization sequence will be computer generated. A unique record number will be generated and the allocation will be disclosed. To achieve a balanced distribution of the treatments among participating centres, randomization will be stratified.

For those patients who do not consent to participate, an 'Ineligible/Declined' form will be completed by a local clinical team member, detailing non personal data, including the reason(s) for the participant declining, or the ineligibility criterion. These data will be recorded in the study database.

Patient and Public Involvement

The patient organisation Bekken4all was consulted in the initial preparation phase of the study proposal to make sure that this considered relevant in a patients perspective. The patient organisation is actively involved in further preparing the study protocol. Special attention is paid to patient load of the trial and to patient related outcome. Furthermore the patient organisation assisted in preparing patient information. A contact person was installed whom participants can address in case of questions. Several meetings are organised during inclusion to assure progress; another meeting when analysing results and a final meeting when preparing conclusive paragraphs and implementation.

Participant time line

During the preparation phase (3-6 months) the logistic infrastructure of the trial was set up in collaboration with all participating centres and the patient federation. Eligible patients are recruited in 10 hospitals across the Netherlands. Inclusion started in October 2020 in the Proctos Kliniek as first centre after which other participating centres followed. It is expected that around 50% of those eligible will agree to be randomized. From experience, recruitment rate will always be lower than anticipated, therefore rate of inclusion has been set at the lower rate of inclusion speed. Trained research personnel will take care of and assist with inclusion, randomization and data synthesis, so that adequate data collection is maximized and warranted. Based on these numbers the recruitment period is anticipated to last 12-18 months. It is estimated that 360 patients will have been randomized and included by then. The follow up period will be 24 months. The data analysis phase is expected to be finalized in 6 months.

Recruitment

It is recognized that, when given the choice between a non-invasive and an invasive medical procedure a substantial proportion of patients may choose the non-invasive procedure. Therefore, in order to maximize recruitment patients will be screened before randomization. During a consecutive telephone recruitment appointment or an email information will be given and patient's treatment preference will be explored. This appointment is regarded as an integral part of the information exchange necessary for informed decision making. Using this approach, rate of recruitment will also be optimised. A log of these screening appointments will be kept.

A research nurse/consultant in every participating centre, responsible for the support and care of patients in the trial, may further improve accrual rate.

Data collection

All medical, quality of life and cost data will be collected at the individual hospitals before central collection into the trial database. Data collection will be facilitated by case record forms in Castor. No hospital patient identification numbers will be revealed to the coordinating centre. All patient data are coded and identified by means of a randomization number. This randomization number does not include initials or date of birth from the patient. The local investigator will have a decoding list with randomization numbers and hospital patient identification numbers of his patients in the investigator site file. At each trial operation/procedure, the performing surgeon(s) are noted in the case record form.

In accordance to section 10, subsection 4, of the Medical Research Involving Human Subjects Act (WMO), the investigator will inform the subjects and the reviewing accredited medical ethical committee if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

Statistical analysis

Data will be analyzed according to the intention-to-treat and the per-protocol principle. No interim analysis is planned. Analyses will be done using SPSS version 26.0. The primary outcome and key secondary outcome, namely quality of life and recurrence, will be analyzed using a one sided alpha with a significance level of 0.025. Descriptive methods will be used to assess quality of data, homogeneity of treatment groups and endpoints. Normality of the data will be analyzed with histograms. The mean difference in the QALYs between the two groups will be assessed through linear regression in which stratification factor (participating center) will be included, together with the lower bound of the 95% confidence interval. If the lower bound of the 95% confidence interval is higher/less negative than -0.05 QALY difference and the 95% confidence interval does not include this non-inferiority limit in both the intention to treat and per-protocol analysis, non-inferiority is considered proven for this endpoint. The non-inferiority boundary for recurrence at one year post procedure is set on a difference of 10%. Rubber band ligation performed in two sessions will not be inferior compared to haemorrhoidectomy only when the primary outcome appear to be non-inferior in both the intention-to treat and the per-protocol analysis. Patients excluded from the per-protocol analysis will be those who non-complied with eligibility, missed windows, consent and treatment issues, which included patients who did not receive their allocated treatment. Secondary outcomes will be described by reporting differences with 95% confidence intervals and will be analyzed using either a two-sided t-test or Mann-Whitney U test for continuous data and a Chi Square test for categorical data. A p-value of <0.05 is considered a threshold for significance. With several questionnaires on different time points a mixed model will be used to analyze repeated measurements.

Some missing data can be expected, we will use multiple imputations when more than 5% data is missing. If missing data is at random this will be handled through multiple imputations with predictive mean matching.

Cost effectiveness analysis (CEA)

General considerations

We hypothesized that rubber bad ligations is non-inferior to a haemorrhoidectomy for the outcome quality of life. The economic evaluation of rubber band ligations against haemorrhoidectomy will be performed as a cost utility analysis from a societal perspective with the cost per QALY as the main outcome measurement. The cost-utility analysis can be used for policy making and composition of a guideline. We will base the cost utility analysis (CUA) on a time horizon of 24 months, because we expect that differences in health outcomes and costs will be presented in the first 24 months. No discounting of effects and costs will be done. Furthermore a CUA with a lifelong time horizon will be made using extrapolation and model based techniques. To account for uncertainties a probabilistic sensitivity analysis will be performed.

Incremental cost-effectiveness ratios will be calculated as the difference in costs per QALY sampling variability in the 24 month time horizon. CUA will be accounted for by bias-corrected and accelerated non-parametric bootstrapping. Results will be reported along with their 95% confidence intervals and displayed graphically with cost-effectiveness planes and with cost-effectiveness acceptability curves. One-way and multi-way sensitivity analyses will be done for the unit costs of health care.

Cost analysis

Medical costs, patient costs and productivity losses will be included in the evaluation. The medical costs cover the costs of surgery, anesthesia, theater, peri-operative materials, inpatient stay at the ICU and the wards and medications. The patient costs include out-of-the pocket expenses like over-the-counter medication and health care related travel costs. Productivity losses are costs resulting from being absent and decreased productivity during work.

Hospital health care utilization will be retrieved from case report forms (CRF) and hospital information systems. Data on out-of-hospital health care will be gathered with the iMTA Medical Consumption Questionnaire (iMCQ) adjusted to the study setting. The productivity losses will be documented with the iMTA Productivity Cost Questionnaire (iPCQ). Questions on out-of-pocket expenses will be added to these patient questionnaires. Patients will be asked to fill in questionnaires at 1 week, 6 weeks, 6, 12 and 24 months after inclusion in the study.

Costs will be price indexed based on consumer price indices (CPI). Costs will be calculated for individual patients as the product sum of the resource use and the respective unit costs.

Patient outcome analysis

Patients will be asked to complete the EQ-5D-5L health status questionnaire at 1 week, 6 weeks, 6, 12 and 24 months after randomization. These questionnaires will be included in the CRFs. The EQ-5D-5L scoring profiles can be converted into a health utility score based on general population based Dutch tariffs [18]. QALYs will be calculated for each patient after linear interpolation between the successive health utility assessment over time.

Budget impact analysis (BIA)

General considerations

The budget impact of rubber band ligations compared to haemorrhoidectomy will be assessed from governmental and insurer perspectives in accordance with the ISPOR guidelines [19,20]. The governmental perspective will be from both the broad societal perspective as well as the budgetary health care framework (BKZ) and can be used to help setting priorities in health care optimization. The insurers perspective can be used to examine the net financial consequences of treating third degree haemorrhoids by two sessions of rubber band ligation first. The budget impact analyses can be used to guide reimbursement decisions and price and volume negotiations between insurer and health care provider.

The budget impact study will reflect the net savings of rubber band ligations compared to haemorrhoidectomy. The time horizon of the budget impact will be three years and will be presented per year.

Several scenarios will be examined, full implementation, partial implementation (50%, 75%) and gradual implementation over the years. Sensitivity analyses will be performed for the percentage of patients in which the rubber band ligation will be performed as well as sensitivity analysis for differences in number of patients with a relapse.

Cost analysis

For the budget impact analysis from a governmental societal perspective the most recent guidelines for (unit) costing in health care research will be applied [21]. In case of impact assessments concerning premium financed health care and from the insurer perspective, existing tariffs at the time of analysis will be used (DBC costing).

Other study parameters

Baseline characteristics will be collected and described with frequencies (numbers, mean or median with respectively percentages, standard deviation or quartiles). Differences between groups will be analyzed using Independent Students T-test for normally distributed numerical data, Mann-Whitney U tests for not normally distributed numerical data and chi-square testing for categorical data.

ETHICS AND DISSEMINATION

Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki and in accordance with the WMO and other European guidelines, regulations and acts such as the GDPR (General Data Protection Regulation (in Dutch: Uitvoeringswet AVG). The protocol has been approved by the Medical Ethics Review Committee of the Amsterdam University Medical Centres, location AMC. Findings will be disseminated in peer-reviewed journals and presented at conferences, whether they are positive, negative or inconclusive.

Recruitment and consent

The informed consent procedure should be performed by the treating physician or a representative that is aware of the details and complications of both treatments included in the trial. Therefore, it is the trial's preference that the consent is taken by the treating physician. The information offered to the patient or representative contains: - A statement that the trial involves research - A full and fair explanation of the procedures to be followed - A full explanation of the nature, expected duration, and purpose of the study - A description of any reasonable foreseeable risks or discomfort to the patient - A description of any benefits which may reasonably be expected - A statement that patient data will be handled with care and confidentiality and the period of time the data is saved (15 years) - A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits, in which case the patient will receive standard treatment with the same degree of care. - Patients are given ample time to decide whether or not to participate in the study. Minors and legally incompetent adults are excluded from the trial.

Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO. The sponsor has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

Methods of dissemination of results

Before starting recruitment the trial protocol will be presented at a meeting of the Dutch Society of Surgery. Initiation of the trial is also made knowledgeable at the website of this same society, as to reach the majority of surgeons/proctologists. When the trial has been

completed results will be discussed first during a meeting of the Dutch Society Coloproctology/Surgery. In this session experiences from other surgeons treating haemorrhoids will be heard, plans following the trial outcome will be outlined and practical aspects of implementation will be discussed. This will be followed by presentation of results at the annual meeting of the Dutch Society of Surgeons (NVvH). There will then be enough support to adjust the Dutch proctology guideline. We expect several manuscripts prepared from this research to be published in high impact peer reviewed journals, including publication of this protocol itself. We will publish the results and a lay summary on the study website upon study completion.

The techniques under investigation are techniques that are long-existing and wide spread so no extra training is expected to be required.

The actual behaviour change of the health care providers may be however hindered by lacking to acknowledge the reason of change/adjustment of treatment. It is not unusual to encounter reluctance on changing long standing habits. Education as proposed is one way to tackle this. Recommendations and education will be implemented in the curriculum of general surgery and proctology trainees. Another way is to use focus groups of patients sharing their experiences. These experiences will be shared with the patient federation.

Monitoring and safety

Monitoring will be performed in compliance with Good Clinical Practice (GCP) and other rules and regulations in order to achieve high quality research and secure patient safety. Qualified and independent monitors from the Leading the Change trial agency will have access to the data and source documents of the trial. Based on the Site Specific Monitoring program of the Leading the Change trial agency, site evaluation visits will be performed to review the quality of the participating sites. All (serious) adverse events, suspected unexpected serious adverse reactions (SUSAR) and any other significant problems are reported to the Medical Ethics Review Committee (MERC) using an online submission system.

A DSMB is not necessary for this study as it compares two already well established treatment modalities for haemorrhoidal disease which will not pose additional risk to the subjects in the study.

Annual progress report and amendments

The sponsor/investigator will submit a summary of the progress of the trial to the accredited MERC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments. All substantial amendments will be notified to the MERC and to the competent authority.

Public disclosure and publication policy

Main presentations and main publications will be in the name of the Study Group. This will apply when the work underpinning a publication has been carried out by a group and no one person can be identified as having substantially greater responsibility for its contents than others. In such cases authorship will be presented by the collective title and there will be a footnote of the names of the people and institutions represented. Other manuscripts, such as describing satellite studies, will have individual authorship. Publication or presentation of data can only be possible when the authors state that the corresponding patients were included in the trial. If a centre violates these rules, exclusion from the trial and exclusion from authorship will be the consequence. Decisions on authorship should be justified to, and require agreement from the Project Management Group. The sponsor will have no influence on implementation of the research and content of publications. Publication of data will not take place until accrual of patients has been completed.

Data sharing statement

Data will be available upon reasonable request. This will include deidentified participant data and statistical codes. After an embargo period the data will be accessible for further research and verification. The request should be made to the corresponding author and will be considered by the HollAND trial project group.

COLLABORATORS

The HollAND projectgroup consists of the trial governors: dr I.J.M. Han-Geurts, surgeon Proctos Kliniek and prof dr W.A. Bemelman, head of Surgery AMC;
The HollAND Trial Steering Committee: prof dr W.A. Bemelman, dr I.J.M. Han-Geurts, surgeon Proctos Kliniek**,** dr C.I.M. Baeten, surgeon Groene Hart Ziekenhuis**,** dr E.R. de Graaf, surgeon Ysselland Hospital**,** dr S.M.M. de Castro, surgeon OLVG, dr A.H.W. Schiphorst, surgeon Diakonessenhuis, dr S. van Dieren, epidemiologist/statistician department of Surgery AMC.

Contributors

IJMH, WAB and SvD have all contributed to conception and design of this trial protocol. IJMH and WAB initiated the project and are de chief investigators. The protocol was drafted by IJMH and was refined by WAB. Statistical advice was provided by SvD. LD was responsible for drafting the manuscript. All authors have read and approved the final manuscript.

Trial sponsor

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COMPETING INTERESTS

None declared.

Protocol version 8, d.d.22-07-2020

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CHAPTER 3

HAEMORRHOIDECTOMY VERSUS RUBBER BAND LIGATION IN GRADE III HAEMORRHOIDAL DISEASE: A LARGE RETROSPECTIVE COHORT STUDY WITH LONG-TERM FOLLOW-UP

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ABSTRACT

Background

Standard therapy for grade III haemorrhoids are rubber band ligation (RBL) and haemorrhoidectomy. The long term clinical and patient reported outcomes of these treatments in a tertiary referral centre for proctology were evaluated.

Methods

A retrospective analysis was performed in all patients with grade III haemorrhoids who were treated between January 2013 and August 2018. Medical history, symptoms, re-interventions, complications and patient reported outcome measurements (PROM) were retrieved from individual electronic patient files, that were prospectively entered as standard questionnaires in our clinic.

Results

Overall, 327 patients (163 males) were treated by either RBL (n=182) or haemorrhoidectomy (n=145). Median follow up was 44 months. Severity of symptoms and patient preference led to the treatment of choice. The most common experienced symptoms were prolapse (83%) and blood loss (70%). Haemorrhoidectomy was effective in 96% of the cases as a single procedure, while a single RBL procedure was only effective in 52%. Thirty-five percent of the RBL group received a second RBL session. Complications were not significant different, 11 (8%) after haemorrhoidectomy versus 6 (3%) after RBL. However, four fistulas developed after haemorrhoidectomy and none after RBL ($p<0.05$). Pre-procedure PROM score was higher in the haemorrhoidectomy group whereas post procedure PROM score did not significantly differ between the groups.

Conclusion

Treatment of grade III haemorrhoids usually requires more than one session RBL whereas one time haemorrhoidectomy suffices. Complications were more common after haemorrhoidectomy. Patient related outcome did not differ between procedures.

INTRODUCTION

Haemorrhoids are one of the most common anorectal disorders [1] with an estimated prevalence up to 39% in the general population by screening colonoscopies. Of these, 45% experienced complains [2]. Patients suffering from haemorrhoidal disease complain of blood loss, soiling, anal pain, prolapse and pruritus.

Initial management of haemorrhoids is conservative and consists of lifestyle-, diet-, and toilet behavior advice [3]. In case of persisting symptoms in grade II and III haemorrhoids, the next step is usually a nonsurgical office based procedure like rubber band ligation (RBL), injection sclerotherapy or infrared coagulation. The most popular nonsurgical procedure is RBL [4,5] which is considered first line therapy for grade I-III in several guidelines [6–8]. Although complications are rare, recurrence is common and repeated rubber banding may be required [9]. Surgery is reserved for grade IV haemorrhoids or those which failed nonsurgical treatment [10,11]. Besides traditional excisional haemorrhoidectomy, multiple other procedures have been developed with the intention to decrease postoperative discomfort such as the haemorrhoidal artery ligation (HAL), stapled haemorrhoidectomy with mucopexy (SH), haemorroidoplasty and radiofrequency ablation [9,12–14]. Despite the variety of surgical procedures, traditional excisional haemorrhoidectomy has proven to be the most clinical- and cost effective procedure and is therefore still considered the gold standard [18,21].

A recent national survey amongst Dutch colorectal surgeons demonstrated varying practices in treatment of haemorrhoids [16]. A similar survey was conducted in Italy including more than 32000 patients [17]. Literature data on the clinical outcome of treatment for specifically grade III haemorrhoids, are rare. The only published systematic review, in which three small heterogeneous trials were analyzed, was in favor of haemorrhoidectomy because off a lower frequency of retreatment [18]. Dutch, and recently developed European (ESCP) guidelines provides guidance on the most effective (surgical) treatment for patients with haemorrhoidal disease [19,20]. In summary, RBL is the preferred treatment in grade I and II with a maximum of four sessions and in grade IV surgical intervention is recommended. In case of grade III, both guidelines are inconclusive; RBL can be considered as first treatment before surgery is considered [19].

The aim of the present study was to evaluate clinical and patient reported results of treatment of grade III haemorrhoids by RBL and excisional haemorroidectomy in a tertiary referral center.

PATIENTS AND METHODS

Study design and study population

The Proctos Clinic is a tertiary center for proctology with five experienced proctologic surgeons. This single center cohort study was conducted between January 1st 2013 and August 1st 2018. All patients aged 18 years and above diagnosed with grade III haemorrhoids and treated by RBL or haemorrhoidectomy, were included. All patients gave written informed consent for the procedure. Exclusion criteria were injection sclerotherapy or RBL in the past three years, prior proctologic surgical interventions, anal or rectal radiotherapy, anorectal malignancy, known inflammatory bowel disease (IBD) or spinal cord injury.

Diagnosis and grading was established by the treating surgeons by medical history, physical examination and proctoscopy. When indicated, a colonoscopy was performed to exclude pathology other than haemorrhoids. Depending on severity of symptoms, RBL and haemorroidectomy were both explained and offered to all patients presenting for the first time with symptomatic haemorrhoids grade III unless contra indicated, following Dutch and ESCP guidelines. After initial clinical assessment and counseling definite choice of treatment was made following the concept of shared decision making.

Demographic and clinical variables were prospectively recorded and could be retrieved from medical records. Follow-up data were recorded for a minimum of one year after last intervention. As part of our policy and patient care, upon visiting our clinic all patients are asked for consent of using their medical data anonymous for future research and permission to approach them for subsequent follow up. In case permission is not granted, a notification in the electronic patient file is made.

Primary and secondary endpoints

The primary outcome was clinical effectiveness measured as re-intervention within one year post procedure.

Secondary outcomes were: 1) number of re-interventions within one year 2) post-operative complications (haemorrhage requiring hospitalisation, emergency reoperation or blood transfusion; acute haemorrhoidal thrombosis; peri-anal fistula; urinary retention requiring catheterization, fissure in ani; faecal incontinence) and 3) the PROM score.

Complications as haemorrhages and anal fistulas were classified by Clavien-Dindo (CD) as shown [21]. Only grade 2 and above were documented.

The proctology specific PROM score (Proctoprom) is a questionnaire comprising of five questions concerning impact of proctologic symptoms on well-being (suffering from anal symptoms during daily activities, toilet visit, social activities, relationship and intimacy and worrying about complaints) and is used for many years in our clinic to evaluate the treatment. The PROM questionnaire has a score range from 0 to 10 per question and the actual score is the mean of the five questions, 0 being perfect and 10 could not be

worse. All items but one are mandatory. If four items are scored, the PROM score is calculated as the average of the four questions. In February 2020 the validated Proctoprom was published [22]. The questionnaires were recorded during the first outpatient visit (PROM1) and after the intervention (PROM2). Unfortunately, PROM2 was not collected after their last visit to the clinic in all patients. Therefore, all patients were approached by email and received another questionnaire in 2019, thus extending the follow up by PROM2.

Interventions

RBL was performed in an outpatient setting. Via the proctoscope (Sapi Med® 18 mm) a device (Hemoband Disposable Ligator®) was placed and the rubber band was applied at the base of the haemorrhoid. A maximum of 3-4 bands was used per session. Oral analgesics were recommended before the intervention to reduce pain afterwards.

Traditional excisional haemorrhoidectomy was performed by using the closed technique (Ferguson) [11] with diathermy with patient positioned in lithotomy position. The procedure was performed under anesthesia in a day-care setting. All patients received post-operative laxatives and oral analgesics. Opioids were administered when necessary. No antibiotics were prescribed.

All interventions were performed by one of the five experienced proctologic surgeons.

Statistical analysis

Descriptive statistical analysis (frequency, percentage, mean, interquartile range) were performed to describe the research sample and questionnaire items. Categorical outcome data was analysed using the Chi-square test. To evaluate treatment the two PROM questionnaires (before and after procedure) were compared in each group using the paired t-test. Comparison between these groups was measured with the unpaired samples t-test. A two sided p-value of <0.05 was considered statistically significant. SPSS Statistics for Windows, version 25.0, was used.

RESULTS

Patient and treatment characteristics

Overall, 552 patients were referred with haemorrhoidal disease grade 3 and treated by RBL or haemorrhoidectomy. A total of 225 patient were excluded due to exclusion criteria and 327 were entered in the study. They were treated by RBL (n=182) or haemorrhoidectomy (n=145). The median age was 54 (range 24-92) and did not differ between the groups. Males and females were equally distributed in both groups.

Although grade III haemorrhoids are defined by prolapse, 17% did not experience this as a main symptom (table 1). There were no significant differences in distribution between treatment groups in number of piles affected.

Table 1. Baseline characteristics with patient reported symptoms.

	RBL (n=182)	Hemorrhoidectomy (n=145)	P-value
Gender, n (%)			*0.657*
Male	93 (51)	70 (48)	
Female	90 (49)	76 (52)	
Age, median (range)	55 (26-92)	52 (24-78)	*0.078*
Symptoms, n (%)			
Blood loss	125 (69)	103 (71)	*0.717*
Soiling	56 (31)	52 (36)	*0.346*
Anal pain	59 (32)	59 (40)	*0.133*
Prolapse	151 (83)	121 (83)	*1.0*
Pruritis	23 (13)	23 (16)	*0.427*
Number of piles			
1 pile	88 (28)	64(21)	*0.106*
2 piles	49 (16)	57 (18)	*0.075*
3 piles	28 (9)	24 (8)	*0.793*

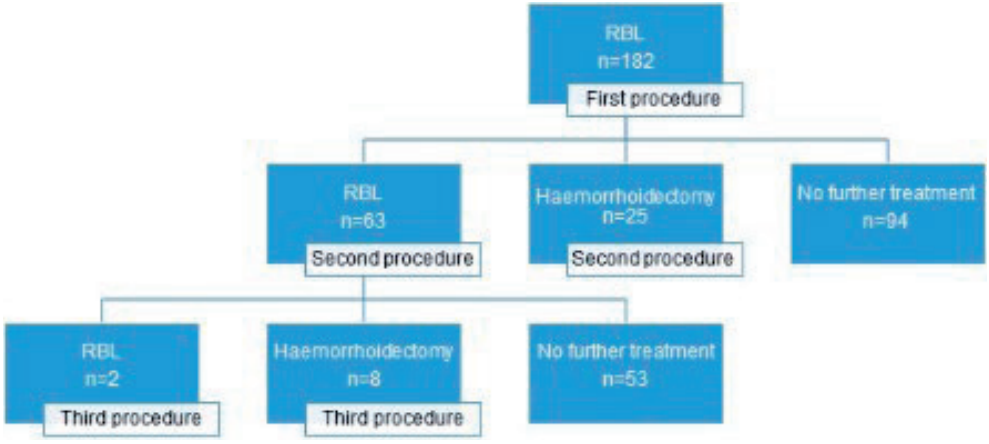

Figure 1. Flowchart of further treatment after rubber band ligation (RBL) within 1 year.

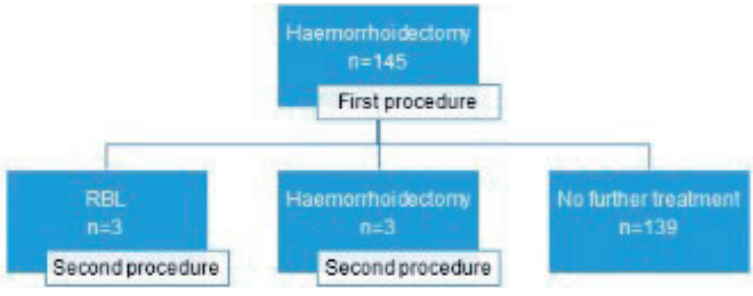

Figure 2. Flowchart further treatment after hemorrhoidectomy within 1 year. RBL, rubber band ligation.

Table 2. Complications after first treatment.

	RBL (n=182)	Hemorrhoidectomy (n=145)	P-value
Hemorrhage	3	0	0.120
Urinary retention	1	4	0.106
Acute thrombosed hemorrhoid	1	2	0.434
Fistula ani	0	4	0.024
Fecal incontinence	0	0	-
Fissure in ani	1	1	0.747
Total	6	11	0.083

In 94 (52%) a single RBL was sufficient. From the 88 patients who needed further treatment, 63 (72%) underwent a second RBL session within one year and 25 (28%) patients underwent a haemorrhoidectomy (fig 1). From the patients who underwent a haemorrhoidectomy, 139 (96%) were treated by this single procedure (fig 2).

Complications

Complications following haemorrhoidectomy and RBL occurred in 11 (8%) versus 6 (3%) patients respectively, this difference was not significant (table 2). Four fistulas developed after haemorrhoidectomy and none in the RBL group ($p<0.05$). All four complications are classified as CD 3 (major). Two were intersphincteric fistulas and both were noticed four weeks after haemorrhoidectomy. One was treated by seton placement followed by fistulotomy and one by suturing the internal opening and filling the fistula tract with Permacol paste. Two fistulas were subcutaneous, of which one was noticed eight weeks and one 16 weeks after haemorrhoidectomy. Both were treated by fistulotomy.

Post banding haemorrhage developed in three patients of which two can be classified as CD 2 (minor) and one as CD 3 (major), all three needed hospital admission. In one patient the haemorrhage occurred under anticoagulation requiring blood transfusion and in one patient blood transfusion was indicated but the patient refused for religious reasons. In another patient the haemorrhage occurred after four weeks and required an emergency re-operation.

One of the 33 patients, who underwent a haemorrhoidectomy after primary RBL treatment, an abscess developed that required drainage.

Patient reported outcome measurements score

The baseline PROM1 score before the procedure was available in 229 patients (70%), 125 in the RBL group and 104 in the haemorrhoidectomy group (fig 3). The PROM2 (post procedure) was available in 195 patients (60%), 106 in the RBL group and 89 in the haemorrhoidectomy group. In 142 patients both scores were available. There were no differences in PROM score between the groups who returned one of the two questionnaires and those who returned both. Therefore, both groups were combined.

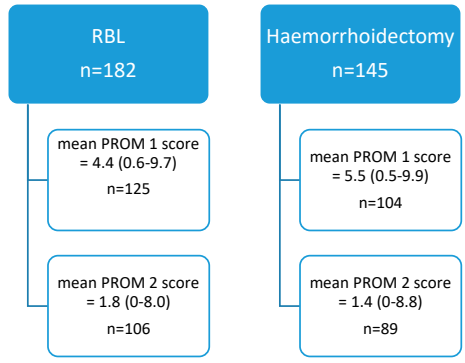

Figure 3. Flowchart of PROM scores. PROM score ranges from 0 to 10 with 0 being perfect and 10 could not be worse. PROM 1 was administered during the first outpatient visit and PROM 2 after treatment.

The mean PROM1 score in RBL was 4.4 (0.6-9.7) and in the haemorrhoidectomy group 5.5 (0.5-9.9), which was a significant difference ($p<0.001$). The median follow up with the PROM2 was 44 months (range 10-76). The PROM2 was significantly decreased after both RBL (1.8, $p<0.001$) and haemorrhoidectomy (1.4, $p<0.001$). With the independent samples T-test no significant difference was found between the final PROM2 (post procedure) score between the RBL and haemorrhoidectomy group ($p=0.087$). The mean PROM2 after two sessions RBL was 2.3. When comparing the PROM2 in patients who underwent two sessions RBL (mean 2.3) and patients who underwent one haemorrhoidectomy (mean 1.4) this difference was statistically significant ($p=0.015$).

DISCUSSION

This study describes the clinical results of traditional excisional haemorrhoidectomy and RBL in grade III haemorrhoids in a tertiary center for proctology. This is the first study reporting on outcomes using a proctology specific PROM concerning patient's well-being and social activities – instead of symptom severity – at a long term follow up. RBL is often considered treatment of choice in grade III haemorrhoids as it is a faster, less expensive way and does not require anesthesia compared to haemorrhoidectomy. However, in our series, we found that 44% of patients underwent haemorrhoidectomy. After initial consultation, performing physical examination and proctoscopy, extensive informative was given on the disease and treatment options were discussed. Patients' choice of treatment was made by shared decision-making. It is likely that patient preference and perhaps also doctors preference is largely responsible for the relatively high numbers of surgery in this study. Doctors preference is a phenomenon not unknown and may be diminished by increasing level of evidence for best treatment [16].

The clinical effectiveness of haemorrhoidectomy in this study, defined as no need for re-intervention, is in concordance with existing literature [13,18,23]. The proportion of patients in our study who needed only one or two RBL sessions in one year was 81%. In current literature the success rate of RBL, as a single procedure, varies between 49% and 88% [9,13,18,24,25]. When considering repeated banding as part of the treatment, as has been suggested by the authors of the HubBle trial [9], both procedures are equally effective, as shown in the current study. The wide variation in success rates reported in the literature of RBL and haemorhroidectomy can be explained by heterogeneity in outcome reporting making comparison of results difficult and hard to interpret. Van Tol recently developed the first European Society of Coloproctology Core Outcome Set for haemorrhoidal disease in an international Delphi study with the perspective to improve the quality and uniformity of future research [26]. The PROM in this study attempts to give insight in severity of patient's complaints. Regrettably, in our study follow-up PROM data had a wide range. Taking a convalescence period of 6-12 weeks into account evaluation of treatment with a PROM questionnaire by then would be ideal. In study context this may be extended to 12 months.

More post-operative complications were observed in the haemorrhoidectomy group compared to the RBL group (p=0.08). Although haemorrhage is more often described after haemorrhoidectomy [18], this was not the case in our study. The only three, relevant, post procedure bleeding occurred in patients who underwent RBL. This might be due to heterogeneity as none of the included studies in this systematic review clearly described how this outcome was defined [18]. Oozing blood during haemorrhoidectomy can occur but can be managed adequately during surgery. Post banding haemorrhage is a well-known complication, often classified as minor and occurs mostly after a few days. The bleeding focus is often not so easily visible and therefore more difficult to control. One patient in our study developed a haemorrhage after four weeks which is quite late. In rare cases post banding haemorrhage may be life threatening [27].

In literature, post RBL or post-operative pain has frequently been measured using a visual analog scale or documented as mild, moderate or severe pain [9,25]. In our clinic, patients are telephone interviewed by a physician assistant to evaluate well-being a few days after the procedure. This was, unfortunately, not documented by a categorical scale.

Other complications can be pelvic infections. Although serious infections following RBL are rare, pelvic sepsis can be lethal if not early recognised [28–32]. In our cohort, there were no such complications. Unfortunately, in our study 4/145 post-operative fistulas were reported after haemorrhoidectomy (p=0.024). This compared to 2/358 in the eTHoS trial [13].

Patients undergoing haemorrhoidectomy had a significantly higher initial PROM than those who underwent RBL (5.5 versus 4.2). This suggests that patients treated by haemorrhoidectomy suffered from more severe or disabling complaints and were therefore

treated by a more invasive procedure than those with milder complaints. The number of affected piles did not seem important in this aspect as 3 piles haemorrhoids were equally distributed among both groups. PROM2 in patients who underwent two sessions RBL was significantly higher than in patients who underwent one haemorrhoidectomy, which suggests that patients where better off after surgery. There is no comparative literature on this issue.

The most widely used description for haemorrhoidal disease is Goligher's classification, which ranks severity of prolapse into four grades. The choice of treatment is mostly based on this gradation. However, the experienced symptoms do not always reliably relate to Goligher's classification [33]. Furthermore, the classification does not take into account symptoms as pain, itching, bleeding or soiling, neither the amount of piles prolapsing. A single prolapsed pile, for instance, can be classified the same as a full circumferential prolapse. This makes evaluation of treatments for a specific grade of haemorrhoidal disease less reliable. We believe patient reported symptoms are a more reliable display of the actual situation and patient burden (table 1) and explains the patient reported prolapse rate of 83%.

This study was limited due to its retrospective character. Firstly, the primary outcome of clinical effectiveness could only be measured by need for re-intervention. This is, as described above, unfortunately a measurement that is relative since it is unknown if the patient was actually content when treated by one or more procedures or had subsequent treatment elsewhere. Secondly, the follow up of the PROM2 varied widely (median 44 months with interquartile rang 10-76). Forty percent of the patients did not completed the PROM2 (post procedure). Furthermore, it is unknown if patients fill in the PROM 2 while under treatment elsewhere.

This paper demonstrates the need of sufficiently large randomised trials comparing treatments focused on patient related outcome. Decision making, in order to maximize outcome, should be supported by evidence and by patient related outcome measurements. In our opinion, evaluation of treatment with a PROM questionnaire would be of most value between 6 weeks and 3 months. In study context this may be extended to 12 months. Further, quality of life and a cost-effectiveness analysis could clarify the impact of the chosen intervention on the patient's life and Dutch national healthcare system. A large multicenter randomised trial comparing haemorrhoidectomy and RBL has recently started in the Netherlands.

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CHAPTER 4

IS THE GOLIGHER CLASSIFICATION A VALID TOOL IN CLINICAL PRACTICE AND RESEARCH FOR HAEMORRHOIDAL DISEASE?

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ABSTRACT

Background

The most widely used classification for haemorrhoidal disease (HD) is Goligher classification, which ranks presence and severity of prolapse into four grades. Since physicians base this gradation on medical history and physical examination, it might be prone to interobserver variability. Furthermore, the gradation impacts the treatment of choice which makes reproducibility of utmost importance.

Methods

In this study we determined the interobserver variability of Goligher classification among surgeons in the Netherlands. We asked gastrointestinal surgeons and residents who routinely treat HD to review 25 photographs (with given timing as during rest or push) of patients with HD and classify the gradation using the Goligher classification. Interobserver variability was assessed using Fleiss' Kappa test.

Results

From the respondents, 87% indicated to use the Goligher classification in clinical practice. Eighty-one percent did find the classification helpful and 63% classified by the Goligher and followed the guideline for treatment of HD accordingly. The interobserver variability showed an overall fair strength of agreement, with a Fleiss' Kappa (κ) of 0.376, (95% CI 0.373-0.380). The κ statistic for grade I, II, III and IV was respectively 0.466, 0.206, 0.378 and 0.522.

Conclusion

The fair interobserver variability is disappointing and demonstrates the need for a more reliable – and international agreed – classification for HD. A new classification should enable more uniformity in treating HD and comparing outcomes of future trials and prospective registries. The protocol for a Delphi study for a new classification system is currently being prepared and led by an international research group.

INTRODUCTION

Haemorrhoidal disease (HD) is one of the most common proctologic disorders with a prevalence up to 39% in the general population [1]. The most widely used classification system for HD is the Goligher system [2], which ranks the presence and severity of prolapse into four grades. Physicians base this gradation on medical history and physical examination, using also subjective criteria to grade HD.

The Goligher classification is used in many guidelines and thereby impacts the choices for treatment of HD worldwide. Furthermore, when comparing outcomes of different procedures for HD in studies based on the Goligher grading, its reliability and reproducibility is of utmost importance. In daily practice, it is perceived that there might be a large interobserver variability due to this mix of subjectivity and objectivity. Therefore concerns exist about suitability of this grading instrument to guide treatment and research. To our knowledge, the interobserver variability has never been investigated and thus remains unknown.

An important shortcoming of the Goligher classification is that it only describes a single symptom, not taking into account the number of affected piles or accompanying symptoms, i.e. pain, itching, bleeding or soiling and their impact on quality of life. Although the classification estimates the severity of prolapse, more disease burden does not automatically lead to a higher grade. This makes it difficult to evaluate and compare treatment strategies. Selection of study population is nearly always based on the Goligher classification. However, due to the abovementioned shortcomings, studies have almost never used the change in Goligher's grade as primary endpoint, but rely on a wide variety of different end-points such as patient-reported outcome measurements or clinical outcomes, e.g. complications or recurrence symptoms defined in many different ways. Several efforts were made to classify HD in a different manner with scores based on haemorrhoidal development and symptom-based severity [3–7]. However, none of these classifications have been successful as the Goligher still remains the most used classification system in guidelines [8–10]. It has been pointed out that the simplicity of this classification is one of the main reasons for its widespread continued use over decades.

No previous study has examined the interobserver variability between physicians on assessing HD using the Goligher classification. This study aims to determine this endpoint among gastrointestinal surgeons and residents – who treat and classify haemorrhoids most frequently – and to demonstrate the need for a more reproducible and reliable classification. This could improve evaluation of treatment options for haemorrhoids and consequently improve care.

METHODS

Study design

A single choice survey was composed. The survey started with six questions concerning baseline characteristics and the use of the Goligher classification in routine clinical practice. Thence the survey continued with 25 patients cases with different grades of HD. Photographs were provided with additional information concerning timing of the photo, during rest or strain (figure 1a and 1b, example of photographs used is the survey, during rest and strain), as well as medical history regarding all aspects of the Goligher classification; the presence and reducibility of prolapse. The survey was created in Survio [11] and the definitions of the four grades were described on top of the form as a reminder [Table 1]. All authors conducted a pilot for testing feasibility and validity. The finalized version was sent by email on April 19th 2021 and was available online until July 5th 2021. One email reminder was sent during the period of online availability of the survey. Observers were asked to review these cases and classify the gradation from I till IV using the Goligher classification. The Medical Ethics Review Committee of the Amsterdam University Medical Centers, location AMC, confirmed that the study was not subjected to the Medical Research Involving Human Subjects Act (WMO).

Subjects

Photographs of patients with different grades of HD were obtained from electronic health records and captured during proctoscopy, before surgical intervention or taken by patients themselves. After verbal consent and a note in patients' health record the photographs were saved anonymously. Using a two sided alpha of 0.05 and a power of 80% a total amount of 24 photographs for 6 raters were needed to detect a statistical significant difference in kappa between 0.6 and 0.8.

Observers

All members of the Dutch Workgroup Coloproctology, as well as Dutch gastrointestinal and colorectal surgeons, fellows and residents were invited to participate in the study. We used the email database of our previous survey concerning the management of anal fistulas among Dutch gastrointestinal surgeons [12]. Known invalid domains were removed and the list was checked globally by contact information that was retrieved from the Dutch Association of Surgery. In addition, a link to the survey was disseminated via the social media platform of the Dutch Workgroup Coloproctology as a reminder.

Data analysis

The interobserver agreement was assessed by using Fleiss' Kappa test. Overall k coefficient was reported as well as the agreement for each gradation separately. Agreement was classified as follows: poor agreement (0.00-0.20), fair (0.21-0.40), moderate (0.41-0.60),

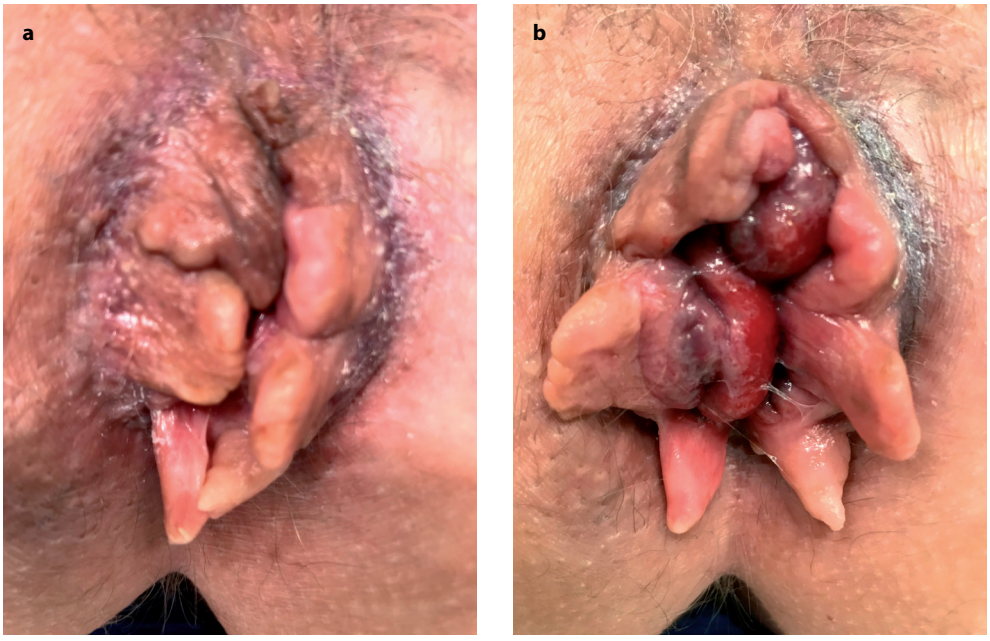

Figure 1. Photographs used in the survey, during rest (**a**) and strain (**b**). The patient case in the survey described a 52-year-old women with daily complaints of soiling and blood loss. She wears a panty liner. She is aware of a prolapse but that is nother main concern and she does not manually reduce it. There are no complaints of itching or pain. Results of the survey were as follows: grade I; 1 (1%), grade II; 41 (43%), grade III; 43 (45%), grade IV 10 (11%).

substantial (0.61-0.80), and almost perfect agreement (0.81-1.00). P values of <0.05 were considered significant. Data were analyzed using SPSS Statistics software version 26.0.

RESULTS

A total of 329 gastrointestinal surgeons, fellows and residents were sent an invitation email. Nine email addresses had an invalid domain and did not receive the invitation. Ninety-five (29%) respondents completed the survey, 86 by answering the email invitation and 9 by the web link on the social media platform of the Dutch Workgroup Coloproctology. Respondents characteristics and questions concerning the use of the Goligher classification in routine practice are shown in Table 2. Most respondents were gastrointestinal surgeons (84%) and the vast majority (65%) treated patients with HD on a weekly basis. Eighty-seven percent used the Goligher classification when treating patients with HD and two respondents indicated to use both the Goligher classification and descriptive diagnosis. The majority (81%) regarded the Goligher classification a helpful tool . Of all respondents, 63% based their treatment on the Goligher classification and followed the Dutch national guideline for treatment of HD accordingly. Sixteen percent of the respond-

Table 1. Definitions of the four grades of Goligher Classification.

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

Table 2. Respondents characteristics and questions concerning the use of the Goligher classification in routine practice.

	N (%)
Specialty	
Surgeon	79 (84)
Fellow	7 (7)
Resident in training	8 (8)
Physician assistant/nurse practitioner	1 (1)
Regularity of treatment	
Daily	18 (19)
Weekly	62 (65)
Monthly	8 (8)
A few times in a year	7 (7)
Do you use a classification for haemorrhoids?	
Yes, the Goligher classification	83 (87)
No (e.g. descriptive diagnosis)	10 (11)
Yes, otherwise, namely..	2 (2)
The Goligher classification determines the grading on the basis of:	
Medical history	11 (12)
Physical examination	5 (5)
Proctoscopy	7 (7)
A combination of the above	72 (76)
Do you find the Goligher classification is a helpful classification	
Yes	77 (81)
No	18 (19)
To what extent do you link your treatment to the grading?	
I do not	20 (21)
I classify and I follow the guideline in the policy of treatment options.	60 (63)
Otherwise, namely.	15 (16)

ents stated that there was a broad spectrum of clinical parameters that was relevant for the choice of treatment. They indicated that the decision making was dependent on the patients complaints, findings at physical examination, comorbidity and patients' preference.

Overall, there was only a fair strength of agreement, with a Fleiss' Kappa (κ) of 0.376, (95% CI 0.373-0.380). Respondents agreed the most when it concerned grade IV HD with a κ statistic of 0.522 (moderate). Also grade I with a κ of 0.466 had a moderate agreement.

There was a slightly lower agreement for grade II and III HD, with a κ statistic of 0.206 and 0.378 (fair), respectively.

DISCUSSION

Although the Goligher appears a simple classification, as based on a single pathological parameter, the present study shows only a fair overall interobserver agreement. The classification uses the presence and severity of prolapse for grading HD, but apparently there are unclear demarcations. The agreement for grade I and IV HD was still moderate. Differentiation between grade II and III HD appeared to be the hardest, as reflected by only fair agreement between respondents, with a κ statistic of 0.206 and 0.378 respectively.

According to the definitions in the Goligher classification, the differentiation between grade II or III HD mainly depends on the patients' medical history (manual reduction), as prolapse and reducibility is not always provocable at physical examination. Patients may also mention reducibility when a concurrent anal polyp or skintag is present and not all patients may admit to the need for manual reduction of their prolapse. This mix of morphological aspects and the subjective information may lead to different interpretation and therefore classification. Medical history and doctors assessment could provide well enough information in diagnosing grade I. Concerning grade IV HD, those can be misinterpreted because of the external component [13, 14]. This external component can also be a thrombosed haemorrhoid or a skintag, which should not be classified by the Goligher system.

The initial intention of the Goligher classification is to grade HD by a single symptom that both causes complaints and defines the anatomy of the prolapse. The classification does not take into account symptoms as pain, itching, bleeding or soiling, neither the actual number of prolapsing piles. This means that a single prolapsing pile can be classified the same as a full circumferential prolapse with itching, bleeding and soiling. The disparity between symptoms and grading is described by Gerjy [14]. The authors showed that HD is a polysymptomatic disease whereby symptoms do not reliably relate to the Goligher classification. This hampers the adequateness of its use in research, e.g. for determining the inclusion of patients in studies evaluating different treatment strategies for HD.

Although 81% of the respondents found the Goligher classification as helpful, only 63% routinely used it in their decision making process. The choice of treatment should therefore depend on a greater number of factors, i.e. the severity of complaints, gender, age, comorbidities and the presence of skin tags or fecal incontinence. Nevertheless, according to the current practice, a low-invasive treatment (e.g. rubber band ligation) is the preferred choice for grade II, while surgical treatment is reserved for grade IV HD. The treatment of choice for grade III HD is still under debate and currently investigated by the

Holland trial, a Dutch initiative comparing rubber band ligation and haemorrhoidectomy from a patient's perspective [15].

Several authors have developed alternative scoring systems to overcome the above-mentioned limitations [4–7, 14, 16–19]. Nevertheless, none of these well-designed classifications have been frequently – and internationally – used in clinical practice. An explanation for the difficult implementation of other classifications may rely on their relative complexity, compared to the Goligher system. Replacing this classification would be quite challenging. As suggested by Rubbini et al, having clinical experiences and professional skills become so widespread, it is recommended to initiate an innovation of such importance only if shared from the beginning by the generality of proctologists [20]. A recent survey among members of the European Society of Coloproctology (ESCP) has shown the need for a new classification system. Currently, the protocol for the development of a new classification system for HD has been initiated by our research group. The intention is to merge objective and subjective findings by performing a Delphi study that will involve clinicians and patients from ESCP member countries. Van Tol et al. already described a core outcome set for HD and showed five symptom domains that should be taken into account when studying patients with this condition [21].

The current study has a number of limitations. The response rate was low (29%). The questionnaire was sent to all members of the Dutch Coloproctology Working group that consists of members that have large experience and affiliation in treating anorectal disease, with 38 (40%) respondents coming from this workgroup. Other respondents were gastrointestinal surgeons and residents with unknown familiarity with anorectal disease. This may have influenced the outcome of the present study, but in a subgroup analysis, no differences were found.

In the design of the study, we aimed to grade HD by presenting the patients' medical history, including the reducibility of the prolapse, and simulate the anorectal assessment by using photographs during rest and/or strain. However, the actual physical examination with digital rectal examination and, if necessary, proctoscopy is standard practice when grading by the Goligher classification. Performing digital rectal examination can provide more information of the tissue of the external component and therefore might distinguish between different diagnosis. Although all respondents were subjected to the same experimental conditions, this limitation in assessment may have augmented the variability of responses between participants. On the other hand, reviewing the gradation still is partially subjective and there is no right or wrong.

In summary, the present study shows only a fair interobserver variability among gastrointestinal surgeons in the Netherlands for grading HD by the Goligher classification. Results also showed that physicians find the classification helpful but do not completely depend their treatment on it.

CONCLUSION

The only fair interobserver variability in grading HD according to the Goligher classification is in accordance with the inadequacy perceived in daily practice and demonstrates the need for a more reliable, and internationally accepted grading system incorporating objective and subjective factors of HD. New classification systems should enable more uniformity of treatment of HD and a more uniform and consistent comparison of outcomes in future trials and prospective registries. The protocol for a Delphi study for a new classification system, preceded by a survey among gastrointestinal surgeons, is currently being prepared and led by an international research group.

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PART II

CRYPTOGLANDULAR PERIANAL FISTULA-IN-ANO AND CHRONIC ANAL FISSURE

CHAPTER 5

MANAGEMENT OF CRYPTOGLANDULAR FISTULA-IN-ANO AMONG GASTROINTESTINAL SURGEONS IN THE NETHERLANDS

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ABSTRACT

Introduction

Management of cryptoglandular fistula-in-ano (FIA) can be challenging. Despite Dutch and international guidelines determining optimal therapy is still quite difficult. The aim of this study was to report current practices in the management of cryptoglandular FIA among gastrointestinal surgeons in the Netherlands.

Methods

Dutch surgeons and residents who are treating FIA regularly were sent a survey invitation by email. The survey was available online from September 19th to December 1st 2019. The questionnaire consisted of 28 questions concerning diagnostic and surgical techniques in the treatment of intersphincteric and transsphincteric FIA.

Results

In total, 147 (43%) surgeons responded and completed the survey. Magnetic resonance imaging was the preferred diagnostic imaging modality (97%) followed by the endo-anal ultrasound (12%). In case of a high FIA 86% used a non-cutting seton. Most respondents removed a seton between 6 weeks and 3 months (n=84, 58%). Fistulotomy was the procedure of preference in low transsphincteric (86%) and low intersphincteric FIA (92%). Mucosal advancement flap (MAF) and ligation of intersphincteric fistula tract (LIFT), with 78% and 46%, respectively were the procedures that were applied most often in high transsphincteric FIA. In high intersphincteric FIA 67% performed a MAF and 33% a fistulotomy. Thirty-three percent of all respondents stated that they habitually closed the internal fistula opening, half of them used a Z-plasty. For debridement of the fistula tract the preferred method was curettage (78%).

Conclusions

Dutch gastrointestinal surgeons use various techniques in the management of FIA. Novel promising techniques should be investigated adequately in sufficient large trials to increase consensus. A core outcome measurement and a prospective international database would help in comparing results. Until then, treatment should be adjusted to the individual patient, governed by fistula characteristics and patient choice.

INTRODUCTION

Fistula-in-ano (FIA) has been challenging to manage for thousands of years. Hippocrates was the first who described and analyzed the etiology and technique of healing this troublesome benign disease [1, 2]. Yet, therapy for FIA has not fundamentally changed. Therapy is aimed at closure of the fistula and symptom relief whilst minimizing functional impairment. Despite current Dutch and international guidelines, determining optimal therapy is still quite difficult in the individual patient. A probable cause is the scarce evidence regarding the best practice in treating FIA [3–6]. This concerns all areas of management: diagnostics, operative treatment, follow-up and treatment of recurrent disease. Ideally, surgical management aims to heal fistula with preservation of fecal continence. Simple FIA can be safely treated by fistulotomy (lay open) with high healing rates between 80-100% [7–9]. Complex fistulas are more challenging for the surgeon due to the higher risk of fecal incontinence and recurrence [10, 11]. These fistulas are often treated by seton placement prior to subsequent sphincter-preserving surgery. Sphincter-preserving techniques include mucosal advancement flap (MAF) with reported healing rates between 70-80% [12, 13], and ligation of the intersphincter fistula tract (LIFT) with a reported healing rate of 69% for cryptoglandular FIA [14–16]. Other sphincter-sparing procedures that have been developed are: tissue-adhesive and biomaterials, stem cells, fistula laser closure (FiLaC™), video assisted anal fistula treatment (VAAFT) and over-the-scope clip (OTSC®). Some of these procedures have been quickly adopted, without a prior pilot or implementation study. Also, technical variations of procedures are performed in an attempt to improve outcome [11, 17–19].

The question still remains, which procedure leads to optimal outcome for the individual patient suffering from FIA? Many studies have attempted to answer this question by comparing techniques through evaluating outcome measurements such as fecal incontinence, recurrence and/or fistula closure. Data are often difficult to compare due to heterogeneity between studies. For that reason a core outcome set (COS) for perianal fistula is currently under development including patient related items [20].

Our objective was to assess the contemporary approach in surgical management of cryptoglandular FIA in the Netherlands and to determine whether current management follows current guidelines.

MATERIALS AND METHODS

Design of the survey

The survey consisted of 28 questions, formulated by two authors (IH and LD). In order to compare our results with the management of cryptoglandular FIA worldwide, the questions were partially based upon the international survey developed by Ratto et al [21]. The

questions were reviewed by three co-authors (gastrointestinal- and colorectal surgeons) after which the survey was edited and co-authors conducted a pilot for testing validity.

The survey consisted of topics concerning baseline characteristics such as respondents function, sex, workload, type of hospital, years of experience in management of cryptoglandular FIA and number of cases treated per year. Seton use was assessed by questions covering material and duration. Other questions assessed diagnostic techniques, surgical approach, (not) dealing with an internal opening and expertise with the different surgical approaches. If the question mentioned 'high intersphincteric' FIA, it was generally described as a intersphincteric FIA with a high internal opening. The survey was in Dutch and was created using a web-based program called SurveyMonkey. Ten questions were multiple-choice and 18 were single-answer questions (appendix 1 the English translationis provided in appendix 1). It was explicitly stated in the invitation that all questions were related to cryptoglandular fistulas only.

The survey was sent by email to all members of the Dutch Working Group Coloproctology as well as to all gastrointestinal- and colorectal surgeons, fellows and residents of each hospital in the Netherlands treating FIA regularly. Data was checked by calling the local secretariats. Contact information was retrieved from the Dutch Association for Surgery. One email reminder was sent during the period of online availability of the survey. A link to the survey was disseminated via LinkedIn and via the newsletter of the Dutch Workgroup Coloproctology as a reminder. The survey was available online from September 19th to December 1st 2019. As this study did not apply the Medical Research Involving Human Subjects Act (WMO), approval by the ethics committee was not required.

Data analysis

To prevent missing data all questions were mandatory with automated skip logic. The web-based program automatically collected all data after which the data was exported to a Microsoft Excel spreadsheet and then imported to SPSS. Descriptive analyses were performed on all data. Categorical outcome data across groups was analysed using the Chi-square test. IBM SPSS version 25 was used.

RESULTS

Respondents characteristics

In total, 342 invitations were sent by email to gastrointestinal surgeons, fellows and residents. Four email addresses with an invalid domain were excluded. One hundred and forty-six respondents (43%) completed the survey, 117 by answering the email invitation and 29 by using the web link. Respondents' characteristics are shown in table 1. Most respondents (52%) had more than 10 years of experience with treating FIA. Only 33% performed more than 30 procedures per year. Patients who had their first appointment in the

Table 1. Respondents characteristics. mc=multiple choice, FIA = fistula-in-ano.

	N (%)
Gender	
Male	103 (71)
Female	42 (29)
Specialty	
Gastrointestinal surgeon	108 (75)
General surgeon	12 (8)
Fellow	6 (4)
Resident (in training)	19 (13)
Work load	
Fulltime	113 (78)
Part-time	32 (22)
Type of hospital	
Academic	14 (10)
Non-academic (peripheral)	124 (86)
(Private) clinic	7 (5)
First visit contact outpatient clinic (mc)	
Surgeon	142 (98)
Fellow	51 (35)
Resident (in training)	74 (51)
Resident (not in training)	26 (18)
Physician's assistant or nurse practitioner	10 (7)
Experience treating anal fistulas	
1-5 years	35 (24)
5-10 years	34 (23)
10-20 years	51 (35)
> 20 years	25 (17)
Experience in total FIA procedures per year	
> 50	20 (14)
30-50	27 (19)
10-30	72 (50)
0-10	26 (18)

outpatient clinic were mostly counseled by a surgeon or resident. Overall, no significant differences in management were seen regarding experience in number of surgical procedures performed per year.

Diagnostic imaging

Table 2 shows the diagnostic imaging modalities used by respondents. Diagnostic imaging was commonly used in case of complex fistulas (n=133, 78%) and recurrent fistulas (n=92, 63%). The respondents who answered 'always' (n=19, 13%) were not included. Magnetic resonance imaging (MRI) was used far more often (97%) than endo-anal ultrasound (12%).

Table 2. Diagnostic techniques used by respondents. mc=multiple choice; FIA=fistula-in-ano; MRI=-magnetic resonance imaging; CT=computed tomography.

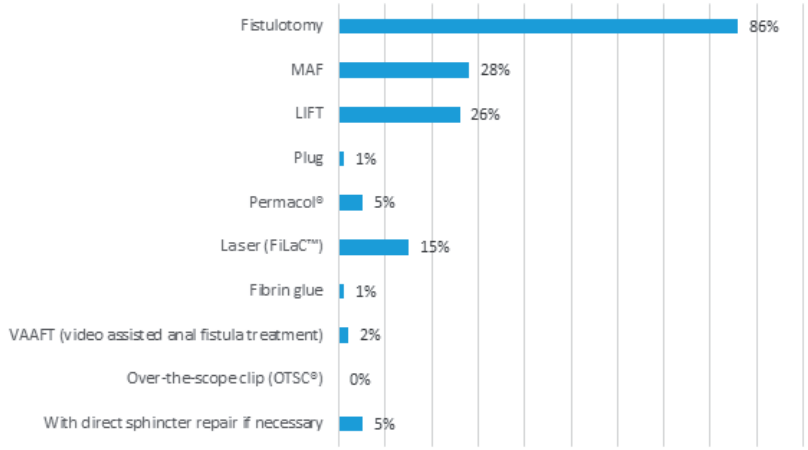
	N (%)
Reason for diagnostic imaging (mc)	
Recurrent FIA	92 (63)
Complex FIA	113 (78)
Prior to seton placement	26 (18)
Prior to surgical procedure	49 (34)
Prior to abscess drainage	0 (0)
Always	19 (13)
Type of diagnostic technique (mc)	
MRI	141 (97)
CT	0 (0)
Endo-anal ultrasound	18 (12)
No diagnostic technique at all	1 (1)

Table 3. Seton treatment by respondents. mc=multiple choice, sa=single answer; FIA=fistula-in-ano.

	N (%)
Use of seton placement (mc)	
Always	13 (9)
Purulent FIA	67 (46)
High FIA	112 (77)
Recurrent FIA	51 (35)
Never	2 (1)
Type of seton use (mc)	
Silicone (e.g. vessel loop)	98 (68)
Comfort Drain	57 (39)
Surgical thread (e.g. mersilene)	25 (17)
SuperSeton®	19 (13)
Time to remove seton (sa)	
< 6 weeks	1 (1)
Between 6 weeks and 3 months	84 (58)
> 3 months	32 (22)
Till next surgical procedure	28 (19)

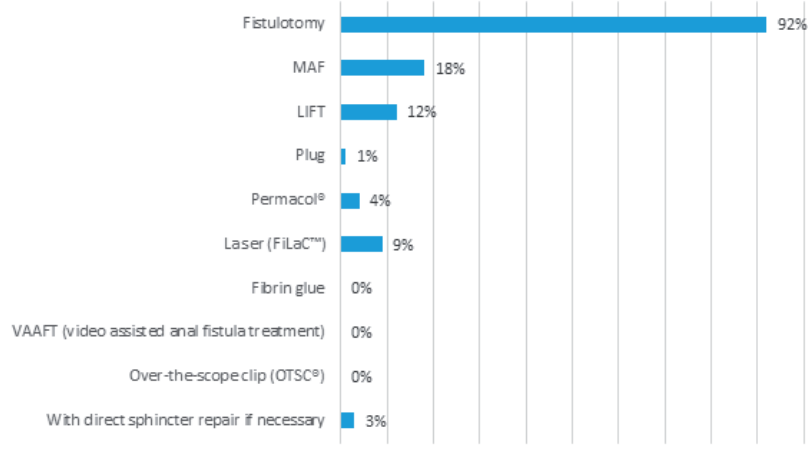
Seton treatment

The main reason for seton placement was the complexity of the fistula in 112 respondents (77%), followed by the presence of excessive inflammation/suppuration in 67 respondents (46%). Nine percent of respondents indicated to use a seton in all cases whereas only one respondent never uses a seton (table 3). Silicone was the most commonly used type of seton (68%), followed by the Comfort Drain and SuperSeton® (39% and 13% respectively), which are characterized by the absence of knots. Fifty-eight percent of the respondents removed the seton between 6 weeks and 3 months, while 19% left it in place until the next surgical procedure.



MAF=mucosal advancement flap; LIFT=ligation of intersphincteric fistula trac.

Figure 1. Choice of treatment for low transsphincteric fistula-in-ano (multiple-choice).



MAF=mucosal advancement flap; LIFT=ligation of intersphincteric fistula tract.

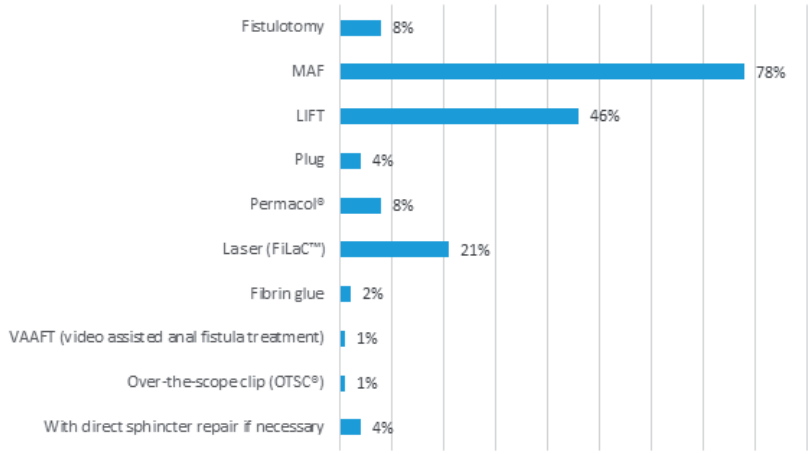
Figure 2. Choice of treatment for low intersphincteric fistula-in-ano (multiple-choice).

Surgical techniques and experience

Low fistula-in-ano

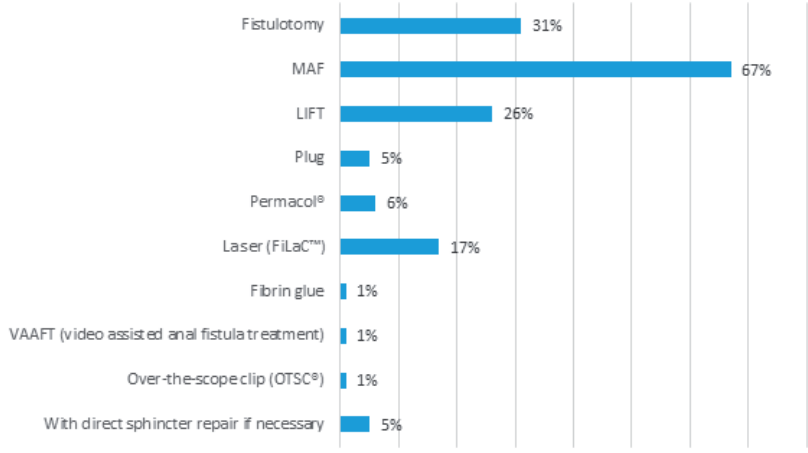
Figures 1 and 2 illustrates the choice of surgical techniques in low transsphincteric and intersphincteric FIA. Fistulotomy was performed by the majority of the respondents, 86% and 92% respectively. Still, more than 25% of respondents indicated that they treated low transsphincteric FIA with MAF or LIFT (28% and 26% respectively). For low intersphincteric FIA this was 18% by MAF and 12% by LIFT.

Eighty-one percent of the respondents had experience with MAF technique, compared to 59% with LIFT (figure 5).



MAF=mucosal advancement flap; LIFT=ligation of intersphincteric fistula tract.

Figure 3. Choice of treatment for high transsphincteric fistula-in-ano (multiple-choice).



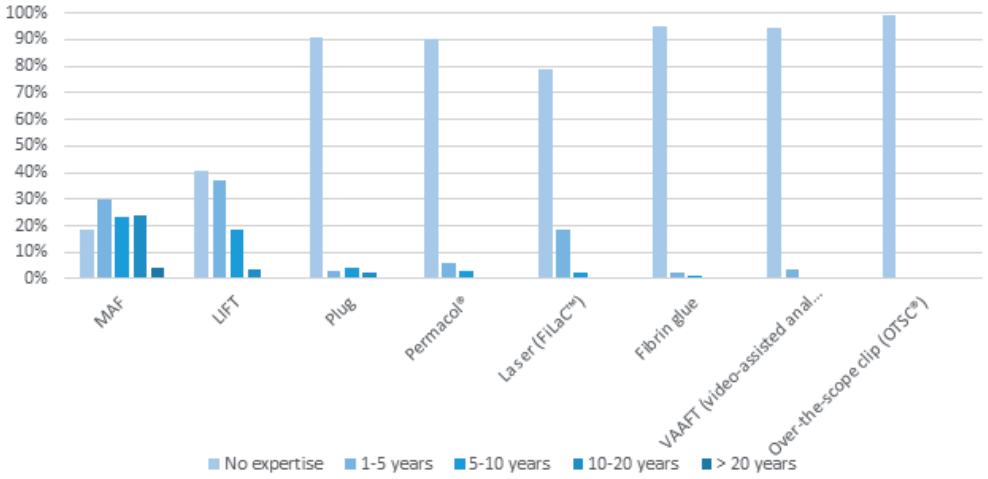
MAF=mucosal advancement flap; LIFT=ligation of intersphincteric fistula tract.

Figure 4. Choice of treatment for high intersphincteric fistula-in-ano (multiple-choice).

High fistula-in-ano

In case of high transsphincteric FIA most respondents performed a MAF (78%) or LIFT (46%) (figure 3). Twenty-one percent of the respondents treated high transsphincteric fistula with FiLaC™ while almost 80% did not have any experience with this procedure (figure 5). The preferred treatment modality for intersphincteric FIA with a high internal opening was more diverse with MAF in first place (67%) followed by fistulotomy (31%) (figure 4). LIFT (26%) and FiLaC™ (17%) were also frequently performed in intersphinctericFIA.

Experience with techniques other than MAP and LIFT was limited. Personal experience with plug, Permacol® and fibrin glue was between 5 and 10%. Most respondents had



MAF=mucosal advancement flap; LIFT=ligation of intersphincteric fistula tract.

Figure 5. Personal expertise with different techniques.

no experience with more novel approaches like VAAFT (94%) and only one respondent had experience with the OTSC®.

Internal opening

Thirty-three percent of all respondents declared that they closed the internal fistula opening when performing any procedure that allows closure, while 9% never did (table 4). When performing LIFT 23% indicated that they closed the internal opening. Fifty percent of the respondents who closed the internal fistula opening used a Z-suture and 39% used a normal suture. The remaining 11% closed the internal fistula opening in a different manner. If the internal fistula opening was not found, the majority (66%) did a fistulectomy or core out of the fistula tract, 31% did an excoriation of the fistula tract and 3% did nothing. The preferred method for debridement of 35 (78%) respondents was curettage, 6 (13%) used a brush, 2 (1.4%) used the diathermy needle, 1(0.7%) used a gauze and one a scalpel.

DISCUSSION

Despite the high prevalence of FIA and a plethora of scientific literature on the subject, there is still no clarity about what is best practice. The present study provides an overview of the current approach in management of FIA amongst gastrointestinal surgeons in the Netherlands.

FIA is most often classified using Parks classification: intersphincteric, transsphincteric, suprasphincteric and extrasphincteric [22]. To aid decision making in determining the choice of procedure, FIA can be described as high or low, based on the nature of the

Table 4. In what circumstances was the internal fistula opening closed (multiple-choice). MAF= mucosal advancement flap; LIFT=ligation of intersphincteric fistula tract; VAAFT=video-assisted fistula treatment; OTSC=over-the-scope clip.

	Total N (%)
Always	33 (23)
Never	13 (9)
When performing a MAF	90 (62)
When performing a LIFT	34 (23)
When performing a plug	5 (3)
When performing Permacol	10 (7)
When performing laser	12 (8)
When performing fibrin glue	0 (0)
When performing VAAFT	2 (1)
When performing OTSC®	0 (0)

primary tract. Low fistulas are subcutaneous, intersphincteric or low transsphincteric (involving no more than 1/3 of external anal sphincter), and high fistulas are higher transsphincteric, suprasphincteric or extrasphincteric [23].

Preoperative assessment of anatomy in recurrent and complex anal fistulas by diagnostic imaging has been shown to improve surgical outcome [24] and is therefore recommended in international guidelines [3–6]. Recurrence of perianal fistula is often due to secondary fistula extensions missed during initial surgery. Delineating the fistula pattern prior to surgery with MRI or three-dimensional (3D)-endoanal ultrasound (3D-EAUS) can help to avoid iatrogenic sphincter damage. Both imaging techniques have proven to be superior to examination under anesthesia (EUA) in identifying secondary tracts and identification of the internal orifice [25]. In experienced hands 3D-EAUS has an excellent sensitivity and specificity in mapping of fistula tracts [26]. Main limitations of 3D-EAUS lie in the identification of pelvirectal abscesses and supralevator tracts. MRI has advantages as soft tissue contrast, operator independence, but has higher costs, a longer execution time and often lower availability. In the cases of complex disease and/or no clear diagnosis at 3D-EAUS, MRI can be a complementary diagnostic tool to previous 3D-EAUS. The majority of the respondents indicated that they used imaging preceding surgery in complex and recurrent fistula. MRI was used far more often than EAUS (97% versus 12%). This is in contrast to the international study by Ratto where a greater proportion of respondents (70%) is familiar with the use of EAUS. It can be assumed that reliance on 3D-EAUS will be higher in hospitals with availability of this device and where surgeons do their own imaging in an outpatient setting as is, to our knowledge, more customary in several European countries. As every corrective procedure for anal fistula has its own specific indications and complications, accurate assessment of a patient' s anal anatomy and anal fistula by high quality imaging may thus lead to patient tailored advice and treatment.

Setons are frequently used for several reasons. Loose setons are often used for drainage, reducing inflammation and are usually left in place until the acute inflammation has

resolved [11]. They are also often used in two-staged surgery preceding a sphincter preserving procedure [27, 28]. There is however no evidence that this leads to better outcome [29–31]. In case there is no intention to perform subsequent surgery a seton can also be left in situ for an indefinite period of time. There are many different types available made out of diverse materials [32]. It is obvious that efforts to make a seton as comfortable as possible will be much appreciated by the patient. A knot-free seton is proven to be associated with improved quality of life [33]. With 39% of respondents choosing a Comfort Drain and 13% a SuperSeton®, the results of our study suggest that attention is being paid to make wearing a seton more agreeable. It has to be noted however, that also when no commercially produced knotless setons are available, an effort can (and should) be made to make the seton comfortable. Moreover, it should be noted that knotless setons may be more prone to being lost by the patient than knotted setons [34]. The majority of the respondents is accustomed to leaving the seton in situ for a considerable period of time. Fifty-eight percent of the respondents removed the seton between 6 weeks and 3 months. There is no consensus on timing of removal in the literature. The review by Subhas et al, describing variations in materials and techniques in treatment with setons, reports an average duration varying from 14 days till 14 months [32]. Interestingly, what happens to fistulas after loss or removal of a seton without additional surgical therapy is unknown.

The majority of the respondents treated low intersphincteric (86%) and low transsphincteric FIA (92%) with fistulotomy. This data are in line with the literature [35]. Quite a few of the respondents indicated that they perform a MAF or a LIFT procedure in case of low intersphincteric FIA, in contrast to guideline recommendations. It would be interesting to know if this concerns a select patient group, for example female patients with an anteriorly located FIA, or patients with already compromised continence. Although the survey contained questions on low transsfincteric and low intersphincteric FIA, distinguishing between low inter- and low transsfincteric FIA is of dubious importance since it has no consequences for therapy.

Postoperative impaired continence after fistulotomy for low and mid FIA (lower 2/3 of external anal sphincter) is reported in up to 22% of patients [36]. The existing literature suggests there is a positive effect on postoperative continence after fistulotomy and fistulectomy with primary sphincter repair [37–40]. Direct sphincter repair was performed by 3 to 5% of the respondents in our study. In the international study by Ratto 9-19% performed direct sphincter repair following fistulotomy for intersphincteric and transsphincteric FIA [21]. As Ratto mentioned, this difference could be due to variations across geographic regions. It is noteworthy that no long-term results of this technique are available. Moreover, when evaluating the long-term results of sphincterplasty for patients with fecal incontinence, studies invariably describe a decrease in continence over the years.

In high FIA there is little standardisation in sphincter preserving techniques, complicating interpretation of study results. In our enquiry MAF was the most applied technique,

followed by LIFT. Both strategies are well established and show no significant difference in overall healing and recurrence rate, as confirmed in a recent systematic review [16]. Incontinence rates were, however, significantly higher after MAF which might give LIFT a more favorable position in determining optimal procedure. It must be mentioned that owing to small numbers no separate analyses were performed concerning incontinence outcome in patients with cryptoglandular or Crohn's FIA. Experience with MAF for high anal fistula was substantial which is in contrast to the survey by Ratto where surgeons were much less eager to perform a MAF, possibly due to its technically demanding character. Still, 8% of the participants treated high transsfincteric FIA with fistulotomy. The risk for impaired continence can be substantial [23]. When considering this approach in the individual patient it is advisable to carefully evaluate sphincter function and anatomy before surgery in order to estimate risk.

Almost 1/3(31%) of the respondents performed a fistulotomy in patients with a intersphincteric FIA with a high internal opening. This is in accordance with current guidelines [3, 5, 6] where this type of fistula is classified as 'simple' FIA. In an elegant study, incorporating pre- and postoperative sonography, Garcés-Albir et al concluded that fistulotomy of the intersphincteric FIA, which involved less than 2/3 of the total length of the external anal sphincter, is a safe and effective treatment for patients without risk factors for fecal incontinence prior to surgery [41].

Experience with techniques other than MAF and LIFT was limited. Less than 10% of the respondents was familiar with more novel surgical approaches such as OTSC® and VAAFT. This was also the case for biomaterials and tissue-adhesive techniques like the anal fistula plug, fibrin glue and Permacol®. With 21% in this study compared to 10% in the study by Ratto [21] the FiLaC™ seems to be the most popular of these, although evidence of superiority of this procedure is not convincing [42, 43]. At the present time, it would seem prudent not to apply untested methods in our patients outside of trials or adequate prospective registries. Moreover, in our opinion, companiesoffering such technology should insist on only applying their new techniques within prospective registry.

FIA recurrence is significantly associated with an undetected internal fistula opening [44, 45]. Ninety-six percent of the respondents who did not find an internal opening proceeded to curettage of the fistula tract.

In the original description of the LIFT technique the intersphincteric tract is sutured twice, namely at the point where it passes the internal and external anal sphincter. The internal orifice is left open. Of the respondents**,** 23% closed the internal opening, even though this was not described in the original LIFT technique [46]. Applying a procedural variation with the intention of improving results isunderstandable. However it makes comparing results of fistula surgery difficult. A database exactly decribing the procedure performed and patient characteristics would be of great help to evaluate results and determine best outcome instead of developing more and more procedures based on the same underlying mechanism of the origin of the FIA.

The strength of the present study was the response rate with 43%of respondents also considering the fact that the survey invitation was not individualized [47]. The subject of the study is partially responsible for the high response rate since it was of great interest to most respondents. Forty-seven percent of the respondents were members of the Dutch Coloproctology Working group, a well-known coloproctology society in the Netherlands.

Some limitations of the study should be mentioned. The most important one is probably the classification of fistula which is, to a certain extent, surgeon dependent. This might have caused confusion when answering the questions and might have influenced our results. Another limitation may be the personal interpretation of the answer options resulting in intrinsic selection bias. The questionnaire was sent to all members of the Dutch Coloproctology Working group. Its members are all practicing and interested in colorectal disease but also include residents besides gastrointestinal surgeons. Efforts were made to send the survey to all known surgeons who were not members of the Workgroup but still known to be familiar with anorectal disease. This was done by calling the secretariat of each hospital. Nevertheless, it is likely that not all surgeons were reached. Software related issues could also have jeopardized the response rate because personalized correspondence was not possible.

In summary, this study shows consistency in the treatment of low FIA between respondents, whereas in high FIA treatment is more variable. The results also suggest that there is a lack of consensus regarding performing diagnostic imaging, seton placement and how to manage the internal fistula opening.

CONCLUSION

Varying practices are seen among gastrointestinal surgeons concerning the management of FIA and a considerable part of the respondents appear to treat FIA differently than recommended in guidelines. Novel promising techniques should be investigated adequately in sufficiently large trials and in prospective registries to increase consensus. The development of a Core Outcome Set for FIA may improve the quality and uniformity of future research. Treatment should be patient tailored with meticulous assessment of fistula characteristics prior to surgery in order to obtain the best results, but with a consistent practice of laying open low FIA and sphincter-preserving techniques for high transsphincteric FIA.

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APPENDIX 1

Personal data

1. You are a
   a. Colorectal surgeon
   b. General surgeon
   c. Fellow
   d. Surgical resident (in training)
   e. Other

2. Gender
   a. Male
   b. Female

3. Do you work
   a. Fulltime
   b. Part-time

4. Where do you work?
   a. Academic hospital
   b. Non-academic hospital
   c. (Private) clinic

5. When a patient with FIA visits the outpatient clinic, he is seen by *(mc)*
   a. The specialist
   b. The fellow
   c. The surgical resident in training
   d. The surgical resident not in trainig
   e. The nurse practitioner or physician assistant

6. Personal experience with surgical management of FIA?
   a. 1-5 years
   b. 5-10 years
   c. 10-20 years
   d. > 20 years

7. How many surgical procedures do you perform per year?
   a. 0-10
   b. 10-30
   c. 30-50
   d. > 50

Diagnostic technique

8. When do you use diagnostic imagine? *(mc)*
    a. Recurrent FIA
    b. Complex FIA
    c. Prior to seton placement
    d. Prior to surgical procedure
    e. Prior to abscess drainage
    f. Always

9. What diagnostic technique do you use? *(mc)*
    a. MRI
    b. CT
    c. Endo-anal ultrasound
    d. No diagnostic technique at all

Seton treatment

10. When do you use seton placement? *(mc)*
    a. Always
    b. Purulent FIA
    c. High FIA
    d. Recurrent FIA
    e. Never

11. What type of seton do you use? *(mc)*
    a. Silicone (e.g. vessel loop)
    b. Comfort drain
    c. Surgical thread (e.g. mersilene)
    d. SuperSeton®

12. What moment do you remove the seton?
    a. < 6 weeks
    b. Between 6 weeks and 3 months
    c. > 3 months
    d. Till next surgical procedure

Surgical techniques

13. Which surgical treatment do you perform in a patient with a low transsphincteric FIA? *(mc)*
    a. Fistulotomy
    b. Mucasal advancement flap (MAF)

c. Ligation of the intersphincteric fistula tract (LIFT)
d. Plug
e. Permacol paste
f. Laser (FiLaC™)
g. Fibrin glue
h. Video assisted anal fistula treatment (VAAFT)
i. Over-the-scope-clip (OTSC®)
j. With direct sphincter repair if necessary

14. Which surgical treatment do you perform in a patient with a high transsphincteric FIA? *(mc)*
    a. Fistulotomy
    b. Mucasal advancement flap (MAF)
    c. Ligation of the intersphincteric fistula tract (LIFT)
    d. Plug
    e. Permacol paste
    f. Laser (FiLaC™)
    g. Fibrin glue
    h. Video assisted anal fistula treatment (VAAFT)
    i. Over-the-scope-clip (OTSC®)
    j. With direct sphincter repair if necessary

15. Which surgical treatment do you perform in a patient with a low intersphincteric FIA? *(mc)*
    a. Fistulotomy
    b. Mucasal advancement flap (MAF)
    c. Ligation of the intersphincteric fistula tract (LIFT)
    d. Plug
    e. Permacol paste
    f. Laser (FiLaC™)
    g. Fibrin glue
    h. Video assisted anal fistula treatment (VAAFT)
    i. Over-the-scope-clip (OTSC®)
    j. With direct sphincter repair if necessary

16. Which surgical treatment do you perform in a patient with a high intersphincteric FIA? *(mc)*
    a. Fistulotomy
    b. Mucasal advancement flap (MAF)
    c. Ligation of the intersphincteric fistula tract (LIFT)

d. Plug
e. Permacol® paste
f. Laser (FiLaC™)
g. Fibrin glue
h. Video assisted anal fistula treatment (VAAFT)
i. Over-the-scope-clip (OTSC®)
j. With direct sphincter repair if necessary

Experience surgical approaches

17. What is your experience with the MAF?
    a. No experience
    b. 1-5 years
    c. 5-10 years
    d. 10-20 years
    e. > 20 years

18. What is your experience with the LIFT procedure?
    a. No experience
    b. 1-5 years
    c. 5-10 years
    d. 10-20 years
    e. > 20 years

19. What is your experience with treatment with a plug?
    a. No experience
    b. 1-5 years
    c. 5-10 years
    d. 10-20 years
    e. > 20 years

20. What is your experience with Permacol® paste?
    a. No experience
    b. 1-5 years
    c. 5-10 years
    d. 10-20 years
    e. > 20 years

21. What is your experience with the laser (FiLaC™)?
    a. No experience
    b. 1-5 years

c. 5-10 years
d. 10-20 years
e. > 20 years

22. What is your experience with fibrin glue?
    a. No experience
    b. 1-5 years
    c. 5-10 years
    d. 10-20 years
    e. > 20 years

23. What is your experience with the video assisted anal fistula treatment (VAAFT)?
    a. No experience
    b. 1-5 years
    c. 5-10 years
    d. 10-20 years
    e. > 20 years

24. What is your experience with the Over-the-scope-clip (OTSC®)
    a. No experience
    b. 1-5 years
    c. 5-10 years
    d. 10-20 years
    e. > 20 years

Internal opening

25. When do you close the internal opening? *(mc)*
    a. Always
    b. Never
    c. When performing a MAF
    d. When performing a LIFT
    e. When performing a plug
    f. When performing Permacol® paste
    g. When performing laser (FiLaC™)
    h. When performing fibrin glue
    i. When performing VAAFT
    j. When performing (OTSC®)

26. How do you close the internal opening?
    a. Z-suture
    b. Normal suture
    c. Not applicable, I do not close the internal opening
    d. Otherwise, namely..

27. What if you do not find an internal opening?
    a. Only fistulectomy or core out of the fistula tract
    b. Excoriation of the fistula tract
    c. I do nothing

28. How do you perform the excoriation?
    a. With a curette
    b. With a brush
    c. With a gauze
    d. Otherwise, namely…

CHAPTER 6

MANAGEMENT OF CHRONIC ANAL FISSURE, RESULTS OF A NATIONAL SURVEY AMONG GASTROINTESTINAL SURGEONS IN THE NETHERLANDS

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ABSTRACT

Background

Chronic anal fissure (CAF) is a common, bothersome condition frequently accompanied by pelvic floor complaints. Despite current guidelines, optimal management is challenging. The aim of this study is to evaluate current management of CAF among gastrointestinal surgeons in the Netherlands.

Methods

Dutch gastrointestinal surgeons and residents were sent a survey invitation by email, which was available online between June 2021 and September 2021. The questionnaire consisted of 21 questions concerning work experience, physical examination, diagnostic- and surgical techniques and follow-up.

Results

Overall, 106 (33%) surgeons completed the survey. Most respondents (59%) had at least 10 years of experience in treating CAF. Only 23% always addressed pelvic floor complaints. Fifty-one percent performed digital rectal examination and 22% always, or almost always, examined the pelvic floor muscles. Most respondents started treatment with fibers and/or laxatives and ointment (96%). Diltiazem was in 90% the preferred ointment. Twenty-two percent referred patients for pelvic floor physical therapy. Botulinum toxin was in 54% performed under general- or spinal anesthesia or sedation. The surgical procedure of choice was fissurectomy (71%) followed by lateral internal sphincterotomy (27%). Fissurectomy was in 51% always combined with botulinum toxin. Fifty-seven percent of the respondents preferred a physical follow-up appointment.

Conclusion

Guideline recommendations are largely followed in the Netherlands, starting with conservative measures followed by surgical procedures. Surgeons do not consistently assess pelvic floor complaints, nor do they routinely examen the pelvic floor muscles. Awareness of pelvic floor dysfunctions is important in order to refer patients for pelvic floor physical therapy.

INTRODUCTION

Chronic anal fissure (CAF) is defined as a longitudinal ulcer in the squamous epithelium with persisting symptoms for longer than four to six weeks or recurrent fissures [1, 2]. Patients usually experience anal pain, during and immediately after defecation, which may last several hours and therefore has a substantial impact on daily activities and quality of life [3, 4]. Despite current Dutch and international guidelines optimal management of CAF is quite challenging, mainly because of its recurrent nature, therapy compliance and the variety of non-operative and operative treatments [5, 6].

Treatment of CAF has undergone an alteration in the last two decades from invasive to non-invasive, reserving surgical interventions for lesions refractory to conservative therapy[7]. Initial conservative management are comprised of lifestyle advice, fibre intake and/or use of laxatives and ointments. The use of ointments is aimed at reducing elevated internal sphincter tone and consequently increase the anodermal vascular blood flow, for which nitro-glycerine as well as calcium channel blockers may be prescribed. Botulinum toxin (BT) can be considered as an alternative or as a step-up approach when standard conservative therapy fails [5, 6]. In addition, various surgical procedures are possible such as fissurectomy, advancement flap repair and lateral internal sphincterotomy (LIS). Currently, LIS is considered the golden standard[6, 8] with healing rates of 90-100% but with a potential risk of incontinence [1, 9-12].

Although most anal fissures probably heal spontaneously or with conservative measures, a percentage tend to recur or persist. A proportion of these patients have a history of constipation and obstructed defecation due to an unrecognized pelvic floor dysfunction. Consequently, these patients have complaints of excessive straining, incomplete evacuation and hard stools together with infrequent stooling which might be due to, for instance, dyssynergia [13, 14]. Dyssynergia can primarily lead to anorectal pain but can also evolve secondary to disorders causing anorectal pain [15].

Pelvic floor dysfunctions are associated with urological, bowel, gynaecological and sexual complaints and chronic pelvic pain [16, 17] and can be treated with pelvic floor physical therapy. It is unknown if surgeons treating these patients are sufficiently aware of this condition in patients with CAF.

Although Dutch and international guidelines are largely based on high-quality evidence, recommendations are ambiguous. As a result there is variation in clinical practice. The aim of this study is to evaluate current practice in the management of CAF among gastrointestinal surgeons in the Netherlands.

MATERIALS AND METHODS

Design of the survey and participants

This study was performed and reported according to the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) [18]. As this study did not apply the Medical Research Involving Human Subjects Act (WMO), approval by the ethics committee was not required. The survey was written in Dutch, consisted of 21 questions and was created using a web-based program called Survio [19]. The closed-survey (i.e. only accessible through invitation) was sent by email to all members of the Dutch Working Group Coloproctology as well as to gastrointestinal surgeons, fellows, and residents of each hospital in the Netherlands. We used the email database of our previous survey among Dutch gastrointestinal surgeons concerning the management of anal fistulas [20]. Known invalid domains were removed and the list was checked globally by contact information that was retrieved from the Dutch Association of Surgery. The survey was accompanied by an invitation email explaining the objectives of the study and length of time of the survey (<10 min). One reminder email was sent after 4 days, the second after 10 weeks. No time limit was set for filling in the survey. The survey was available online from June 25th, 2021, to September 30th, 2021.

Survey

The survey consisted of 21 questions, formulated by all five authors. The questions were reviewed by two colorectal surgeons and one urologist, after which the survey was edited. All authors conducted a pilot for testing validity. The survey consisted of topics concerning baseline characteristics such as respondents' function, type of hospital, years of experience in treating CAF and number of surgical procedures – including botulinum toxin injections – per year. Other questions assessed medical history and physical examination with attention to pelvic floor complaints and dysfunctions; diagnostics techniques; surgical approaches; follow-up and presumed effect of treatment. Seventeen questions were single-choice, two were multiple-choice and two questions required a number. The participants were given the chance to review and change their answers. The survey was tested for completeness, usability and technical functionality before submission. The survey was voluntary and no incentives were offered.

Statistical analysis

All statistical analyses were performed using Statistical Packages for Social Sciences (SPSS, Chicago, Il, USA, version 26.0). To prevent missing data, all questions were mandatory with automated skip logic. The web-based program Survio automatically collected all data after which the data were exported to a Microsoft Excel spreadsheet and then imported to SPSS. Descriptive analyses were performed on all data. Categorical outcome data across groups were analysed using the Chi-square test.

RESULTS

Respondents' characteristics

In total, 329 invitations were sent by email to gastrointestinal surgeons, fellows, and residents. Nine email addresses with an invalid domain did not receive the invitation. Hundred-and-six (33%) surveys returned and were completely answered. Forty- one responses were excluded since they did not complete. Respondents' characteristics are shown in table 1. Eighty-one percent of the respondents were gastrointestinal surgeons and 89% worked in a general hospital. Fifty-nine percent of the responders had at least 10 years of experience with treating CAF and 61% performed more than 10 procedures for CAF per year, including botulinum toxin (BT).

Medical history and physical examination

From the respondents, 28% never or almost never asked and only 23% always or almost always asked for complaints in other domains of the pelvic floor. A subgroup analysis showed that respondents with more than 10 years of experience in treating CAF slightly more often asked for pelvic floor complaints than respondents with less than 10 years of experience, although not significant.

Half of the respondents performed digital rectal examination and 23% performed proctoscopy. Only 22% of the respondents indicated that they always, or almost always, performed physical examination of the pelvic floor muscles, whilst 37% never or almost never did.

Treatment

Ninety-six percent started treatment with fibers and/or laxatives and ointment. In 90% of the respondents, diltiazem was the preferred ointment. Fifty-six percent prescribed ointment for a period of 6 weeks followed by 27% who continued ointment for 12 weeks. Most of the respondents (72%) felt they had enough time to give the patient instructions or advice regarding the use of laxatives, lifestyle and ointment. Twenty-two percent of the respondents referred to a pelvic floor therapist and they always combined this with fibers and/or laxatives.

BT injections were given by 77% of the respondents mainly under general- or spinal anesthesia or sedation (42%). Almost half of the respondents repeated BT injections twice and more than 76% never performed BT in the levator ani muscle.

Fissurectomy was the most popular operative procedure (71%), followed by LIS (27%). More than half of the respondents always, or almost always, used BT intersphincteric in case they performed a fissurectomy. When BT injections were performed under anesthesia, only 27% performed a fissurectomy simultaneously.

Follow-up

Fifty-seven percent scheduled a physical follow-up check in the outpatient clinic. Forty-three percent referred a patient with CAF to another specialist at least once. A percentage of 57% estimated their patients to be symptom-free after 1 year in 50-75% of the cases. Thirty percent of the respondents had the feeling they always or almost always treat these patients satisfactorily.

DISCUSSION

Implementation of Dutch and international guidelines for chronic anal fissure in daily practice varies. The present study provides an overview of the current approach in management of CAF amongst gastrointestinal surgeons in the Netherlands.

The pelvic floor plays a major role in defecation and continence. Furthermore, pelvic floor dysfunctions are prevalent in patients with chronic anal pain syndromes [21, 22]. However, 28% of the respondents never or almost never asked for any pelvic floor complaints in patients with CAF and only 23% always asked about this topic. Complaints of pelvic floor disorders vary and are often complex, making these disorders less widely recognized [23]. A survey by Nicolai et al. about addressing pelvic floor complaints among Dutch gastroenterologists showed that one of the reasons for not asking about pelvic floor complaints was a lack of knowledge about pelvic floor disorders [24]. In our survey we did not inquire the reason for not asking for pelvic floor complaints, but this would be probably the same in gastrointestinal surgeons. We feel that knowledge about pelvic floor dysfunctions is beneficial in the treatment of anorectal disorders since this might result in a referral to another specialist in an early stage.

The study shows that there is moderate consensus among the respondents concerning performing physical examination in patients with CAF. Only half of the respondents performed digital rectal examination and 37% never or almost never examined the pelvic floor muscles. Seniority in experience did not differentiate. In case of expecting a CAF, reason for not performing digital rectal examination could be the assumption that its contradicted or should be kept to a minimum because of associated pain. However, careful digital rectal examination is important to obtain information on anorectal anatomy and function [25, 26]. When identifying pelvic floor muscle dysfunction, patients can be appropriately referred to a pelvic floor physical therapist if necessary.

Most of the respondents is accustomed to start with conservative measures as lifestyle, the increase of fluid, fibers, laxatives and ointment, which is according to current guidelines [5, 6, 27-29]. Diltiazem ointment was the preferred local treatment. Duration of application varies in studies and guidelines, but mostly a duration of at least 6 weeks is recommended [30-32]. In our study 56% of the respondents indicated to prefer a duration of 6 weeks. Forty percent preferred a longer therapy duration, except for 4 respondents.

Most respondents did have enough time to give instructions in the consulting room. This is important, since information about patient' complaints, lifestyle advice, laxative- or ointment and its use requires an explanation by the clinician [2, 33]. Pelvic floor dysfunctions can effectively be treated with pelvic floor physical therapy, but only 22% of the respondents referred to this treatment modality, a missed opportunity. The clinical effect of pelvic floor physical therapy in patient with CAF is currently investigated by the Pelvic floor Anal Fissure (PAF) study [34].

Botulinum toxin injections were performed in the outpatient's clinic by less than half of the respondents of whom 90% performed this without local anesthetics, excluding the 23 respondents who did not perform this procedure at all. More than half of the respondents (54%) performed BT injections under general- or spinal anesthesia or sedation which is in accordance with a recent survey among members of the American Society of Colon and Rectal Surgeons (ASCRS) [35]. In current literature, there is no consensus on dose, site or number of injections [29, 36]. This corresponds with the results of our study showing no consensus on how often one should repeat BT. Nevertheless, BT remains an effective treatment in recurrent anal fissures as well as in patients with therapeutic failure of prior BT injection [7, 37].

In case BT was performed under anesthesia, only 27% always or almost always simultaneously performed fissurectomy and another 27% does this in more than half of the cases. This is comparable to the results of a survey among American surgeons [35]. When performing fissurectomy, 51% always or almost always simultaneously injected BT and 23% did this in more than half of the patients. The clinical effect of this combined procedure was recently confirmed by Roelandt et al. They found that BT injections significantly increased the efficiency of fissurectomy, with a healing rate of 90%, compared to 81% in fissurectomy alone [38].

Fissurectomy was the surgical procedure of choice in our study (71%), followed by LIS (27%). LIS is the preferred treatment for refractory anal fissures and is still considered the golden standard since LIS has superior healing rates [5, 6], although (minor) fecal incontinence is a potential risk [8-11]. Guideline recommendations differ on this subject. The ASCRS guideline favours LIS [6], the Dutch guideline however, recommends LIS only for refractory fissures when previous treatment fails [5].

The follow-up was diverse in our survey. Twenty-one percent of the respondents stated that they scheduled a telephone call follow-up check after starting the treatment. This is quite interesting given the fact that it concerns a chronic disorder which has a large impact on quality of life and increased heath care utilization [39]. Besides that, chronic pelvic pain is often accompanied by pelvic floor dysfunctions [40]. A physical diagnostic follow-up should be performed since physical rectal examination is important to monitor clinical healing of the fissure and investigation of the anal sphincter tone. A physical follow-up will probably better monitor patients' wellbeing and subsequently ensure that the patient does not end up in a vicious circle of pain again. Forty-three percent referred

a patient to another specialist at least once last year. No recommendations are made in clinical guidelines concerning follow-up period or when to refer a patient to another specialist.

This study has some limitations that should be mentioned. First, the response rate of 33% may have caused non-response bias. This response rate is, however, was less compared to earlier published response rates of online surveys [41, 42]. Second, the questionnaire was sent to all members of the Dutch Coloproctology Working group that consists of members that have large experience and affiliation in treating anorectal diseases. Of all respondents, 33% came from this group. This may have caused selection bias. Third, we used a non-validated questionnaire and respondents were self-reported. Self-reports may have resulted in an overestimation of history-taken practices and to our knowledge, validated questionnaires are not available in this field.

CONCLUSION

Guideline recommendations in treating CAF are largely followed and consistent among most gastrointestinal surgeons in the Netherlands. Initial treatment consists of conservative measures followed by surgical procedures. Surgeons do not consistently assess pelvic floor complaints, nor do they routinely examine the pelvic floor muscles. Awareness of pelvic floor dysfunctions in patients with CAF is important in order to refer patients for pelvic floor physical therapy.

What does this paper add to the literature?
Gastrointestinal surgeons in the Netherlands have not yet been surveyed regarding their current management concerning chronic anal fissure. The paper discusses similarities and discordances between surgeons and compare these to current Dutch and international guidelines. Furthermore, it emphasizes the focus of the pelvic floor in current management of CAF.

Table 1. CAF= chronic anal fissure; BT=botulinum toxin; SC= Single Choice; MC= Multiple Choice.

Respondents' characteristics	N (%)
What is your medical specialty?	
Gastrointestinal surgeon	86 (81)
General surgeon	7 (7)
Fellow	2 (2)
Resident in training	8 (7)
Physician assistant/nurse practitioner	3 (3)
What type of hospital are you working?	
Academic	4 (4)
Non-academic (peripheral)	94 (89)
(Private) clinic	8 (7)
How many years of work experience do you have as a medical specialist in the treatment of CAF?	
1-5 years	19 (18)
5-10 years	24 (23)
10-20 years	35 (33)
>20 years	28 (26)
How many procedures for CAF (incl botulinum toxin) do you perform per year?	
0-10	41 (39)
10-30	41 (39)
30-50	19 (18)
>50	5 (5)
Medical history and physical examination	
How often do you ask a patient with CAF about pelvic floor complaints (gynaecology, urology, sexuology)? **SC?*	
Never/almost never	30(28)
In less than half of the cases	38 (36)
In more than half of the cases	14 (13)
Almost always/always	24 (23)
In case you expect CAF by medical history, which physical examination and/or diagnostics do you do? **MC*	
None	1 (1)
Inspection	103 (97)
Digital rectal examination	54 (51)
Proctoscopy	24 (23)
Endo-anal ultrasound	6 (6)
Do you examine the pelvic floor muscles by a patient with CAF (squeeze, relaxation and push of the levator ani muscle and external anal sphincter)? **SC*	
Never/almost never	39 (37)
In less than half of the cases	26 (24)
In more than half of the cases	18 (17)
Almost always/always	23 (22)
Treatment	
Which treatment do you initiate when treating a patient with CAF? (assuming the general practitioner has not already done this) **MC*	
Lifestyle advice by nutrition advice and toilet behaviour	79 (74)
Fibers/laxatives and ointment	102 (96)
Pain medication (local and/or systemic)	43 (41)
Pelvic floor physical therapy	23 (22)
Botulinum toxin	2 (2)

Respondents' characteristics	N (%)
Which ointment do you prescribe for CAF? **SC*	
Lidocaine	1 (1)
Isosorbide dinitrate	9 (8)
Diltiazem	96 (90)
Other	0 (0)
In case of isosorbide dinitrate or diltiazem, what was your recommendation concerning duration of application? (number)	
16 weeks	1 (1)
12 weeks	29 (27)
8 weeks	13 (12)
6 weeks	59 (56)
4 weeks	1 (1)
3 weeks	1 (1)
2 weeks	2 (2)
Do you feel you have enough time to instruct and advice the patient regarding the use of laxatives, lifestyle and ointment? **SC*	
Never/almost never	4 (4)
In less than half of the cases	7 (7)
In more than half of the cases	19 (18)
Almost always/always	76 (72)
How do you perform the botulinum toxin (BT) injections? **SC*	
Outpatient clinic, without anesthesia	34 (32)
Outpatient clinic, with local anesthesia	4 (4)
General- or spinal anesthesia or sedation	45 (42)
Not applicable, I do not perform this procedure	23 (22)
How often do you repeat BT injections? **SC*	
One time	16 (19)
Two times	41 (49)
More than two times	22 (27)
I do not repeat	4 (5)
Do you simultaneously give BT in the levator ani muscle when treating CAF? **SC*	
Never/almost never	63 (76)
In less than half of the cases	13 (16)
In more than half of the cases	6 (7)
Almost always/always	1 (1)
What is your preferred surgical procedure for CAF (except BT)? **SC*	
Fissurectomy	59 (71)
Lateral internal sphincterotomy (LIS)	22 (27)
Advancement flap repair	2 (2)
In case you perform a fissurectomy, do you simultaneously give BT intersphincteric? **SC*	15 (18)
Never/almost never	7 (8)
In less than half of the cases	19 (23)
In more than half of the cases	42 (51)
Almost always/always	
In case you perform BT under anesthesia, do you simultaneously perform a fissurectomy? **SC*	
Never/almost never	24 (29)
In less than half of the cases	15 (18)
In more than half of the cases	22 (27)
Almost always/always	22 (27)

Respondents' characteristics	N (%)
Follow-up	
How do you manage the follow-up after starting a treatment? **SC*	
No follow-up	0 (0)
Physical appointment	60 (57)
Telephone call	22 (21)
According to the needs of the patient	24 (23)
How many times did you refer a patient with CAF to another specialist last year? (number)	
0 times	61 (58)
1-5 times	42 (40)
6-10 times	3 (3)
What percentage of your patients do you estimate to be symptom-free a year after starting the treatment? **SC*	
0-25%	0 (0)
25-50%	9 (8)
50-75%	60 (57)
75-100%	33 (31)
I do not know	4 (4)
Do you feel you can treat patients with CAF satisfactorily? **SC*	
Never/almost never	0 (0)
In less than half of the cases	2 (2)
In more than half of the cases	72 (68)
Almost always/always	32 (30)

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PART III

FAECAL INCONTINENCE

CHAPTER 7

TO WHAT EXTENT ARE ANORECTAL FUNCTION TESTS COMPARABLE? A STUDY COMPARING DIGITAL RECTAL EXAMINATION, ANAL ELECTROMYOGRAPHY, 3 DIMENSIONAL HIGH RESOLUTION ANAL MANOMETRY AND TRANSPERINEAL ULTRASOUND

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ABSTRACT

Background

Anorectal function tests are helpful for objective investigation of anorectal (dys)function. A variety of tests are available, but there is no recommendation when to perform which test. Furthermore, which test is the most accurate is controversial and the correlation between these tests is not very clear. The aim of our study was to examine the correlation of anal pressures and the possibility to diagnose pelvic floor dyssynergia between digital rectal examination (DRE) and several anorectal function tests.

Methods

Between January 2020 and April 2022, all men and women aged 18 to 80 years, treated at the Proctos Clinic, who were referred for pelvic floor physical therapy (PFPT) by the surgeon and underwent anorectal function tests, were included. DRE was performed to establish the anal pressure at rest, and during squeeze and straining. Anorectal function tests included 3D High resolution anal manometry (3D-HRAM), balloon expulsion test (BET), transperineal ultrasound (TPUS) and surface electromyography (s-EMG).

Results

A total of 50 patients, 37 (74%) females, were included. Median age was 51 years. Twenty-three (62%) females had a history of two or more vaginal deliveries. Most frequent reason for referral for PFPT was faecal incontinence in 27 (54%) patients. The assessed pressures and pelvic floor function measured with DRE by the surgeon and the pelvic floor physical therapist during rest, squeeze and straining correlated in 78%, 78% and 84%, respectively. Correlation between DRE and 3D-HRAM or s-EMG, was better for squeeze pressures than resting pressures. The correlation between s-EMG and 3D-HRAM was better during squeeze than at rest with an agreement of 59% and 37% respectively.

Conclusion

DRE by an experienced investigator is of sufficient value for daily clinical practice to detect dyssynergia and to measure sphincter tone. Commonly performed anorectal function tests correlate poorly with DRE and with other anorectal function tests. When conservative treatment fails, further investigation is warranted, however these results should be interpreted with caution.

What does this paper add to the literature?

Anorectal function tests as the 3D high resolution anorectal manometry, balloon expulsion test, surface electromyography and transperineal ultrasound are all frequently performed in the diagnostic work-up in patients with defaecation disorders. No previous study has compared these tests regarding their outcomes, nor has the interrater agreement been measured regarding the digital rectal examination by two experienced observers. Furthermore, transperineal ultrasound is in all probability not frequently used and therefore underexposed in the diagnostic workup of patients with dyssynergic defaecation.

INTRODUCTION

Anorectal function disorders like faecal incontinence and chronic constipation are very common. Generally, a conservative approach with life style advices, fibers, laxative and pelvic floor physical therapy will improve complaints in many patients. When unsuccessful, or the underlying cause seems unclear, these patients are referred to a specialist for further evaluation of anorectal function and possible therapy [1]. Besides digital rectal examination (DRE), a variety of tests are available to evaluate anorectal function. One may then objectively assess e.g. low or high tone of the anal sphincter, paradoxical contraction or inadequate relaxation of the pelvic floor.

Available tests are for example; anorectal manometry (ARM), 3 dimensional high resolution anorectal manometry (3D-HRAM), balloon expulsion test (BET), surface electromyography with or without an intra anal probe (s-EMG), transperianal ultrasound defaecography and the classical defaecography. Although some studies suggest that DRE alone is a useful tool to identify anorectal disorders [2, 3], others propose that anorectal function tests objectively evaluate anorectal function and might provide a predictive value for treatment results and influence management [4-9]. Which anorectal function test is the most accurate, is under debate.

The s-EMG with intra-vaginal or -anal electrode probes is commonly utilized by the pelvic floor physical therapist to confirm DRE and evaluate therapy [5, 10]. ARM is often considered the gold standard to measure anal pressures, however lack of reproducibility mentioned in several studies makes the test questionable [11-16]. Few studies compared ARM with anal s-EMG and showed limited concordance [17-19]. A more recent study compared ARM with DRE to determine dyssynergia and concluded that there was a moderate agreement [20].

According to the ROME IV criteria dyssynergia is established by two out of three anorectal function tests: first; abnormal anorectal evacuation pattern measured with ARM or EMG, second; abnormal BET, and third; impaired rectal evacuation diagnosed on imaging studies (e.g. defaecography) [7]. Furthermore, examinations as DRE and transperineal ultrasound are not mentioned in this context and a clear gold standard for one of these tests is not suggested. One could wonder whether a restricted use of these additional tests is justified. Could we rely on DRE and use additional tests only in complex patients?

Another reason to perform anorectal function tests is an attempt to objectively measure the anal pressures. Since there is no gold standard, a reappraisal for DRE by experienced investigators seems worthwhile investigating.

The Proctos Clinic is a tertiary referral center for specialized proctological care with experienced surgeons, a pelvic floor physical therapist and a fully equipped anorectal function laboratory. The aim of our study was to examine the correlation of the anal pressures between DRE, 3D-HRAM and the s-EMG. DRE, 3D-HRAM, s-EMG, BET and the trans-perineal ultrasound were compared to diagnose dyssynergia. Furthermore, we sought to assess the level of agreement between DRE performed by the surgeon and the pelvic floor physical therapist.

METHODS

Study population

The Proctos Clinic is a tertiary referral center for anorectal function complaints. Between January 2020 and April 2022, men and women aged 18 to 80 years, who underwent anorectal function tests and were referred for pelvic floor physical therapy (PFPT), were invited to participate in the study. Exclusion criteria were noncompliance with verbal instruction in Dutch and current psychiatric disorders. Patients in whom the timeframe was more than 4 weeks between the tests were excluded as the measurements may not be comparable.

Patients' first visited the surgeon, who performed a DRE and a transperineal ultrasound and counseled the patients for the study. Subsequently, patients were asked to participate in case they were referred for 3D-HRAM, BET and pelvic floor physical therapy. The pelvic floor physical therapist also performed DRE and s-EMG at first visit. The pelvic floor physical therapist was blinded for the DRE of the surgeon and also for the results of de 3D-HRAM, BET and transperineal ultrasound. All appointments were scheduled within 4 weeks. Results of the different tests were prospectively recorded. All patients signed a written informed consent before entering the study. The study was approved by the Medical Ethics Review Committee of the Amsterdam University Medical Centres, location AMC.

Anorectal investigations

Digital rectal examination

DRE was performed by all five surgeons and the pelvic floor physical therapist in the same standardized way. The procedure of DRE was explained to the patient. During the assessment the patient was lying on his/her left side with the knees flexed at 90.[0.] The examin-

ers used non-allergic gloves lubricated with water-based gel. All patients were asked to empty their bladder before the assessment. After careful insertion of the index finger, the sphincter tone was assessed at rest and scored as low, normal- or high (table 1). Squeeze tone was evaluated as the increment in pressure and scored similar. Then the patient was asked to squeeze for 30 seconds. The squeeze pressure was scored as low, normal or high. Subsequently, the examiner placed his/her left hand on the patient's abdomen and the patient was asked to push and bear down. Push effort was scored as relaxation, indifferent or paradoxical contraction.

Surface electromyography

Pelvic floor muscle tone and function were measured with EMG (mV) [10] with an intra-anal probe (Maple,®Novuqare Pelvic Health B.V. CE 0344, Rosmalen, the Netherlands). This is a probe with a matrix of 24 electrodes enabling measuring EMG signals from the different sides and layers of the pelvic floor muscles. The EMG probe is placed intra-anal, with the reference electrode placed on the spina iliaca anterior superior. Patients were asked to perform four consecutive tasks: 1) one minute rest where patients were instructed to feel the pelvic floor in rest 2) three maximum voluntary contractions where patients were instructed to perform a controlled contraction and relaxation of the pelvic floor muscles 3) one endurance contraction where patients were instructed to contract the pelvic floor muscles at such a level that they could hold for 30 seconds and 4) one push effort where the patient was asked to bear down. The examiner was holding the probe to keep it in place. From these s-EMG measurements, mean EMG amplitudes per electrode were calculated. A sustained increase in surface s-EMG activity (>50% increase from baseline) on attempted bearing down was defined as dyssynergia. The EMG values are presented as absolute values (mV). Normal values have not been published yet. For this reason the pelvic floor physical therapist estimated the normal values for men and women on clinical experience and a recent study where EMG values where measured during PFPT in patients with a chronic anal fissure [21](table 1). Results of the one year follow-up will be published shortly.

3D high resolution anal manometry (3D-HRAM)

The 3D-HRAM was performed by a nurse continence specialist and, the methods are previously described [22]. The anorectal probe has 256 pressure sensors on 16 lines, each line having 16 circumferential sensors. The probe, which is covered by a disposable sheath, has a diameter of 10.75 mm, a length of 64 mm and an internal lumen to inflate the balloon (3.3 cm long with a capacity of 400cc). Patients underwent the test in the left lateral position. Patients were asked to use a MICROLAX® enema the night before and the morning of the test. Pressures were measured at rest, during squeeze and during straining according to the London protocol (Carrington IAPWG 2019). Analysis of the manometry data was performed with ManoView (Given Imaging, Duluth, GA, USA). The mean rest-

Table 1. Summary of anorectal function tests and their categorized outcomes. DRE = digital rectal examination; 3D-HRAM = 3 dimensional high resolution anorectal manometry; s-EMG = surface electromyography; BET = balloon expulsion test.

	Mean resting pressure	Mean squeeze pressure	Push	Evacuation
DRE surgeon	1. Low 2. Normal 3. High	1. Low 2. Normal 3. High	1. Relaxation 2. Indifferent 3. Paradoxical	-------
DRE pelvic floor physical therapist	1. Low 2. Normal 3. High	1. Low 2. Normal 3. High	1. Relaxation 2. Indifferent 3. Paradoxical	-------
3D-HRAM	1. Low: 0-49 mmHg 2. Normal: 50-100 mmHg 3. High: >100 mmHg	1. Low: 0-49 mmHg 2. Normal: 50-200 mmHg 3. High: >200 mmHg	1. Relaxation 2. Indifferent 3. Paradoxical	-------
s-EMG	Women 1. Low: 0-2.0 2. Normal: 2.1-5.0 3. High: ≥ 5.1 Men 1. Low: 0-3.0 2. Normal 3.1-6.0 3. High: ≥ 6.1	Women 1. Low: 0-6.0 2. Normal: 6.1-15.0 3. High: ≥ 15.1 Men 1. Low: 0-9.0 2. Normal: 9.1-18.0 3. High: ≥ 18.1	1. Decrease of electrical activity (relaxation) 2. Indifferent 3. Increase of electrical activity (paradoxical)	-------
Transperianal echo	-------	-------	1. Relaxation 2. Indifferent 3. Paradoxical	1. Yes 2. No
BET	-------	-------	-------	1. <1 min = normal 2. >1 min = abnormal

ing pressure (MRP) and mean squeeze pressure (MSP) were measured by the software and were additional visually reviewed by the gastroenterologist RF. Figure 1 and figure 2 shows examples of the pressure profile during rest (MBP) and during squeeze (MSP) with ManoView. Normal values have been published by several authors and show a large range [14, 23-28]. Based on these studies we considered an anal rest or squeeze pressure lower than 50 mmHg as 'low'. For comparison with the other tests, the anal pressures were categorized as described in table 1.

The balloon expulsion (BET)

A non-sterile disposable balloon (BARD, Covington, USA) was filled with 50cc water or until the patients felt a desire to defaecate. Balloon expulsion time differs in literature. According to several studies, evacuation within 1 minute was considered as normal [28-30]. The BET was performed by a nurse continence specialist in our clinic and results were scored <1 minute or >1 minute [1](table 1).

Transperineal ultrasound (TPUS)

This was performed with a standard BK Medical scanner (BK Medical ApS, Herlev, Denmark) and a transducer (BK Medical, type 2C9, 13 MHz). The patient was lying supine with

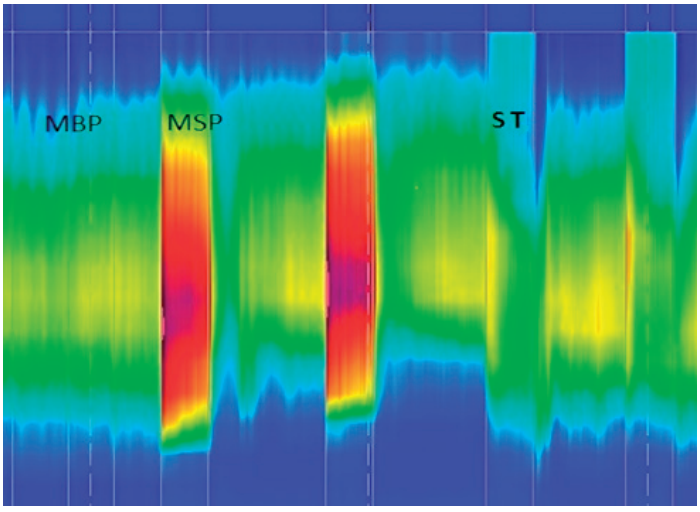

Figure 1. 3D-HRAM. Normal pressure profile during rest (MBP), increase during squeeze (MSP), and decrease during straining (ST).

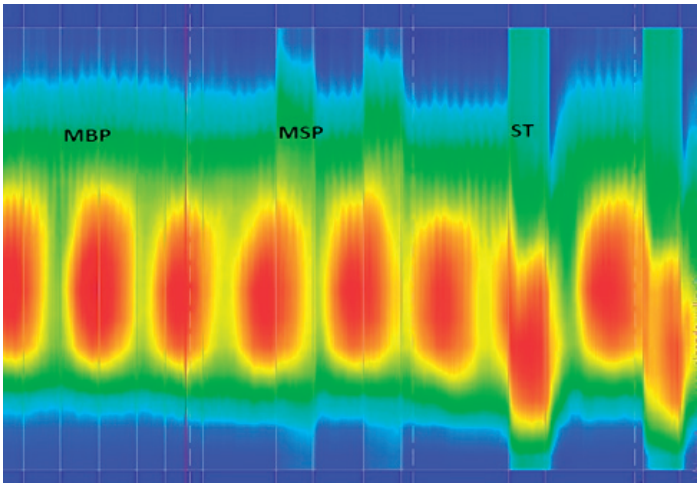

Figure 2. 3D-HDRAM. Dyssynergia. A high basal pressure (MBP) profile is seen with no changes in pressure during maximal squeeze (MSP) and straining (ST).

the legs flexed. As with the 3D-HRAM, patients were asked to use a MICROLAX® enema the night before and the morning of their appointment. Transperineal ultrasound was performed using a conventional curved array probe rested on the perineum to gain dynamic two-dimensional mid plane sagittal views. For the real time movement 50 ml echo lucent gel was introduced in the rectum. The patient was asked to squeeze, bear down and cough while views were digitally recorded. The movements during straining were categorised as relaxation, indifferent and paradoxical contraction. Evacuation of gel during straining was categorised as yes or no (table 1).

Table 2. Patient characteristics.

	No. patients
Gender	
Male, n(%)	13 (27)
Female, n(%)	37 (74)
Median age, years (SD)	51 (15)
Indication, n(%)	
Fecal incontinence	27 (54)
Obstructed defecation	10 (21)
Chronic anal fissure	3 (6)
Haemorrhoidal disease	2 (4)
Other	8 (17)
Vaginal parity, n(%)	
0	7 (19)
1	7 (19)
2	14 (38)
≥3	9 (24)
Rectal surgery in the past, n(%)	9 (18)
Radiotherapy in de past, n(%)	1 (2)
Urologic or gynecologic surgery in the past, n(%)	10 (20)
Neurological or connective tissue disease, n(%)	3 (6)
Pelvic floor physical therapy in the past, n(%)	31 (62)

Statistical analysis

All statistical analyses were performed using SPSS (IBM, SPSS Statistics 28). Continuous data were described as mean or median depending on the distribution, including range and standard deviation. Statistical analysis was performed by comparing categorical results of anal pressures with descriptive statistics using crosstabs, namely; the resting and squeeze pressures and straining movement of DRE by the surgeon and pelvic floor physical therapist, 3D-HRAM, s-EMG, transperineal ultrasound (with echo lucent gel) and BET. The interrater agreement for DRE, which included tone during rest and squeeze and straining movement, between the referring surgeon and the pelvic floor physical therapist was assessed by using the Cohen's Weighted Kappa test. Agreement was classified as follows: poor agreement (0.00-0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80), and almost perfect agreement (0.81-1.00). P values of <0.05 were considered significant.

RESULTS

Patients, demographics and clinical characteristics

Between January 2020 and April 2022, 56 patients were referred for PFPT by the surgeon and underwent anorectal function tests in the diagnostic work-up. Six patients were excluded due to incomplete data because the patient cancelled an appointment or when treatment started between the different tests. The appointment for the 3D-HRAM was always prior to, or at the same day as the PFPT.

Demographics and clinical characteristics of the study group are detailed in Table 2. A total of 37 (74%) females were included and median age was 51 years. Twenty-three (62%) females had two or more vaginal deliveries. Thirty-one (62%) patients previously received PFPT. Most frequent indication for referral for PFPT was faecal incontinence in 27 patients (54%).

Interrater agreement digital rectal examination

The assessed sphincter tone and pelvic floor muscle function with DRE by the surgeon and the pelvic floor physical therapist during rest, squeeze and straining correlated in 78%, 78% and 84%, respectively. This resulted in substantial agreement for assessing the resting tone with a Cohen's Weighted Kappa (κ) of 0.749 (95% CI 0.612-0.886). In the assessment of the squeeze tone this was somewhat lower, but still substantial, with a (κ) of 0.620 (95% CI 0.432-0.807). When assessing straining, they agreed almost perfect with a (κ) of 0.819 (95% CI 0.700-0.938).

The prolonged squeeze (30 seconds) was only performed by few surgeons and therefore, we omitted this variable from the analysis.

Digital rectal examination by the surgeon and pelvic floor physical therapist and anorectal manometry (n=46 and n=45)

When classifying the resting tone and pressure as low, normal or high, 23 (47%) patients were assessed similar by the surgeon's DRE and the 3D-HRAM. In the assessment of squeeze tone and pressures this was somewhat better with 31 (65%) patients. DRE of the pelvic floor physical therapist was similar to 3D-HRAM in 26 (53%) and 32 (65%) patients in the assessment of the resting and squeeze tone and pressure respectively.

Digital rectal examination by the surgeon and pelvic floor physical therapist and surface electromyography (n=49 and n=50)

The resting tone assessed by the surgeon's DRE and s-EMG activity was similar in only 18 (36%) patients. For squeeze this was 32 (65%). DRE by the pelvic floor physical therapist correlated in 18 (36%) and 41 (82%) patients with s-EMG in the assessment of resting tone and squeeze tone. The surgeon and the pelvic floor physical therapist both classified the resting tone with DRE in respectively three and four patients as 'low' while s-EMG activity assessed 'high'. One patient with a chronic anal fissure was classified 'high' for squeeze tone with DRE by both the surgeon and pelvic floor physical therapist but classified 'low' with s-EMG.

Anorectal manometry and surface electromyography (n=49)

When the results are categorized as low, normal and high, the 3D-HRAM and s-EMG correlated well in only 18 (37%) patients when comparing the resting pressure and electric activity. With 29 (59%) patients this was better when comparing the squeeze tone and electric activity. Overall, four patients who were classified as 'low' on the 3D-HRAM were

classified 'high' with s-EMG activity concerning resting pressure and one patient vice versa during squeeze pressure.

Comparing detecting dyssynergia

BET and evacuation of gel during TPUS (n=19)

Four patients were not able to evacuate the gel despite being able to expel the balloon within one minute. Three patients evacuated the gel – of whom two not completely – while they were not able to expel the balloon within one minute (table 3).

Table 3. Balloon expulsion test (BET) versus evacuation of gel during transperineal ultrasound (TPUS).

		Evacuation of gel during TPUS		
		Yes	**No**	**Total**
BET	<1 minute	5	4	9
	>1 minute	3	7	10
Total		8	11	19

TPUS and evacuation of gel during TPUS (n=24)

Half of patients who underwent TPUS with echo lucent gel evacuated the gel (table 4). Nineteen patients were classified as 'indifferent' regarding the straining movement.

Table 4. Transperineal ultrasound (TPUS) versus evacuation of gel during TPUS

		Evacuation of gel during TPUS		
		Yes	**No**	**Total**
TPUS	Relaxation	3	0	3
	Indifferent	9	10	19
	Paradoxical	0	2	2
Total		12	12	24

TPUS and BET (n=23)

Eighteen patients were classified 'indifferent' on the transperineal ultrasound (table 5). Almost half of them expelled the balloon within one minute and the other half in more than one minute or not at all. One patient showed normal 'relaxation' of the puborectalis muscle when straining on TPUS, whereas he was not able to expel the balloon within one minute.

Table 5. Transperineal ultrasound (TPUS) versus balloon expulsion test (BET).

		BET		
		< 1 minute	**> 1 minute**	**Total**
TPUS	Relaxation	1	3	4
	Indifferent	10	8	18
	Paradoxical	0	1	1
Total		11	12	23

S-EMG versus BET (n=37)

Thirteen patients (35%) were classified as 'paradoxical' of whom almost half was able to expel the balloon within one minute and half could not (table 6). Fourteen patients were classified as 'indifferent' of whom nine was not able to expel the balloon within one minute.

Table 6. Surface electromyography (s-EMG) versus balloon expulsion test (BET).

		BET		
		< 1 minute	**> 1 minute**	**Total**
s-EMG	Relaxation	7	3	10
	Indifferent	5	9	14
	Paradoxical	6	7	13
Total		18	19	37

3D-HRAM with BET (n=37)

Four out of 10 patients (40%) who showed paradoxical straining on the 3D-HRAM were able to expel the balloon within one minute while five out of the 16 patients (31%) who showed normal relaxation could not expel the balloon within one minute (table 7).

Table 7. 3D high resolution anorectal manometry (3D-HRAM) versus balloon expulsion test (BET).

		BET		
		< 1 minute	**> 1 minute**	**Total**
3D-HRAM	Relaxation	11	5	16
	Indifferent	3	8	11
	Paradoxical	4	6	10
Total		18	19	37

DRE by the surgeon versus BET (n=37)

Half of the 10 patients who were classified as 'indifferent' were able to expel the balloon within one minute (table 8). Of the patients who were assessed as normal 'relaxation' or 'paradoxical' respectively 9 of 15 (67%) and 4 of 12 (33%) were able to expel the balloon within one minute.

Table 8. Digital rectal examination (DRE) of the surgeon versus balloon expulsion test (BET).

		BET		
		< 1 minute	**> 1 minute**	**Total**
DRE surgeon	Relaxation	9	6	15
	Indifferent	5	5	10
	Paradoxical	4	8	12
Total		18	19	37

DRE by the pelvic floor physical therapist versus BET (n=37)
Results are almost similar with the DRE by the surgeon.

S-EMG versus TPUS (n=32)
Twelve patients (37%) showed the same results concerning classifying the puborectalis muscle movement in these tests (table 9).

Table 9. Surface electromyography (s-EMG) versus transperineal ultrasound (TPUS).

		TPUS			
		Relaxation	**Indifferent**	**Paradoxical**	**Total**
s-EMG	Relaxation	2	6	0	8
	Indifferent	3	9	1	13
	Paradoxical	0	10	1	11
Total		5	25	2	32

S-EMG versus evacuation of gel during TPUS (n=24)
Two patients were not able to evacuate the gel while they showed a decrease in electric activity which corresponds with relaxation of the pelvic floor muscles (table 10). One patient evacuated the gel completely during TPUS but showed an increase in electric activity with the s-EMG. This patient did not show paradoxical movement on the other tests.

Table 10. Surface electromyography (s-EMG) versus evacuation of gel during transperineal ultrasound (TPUS).

		Evacuation of gel during TPUS		
		Yes	**No**	**Total**
s-EMG	Relaxation	6	2	8
	Indifferent	5	4	9
	Paradoxical	1	6	7
Total		12	12	24

3D-HRAM versus TPUS (n=32)
In 8 (25%) patients the test showed the same results (table 11). TPUS was often classified as 'indifferent' in 25 (78%) patients.

Table 11. 3high resolution anorectal manometry (3D-HRAM) versus transperineal ultrasound (TPUS).

		TPUS			
		Relaxation	**Indifferent**	**Paradoxical**	**Total**
3D-HRAM	Relaxation	3	13	0	16
	Indifferent	2	3	0	5
	Paradoxical	0	9	2	11
Total		5	25	2	32

3D-HRAM versus evacuation of gel during TPUS (n=24)

Two patients were classified as 'paradoxical' but were able to evacuate the gel during TPUS (table 12). Also three patients could not evacuate while they showed normal 'relaxation' on the 3D-HRAM.

Table 12. 3 dimensional high resolution anorectal manometry (3D-HRAM) versus evacuation of gel during transperineal ultrasound (TPUS).

		Evacuation of gel during TPUS		
		Yes	**No**	**Total**
3D-HRAM	Relaxation	8	3	11
	Indifferent	2	3	5
	Paradoxical	2	6	8
Total		12	12	24

3D-HRAM versus s-EMG (n=50)

Twenty-six (52%) patients showed similar results in both tests (table 13). S-EMG was more often classified as 'indifferent' and one patient was classified 'paradoxical' while normal 'relaxation' was measured using 3D-HRAM.

Table 13. 3 dimensional high resolution anorectal manometry (3D-HRAM) versus surface electromyography (s-EMG).

		s-EMG			
		Relaxation	**Indifferent**	**Paradoxical**	**Total**
3D-HRAM	Relaxation	9	13	1	23
	Indifferent	3	5	3	11
	Paradoxical	0	4	12	16
Total		12	22	16	50

TPUS versus DRE by the surgeon (n=32)

In 17 patients (52%) the tests showed similar results. Twenty-five (78%) patients were classified 'indifferent' with TPUS (table 14).

Table 14. Transperineal ultrasound (TPUS) versus digital rectal examination (DRE) by the surgeon.

		DRE surgeon			
		Relaxation	**Indifferent**	**Paradoxical**	**Total**
TPUS	Relaxation	5	0	0	5
	Indifferent	6	10	9	25
	Paradoxical	0	0	2	2
Total		11	10	11	32

TPUS versus DRE by the pelvic floor physical therapist (n=32)

Results are almost similar with the DRE by the surgeon.

DRE by the surgeon versus evacuation of gel during TPUS (n=24)

One patient showed 'paradoxical' straining during DRE by the surgeon but could evacuate the gel during the TPUS at the same day (table 15). One patient could not evacuate the gel while the surgeon classified 'relaxation' with DRE.

Table 15. Digital rectal examination (DRE) by the surgeon versus evacuation of gel during transperineal ultrasound (TPUS).

		Evacuation of gel during TPUS		
		Yes	**No**	**Total**
DRE surgeon	Relaxation	7	1	8
	Indifferent	4	5	9
	Paradoxical	1	6	7
Total		12	12	24

DRE by the pelvic floor physical therapist versus evacuation of gel during TPUS (n=24)

Results are almost similar with DRE by the surgeon except that DRE in two patients were classified as 'relaxation' while they could not evacuate the gel.

S-EMG versus DRE by the surgeon (n=50)

In 26 (52%) patients the test results were similar. S-EMG classified 'indifferent' in 22 (44%) patients (table 16). One patient was classified 'paradoxical' with s-EMG but classified 'relaxation' by the surgeons' DRE.

Table 16. Surface electromyography (s-EMG) versus digital rectal examination (DRE) by the surgeon.

		DRE surgeon			
		Relaxation	**Indifferent**	**Paradoxical**	**Total**
s-EMG	Relaxation	9	3	0	12
	Indifferent	7	8	7	22
	Paradoxical	1	6	9	16
Total		17	17	16	50

S-EMG versus DRE by the pelvic floor physical therapist (n=50)

In 31 (62%) patients the test results were similar (table 17).

Table 17. Surface electromyography (s-EMG) versus digital rectal examination (DRE) by the pelvic floor physical therapist.

		DRE pelvic floor physical therapist			
		Relaxation	**Indifferent**	**Paradoxical**	**Total**
s-EMG	Relaxation	12	0	0	12
	Indifferent	6	10	6	22
	Paradoxical	0	7	9	16
Total		18	17	15	50

3D-HRAM versus DRE by the surgeon (n=50)

In 26 (52%) patients the test results were similar (table 18). Five patients were classified as 'paradoxical' straining by the surgeon while these patients showed 'relaxation' on 3D-HRAM. The other way around; one patient was classified 'paradoxical' with 3D-HRAM but the surgeon classified DRE as 'relaxation'.

Table 18. 3D high resolution anorectal manometry (3D-HRAM) versus digital rectal examination (DRE) by the surgeon.

		DRE surgeon			
		Relaxation	**Indifferent**	**Paradoxical**	**Total**
3D-HRAM	Relaxation	12	6	5	23
	Indifferent	4	5	2	11
	Paradoxical	1	6	9	16
Total		17	17	16	50

3D-HRAM versus DRE by the pelvic floor physical therapist (n=50)

Results were almost similar to the surgeon's DRE.

DISCUSSION

The present study provides an overview of the correlation between outcomes of frequently performed anorectal function tests and compare their ability to measure dyssynergia. Furthermore this study measured the level of agreement between DRE performed by the surgeon and the pelvic floor physical therapist in a tertiary referral center.

Despite the surgeons and the pelvic floor physical therapist being experienced, performing several digital rectal examinations per day, the agreement of the anal tone between their DRE was not perfect. The assessed tone during rest, squeeze and straining did not correlate in 22%, 22% and 16% respectively. To the best of our knowledge no literature concerning the interrater agreement of DRE has been published. Interrater agreement has only been studied in vaginal digital assessment concerning the pelvic floor function and digital rectal examination in the context of prostate cancer [31-33]. Overall, the agreement was substantial to almost perfect. The small differences in classification of DRE between the surgeon and pelvic floor physical therapist may be explained by differences in interpretation of the indifferent movement of the pelvic floor. Not a single examination was classified both as relaxation and paradoxical movement.

The correlation between the surgeons' DRE, pelvic floor physical therapists' DRE and the 3D-HRAM in our study was moderate and somewhat better for squeeze tone/pressures than resting tone/pressures. Several studies compared DRE with ARM and showed an overall good agreement of pressures, however similar to our study, slightly better for squeeze pressures, but results are not consistent [9, 15, 34-39]. For example, the study

by Beatrice et al showed that DRE correlates well, but not perfectly, with the ARM for resting pressures, r=0.71 (p<0.001) [9]. However, Orkin et al observed an excellent agreement between DRE and the ARM for resting pressures (r=0.82) and for squeeze pressures (r=0.81) [34]. In contrast, Soh et al described a poor agreement between DRE and ARM for resting pressures with a k-coefficient of 0.01 and a moderate agreement for squeeze pressure with a k-coefficient of 0.42 [35]. Pinto et al showed a moderate to strong agreement for resting pressure with a Gamma index of 0.7 and a strong correlation of the squeeze pressures with a Gamma of 0.96 [37]. All studies – including ours – report that the examinations were performed by experienced examiners but the results vary considerably. Nevertheless, ARM can be performed with a variety of types of equipment, techniques and study protocols, making results less reproducible and thus difficult to compare [40, 41]. A recent study by Prichard et al described even significantly different results during ARM between operators despite using similar instructions to patients [16]. Even a small difference in outcome could lead in a different interpretation. It must be noted that in contrast to most ARM studies we used the 3D probe.

DRE correlated better with 3D-HRAM in patients referred for faecal incontinence. With 54% this was the largest group in this study. However, defining 'normal' resting and squeeze pressures for ARM values is quite difficult. There is obviously an overlap since several studies showed different values for normal and abnormal resting and squeeze pressures for ARM [14, 23-28]. To be accurate in comparing between groups, the pressures should be adjusted according to age, gender and parous and nulliparous females. But these differences were small and to make comparisons between tests manageable in this study we did not differentiate.

The surgeons' DRE and the pelvic floor physical therapist's DRE were compared to the s-EMG and showed some discrepancies. The surgeon's DRE and the pelvic floor physical therapist's DRE were categorized as 'low' whereas the s-EMG categorised 'high' in three and four patients, respectively. However, one patient was categorised 'high' with DRE and 'low' with s-EMG. This can probably be explained by the fact that patients who can hardly control their external anal sphincter might overcompensate with their levator muscle. As we measured with s-EMG, the mean of the total electrical activity of the external anal sphincter including the levator muscle, the EMG activity might be higher than expected. When retrospectively assessing the 3D-HRAM, these patients showed indeed higher pressures of the posterior levator muscle on the 3D image in contrast to the sphincter and vice versa for the patient with a chronic anal fissure. Furthermore, high tone on the levator muscle with DRE might be turgor which is not measured with s-EMG. For this reason comparing s-EMG with other tests might not be appropriate and should probably be used only to confirm physical examination and biofeedback registration.

The correlation between s-EMG and the 3D-HRAM was better for squeeze pressures and electric activity than resting pressures and electric activity with an agreement of 59% and 37% respectively. A study from 1989 also showed limited concordance with a correla-

tion coefficient of 0.55 ($p<0.001$) between the maximum squeeze pressure with ARM and maximum contraction pattern with de EMG [17]. Regarding diagnosing dyssynergia while straining with s-EMG and 3D-HRAM, our results were not in line with the results by Chiarioni et al [30]. In our study, s-EMG and ARM were concordant in 52% while Chiarioni et al described an agreement of 88% for classifying patients' dyssynergic or not dyssynergic. Both tests are used to test the anorectal function but are used for different purposes in clinical practice. The question that remains is how relevant small differences are in clinical practice.

The results of the six different function tests used to diagnose pelvic floor dyssynergia, namely DRE by both the surgeon and the pelvic floor physical therapist, 3D-HRAM, s-EMG, BET and transperineal ultrasound (with echo lucent gel) were to some extent comparable. Although most comparisons were statistically significant, the correlation remained low. Discrepancies with TPUS could be explained by the non-anatomical supine position of the test and the fact that the patient is not in private environment. Three patients who evacuated the gel – although not completely – but were not able to expel the balloon within 1 minute, were referred for PFPT because of faecal incontinence. It is very likely that these patients lost the gel by leaking, not because of the push effort. This makes these tests not suitable to compare.

Furthermore, the tests are performed in different postures; the balloon expulsion is performed in a private setting, in sitting position, whereas the other tests are performed by an examiner with the patient lying in the left lateral position. 3D-HRAM measures the anorectal pressures, s-EMG measures electrical activity and TPUS is visually assessed by the doctor were evacuating echo lucent gel might support their findings. Some discrepancies cannot be explained except the snapshot nature of the tests. It is known that the diagnostic accuracy of ARM is limited for discriminating between healthy people and patients with functional constipation [42]. Unfortunately, previous studies with TPUS assessed its accuracy for detecting rectocele, intussusception or enterocele, or used a total pelvic floor ultrasound without echo lucent gel. No previous studies reported its accuracy to diagnose dyssynergia. However, based on our experience the TPUS is a low cost and easy tool for surgeons to perform. Surgeons are able to perform their own test in the outpatient clinic and, moreover, it has comparable results with the classical defaecography [43] which makes it worth considering it a relevant anorectal function test. The BET is a frequently used test for assessing defaecatory dysfunction since it is a simple and low-cost procedure. Different protocols are used to perform the procedure; air filled or water-filled balloon, lying or seated position. Time values that are considered abnormal range from 1 till 5 minutes [28-30, 44, 45]. In our study, a balloon expulsion time of more than 1 minute was considered prolonged. This was categorised as dyssynergia by the 3D-HRAM in 32% of the cases. In contrast to older studies more recent studies demonstrated poor agreement between BET and ARM [46, 47].

According to the ROME IV criteria, dyssynergic defaecation is established by two out of three tests: 1) ARM or s-EMG; 2) balloon expulsion test or 3) defaecography. Remarkable is that the ARM or the s-EMG should be abnormal and that DRE and the transperineal ultrasound are not mentioned in this work-up [7]. This might be confusing and suggests that none of the tests can be considered as golden standard. Furthermore, anorectal function tests provide additional workload and costs whereas DRE is widely available and dyssynergia is a wide spread phenomena. The ROME IV criteria are merely used to standardize patients in an attempt to objectivize dyssynergia. Also Bordeianou et al had their doubts about which test to assign highest value, the s-EMG, BET or ARM, prior to referral to the pelvic floor physical therapist with dyssynergia [48].

Undoubtedly this study has a number of limitations which should be acknowledged. First, the surgeons and the pelvic floor physical therapist were unblinded to the patients' medical history when performing the DRE which likely has influenced the results by information bias. Secondly, although all surgeons and the pelvic floor physical therapist were given instructions before the study started on how to perform a complete structured DRE and systematically describe the physical examination in the electronic health record, variety in performing and assessing DRE is insurmountable. The single observer for all 3D-HRAM results might be a lowness or a strength in this study. A considerable limitation of this study is that we were not able to use controlled normal s-EMG values since they have not yet been published. Furthermore, the results of the study would have had more relevance if there was a gold standard or known sensitivity of the tests. This issue is also reflected in the ROME IV criteria for dyssynergic defaecation as mentioned above. Unfortunately, not all patients underwent all tests due to logistic problems in the outpatient clinic concerning the tests in the context of the study. Consequently, some patients did not undergo the BET or the TPUS. Lastly, there might have been interpretation bias by assessing straining movement of the pelvic floor. It is not known how 'indifferent' movement of the pelvic floor is defined among the examiners; does this mean 'no movement' or also 'relaxation but not enough'? This probably resulted in different outcomes.

This study showed that squeeze pressures were more often similarly categorized than resting pressures in anorectal function tests. It further shows that the surgeons' DRE and the pelvic floor physical therapist's DRE more often similar assessed in comparison to anorectal functions tests as 3D-HRAM, s-EMG or TPUS. Still, the correlation between all tests is quite disappointing and this raises questions regarding when to perform these tests in addition to DRE. Or does this mean that we can suffice with an expert's DRE when referring to the pelvic floor physical therapist for dyssynergia? The pelvic floor physical therapist will evaluate therapy with his/her own DRE with or without s-EMG, not with ARM or transperineal ultrasound. Perhaps we should only perform anorectal function tests in patients who are refractory to conservative treatment like lifestyle and pelvic floor physical therapy, or when more invasive procedures like surgery or botox e.g. are considered. Furthermore, these tests are valuable when evaluating new (surgical) therapies.

CONCLUSION

This study shows that DRE has a good correlation amongst experienced investigators. Since commonly performed anorectal function tests correlate poorly with DRE, and with other anorectal function tests, DRE by an experienced investigator suffices in daily clinical practice. When conservative treatment fails, further investigation is warranted, however these results should be interpreted with caution.

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CHAPTER 8

PROSPECTIVE COHORT STUDY OF HIGH-VOLUME TRANSANAL IRRIGATION IN PATIENTS WITH CONSTIPATION AND/OR FAECAL INCONTINENCE

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Submitted

ABSTRACT

Aim

To determine the clinical efficacy of high-volume transanal irrigation (TAI) in patients with constipation and/or faecal incontinence, using validated symptom and quality of life questionnaires.

Method

Prospective cohort study of 114 consecutive patients with constipation and/or faecal incontinence (Rome-IV defined) who started TAI. A comprehensive questionnaire was completed at baseline, 4, 12, 26 and 52 weeks follow-up. Primary objective: significant symptom reduction (≥30%; Cleveland Clinic constipation score [CCCS] and St Marks incontinence score [SMIS]) at 52 weeks. Secondary objectives: 1) continuation rates of TAI, 2) effect on quality of life (QOL), and 3) identification of predictors for continuation.

Results

A total of 59 (51.8%) patients with constipation, 26 (22.8%) with faecal incontinence, and 29 (25.4%) with coexistent symptoms were included. Reduction of constipation symptoms was not observed. Median PAC-QOL scores decreased on most domains, indicating QOL improvement. Reduction of faecal incontinence occurred in 5/9 (55.6%) patients with faecal incontinence and in 3/10 (30.0%) patients with coexistent symptoms. Median SMIS per-individual decreased in patients with faecal incontinence (3; IQR -5–3) and in patients with coexistent symptoms (2; IQR 0–4). Median FI-QOL scores increased on most domains, indicating QOL improvement. At 52 weeks, 41 (36.0%) patients continued TAI, 63 (55.2%) stopped and 10 (8.8%) patients were lost to follow-up. No clinical characteristics predicted continuation.

Conclusion

TAI reduced symptoms of faecal incontinence but not constipation. One-third of patients continued TAI at 52 weeks. QOL related to both constipation and faecal incontinence improved. No clinical characteristics were found to predict continuation.

What does this paper add to the literature?

this is one of the first cohort studies in which the clinical efficacy of high-volume transanal irrigation in patients with constipation and/or faecal incontinence was evaluated using validated symptom and QOL questionnaires. Further, we provide detailed results on irrigation parameters, which can be helpful for therapists to guide patients.

INTRODUCTION

Treatment of faecal incontinence and chronic constipation with transanal irrigation (TAI) is gaining popularity, and an increasing number of studies have been published during the past two decades reporting success rates in both adults and children. [1, 2] A systematic review and meta-analysis conducted in 2010 reported excellent success rates in children. [1] In adults, TAI was shown to be successful in 45% of patients with chronic constipation, in 47% of patients with faecal incontinence and in 59% of patients with coexistent symptoms (data based on 1,229 patients in 17 studies). [1] Similar results have been reported in a recent systematic review in adults. [2] Further, a large study in 348 patients with constipation and/or faecal incontinence showed successful treatment in 47% at a mean follow-up of 21 months. [3] This observation was confirmed by a study in 507 patients, of whom 216 (43%) still used TAI at a follow up of 12 months. [4]

A number of clinical trials have been performed in specific patient groups. A randomised controlled trial compared TAI with conservative management in 87 patients with spinal cord injury. [5] Improvement of constipation, faecal incontinence and related quality of life (QoL) was demonstrated. Three clinical trials showed that TAI improves symptoms and QoL in patients with low anterior resection syndrome. [6-8] A recent report of the Chronic Constipation Treatment Pathway (CapaCiTY) research programme showed a reduction in the Patient Assessment of Constipation Quality of Life score (PAC-QoL) at 3 months, which was larger in the group of patients using high-volume irrigation (which was preferred over low-volume irrigation by the majority of patients). [9]

In contrast to stronger evidence in these specific patient groups, most other studies to date had methodological limitations, reporting cross-sectional or retrospectively collected data over a short follow up period (several weeks to months), or reporting on small patient groups. Further, validated scoring systems to report on QoL were not routinely used, which makes it hard to interpret and compare the results of different studies. There is a need for prospective studies using validated symptom severity and QoL measures to validate the success rate. In this prospective cohort study, the primary objective was to determine the effect of high-volume TAI on reduction of symptoms of constipation and/or faecal incontinence at 52 weeks follow up. Secondary objectives included: 1) continuation rates of TAI, 2) the effect of TAI on QoL, and 3) evaluation of predictors for continuation.

METHODS

Study population

We prospectively recruited 114 consecutive adult patients naive to TAI with either the Navina™ Classic or Smart system, referred by 26 different centres in the Netherlands to "Wellspect HealthCare" or the wholesale company "Hoogland Medical" between Febru-

ary 2018 and September 2020. All patients had to satisfy the Rome IV criteria for functional constipation (minimum of ≥2 symptoms: during more than one-fourth [25%] of defaecations: (a) straining; (b) lumpy or hard stool; (c) feeling incomplete evacuation; (d) feeling anorectal obstruction; (e) manual manoeuvres; and (f) <3 defaecations per week) [10] and/or the Rome IV criteria for faecal incontinence (>monthly episodes to solid or liquid stools). [11] All participating patients underwent treatment with TAI according to routine care. Patients were allowed to decide to use either the Classic (manual pump) or Smart (electronic pump) system. During a face-to-face visit, all patients were instructed by a conservative management nurse to start TAI on a daily basis with 500–1000 mls of water. Frequency of TAI and the volume of water were adjusted during follow-up (frequent telephone clinics).

Study questionnaire

Data were collected using a comprehensive questionnaire completed at five different time points: baseline (just before starting the first irrigation, face-to-face visit with the conservative management nurse), 4, 12, 26 and 52 weeks of follow up. The baseline questionnaire incorporated questions on demographics, obstetric, surgical and medical history, and previous treatment. Validated symptom severity and QoL scores were completed in both at baseline and during follow up, including the Rome IV criteria for functional constipation [10] and faecal incontinence, [11] Cleveland Clinic constipation score (CCCS; 0–30; higher score indicates more severe symptoms), [12] St Marks incontinence score (SMIS; 0–24; higher score indicates more severe symptoms), [13] PAC-QoL (1–4; higher score indicates worse QoL), [14] fecal incontinence quality of life (FI-QoL; 1–4; higher score indicates better QoL) score [15] and Bristol stool form scale.[17] QoL questionnaires (PAC-QoL and FI-QoL) were not included in the questionnaire at 12 weeks follow up. Completeness of evacuation after irrigation (VAS score), treatment satisfaction (VAS score) and side effects were also recorded at each follow up appointment. In case of discontinuation of TAI, patients were asked to provide the main reason for discontinuation. At follow up, irrigation parameters (frequency, volume [mls] and duration [minutes] of irrigation) were evaluated. The questionnaire data were collected on paper (baseline visit) or digitally via a secured data management platform (Castor) depending on patients' preference. All data were stored on the data management platform.

Sample size

The sample size was based on the primary end point of the study: reduction of symptoms at 52 weeks measured using CCCS and SMIS. According to previously published results, we estimated that patients had a median SMIS of 9 (standard deviation 4.5) and a median CCCS of 13 (standard deviation 4.5) at baseline. [5] Patients were divided in 3 groups: primary symptoms of constipation, primary symptoms of faecal incontinence, and symptoms of both constipation and faecal incontinence (based on the Rome IV criteria for

functional constipation [10] and/or faecal incontinence [11]; these symptoms frequently co-exist [16]). A 30% scale reduction with a variance estimate conservatively set at a standard deviation of 4.5 was considered clinically relevant. A power of 90% and a significance level of 5% was used. To detect a median change of 3.9 in CCCS pre versus post irrigation, 17 patients with primary symptoms constipation had to be included. To detect a median change of 2.7 in SMIS pre versus post irrigation, 32 patients with primary symptoms of FI had to be included. To detect a median change of 6.6 in CCCS and SMIS pre versus post irrigation, 8 patients with symptoms of both constipation and faecal incontinence had to be included. Different studies (including a study from our centre) have reported a dropout of approximately 50% of patients after 1 year follow-up. [3, 17, 18] Therefore we aimed to recruit a total number of 34 patients with constipation, 64 patients with faecal incontinence and 16 patients with both constipation and faecal incontinence (total number of patients 114).

Data analysis

All data were presented in the total group, as well as per Rome IV classification. Descriptive statistics were used to report the results, including median (interquartile range [IQR]) for continuous variables. For variables with missing data, multiple imputation was performed. Clinical characteristics were compared between groups using chi-square and Mann-Whitney-U test. Kaplan-Meier curves were plotted to show continuation rates in: 1) the total group, and stratified per: 2) symptom group, 3) sex and 4) device group (Navina™ Classic vs Smart). Reduction in symptoms was measured per entire group (median, IQR), and also per individual (median, IQR) to confirm that symptom improvement was not secondary to drop-out of patients with more severe symptoms. Multivariable logistic regression was used to identify independent factors associated with continuation of TAI at 52 weeks, with results presented as effect sizes (odds ratio) with 95% confidence intervals. Statistical analysis was performed using Graphpad Prism 9.0 and R Studio.

Ethical approval

Ethical approval was granted by the VU University Medical Centre Research Ethics Committee (reference number 2017.533) on 4th January 2018.

RESULTS

Study participants

Demographics and clinical characteristics of the total study group and subgroups according to the Rome IV criteria for functional constipation and faecal incontinence are detailed in Table 1. In total, 59 (51.8%) patients were included with functional constipation in isolation, 26 (22.8%) patients with faecal incontinence in isolation, and 29 (25.4%) with coex-

istent symptoms. Patients with faecal incontinence in isolation (median age = 69 years; IQR 64–75) were significantly older than patients with functional constipation in isolation (median age = 51 years; IQR 36–60) or coexistent symptoms (median age = 59 years; IQR 46–63; p <0.0001). Males were most often referred for treatment of functional constipation in isolation. Median BMI in the total group was 25.1 kg/m^2. Females with faecal incontinence in isolation or coexistent symptoms were more likely to be parous compared to females with functional constipation in isolation (p <0.0001). Pelvic surgery was more often performed in patients with faecal incontinence in isolation compared to patients with functional constipation (65.4% vs 33.9%; p = 0.007). A history of anal/perineal surgery was frequently reported in patients with faecal incontinence in isolation or coexistent symptoms (34.6% and 37.9%, respectively). Neurological conditions were most common in patients with functional constipation (32.2%). Two-third of all patients underwent pelvic floor physiotherapy (+/- biofeedback), and 6 patients (5.3%) tried TAI with another device before entering the study.

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Symptomology at baseline

Bowel symptoms at baseline in the total group and per individual Rome IV criteria are shown in Table 2. Remarkably, most patients with faecal incontinence in isolation reported symptoms of incomplete rectal evacuation (88.5%). Median CCCS was 15 (IQR 11–19) in patients with functional constipation and 13 (IQR 11–18) in patients with coexistent symptoms. Median SMIS was 14 both in patients with faecal incontinence in isolation and in patients with coexistent symptoms. Urge faecal incontinence was the most reported type of faecal incontinence (73.1% in patients with faecal incontinence, 58.6% in patients with coexistent symptoms). Hard stools were most common in patients with functional constipation (54.2%), and half of patients with faecal incontinence reported normal stool consistency.

Continuation of transanal irrigation

At 52 weeks follow up, 41 (36.0%) patients continued TAI, 63 (55.2%) stopped and 10 (8.8%) patients were lost to follow up. Of the patients who stopped TAI, 46 (73.0%) patients stopped due to insufficient symptom improvement (n = 35), side effects (n = 9), other reasons related to the equipment/procedure (n = 4), or a combination of these issues (Table 3). Twenty-five (54.3%) of these stopped within the first 12 weeks after starting TAI. Discontinuation rate was lowest in patients with functional constipation (49.2%), although there were no significant differences when compared with the other two groups (p = 0.397). Abdominal pain (4.8%) and anal pain (3.2%) were most often reported as side effects related to discontinuation. One hospital admission related to irrigation was reported in a patient with coexistent symptoms of functional constipation and faecal incontinence. No bowel perforations or deaths occurred.

Table 1. Demographics and clinical characteristics in 114 with symptoms of functional constipation (*n* = 59), faecal incontinence (*n* = 26), or coexistent symptoms of functional constipation and faecal incontinence (*n* = 29).

Patients per symptom group (Rome IV criteria defined)	**Total group** (*n* = 114)	**Functional constipation** (*n* = 59, 51.8%)	**Faecal incontinence** (*n* = 26, 22.8%)	**Coexistent functional constipation and faecal incontinence** (*n* = 29, 25.4%)
Age, years (median [IQR])	59 (44 – 66)	51 (36 – 60)	69 (64 – 75)	59 (46 – 63)
Sex (*n*, %)				
Female	94 (82.5)	43 (72.9)	25 (96.2)	26 (89.7)
Male	20 (15.7)	16 (27.1)	1 (3.8)	3 (10.3)
BMI (median [IQR])	25.1 (22.3 – 28.0)	24.9 (22.2 – 27.6)	25.9 (22.8 – 30.6)	24.7 (22.1 – 27.2)
Parity (*n*, %)				
Nulliparous[a]	20 (21.3)	16 (37.2)	1 (4.0)	3 (11.5)
Parous[a]	74 (78.7)	27 (62.8)	24 (96.0)	23 (88.5)
Number of deliveries[b]				
1	12 (16.2)	7 (25.9)	2 (9.3)	3 (13.0)
2	30 (40.5)	13 (48.1)	9 (37.8)	8 (34.8)
3	27 (36.5)	6 (22.2)	11 (45.8)	10 (43.5)
≥4	5 (6.8)	1 (3.7)	2 (8.3)	2 (8.7)
Traumatic vaginal delivery[b]	56 (75.7)	19 (70.4)	20 (83.3)	17 (73.9)
Instrumental delivery[b]	10 (13.5)	5 (18.5)	0	5 (21.7)
Caesarean section[b]	10 (13.5)	6 (22.2)	0	4 (17.4)
Surgical history (*n*, %)				
Abdominal/bowel surgery	49 (43.0)	29 (49.2)	9 (34.6)	11 (37.9)
Pelvic surgery, including hysterectomy	53 (46.5)	20 (33.9)	17 (65.4)	16 (55.2)
Rectal surgery	12 (10.5)	5 (8.5)	5 (19.2)	2 (6.9)
Anal/perineal surgery	29 (25.4)	9 (15.3)	9 (34.6)	11 (37.9)
Spinal surgery	10 (8.8)	7 (11.9)	3 (11.5)	0
Medical history (*n*, %)				
Neurological conditions (including spinal	31 (27.2)	19 (32.2)	5 (19.2)	7 (24.1)
surgery)	14 (12.3)	8 (13.6)	4 (15.4)	2 (6.9)
Diabetes	16 (14.0)	8 (13.6)	4 (15.4)	4 (13.8)
Depression				
Previous treatment (*n*, %)				
Pelvic floor physiotherapy (+/- biofeed-	77 (66.6)	35 (59.3)	20 (76.9)	22 (75.9)
back)	6 (5.3)	4 (6.8)	1 (3.8)	1 (3.4)
Transanal irrigation (low or high volume)	4 (3.5)	3 (5.1)	1 (3.8)	0
Percutaneous tibial nerve stimulation	7 (6.1)	3 (5.1)	3 (11.5)	1 (3.4)
Sacral neuromodulation	6 (5.3)	2 (1.8)	2 (7.7)	2 (6.9)
Anal sphincter repair				

Footnote: a. Of females. b. Of parous females.

Other reasons of discontinuation unrelated to insufficient (patient reported) symptom improvement, side effects or reasons related to the equipment/procedure are also listed in Table 3, and occurred in 17/114 (14.9%) patients. The majority of these patients was highly satisfied with TAI (VAS 8/10 (IQR 7–8); data available in 14/17 patients).

Kaplan Meier curves in Figure 1 demonstrate continuation rates of TAI; those who stopped TAI due to reasons of discontinuation unrelated to insufficient symptom

Table 2. Bowel symptoms at baseline.

Patients per symptom group (Rome IV criteria defined)	Total group (*n* = 114)	Functional constipation (*n* = 59, 51.8%)	Faecal incontinence (*n* = 26, 22.8%)	Coexistent functional constipation and faecal incontinence (*n* = 29, 25.4%)
Rome IV criteria functional constipation (*n*, %)				
Straining[a]	75 (65.8)	53 (89.8)	0	22 (75.9)
Lumpy or hard stool[a]	60 (52.6)	38 (64.4)	1 (3.8)	21 (72.4)
Feeling incomplete evacuation[a]	107 (93.9)	58 (98.3)	23 (88.5)	26 (89.7)
Feeling anorectal obstruction[a]	83 (72.8)	58 (98.3)	0	25 (86.2)
Manual manoeuvres[a]	39 (34.2)	24 (40.7)	0	15 (51.7)
<3 defaecations per week	45 (39.5)	32 (54.2)	0	13 (44.8)
Cleveland Clinic constipation score (*n*, %)				
Median score (IQR)	13 (10 – 17)	15 (11 – 19)	7 (5 – 8)	13 (11 – 18)
Frequency of bowel movement[b]	23 (20.2)	17 (28.8)	0	6 (20.7)
Painful evacuation effort[b]	68 (59.6)	42 (71.2)	4 (15.4)	22 (85.9)
Feeling incomplete evacuation[b]	107 (93.9)	58 (98.3)	23 (88.5)	26 (89.7)
Abdominal pain[b]	61 (53.5)	27 (45.8)	17 (65.4)	17 (58.6)
Minutes in lavatory per attempt[b]	50 (43.9)	33 (55.9)	3 (11.5)	14 (48.3)
Assistance for defaecation[b]	52 (45.6)	35 (59.3)	0	17 (58.6)
Unsuccessful attempts per 24 hr[b]	26 (22.8)	17 (28.8)	1 (3.8)	8 (27.6)
Duration of constipation in years[b]	53 (46.5)	32 (54.2)	0	19 (65.5)
Incontinence (*n*, %)[c]				
Solid stool	21 (18.4)	-	14 (53.8)	7 (24.1)
Liquid stool	33 (28.9)	-	12 (46.2)	21 (72.4)
Flatus	52 (45.6)	16 (27.1)	16 (61.5)	20 (69.0)
Type[c]				
Passive	30 (26.3)	-	15 (57.7)	15 (51.7)
Urge	36 (31.6)	-	19 (73.1)	17 (58.6)
Stress	12 (10.5)	-	7 (5.1)	5 (17.2)
Post-defaecation	20 (17.5)	-	11 (42.3)	9 (31.0)
Faecal urgency	58 (50.9)	8 (13.6)	25 (96.2)	25 (86.2)
Pads/plugs	46 (40.4)	7 (11.9)	22 (84.6)	17 (58.6)
Constipation medication (e.g. Loperamide)	19 (16.7)	3 (5.1)	11 (42.3)	5 (17.2)
St Marks incontinence score (median [IQR])	8 (0 – 14)	1 (0 – 5)	14 (12 – 17)	14 (11 – 17)
Stool consistency				
Hard (Bristol 1 – 2)	46 (40.4)	32 (54.2)	3 (11.5)	11 (37.9)
Normal (Bristol 3 – 5)	22 (19.3)	5 (8.5)	13 (50.0)	4 (13.8)
Liquid (Bristol 6 – 7)	24 (21.1)	12 (20.3)	5 (19.2)	7 (24.1)
Variable	22 (19.3)	10 (16.9)	5 (19.2)	7 (24.1)

Footnote: a. ≥25% of defaecations. b. Proportion of patients with a score of ≥2 per symptom category. c. > monthly episodes.

improvement/side effects, and those lost to follow up were censored. In the total group (Panel A), continuation rate decreased to 53.5% at 52 weeks. No difference was found in continuation rates between symptom groups according to the Rome IV criteria (Panel B; functional constipation: 52.1%; faecal incontinence: 56.7%; coexistent symptoms: 53.8%; $p = 0.992$). Differences in continuation rate between sexes were small (Panel C; males: 61.8%; females: 51.5%; $p = 0.431$). Although not statistically significant, patients using the Navina Smart system were numerically more likely to continue therapy until 52 weeks follow up

Table 3. Reasons for discontinuation at 52 weeks follow up in 63 (55.3%) of 114 patients.

Reason	Total group (*n* = 63, 55.3%)	Functional constipation (*n* = 29, 49.2%)	Faecal incontinence (*n* = 16, 61.5%)	Coexistent functional constipation and faecal incontinence (*n* = 18, 62.1%)
Insufficient symptom improvement, *n* (%)	35 (55.6)	19 (65.5)	7 (43.8)	9 (50.0)
Side effects, *n* (%)				
Abdominal pain	3 (4.8)	2 (6.9)	1 (6.3)	0
Nausea	1 (1.6)	1 (3.4)	0	0
Anal pain/irritation	2 (3.2)	1 (3.4)	1 (6.3)	0
Pain and discomfort	1 (1.6)	1 (3.4)	0	0
Collapse during irrigation	1 (1.6)	0	1 (6.3)	0
Hospital admission related to irrigation	1 (1.6	0	0	1 (5.6)
Reasons related to equipment/procedure, *n* (%)	1 (1.6)	1 (3.4)	0	0
Bursting balloon	3 (4.8)	1 (3.4)	2 (12.5)	0
Cumbersome procedure				
Other reasons, *n* (%)				
Spontaneous symptom improvement	8 (12.7)	2 (6.9)	3 (18.8)	3 (16.7)
Physical impairment	2 (3.2)	1 (3.4)	0	1 (5.6)
Perforated diverticulitis unrelated to	1 (1.6)	0	0	1 (5.6)
irrigation	1 (1.6)	0	0	1 (5.6)
Urogenital cancer treatment	2 (3.2)	1 (3.4)	0	1 (5.6)
Unknown reason	1 (1.6)	1 (3.4)	0	0
Colostoma for other bowel disease	4 (6.3)	1 (3.4)	2 (12.5)	1 (5.6)
Other surgery				

compared to those using the Navina Classic system (Panel D; 62.1% vs 38.0%, respectively; $p = 0.061$).

Transanal irrigation parameters and side effects

Supplementary Table 1 shows TAI parameters during follow up. The majority of patients performed TAI between twice per week and 2 times per day. Volume of water used at 52 weeks follow up was lowest in patients with functional constipation in isolation (median 600 mls per procedure). Duration of the procedure was around 30 minutes and remained unchanged throughout the study period. Feeling of complete evacuation after irrigation and treatment satisfaction at 52 weeks were reported to be high in the total group (median VAS of 7 and 8 respectively), and were highest in patients with faecal incontinence in isolation. Side effects during the procedure were commonly reported, abdominal pain/cramping during the procedure occurred in 19.5% at 52 weeks follow up. Of the side effects related to the equipment, dislocation of the catheter was most common. Bursting of the balloon was also reported, in 3 (7.3%) patients at 52 weeks of follow up.

Symptomology and QoL

Symptom severity and QoL scores at baseline and follow up are detailed in Table 4.

Table 4. Symptomology and quality of life scores at baseline, 4, 12, 26 weeks and 52 weeks follow up.

	Total group		**Functional constipation**		**Faecal incontinence**		**Coexistent functional c onstipation and faecal incontinence**	
	Baseline: *n* = 114 4 weeks: *n* = 87 12 weeks: *n* = 70 26 weeks: *n* = 55 52 weeks: *n* = 41		Baseline: *n* = 59 4 weeks: *n* = 42 12 weeks: *n* = 37 26 weeks: *n* = 29 52 weeks: *n* = 22		Baseline: *n* = 26 4 weeks: *n* = 18 12 weeks: *n* = 16 26 weeks: *n* = 13 52 weeks: *n* = 9		Baseline: *n* = 29 4 weeks: *n* = 27 12 weeks: *n* = 17 26 weeks: *n* = 13 52 weeks: *n* = 10	
Patients per symptom group (Rome IV criteria defined)	Median (IQR)	Median (IQR) reduction from baseline per individual*	Median (IQR)	Median (IQR) change from base-line per individual*	Median (IQR)	Median (IQR) change from baseline per individual*	Median (IQR)	Median (IQR) change from baseline per individual*
Constipation								
Cleveland Clinic constipation score								
Baseline	16 (13 – 19)	-	16 (14 – 19)	-	-	-	14 (13 – 18)	-
4 weeks	16 (12 – 18)	0 (-2 – 2)	16 (13 – 18)	-1 (-2 – 2)	-	-	14 (11 – 18)	0 (-2 – 2)
12 weeks	16 (12 – 18)	0 (-2 – 2)	14 (13 – 17)	1 (-1 – 2)	-	-	13 (11 – 16)	2 (-1 – 3)
26 weeks	15 (12 – 18)	1 (-1 – 2)	15 (12 – 19)	0 (-1 – 2)	-	-	14 (12 – 16)	2 (-1 – 4)
52 weeks	15 (12 – 17)	1 (-1 – 2)	15 (13 – 19)	0 (-1 – 1)	-	-	13 (11 – 16)	1 (0 – 3)
PAC-QoL								
Worries/concerns								
Baseline	2.4 (1.5 – 2.8)	-	2.4 (1.7 – 2.8)	-	-	-	2.3 (1.5 – 2.7)	-
4 weeks	2.2 (1.5 – 2.8)	-0.1 (-0.5 – 0.3)	2.3 (1.6 – 2.8)	-0.1 (-0.5 – 0.3)	-	-	2.2 (1.5 – 2.9)	0.1 (-0.2 – 0.2)
26 weeks	2.0 (1.5 – 2.4)	0 (-0.4 – 0.6)	2.2 (1.7 – 2.4)	0 (-0.5 – 0.5)	-	-	2.0 (1.5 – 2.2)	0.2 (-0.3 – 0.6)
52 weeks	1.9 (1.7 – 2.5)	0.1 (-0.4 – 0.4)	1.9 (1.8 – 2.4)	0 (-0.4 – 0.3)	-	-	2.0 (1.5 – 2.6)	0.3 (-0.1 – 0.4)
Physical discomfort								
Baseline	3.0 (2.5 – 3.5)	-	3.0 (2.7 – 3.5)	-	-	-	3.0 (2.3 – 3.8)	-
4 weeks	3.0 (2.3 – 3.2)	0.3 (-0.3 – 0.7)	3.0 (2.5 – 3.3)	0.3 (-0.5 – 0.5)	-	-	2.8 (2.0 – 3.0)	0 (0 – 1.0)
26 weeks	2.5 (2.0 – 3.0)	0.5 (0 – 0.9)	2.5 (2.0 – 3.0)	0.5 (-0.3 – 0.8)	-	-	2.5 (2.0 – 2.7)	0.8 (0.3 – 1.1)
52 weeks	2.5 (2.2 – 3.0)	0.4 (0 – 0.8)	2.8 (2.3 – 3.1)	0.3 (0 – 0.8)	-	-	2.4 (1.7 – 2.6)	0.6 (0.3 – 1.1)
Psychosocial discomfort								
Baseline	1.9 (0.9 – 2.4)	-	1.6 (0.7 – 2.3)	-	-	-	2.0 (1.3 – 2.5)	-
4 weeks	1.6 (0.9 – 2.3)	0 (-0.5 – 0.5)	1.5 (0.8 – 2.3)	0 (-0.5 – 0.6)	-	-	1.9 (1.3 – 2.3)	0.1 (-0.4 – 0.4)
26 weeks	1.6 (0.9 – 2.1)	0.2 (-0.7 – 0.6)	1.5 (0.9 – 1.9)	0.3 (-0.9 – 0.6)	-	-	2.1 (1.0 – 2.2)	0 (-0.3 – 0.3)
52 weeks	1.3 (0.8 – 2.1)	0.1 (-0.2 – 0.6)	1.2 (0.8 – 1.8)	0.1 (-0.3 – 0.6)	-	-	1.7 (1.3 – 2.3)	0.1 (0 – 0.7)

Satisfaction								
Baseline	3.2 (2.4 – 3.5)	-	3.2 (2.6 – 3.6)	-	-	-	3.0 (2.4 – 3.4)	-
4 weeks	2.6 (1.8 – 3.2)	0.4 (-0.2 – 0.8)	2.8 (2.0 – 3.2)	0.3 (0 – 0.8)	-	-	2.2 (1.8 – 3.2)	0.4 (-0.2 – 0.9)
26 weeks	3.3 (2.5 – 3.8)	-0.3 (-0.9 – 0.5)	3.3 (2.5 – 3.8)	-0.5 (-0.9 – 0.5)	-	-	2.8 (2.3 – 3.3)	0.1 (-0.7 – 0.5)
52 weeks	2.4 (2.0 – 2.8)	0.6 (-0.1 – 1.0)	2.5 (2.1 – 2.9)	0.6 (-0.2 – 0.9)	-	-	2.3 (1.9 – 2.8)	0.5 (0.1 – 0.8
Faecal incontinence								
St Marks incontinence score								
Baseline	14 (12 – 16)	-	-	-	14 (12 – 16)	-	14 (10 – 16)	-
4 weeks	14 (9 – 16)	0 (-2 – 3)	-	-	15 (12 – 16)	-1 (-3 – 1)	11 (9 – 16)	2 (-2 – 5)
12 weeks	9 (5 – 15)	3 (0 – 9)	-	-	11 (6 – 15)	3 (0 – 6)	8 (5 – 16)	3 (0 – 9)
26 weeks	8 (5 – 14)	4 (0 – 9)	-	-	11 (8 – 17)	2 (-3 – 4)	14 (8 – 16)	2 (-2 – 5)
52 weeks	11 (7 – 16)	3 (1 – 5)	-	-	9 (6 – 15)	3 (3 – 5)	15 (7 – 16)	2 (0 – 4)
FI-QoL								
Lifestyle								
Baseline	2.3 (1.7 – 2.9)	-	-	-	2.7 (2.1 – 3.1)	-	2.0 (1.6 – 2.7)	-
4 weeks	2.4 (1.8 – 2.6)	0 (-0.3 – 0.4)	-	-	2.6 (2.4 – 2.7)	0.2 (-0.2 – 0.4)	2.0 (1.8 – 2.5)	-0.1 (-0.4 – 0.5)
26 weeks	2.7 (1.9 – 3.1)	-0.1 (-0.8 – 0.1)	-	-	3.0 (2.2 – 3.5)	-0.1 (-0.7 – 0.5)	2.4 (1.9 – 2.8)	-0.2 (-0.9 – 0)
52 weeks	2.6 (2.0 – 3.0)	-0.1 (-0.5 – 0.3)	-	-	2.8 (2.5 – 3.1)	0.1 (-0.4 – 0.4)	2.3 (1.9 – 2.8)	-0.1 (-0.4 – 0.1)
Coping/behaviour								
Baseline	1.8 (1.4 – 2.2)	-	-	-	1.8 (1.4 – 2.2)	-	1.8 (1.6 – 2.3)	-
4 weeks	1.8 (1.4 – 2.3)	0 (-0.3 – 0.3)	-	-	1.7 (1.4 – 2.1)	0 (-0.2 – 0.3)	1.9 (1.3 – 2.4)	0 (-0.5 – 0.2)
26 weeks	2.1 (1.6 – 2.4)	-0.2 (0.4 – 0.2)	-	-	2.0 (1.6 – 2.4)	-0.2 (-0.4 – 0.2)	2.1 (1.4 – 2.4)	-0.2 (-0.8 – 0.3)
52 weeks	2.1 (1.6 – 2.6)	-0.2 (-0.8 – 0.1)	-	-	2.1 (1.8 – 2.7)	-0.4 (-0.9 – 0.1)	1.9 (1.6 – 2.4)	-0.2 (-0.4 – 0.1)
Depression/self-perception								
Baseline	2.7 (2.1 – 3.1)	-	-	-	2.8 (2.3 – 3.3)	-	2.6 (1.9 – 3.0)	-
4 weeks	2.3 (1.7 – 2.8)	0.3 (-0.1 – 0.8)	-	-	2.7 (2.4 – 2.9)	0.2 (-0.1 – 0.5)	1.9 (1.6 – 2.4)	0.4 (-0.1 – 0.9)
26 weeks	2.8 (2.0 – 3.1)	-0.1 (-0.4 – 0.3)	-	-	3.0 (2.7 – 3.5)	-0.2 (0.2 – 0.3)	2.2 (1.7 – 2.9)	-0.1 (-0.4 – 0.4)
52 weeks	2.9 (2.6 – 3.3)	-0.1 (-0.4 – 0.2)	-	-	2.8 (2.6 – 3.4)	0.1 (-0.3 – 0.4)	2.7 (2.2 – 3.0)	-0.2 (-0.5 - -0.1)
Embarrassment								
Baseline	2.0 (1.5 – 2.5)	-	-	-	2.0 (1.1 – 2.6)	-	2.0 (1.7 – 2.3)	-
4 weeks	2.0 (1.7 – 2.7)	0 (-0.3 – 0.3)	-	-	2.0 (2.0 – 2.6)	0 (-0.3 – 0.3)	2.0 (1.7 – 2.5)	0 (-0.3 – 0.2)
26 weeks	2.3 (1.3 – 3.0)	0 (-1.0 – 0.3)	-	-	2.5 (2.0 – 3.0)	-0.2 (-1.2 – 0.3)	2.0 (1.0 – 2.7)	0 (-1.0 – 0.7)
52 weeks	2.3 (1.8 – 3.3)	-0.3 (-0.9 – 0)	-	-	2.7 (2 – 3.4)	-0.2 (-2.0 – 0.2)	2.0 (1.8 – 2.6)	-0.5 (-0.7 - -0.1)

* Positive value indicates improvement of symptoms or quality of life on the St Marks incontinence score Cleveland Clinic constipation score and patient assessment of constipation quality of life (PAC-QoL) questionnaire. Negative value indicates improvement of quality of life on the fecal incontinence quality of life questionnaire (FI-QoL).

Table 5. Multivariate regression analyses of demographics and clinical characteristics predicting continuation of transanal irrigation at 52 weeks in 89 patients.

	Continuation (%)	Odds ratio (95% CI)	*P* value
Indication			
Functional constipation	23/47 (48.9)	-	
Faecal incontinence	9/20 (45.0)	0.89 (0.21 – 3.70)	0.872
Coexistent constipation and incontinence	10/21 (47.6)	0.93 (0.26 – 3.35)	0.912
Age, years (continuous)	-	1.01 (0.97 – 1.05)	0.664
Sex			
Male	10/17 (58.8)	-	
Female	32/71 (45.1)	0.70 (0.10 – 5.02)	0.719
BMI (continuous)	-	1.02 (0.95 – 1.10)	0.543
Parous	27/57 (47.4)	1.59 (0.32 – 7.92)	0.570
Surgical history			
Abdominal/bowel surgery	17/36 (47.2)	1.02 (0.37 – 2.83)	0.976
Pelvic surgery, including hysterectomy	19/41 (46.3)	1.01 (0.35 – 2.94)	0.980
Rectal surgery	4/11 (36.4)	0.56 (0.12 – 2.55)	0.449
Anal/perineal surgery	6/21 (28.6)	0.31 (0.09 – 1.08)	0.065
Spinal surgery	6/10 (60.0)	0.80 (0.13 – 4.97)	0.807
Medical history			
Neurological conditions (including spinal surgery)	16/25 (64.0)	2.58 (0.69 – 9.64)	0.158
Diabetes	7/13 (53.8)	1.04 (0.28 – 3.83)	0.954
Depression	7/13 (53.8)	1.20 (0.32 – 4.60)	0.787

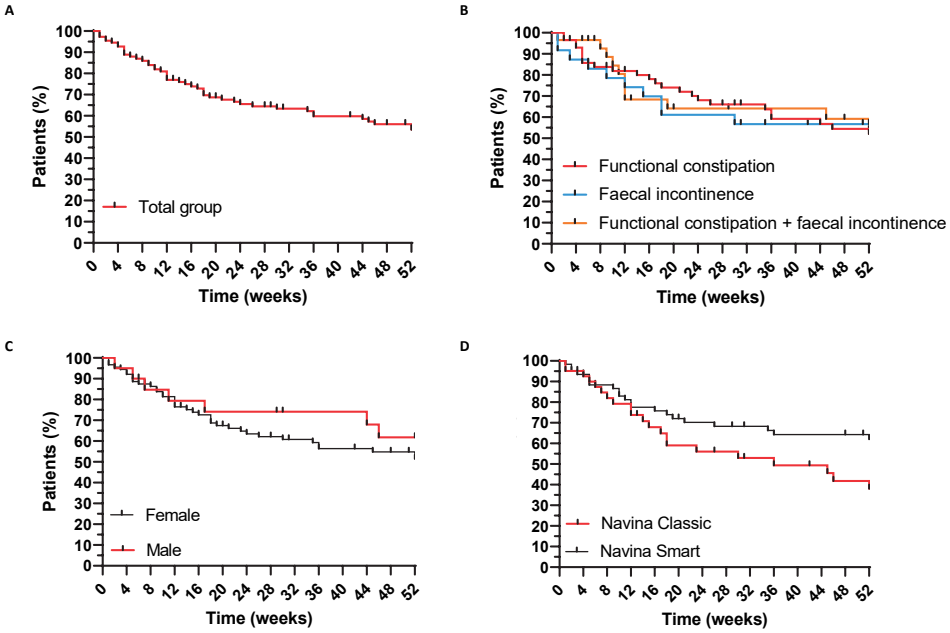
Footnote: 25 patients were excluded from the analyses due to reasons of discontinuation unrelated to insufficient symptom improvement/side effects, or lost to follow up.

Constipation

At 52 weeks follow up, 0/22 (0%) of patients with functional constipation and 0/10 (0%) of patients with coexistent symptoms had ≥30% symptom reduction on the CCCS. Median CCCS showed a minimal decrease (1 point) from baseline through follow up in patients with functional constipation in isolation and also in those with coexistent symptoms. Compared to baseline, CCCS per individual remained similar in patients with functional constipation at 52 weeks follow up, and decreased slightly (1 point) in those with coexistent symptoms. Median PAC-QoL scores decreased (indicating higher functional status of QoL) on all domains, both in patients with functional constipation and in those with coexisting symptoms. Additionally, median scores per individual on most domains decreased at follow up compared to scores at baseline.

Faecal incontinence

At 52 weeks follow up, 5/9 (55.6%) of patients with faecal incontinence and 3/10 (30.0%) of patients with coexistent symptoms had ≥30% symptom reduction on the SMIS. Median SMIS decreased (indicating less severe symptoms) in patients with faecal incontinence in isolation (baseline: 14; 52 weeks: 9) but not in patients with coexistent symptoms (baseline: 14; 52 weeks: 15). Median change in SMIS per individual at 52 weeks follow up compared to baseline was 3 (IQR -5–3) in patients with faecal incontinence in isolation (indicat-



A. Total group.
B. Stratified per symptom group.
C. Stratified per sex.
D. Stratified per device group. 7 patients who changed to the other device during the study were excluded from this analysis.

Figure 1. Kaplan Meier curves showing continuation rates of TAI throughout the study. Those who stopped TAI due to reasons of discontinuation unrelated to insufficient symptom improvement/side effects, other reasons related to the equipment/procedure and those lost to follow up were censored.

ing less severe symptoms), and 2 (IQR 0–4) in patients with coexistent symptoms. Median FI-QoL scores on most domains increased (indicating better QoL) both in patients with faecal incontinence in isolation, and in those with coexistent symptoms. This change was also observed per individual on most domains in both groups.

Factors associated with continuation of TAI

Table 5 demonstrates the independent association of demographics and clinical characteristics with continuation of TAI at 52 weeks. None of the factors was statistically associated with continuation.

DISCUSSION

This prospective study of TAI in patients with constipation and/or faecal incontinence showed that significant reduction of symptoms of faecal incontinence at 52 weeks follow up occurred in 55.6% of patients with faecal incontinence in isolation and 30.0% in

patients with coexistent symptoms. Significant reduction of symptoms of constipation was not observed. In total, 36.0% of patients continued TAI at 52 weeks. QoL related to both faecal incontinence and constipation improved on most domains. We did not identify clinical characteristics to predict continuation of TAI.

Significant reduction of symptoms was only observed in patients with faecal incontinence. The reason that reduction of symptoms of constipation did not occur might be related to the outcome measure which was used for the primary outcome (CCCS). [12] This questionnaire was also used in the first randomised controlled trial in patients using TAI, [5] however, it may be suboptimal to evaluate symptom improvement/deterioration secondary to TAI. For example, the question "duration of constipation" does not reflect symptom severity and will not change as a result of TAI (or after any other therapy). Further, after starting TAI, all patients will score the maximum score on the question "type of assistance", while this does not necessarily reflect more severe symptoms. Also, "minutes in lavatory per attempt" are likely to increase due to TAI (median time of procedure is 30 minutes), again this does not necessarily indicate more severe symptoms. Nonetheless, Christensen *et al.* were able to show a reduction in CCCS in patients starting TAI, [5] the difference in outcome between their and our study remains unclear. The secondary outcomes of our study support the hypothesis that the primary outcome related to constipation was affected by the poor quality of the CCCS: approximately one-third of patients with constipation continued TAI at 52 weeks follow up, those continuing TAI were satisfied with the treatment (VAS 7/10), and QoL improved on most domains.

Several studies have reported the success rate of TAI in patients with constipation and/or faecal incontinence, most of these studies defined successful outcome as continuation of therapy. The continuation rate of our study was slightly lower (36.0%) compared to results of previous studies (43-59%). [1-4, 18] However, another 8.8% was lost to follow up, and 14.9% of patients discontinued treatment due to reasons unrelated to insufficient symptom improvement, side effects or reasons related to the equipment/procedure (e.g spontaneous symptom improvement). Taking this into account, we might conclude that treatment satisfaction may comparable to "success rates" reported by other studies.

We acknowledge study limitations. Although the required total number of patients was recruited (n = 114), the number of patients with faecal incontinence in isolation at 52 weeks follow up was smaller than required for the primary objective (n = 16 vs 32), which might impact on the results related to treatment of incontinence symptoms. Sufficient patients with functional constipation in isolation and coexistent symptoms were recruited. The criticism concerning the primary outcome in constipation was discussed in a previous paragraph. Accepting these limitations, this is one of the few prospective cohort studies in which the effect of TAI on symptoms and QoL was evaluated using validated questionnaires, specifically, with a study duration of ≥12 months. [4] Further, we provide detailed results on irrigation parameters at different follow up points, which can be a helpful guide for therapists to inform patients about the therapy.

Our study did not reveal clinical characteristics to predict treatment continuation. Predicting factors were only found in a few previous studies. Christensen *et al.* reported that patients with neurogenic bowel dysfunction and anal insufficiency more often continued TAI. [3] Further, those with rectal hypersensitivity and anal hypocontractility were also found to continue treatment. These findings have not been validated by others, and data on anorectal physiological investigations are reported infrequently. Studies in which the association of the underlying pathophysiology with treatment success is thoroughly evaluated are yet to be performed (for example, differences between patients with constipation secondary to outlet dysfunction vs those with colonic dysmotility). The only factor which was associated with treatment outcome in the study by Bildstein *et al.* was satisfactory progress after the first training session. [19] This implies that appropriate training and patient support play an important role in success of therapy. Further, as most studies (including the current study) show that TAI may result in symptom reduction, but does not resolve all symptoms, education and expectation management play a key role.

In conclusion, this prospective study evaluating TAI in patients with constipation and/or faecal incontinence demonstrated improvement of symptoms of faecal incontinence and QoL related to constipation and faecal incontinence. In total, 36.0% of patients continued TAI at 52 weeks, the majority of those who continued treatment was highly satisfied.

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Supplementary Table 1. Continuation rates, TAI parameters and side effects at 4, 12, 26 and 52 weeks follow up.

Patients per symptom group (Rome IV criteria defined)	**Total group** (*n* = 114)	**Functional constipation** (*n* = 59, 51.8%)	**Faecal incontinence** (*n* = 26, 22.8%)	**Coexistent functional constipation and faecal incontinence** (*n* = 29, 25.4%)
4 weeks	87 (76.3)	42 (71.2)	18 (69.2)	27 (93.1)
Frequency of irrigation (*n*, %)				
≤Once per week	2 (2.3)	1 (2.4)	1 (5.6)	0
2x per week – 2x per day	85 (97.7)	41 (97.6)	17 (94.4)	27 (100)
>2x per day	0	0	0	0
Volume of irrigation (mls, median [IQR])	800 (500 – 1000)	775 (500 – 1000)	700 (500 – 1000)	800 (600 – 1000)
Duration of procedure (minutes, median [IQR])	30 (15 – 45)	20 (14 – 40)	30 (21 – 30)	40 (20 – 49)
Feeling of complete evacuation after irrigation (VAS, median [IQR])	6 (5 – 8)	6 (4 – 7)	8 (6 – 8)	6 (4 – 8)
Treatment satisfaction (VAS, median [IQR])	7 (5 – 8)	7 (5 – 8)	7 (5 – 9)	7 (5 – 9)
Side effects				
Abdominal pain/cramping	28 (32.2)	12 (28.6)	5 (27.8)	11 (40.7)
Anal pain	14 (16.1)	5 (11.9)	3 (16.7)	6 (22.2)
Dislocation of catheter	14 (16.1)	5 (11.9)	3 (16.7)	6 (22.2)
Autonomic symptoms	7 (8.0)	3 (7.1)	1 (5.6)	3 (11.1)
Busting balloon	7 (8.0)	2 (4.8)	1 (5.6)	4 (14.8)
Anal bleeding	6 (6.9)	1 (2.4)	1 (5.6)	4 (14.8)
12 weeks	70 (61.4)	37 (62.7)	16 (61.5)	17 (58.6)
Frequency of irrigation (*n*, %)				
≤Once per week	1 (1.4)	0	1 (6.3)	0
2x per week – 2x per day	67 (95.8)	36 (97.3)	14 (87.5)	17 (100)
>2x per day	2 (2.8)	1 (2.7)	1 (6.3)	0
Volume of irrigation (mls, median [IQR])	800 (525 – 1000)	1000 (550 – 1000)	800 (500 – 1175)	800 (700 – 1000)
Duration of procedure (minutes, median [IQR])	30 (20 – 45)	20 (20 – 39)	33 (24 – 37)	40 (15 – 45)
Feeling of complete evacuation after irrigation (VAS, median [IQR])	7 (5 – 8)	7 (5 – 8)	8 (5 – 9)	8 (5 – 8)
Treatment satisfaction (VAS, median [IQR])	8 (6 – 8)	6 (6 – 8)	8 (6 – 9)	7 (7 – 8)
Side effects				
Abdominal pain/cramping	21 (30.0)	13 (35.1)	2 (12.5)	6 (35.3)
Anal pain	11 (15.7)	5 (13.5)	2 (12.5)	4 (23.5)
Dislocation of catheter	3 (4.3)	3 (8.1)	2 (12.5)	1 (5.9)
Autonomic symptoms	4 (5.7)	3 (8.1)	0	1 (5.9)
Busting balloon	5 (7.1)	2 (5.4)	0	3 (17.6)
Anal bleeding	4 (5.7)	1 (2.7)	2 (12.5)	1 (5.9)

26 weeks	55 (48.2)	29 (49.2)	13 (50.0)	13 (44.8)
Frequency of irrigation (*n*, %)				
≤Once per week	5 (9.1)	3 (10.3)	0	2 (15.4)
2x per week – 2x per day	50 (90.9)	26 (89.7)	13 (100)	11 (84.6)
>2x per day	0	0	0	0
Volume of irrigation (mls, median [IQR])	900 (600 – 1000)	900 (590 – 1000)	800 (700 – 1300)	1000 (500 – 1000)
Duration of procedure (minutes, median [IQR])	30 (20 – 45)	30 (20 – 45)	30 (20 – 40)	35 (20 – 45)
Feeling of complete evacuation after irrigation (VAS, median [IQR])	7 (5 – 8)	6 (5 – 8)	8 (6 – 8)	7 (6 – 8)
Treatment satisfaction (VAS, median [IQR])	7 (6 – 8)	6 (5 – 8)	8 (7 – 9)	7 (6 – 8)
Side effects				
Abdominal pain/cramping	13 (23.6)	11 (37.9)	0	2 (15.4)
Anal pain	8 (14.5)	4 (13.8)	2 (15.4)	2 (15.4)
Dislocation of catheter	7 (12.7)	7 (24.1)	0	0
Autonomic symptoms	5 (9.1)	3 (10.3)	0	2 (15.4)
Busting balloon	2 (3.6)	0	0	2 (15.4)
Anal bleeding	2 (3.6)	1 (3.4)	0	1 (7.7)
52 weeks	41 (36.0)	22 (37.3)	9 (34.6)	10 (34.5)
Frequency of irrigation (*n*, %)				
≤Once per week	5 (12.2)	2 (9.1)	1 (11.1)	2 (20.0)
2x per week – 2x per day	36 (87.8)	20 (90.9)	8 (88.8)	8 (80.0)
>2x per day	0	0	0	0
Volume of irrigation (mls, median [IQR])	800 (400 – 1000)	600 (365 – 1000)	800 (400 – 1000)	1000 (765 – 1225)
Duration of procedure (minutes, median [IQR])	30 (20 – 40)	30 (20 – 35)	40 (30 – 45)	30 (21 – 43)
Feeling of complete evacuation after irrigation (VAS, median [IQR])	7 (5 – 8)	7 (5 – 7)	9 (8 – 9)	7 (5 – 8)
Treatment satisfaction (VAS, median [IQR])	8 (7 – 8)	7 (6 – 8)	9 (8 – 10)	8 (6 – 8)
Side effects				
Abdominal pain/cramping	8 (19.5)	6 (27.3)	0	2 (20.0)
Anal pain	4 (9.8)	4 (18.2)	0	0
Dislocation of catheter	3 (7.3)	3 (13.6)	0	0
Autonomic symptoms	1 (2.4)	0	0	1 (10.0)
Busting balloon	3 (7.3)	2 (9.1)	0	1 (10.0)
Anal bleeding	4 (9.8)	3 (13.6)	1 (11.1)	0

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SUMMARY

The aim of this thesis was to evaluate current management and current practice in several anorectal diseases. This was done by using patient reported outcome measurements among others and by performing national survey's.

PART I

Treatment for haemorrhoidal disease is generally divided in low-invasive procedures for grade I and grade II haemorrhoids, such as rubber band ligation, and more invasive procedures for grade III and IV, such as a haemorrhoidectomy. Many studies distinguish between comparable surgical procedures as between minimal invasive procedures (e.g. RBL with sclerotherapy) and between more invasive surgical procedures (e.g. haemorrhoidal artery ligation with haemorrhoidectomy). However, there is an overlap in indication for selecting a minimally invasive treatment and an operation for grade II and III haemorrhoids. In **chapter one** the clinical effectiveness of RBL versus haemorrhoidectomy was assessed in a systematic review and meta-analysis. Eight RCT's were included containing a total of 1208 patients with second- and third degree haemorrhoids who underwent RBL or haemorrhoidectomy. The overall methodological quality of the studies was moderate. Outcome measures were diverse and not clearly defined. Recurrence of complaints or need for reintervention was more common after RBL than haemorrhoidectomy. Patients experienced less post-procedural pain after RBL but there was significant statistical heterogeneity due to variations in measuring the pain, or it was not even mentioned. Postoperative bleeding was less common following RBL. However, none of the studies described how this outcome was defined. Urinary retention was more common after haemorrhoidectomy and anal incontinence was described in 5-7.7% in the haemorrhoidectomy group and none in the RBL group. Anal stenosis occurred in one patient in the RBL group versus 1-8.3% in the haemorrhoidectomy group. The length of hospital stay and loss of working days was both in favor of the RBL group. The aim of the study was also to assess the cost effectiveness of both procedures but none of the included trials mentioned costs. Therefore, a multicenter randomised trial was needed with emphasis on economic and patient-related outcomes. In **chapter two** the protocol of this multicenter randomised trial, the HollAND trial, is shown. For grade III haemorrhoids the current national guideline advises to treat either by RBL or haemorrhoidectomy. Even if both procedures have their own advantages and disadvantages, patient expectations and priorities and costs should be taken into account when deciding which procedure to perform. Therefore this

non-inferiority trial with cost-utility analysis is initiated. The hypothesis is that, because RBL is lesser burden on patients, RBL in two sessions in not inferior compared with haemorrhoidectomy on quality of life (QoL) in patients with grade III haemorrhoids. Exclusion criteria are previous anorectal surgery, more than one RBL or sclerotherapy session in the past three years, previous radiation on the pelvis, pre-existing sphincter injury, inflammatory bowel disease, pregnancy, and patients who are medically unfit for surgery. It is necessary to include 180 patients in each group following a total sample size of 360 patients. The primary outcome measure is QoL at 24 months measured with the 5-level EQ-5D, in hospital direct and indirect costs and out-of-hospital postoperative costs. The key secondary outcome is recurrence at one year post procedure. Recurrence is defined with a self-reported dichotomous question: do you feel your symptoms from haemorrhoids are cured or improved compared with before treatment; or unchanged or worse compared with before treatment? This definition is also used in a systematic review and recent clinical trial. Other secondary endpoints are measured with patient-reported outcomes as QoL at 12 moths, severity of faecal incontinence with the Vaizey faecal continence score, complaint reduction with the Haemorrhoid Symptom Score (HSS) and the proctology patient-reported outcome measurement (proctoPROM) and Patient-Reported Outcome Measurement-Haemorrhoidal Impact and Satisfaction Score (PROM-HISS).

In **chapter three** a retrospective analysis was performed in patients with grade III haemorrhoids, who were treated with RBL or haemorrhoidectomy, between January 2013 and August 2018 in a tertiary center for proctology, the Proctos Kliniek. Exclusion criteria were injection sclerotherapy or RBL in the past three years, prior proctologic surgical interventions, radiotherapy of the pelvis, anorectal malignancy, known inflammatory bowel disease and spinal cord injury. Overall, 327 patients were included of whom 182 were treated by RBL and 145 by haemorrhoidectomy. Of the 52% patients who were treated with RBL, a single RBL was sufficient. Thirty-five percent underwent a second RBL session within one year and 14% underwent a haemorrhoidectomy as second treatment. A total of 5% of the patients, who were initially treated with RBL, needed a third treatment. Of the patients who were primarily treated with haemorrhoidectomy 4% needed a reintervention. Complications occurred in 8% after haemorrhoidectomy and in 3% after RBL. The pre-procedure patient-reported-outcome-score, concerning the impact of proctologic symptoms on well-being (proctoPROM), was higher in the haemorrhoidectomy group. This suggests that patients treated by haemorrhoidectomy suffered from more severe or disabling complaints and were therefore treated by a more invasive procedure than those with milder complaints. In both groups the post-procedure proctoPROM was significantly decreased.

The Goligher classification is used in the above mentioned studies and is the most widely used description for the haemorrhoidal disease, which ranks the severity of prolapse into four grades. Physicians base this gradation on medical history and physical examination and the classification therefore might be prone to interobserver variabil-

ity. Furthermore, the classification estimates the severity of prolapse, but more disease burden does not automatically lead to a higher grade. This makes it difficult to evaluate and compare treatment strategies in research. **Chapter four** describes a study were the interobserver variability is determined among surgeons in the Netherlands. A survey with 25 photographs of patients with haemorroidal disease, with given symptoms and timing as during rest or push, were used. A total of 329 gastrointestinal surgeons, fellows and residents were sent an invitation email, of whom 95 (29%) completed the survey. Eighty-seven percent indicated that they use the Goligher classification in clinical practice. A total of 81% of the respondents found the classification helpful and 63% classified haemorrhoidal disease according to Goligher and followed the guidelines for treatment of haemorrhoidal accordingly. The interobserver variability showed an overall fair strength of agreement, with a Fleiss' Kappa (κ) of 0.376 (95% CI 0.373–0.380). There was a moderate agreement for grade I and IV haemorrhoids with a κ statistic of 0.466 and 0.522, respectively. Differentiation between grade II and III haemorroidal disease appeared to be the hardest, as reflected by only fair agreement between respondents, with a κ statistic of 0.206 and 0.378, respectively.

PART II

Fistula-in-ano has been challenging for surgeons for a very long time. Therapy is aimed at closure of the fistula and symptom relief whilst minimizing functional impairment. Despite current Dutch and international guidelines, determining optimal therapy is still quite difficult in the individual patient. Also determining what kind of diagnostics, operative treatment, follow-up and treatment for recurrent disease is appropriate, is not very clear. In **chapter five** current practices in the management of cryptoglandular fistula-in-ano among gastrointestinal surgeons in the Netherlands is reported. A questionnaire with 28 questions concerning diagnostic and surgical techniques was sent to 342 gastrointestinal surgeon, fellows and residents, of whom 147 (43%) responded. Magnetic resonance imaging seemed the preferred diagnostic imaging modality (97%) followed by the endo-anal ultrasound (12%). Most respondents removed a seton between 6 weeks and 3 months, with 58%. Fistulotomy was the procedure of preference in low transsphincteric (86%) and low intersphincteric fistula-in-ano (92%). The mucosal advancement flap and ligation of intersphincteric fistula tract (LIFT) were the procedures that were applied most often in high transsphincteric FIA, with 78% and 46%, respectively. In high intersphincteric fistula-in-ano 67% performed a mucosal advancement flap and 33% of the respondents performed a fistulotomy. Closing the internal fistula opening was done by 33% of all respondents.

In **chapter six** a similar study was done for the current management of chronic anal fissure. Dutch gastrointestinal surgeons, fellows and residents were invited of whom

106 (33%) completed the survey. Patients with chronic anal fissure frequently suffer from pelvic floor complaints which can effectively be treated with pelvic floor physical therapy. However, only 22% of the respondents indicated that they always, or almost always, performed physical examination of the pelvic floor muscles. Half of the respondents performed digital rectal examination. Fifty-six percent prescribed ointment, such as diltiazem, for a period of 6 weeks and 27% for at least 12 weeks. Botulinum toxin injections were performed by 78% of the respondents and mainly under general, spinal anesthesia or sedation (54%). Fissurectomy was the most popular operative procedure with 71%, followed by the lateral internal sphincterotomy (LIS) with 27%.

PART III

Anorectal physiology testing is useful as a diagnostic tool and to evaluate treatment. A variety of tests are available, but there is no guideline with recommendations when to perform which test. Furthermore which test is the most accurate is controversial and the correlation between these tests is not very clear. **Chapter seven** shows a study that prospectively collected data from several anorectal functions tests in the diagnostic work-up of patients who were referred for pelvic floor physical therapy. Anorectal function tests included digital rectal examination (DRE), 3D High resolution anal manometry (3D-HRAM), balloon expulsion test (BET), transperineal ultrasound (TPUS) and surface electromyography (s-EMG). Fifty patients, of which 37 (74%) females, were included. Most frequent indication for referral for pelvic floor physical therapy was faecal incontinence in 27 (54%) patients. Despite experienced surgeons and a skilled pelvic floor physical therapist, who both daily perform several digital rectal examinations, the assessed pressures and pelvic floor function did not correlate in 100%. During rest, squeeze and straining DRE by the surgeon and the pelvic floor physical therapist correlated in 78%, 78% and 84%, respectively. Correlation between DRE and 3D-HRAM or s-EMG, was better for squeeze pressures than resting pressures. The results of the six different function tests regarding diagnosing pelvic floor dyssynergia, namely DRE by both the surgeon and the pelvic floor physical therapist, 3D-HRAM, s-EMG, BET and transperineal ultrasound (with echo lucent gel) were to some extent comparable. Overall, the results of the study suggests that if further investigation with anorectal functions tests is warranted, the results of these tests should be interpreted with caution.

In general, if pelvic floor physical therapy with biofeedback does not suffice in patients with faecal incontinence or constipation, the next step in treatment is transanal irrigation (TAI). **Chapter eight** describes the results of a prospective study were the clinical efficacy of high-volume transanal irrigation (TAI) in patients with constipation and/or faecal incontinence is determined. Patients completed validated symptom and quality of life questionnaires at baseline, 4, 12, 26 and 52 weeks follow-up. A total of 59 (51.8%) patients with con-

stipation, 26 (22.8%) with faecal incontinence, and 29 (25.4%) with coexistent symptoms were included. Reduction of constipation symptoms was not observed. Median PAC-QOL scores decreased on most domains, indicating that quality of life improved. Reduction of faecal incontinence occurred in 5/9 (55.6%) patients with faecal incontinence and in 3/10 (30.0%) patients with coexistent symptoms. Median St Marks incontinence score per-individual decreased in patients with faecal incontinence as well as in patients with coexistent symptoms. Median FI-QOL scores increased on most domains, indicating that quality of life improved. At 52 weeks, 41 (36.0%) patients continued TAI, 63 (55.2%) stopped TAI and 10 (8.8%) patients were lost to follow-up. The study shows that TAI reduced symptoms of faecal incontinence but not constipation, and that QOL related to both constipation and faecal incontinence improved.

FUTURE PERSPECTIVES

This thesis sheds light on the contemporary treatment of benign anorectal disorders. Many medical and surgical techniques used today originated thousands of years ago. Contemporary procedures are largely technical variations of existing procedures in an attempt to improve outcome.

HAEMORRHOIDAL DISEASE

Haemorrhoidal disease is currently one of the most common benign anorectal disabilities. Since management of haemorroidal disease is difficult and guidelines are not clear on what is the optimal treatment, evaluating current practice is necessary to manage sensible and value based health care. The systematic review that we conducted suggest that haemorrhoidectomy has better symptom control in patients with grade II-III haemorrhoids compared with rubber band ligation. However, the studies that were analyzed were of poor quality and therefore an advice about treatment protocol could not be given. Good quality trials with an emphasis on economic and patient related outcomes are needed. Consequently, 'the HollAND trial' was initiated by our project group. It is a multicentre randomised trial in the Netherlands and the first patient was included in November 2019. Along with Sars-Cov-19, inclusion rate was low due to patient preference. An additional problem was that most patients favoured rubber band ligation what would lead to a selection bias. This would hamper the trial and compromises the generalizability of the outcome of the trial. The project group was considering whether another study design would be more suitable. An RCT may be the inappropriate design for a trial comparing treatments of significant different nature (e.g. invasive versus minimal invasive procedure). Since, the RCT has been originally developed for trials comparing the effect of medication to placebo [1]. It can be expected that many eligible trial participants have a treatment preference for such different interventions and decline randomisation. A decreased recruitment could limit generalizability of results to the clinical population (i.e. reduce external validity by randomisation bias). Furthermore, patients randomly allocated to their non-preferred intervention may experience worse outcomes. Especially subjective (patient reported) outcomes are prone to this bias. To overcome such biases, a patient preference trial would be a design in which patients with a preference for a treatment arm will be treated accordingly, whereas patients without a distinct preference will be randomised in the usual way. A recent systematic review and meta-analyses by Wasmann et al concluded that partially randomised patient preference trials (RPPT) could

increase external validity without compromising the internal validity compared with RCTs [2]. To date there is no sufficiently large trial that has answered the research question 'is RBL performed in two sessions not inferior

compared with haemorrhoidectomy on quality of life (QOL) in patients with grade III haemorrhoids. There still is a need for evaluating treatment from the patient's point of view and transparency in surgical and non-surgical treatment outcome for haemorroidal disease.

The Goligher classification describes the severity of haemorrhoidal prolapse in four grades. Generally, the grading is based on medical history, physical examination and also subjective criteria. Haemorrhoidal grading impacts treatment and outcomes of studies and therefore its reliability and reproducibility is of importance. Our study showed only a fair interobserver variability among surgeons in the Netherlands. Apart from the fact that more disease burden does not automatically lead to a higher grade, this demonstrates the need for a more reliable, and internationally accepted grading system incorporating objective and subjective factors of haemorrhoidal disease. New classification systems should enable more uniformity of treatment and a more uniform and consistent comparison of outcomes in future trials and prospective registries. The protocol for a Delphi study for a new classification system, preceded by a survey among gastrointestinal surgeons, is currently being prepared and led by an international research group.

CRYPTOGLANDULAR PERIANAL FISTULA-IN-ANO AND CHRONIC ANAL FISSURE

Determining optimal therapy for fistula-in-ano is still quite difficult in the individual patient. A probable cause is the scarce evidence regarding the best practice in treating fistula-in-ano [3-5]. This may be due to the lack of uniform outcomes in literature. Machielsen et al showed substantial heterogeneity in outcomes, definitions, and measurement instruments reported in studies for cryptoglandular fistula-in-ano [6]. Surgical management aims to heal the fistula with preservation of fecal continence and varying practices are seen among gastrointestinal surgeons concerning the management of fistula-in-ano. A considerable part of the surgeons that responded in our study appear to treat fistula-in-ano differently than recommended in guidelines. Novel promising techniques are sometimes adopted quickly without a prior pilot of implementation study. These techniques should be investigated adequately in sufficiently large trials and in prospective registries with standardised outcome reporting and measurement to increase consensus. Recently a Core Outcome Set is developed of 10 voted outcomes: clinical fistula healing, radiological healing, recurrence, development of additional fistulas, fistula symptoms, incontinence, psychological impact of treatment, complications and reinterventions, patient satisfaction, and quality of life [7].

Optimal management for chronic anal fissure is also challenging and mainly because of its recurrent nature, therapy compliance and the variety of non-operative and operative treatments [8, 9]. Our study showed that guideline recommendations in treating chronic anal fissure are largely followed and consistent among most gastrointestinal surgeons in the Netherlands. Although most anal fissures heal spontaneously or with conservative measures, a percentage tend to recur or persist. Botulinum toxin injections can be considered as a step-up approach when conservative therapy fails. However, there are no consensus guidelines on the optimal dose, site, or number of injections [10]. A recent systematic review and meta-analysis evaluated the efficacy of botulinum toxin injections according to dose and injection sites [11]. They concluded that botulinum injections out of the fissure site offered improved outcomes in the short term compared to injections on both sides and low-dose had a lower risk of short-term incontinence. Unfortunately, some treatments were indirectly estimated from a small number of studies and the dosage of botulinum toxin was dichotomized in low and high. Future studies should be concrete in volume of botulinum toxin and number of injections and sites.

Lateral internal sphincterotomy (LIS) is the preferred treatment for refractory anal fissures and is still considered the golden standard since LIS has superior healing rates [8, 9]. The Dutch guideline recommends LIS for refractory fissures when previous treatment fails but when this point is reached is to date unclear. Research on timing of the next step in treatment of chronic anal fissure would be relevant.

A proportion of the patients with chronic anal fissure has an unrecognized pelvic floor dysfunction while surgeons, apparently, do not consistently assess pelvic floor complaints, nor do they routinely examine the pelvic floor muscles. A recent publication by van Reijn-Baggen et al showed that pelvic floor physical therapy yields a significant and clinical benefit in the time course and should be advocated as adjuvant conservative treatment [12]. Awareness of pelvic floor dysfunctions in patients with chronic anal fissure is therefore very important in order to refer patients for pelvic floor physical therapy.

ANORECTAL FUNCTIONS TESTS

Anorectal function tests are helpful for objective investigation of anorectal (dys)function. The 3D high resolution anorectal manometry, balloon expulsion test, surface electromyography and transperineal ultrasound are all frequently performed in the diagnostic work-up in patients with defaecation disorder, but which test is the most accurate is not clear. Our study showed that DRE has a good correlation amongst experienced investigators but DRE poorly correlate with commonly performed anorectal function tests. A considerable limitation of the study was that we were not able to use controlled normal s-EMG values since they have not yet been published. Furthermore, a gold standard or known sensitivity of the anorectal function tests would be of utmost importance when performing future research in diagnosing anorectal disorders.

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SAMENVATTING

Het doel van dit proefschrift was het evalueren van de huidige behandeling en praktijk van verschillende anorectale aandoeningen. Dit is gedaan door onder andere patiënt gerapporteerde uitkomstmaten en nationale enquêtes te gebruiken.

DEEL I

Behandelingen voor hemorroïden is doorgaans verdeeld in minimaal invasieve ingrepen voor graad I en II hemorroïden, zoals de rubberband ligatie (RBL), en meer invasievere ingrepen voor graad III en IV, zoals de hemorroïdectomie. Veel studies vergelijken chirurgische ingrepen waarbij wordt vergeleken tussen minimaal invasieve ingrepen (RBL met sclerotherapie) en tussen meer invasievere ingrepen (hemorroidale arteriele ligatie met hemorroïdectomie). Er is echter een overlap in indicatie voor het kiezen voor een minimaal invasieve ingreep of een operatie in graad II en III hemorroïden. In **hoofdstuk één** wordt de klinische effectiviteit van RBL en hemorroïdectomie gemeten in een systematische review met meta-analyse. Acht RCT's werden geïncludeerd met totaal 1208 patiënten met graad II en III hemorroïden die een RBL of hemorroïdectomie ondergingen. De totale methodologische kwaliteit van de studies was matig. Uitkomstmaten waren verschillend en niet duidelijk gedefinieerd. Recidiverende klachten en re-interventies kwamen vaker voor na RBL dan na hemorroidectomie. Patiënten ervaarde minder post procedurele pijn na RBL maar er was significant statische heterogenieit. Dit kwam door de variatie in het meten van pijn tussen de studies, of doordat de definitie of meting van de pijn helemaal niet werd geschreven. Postoperatieve bloeding kwam minder vaak voor na RBL. Er was echter niet één studie die de uitkomst 'postoperatieve bloeding' had gedefinieerd. Blaasretentie werd vaker gezien na hemorroïdectomie en incontinentie werd in 5-7,7% gezien in de hemorroïdectomie groep en geen enkele keer in de RBL groep. Anale stenose kwam in één patiënt voor in de RBL groep versus 1-8,3% in de hemorroïdectomie groep. De lengte van de ziekenhuisopname en het gemis in werkdagen was beide in het voordeel van de RBL groep. Het doel van de studie was tevens om de kosteneffectiviteit van beide ingrepen te meten maar geen van de geïncludeerde trials beschreef de kosten. In **hoofdstuk twee** wordt het protocol van de multicentrische gerandomiseerde trial weergegeven; de HollAND trial. De huidige nationale richtlijn adviseert voor graad III hemorroïden een behandeling met RBL danwel hemorroïdectomie. Ook al hebben ingrepen hun eigen voor- en nadelen, patiëntverwachtingen, prioriteiten en kosten zouden moeten worden meegenomen in de beslissing voor welke ingreep wordt gekozen. Daar-

voor is deze niet inferieure trial met kosteneffectiviteitsanalyse opgezet. De hypothese is dat vanwege het gegeven dat RBL minder belastend is voor de patiënten, RBL in twee sessies, niet inferieur is vergeleken met de hemorroïdectomie op de kwaliteit van leven (QoL) in patiënten met graad III hemorroïden. Exclusiecriteria zijn eerdere anorectale chirurgie, meer dan één RBL of sclerotherapie sessie in de laatste drie jaar, eerdere radiatie op het kleine bekken, pre-existent sfincterletsel, chronische inflammatoire darmziekten, zwangerschap, stollingsstoornis, en patiënten die niet voldoende fit zijn voor een operatie. De steekproefgrootte beslaat 360 patiënten waarvan er 180 in elke groep moeten worden geïncludeerd. De primaire uitkomstmaat is kwaliteit van leven op 24 maanden, gemeten met de 5-level-EQ-5D, de directe ziekenhuiskosten en de postoperatieve kosten buiten het ziekenhuis. De belangrijkste secundaire uitkomstmaat is recidief binnen 1 jaar na de ingreep. Een recidief is gedefinieerd met de zelf-gerapporteerde dichotome vraag; zijn de klachten van aambeien verdwenen of verbeterd ten opzichte van vóór de behandeling; of hetzelfde gebleven of verergerd vergeleken met vóór de behandeling? Deze definitie werd tevens gebruikt in een systematische review en recente klinische trial. Andere secundaire uitkomstmaten werden gemeten met patiënt gerapporteerde uitkomsten zoals de kwaliteit van leven (QoL) op 12 maanden, de ernst van fecale incontinentie met de Vaizey fecale continentie score, symptoom vermindering met de 'Haemorrhoid Symptom Score' (HSS) en de 'proctologie patiënt-gerapporteerde uitkomstmaat' (proctoPROM) en 'Patient-Reported Outcome Measurement-Haemorrhoidal Impact and Satisfaction Score' (PROM-HISS).

In **hoofdstuk drie** is een retrospectieve analyse verricht naar patiënten met graad III hemorroïden die tussen januari 2013 tot augustus 2018 in een tertiair verwijscentrum voor proctologie (de Proctos Kliniek) werden behandeld met RBL of een hemorroïdectomie. Exclusiecriteria waren; sclerotherapie of RBL in de afgelopen 3 jaar, eerdere anorectale ingrepen, radiotherapie op het kleine bekken, anorectale maligniteit, bewezen chronische inflammatoire darmziekten en dwarslaesies. Totaal werden 327 patiënten geïncludeerd waarvan 182 patiënten waren behandeld met RBL en 145 patiënten waren behandeld met een hemorroïdectomie. Van de patiënten die waren behandeld met RBL, was 52% geholpen met een enkele behandeling. Van alle patiënten die een RBL had ondergaan, onderging 35% een tweede RBL sessie binnen één jaar en onderging 14% een hemorroidectomie als tweede behandeling. In totaal onderging 5%, van de patiënten die aanvankelijk met RBL waren behandeld, een derde behandeling. Van de patiënten die waren behandeld met een hemorroidectomie, onderging 4% een reinterventie. In 8% van de patiënten traden complicaties op na een hemorroidectomie en in 3% na RBL. De pre-procedurele patiënt gerapporteerde uitkomstmaat score, betreffende de impact van proctologische klachten op de patiënt zijn welzijn (proctoPROM), was hoger in de hemorroidectomie groep. Dit suggereert dat patiënten die werden behandeld voor een hemorroidectomie meer klachten ervaarden en mogelijk daarom werden behandeld met een meer invasievere ingreep dan degene met de mildere klachten. In beide

groepen was de postprocedurele proctoPROM significant lager, en daarmee de klachten beter.

De Goligher classificatie wordt gebruikt in de bovengenoemde studies. Het is tevens de meest gebruikte beschrijving voor hemorroïden waarbij de mate van prolaps wordt verdeeld in vier graderingen. Artsen baseren de gradatie op basis van de anamnese en het lichamelijk onderzoek maar derhalve is de classificatie gevoelig voor interobserver variabiliteit. Bovendien wordt de ernst van de prolaps hoger gegradeerd maar daarmee hangt de mate van klachten van de hemorroïden niet direct samen. Dit maakt het lastig om behandelingen te evalueren in onderzoeksverband. In **hoofdstuk vier** wordt de interobserver variabiliteit gemeten onder chirurgen in Nederland. Er werd een enquête verstuurd met 25 foto's van patiënten met hemorroïden met de bijbehorende anamnese en daarbij de informatie wat betreft het moment waarop de foto genomen was (gedurende rust of tijdens persen). Totaal werden 329 gastro-intestinaal chirurgen, fellows en AIOS'en uitnodigingd via de email, waarna 95 (29%) de enquête hadden ingevuld. Van deze groep gaf 87% aan de Goligher classificatie in de praktijk te gebruiken en vond 81% de classificatie nuttig. Daarentegen gaf 63% aan de classificatie te gebruiken en daarbij ook de richtlijn voor behandeling te volgen. De totale interobserver variabiliteit liet slechts een 'matige' overeenkomst zien, met een Fleiss' Kappa (κ) van 0.376 (95% CI 0.373–0.380). Er was een betere 'redelijke' overeenkomst voor graad I en IV hemorroïden met een κ statistic van 0.466 en 0.522, respectievelijk. Graad II en III hadden een lagere, 'matige', overeenkomst met 0.206 en 0.378 respectievelijk.

DEEL II

De behandeling van perianale fistels is voor chirurgen al voor een heel lange tijd een uitdaging. De behandeling is gericht op klachtenvermindering en het dichten van de fistel terwijl de anale functiebeperking zoveel mogelijk moet worden beperkt. Ondanks de huidige Nederlandse en internationale richtlijnen is het bepalen van de meest geschikte behandeling voor de individuele patiënt nog steeds erg lastig. Ook het bepalen van de diagnostiek, operatieve behandeling, follow-up en welke behandeling het meest geschikt is voor recidieven, is niet duidelijk. In **hoofdstuk vijf** wordt de huidige praktijk in de behandeling van cryptoglandulaire perianale fistels onder gastro-intestinale chirurgen in Nederland beschreven. Een enquête met 28 vragen betreft diagnostiek en de chirurgische techniek, werd verstuurd naar 342 gastro-intestinaal chirurgen, fellows en AIOS'en, waarvan 147 (43%) de enquête had ingevuld. De MRI-scan was de beeldvormende techniek van voorkeur met 43% waarna de endo-anale echografie volgde met 12%. De meeste respondenten verwijderde de seton tussen 6 weken en 3 maanden, met 58%. De fistulotomie was de ingreep van voorkeur voor de laag transsfincterische perianle fistel (86%) en de laag intersfincterische fistel (92%). De mucosale verschuivingsplastiek en de 'ligation

of intersphincteric fistula tract' (LIFT) waren de ingrepen die het meest werden gebruikt voor de hoog transsfincterische fistel met, 78% en 46% respectievelijk. In hoog intersfincterische fistels werd in 67% de mucosale verschuivingsplastiek gebruikt en in 33% de fistulotomie. Het sluiten van de interne fistelopening werd gedaan door 33% van de respondenten.

In **hoofdstuk zes** is een vergelijkbare studie gedaan waar de huidige praktijk voor de behandeling van de chronische anale fissuur is onderzocht. Nederlandse gastro-intestinaal chirurgen, fellows en AIOS'en werden uitgenodigd om een enquête in te vullen waarvan 106 (33%) de enquête hadden ingevuld. Patiënten met een chronische anale fissuur hebben frequent bijkomende bekkenbodemproblematiek welke effectief kan worden behandeld met bekkenbodemfysiotherapie. Tweeëntwintig procent van de respondenten gaf echter aan dat zij altijd, of bijna altijd, bij het lichamelijk onderzoek de bekkenbodemspieren onderzochten. De helft van de respondenten deed rectaal toucher. Van de respondenten schreef 56% zalf voor, zoals diltiazem, voor de periode van 6 weken en 27% voor minimaal 12 weken. Botulinetoxine injecties werd door 78% van de respondenten uitgevoerd waarvan meestal onder algehele anesthesie, spinaal anesthesie of sedatie (54%). De fissurectomie was de meest populaire operatieve ingreep met 71%, gevolgd door de laterale interne sfincterotomie (LIS) met 27%.

DEEL III

Anorectale fysiologische onderzoeken zijn nuttig als diagnostisch instrument en om behandelingen te evalueren. Er is een verscheidenheid aan onderzoeken beschikbaar, maar een richtlijn met aanbevelingen wanneer welk onderzoek moet worden gedaan is er niet. Bovendien is het niet duidelijk welke test het meest nauwkeuring is en welke correlatie de testen met elkaar hebben. In **hoofdstuk zeven** is prospectief data verzameld van verschillende anorectale functie onderzoeken in de diagnostische work-up van patiënten die waren verwezen naar de bekkenbodemfysiotherapeut. Anorectale functie onderzoeken omvatten het rectaal toucher, anorectale 3D manometrie, ballon expulsie test, transperineale echografie en de anale elektromyografie. Er werden 50 patiënten geïncludeerd waarvan 37 (74%) vrouwen. De meest voorkomende indicatie voor verwijzing naar de bekkenbodemfysiotherapeut was fecale incontinentie met 27 (54%) patiënten. Ondanks ervaren chirurgen en een ervaren bekkenfysiotherapeut, die allen meermaals per dag rectaal touchers uitvoeren, correleerden de vastgestelde anale drukken en bekkenbodemfunctie niet voor 100%. Gedurende rust, knijpen en persen correleerde het rectaal toucher van de chirurg en de bekkenfysiotherapeut in respectievelijk 78%, 78% en 84%. De correlatie tussen het rectaal toucher en de anorectale manometrie of de anale elektromyografie was beter voor knijpen dan voor de rustdruk. De resultaten van de zes onderzoeken (rectaal toucher door de chirurg en de bekkenbodemfysiothera-

peut, anorectale 3D manometrie, ballon expulsie test, transperineale echografie en anale elektromyografie) wat betreft het diagnosticeren van dyssynergie waren tot op zekere hoogte vergelijkbaar. De resultaten van de studie suggereren dat indien er verder onderzoek moet worden gedaan met een anorectaal functie onderzoek, de resultaten van die onderzoeken met enige voorzichtigheid moet worden geïnterpreteerd.

Patiënten met fecale incontinentie of constipatie komen, indien bekkenbodemfysiotherapie met biofeedback niet afdoende helpt, in aanmerking voor transanale irrigatie (TAI). **Hoofdstuk acht** beschrijft de resultaten van een prospectieve studie waar is gekeken naar de klinische effectiviteit van hoog volume TAI in patiënten met constipatie en/of fecale incontinentie. Patiënten werden gevraagd om gevalideerde vragenlijsten in te vullen betreft klachten en kwaliteit van leven bij baseline, 4, 12, 26 en 52 weken. In totaal werden er 59 (51,8%) patiënten met constipatie, 26 (22,8%) patiënten met fecale incontinentie, en 29 (25,4%) met beide klachten geïncludeerd. Vermindering van de constipatie klachten werd in het onderzoek niet gezien. De mediane PAC-QOL score verbeterde op de meeste domeinen. Vermindering van fecale incontinentie werd gerapporteerd in 5/9 (55,6%) patiënten met fecale incontinentie, en in 3/10 (30%) patiënten met beide klachten. De mediane St Marks incontinentie score per individu verbeterde in zowel patiënten met fecale incontinentie als in patiënten met beide klachten. De mediane FI-QOL scores verbeterde op bijna alle domeinen. Bij 52 weken waren 41 (36%) patiënten gecontinueerd met TAI en waren er 63 (55,2%) gestopt en 10 (8,8%) waren lost to follow-up. Hiermee laat de studie zien dat TAI de klachten van patiënten met fecale incontinentie verminderd, maar niet van patiënten met constipatie. Daarnaast laat het zien dat TAI de kwaliteit van leven in patiënten met constipatie en fecale incontinentie verbeterd.

PORTFOLIO

Name PhD student: Lisette Dekker PhD period: April 2019 – February 2023 Name PhD supervisor: dr. I.J.M. Han-Geurts / prof. W.A. Bemelman		
1. PhD training		
	Year	**Workload (Hours/ECTS)**
General courses		
– BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2019	0.9
– Practical biostatistics	2019	1.1
– Citation Analysis and Impact Factors	2020	0.1
– Scientific Writing for publication	2020	1.5
Specific courses		
– CE – RCT 19,20,23,24-9-2019	2019	0.6
– CE – SR 18,19,20-5-2020	2020	0.7
Seminars, workshops and master classes		
– Monthly department journal club AMC/UvA	2019-2022	1.0
– Two weekly department research meetings Proctos Kliniek	2019-2022	1.5
Presentations		
– WCP-avond Rotterdam, the Netherlands	2019	0.25
– NVvH Najaarsdag, Ede, the Netherlands	2019	0.25
(Inter)national conferences		
– Chirurgendagen NVvH, Veldhoven, the Netherlands	2019	0,5
– ESCP, Vienna	2019	0,5
– Najaarsdag NVvH, Ede, the Netherlands	2019	0,25
– Lagerhuisdebat fistels, Bilthoven, the Netherlands	2020	0,25
– ESCP Virtual, Vilnius	2020	0,5
– Werkgroep Coloproctology, Utrecht, the Netherlands	2021	0,5
– ESCP Virtual	2021	0,5

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ABOUT THE AUTHOR

Lisette Dekker was born on the 7th of July 1992 in Medemblik, the Netherlands. She attended the first three years of high school at de Dijk in Medemblik after which she went to the Oscar Romero in Hoorn for the last 3 years. After graduating in 2010 she started with medical school and obtained her Bacherlor's degree at the University of Amsterdam and her Master's degree at the Vrije Universiteit Amsterdam. In 2017 she started working as surgical resident, not in training, at the Antoni van Leeuwenhoek hospital in Amsterdam and in 2018 she went to the OLVG oost in Amsterdam for her second job as surgical resident, not in training. In 2019 she started as a medical researcher at the Proctos Kliniek in Bilthoven under supervision of dr. Han-Geurts and prof. dr. Bemelman from the Amsterdam UMC location AMC. She did her PhD trajectory at the department of surgery of the Amsterdam UMC. Her research focused on benign anorectal disease and she finished her PhD thesis in 2022. Lisette lived in Amsterdam from 2014 until 2020 and then moved to Spakenburg. In 2022 she started as a resident not in training at the internal medicine department at Meander MC in Amersfoort. In January 2023 she became resident in training at the department of radiology at Meander MC.