Protocol

LigaSure™ Hemorrhoidectomy (LH) versus Open Hemorrhoidectomy (OH)

- A Randomized Clinical Trial on the long-term effects on hemorrhoidal symptoms.

Version 4, September 1, 2019

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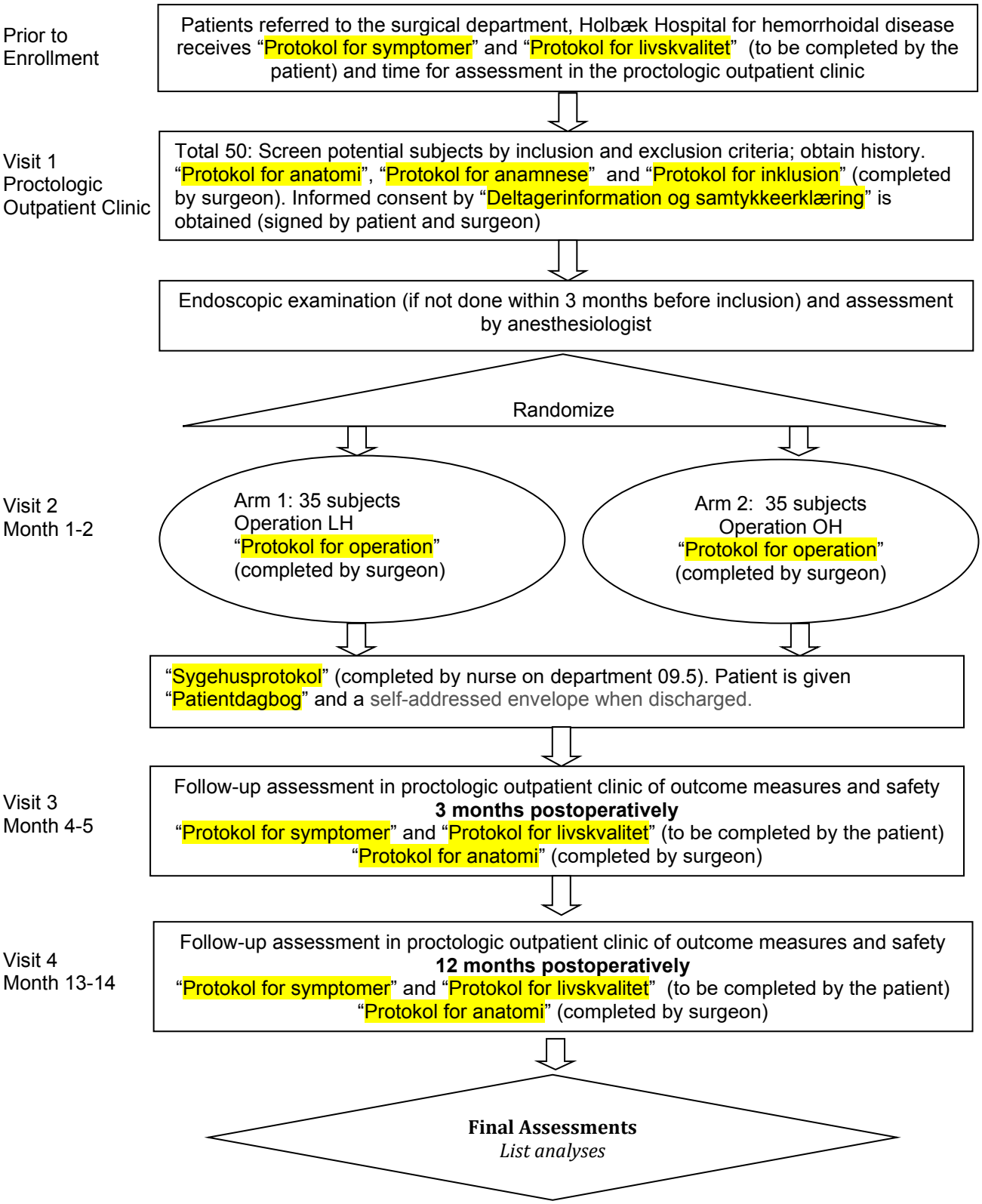
LIST OF ABBREVIATIONS

ASA	American Society of Anesthesiologists (ASA) score
Consort	Consolidated Standards of Reporting Trials
EHR	Electronic Health Record
EQ-5D-5L	Euro Quality of Life – 5 Dimensions – 5 Levels
HAL	Hemorrhoidal Artery Ligation
HDSS	Hemorrhoidal Disease Symptom Score
LH	LigaSure™ Hemorrhoidectomy
N	Number (typically refers to subjects)
OH	Open Hemorrhoidectomy
p.n.	pro necessitate
QoL	Quality of Life
RFIS	Revised Fecal Incontinence Scale
SD	Standard Deviation
SH	Stapled Hemorrhoidopexy
SHS	Short Health Scale
THD	Trans anal Hemorrhoidal Dearterialization
WHO	World Health Organization

PROTOCOL SUMMARY

Title:	*LigaSure™ Hemorrhoidectomy versus Open Hemorrhoidectomy - A Randomized Clinical Trial on the long-term effect on hemorrhoidal symptoms*
Précis:	A randomized clinical trial that will compare two operations used for grade II - IV hemorrhoids. Patients referred to the department of surgery in Holbæk Hospital for hemorrhoids and eligible for operation will be included consecutively. Evaluation will be done by assessing symptoms, quality of life, anal continence and hemorrhoidal anatomy pre- and postoperatively.
Objectives:	Primary: Symptoms related to hemorrhoids one year postoperatively, according to a hemorrhoidal disease symptom score (HDSS) Secondary: 1) Patient satisfaction with the operation. 2) Health related Quality of Life 3) Anal continence as evaluated by two scores for symptoms of incontinence. All one year postoperatively
Population:	Male or female, ASA I-II, aged 18 to 85 at the time of randomization, referred to surgical assessment and presenting with grade II hemorrhoids refractory to banding or sclerosing and grade III og IV hemorrhoids at the surgical department, Holbæk Hospital.
Site:	Single center study. Holbæk Hospital, Surgical Department
Description of Intervention:	Hemorrhoidectomy with either Open Hemorrhoidectomy or LigaSure™ Hemorrhoidectomy
Study Duration:	48 months (from when the study opens to enrollment until completion of follow up.)
Subject Participation Duration:	One year
Estimated Time to Complete Enrollment:	36 months

Schematic of Study Design:



INTRODUCTION

Background

Hemorrhoids is one of the oldest known medical conditions. Description of hemorrhoids is found as early as 2250BC in the code of king Hammurabi in Babylon. Even though first recorded treatment is thought to be found in the "Edwin Smith Papyrus" from 1700BC [1] as of today the treatment of this benign state is still debated. A wide range of prevalence rates of hemorrhoids have been stated in part because of the varying definition ,but the general consensus is that hemorrhoidal disease is a common anorectal disease affecting the quality of life of millions of people worldwide[2] [3]. Operation for hemorrhoid is one of the most common operations for benign disease in Denmark.

Hemorrhoids arise from the normal vascular structures in the anal canal also referred to as anal cushions or sinusoids as they do not contain muscular cells like arteries or veins. These cushions are typically arranged in three main columns or piles in the anal canal forming an important part of the intricate mechanism of the anal canal preventing incontinence[4].

Hemorrhoids is a pathologic term describing the symptomatic abnormal downward displacement and enlargement of the anal cushions[5]. The term hemorrhoidal disease is used when the hemorrhoids cause symptoms.

Treatment of hemorrhoidal disease consists of conservative management with lifestyle and diet changes or local treatment, minor surgery and surgical treatment depending on the severity of disease and symptoms. The staging of internal hemorrhoids in four categories by the Goligher classification[6] is the classification that generally forms the basis of the treatment in Denmark.

Local treatment consists of corticosteroids and anesthetic ointments. Minor surgery includes rubber band ligation and sclerotherapy. Operation is reserved for subjects with prolapse[7], Goligher grade II and IV. Grade II hemorrhoids may be treated by operation if still symptomatic after banding or sclerosing.

The gold standard in the operative treatment of hemorrhoidal is the Milligan-Morgan Hemorrhoidectomy[8] also referred to as hemorrhoidal excision or *Open Hemorrhoidectomy* (OH). The operation can also be performed as a *Closed Hemorrhoidectomy* when the wound is closed with sutures (Ferguson's Hemorrhoidectomy).

The conventional excisional operation has been associated with postprocedural pain and delayed healing of wounds. In recent years there have been suggestions for and a development toward a less traumatic Open Hemorrhoidectomy. Injuries to the internal anal sphincter during dissection is thought to be one cause for pain. The less traumatic operations include dissection of the hemorrhoid preserving the fascia over the internal anal sphincter and also smaller excision of skin and mucosa[9] - the technique used in this study is described in more detail under Methods.

Several new procedures have been proposed in the last decades. Common for all is the implementation of a new technical device, meaning increased operative costs.

Stapled Hemorrhoidopexy (SH) was first described by Longo in 1993 and uses a circular stapler to resect part of the rectal mucosa a couple of centimeters from the dentate line, thus reducing the prolapsed hemorrhoids into the anal canal[10]. The reasoning behind this procedure is that the prolapse of hemorrhoids is the main pathologic factor causing symptoms, and by reducing the prolapse the patient's symptoms may be treated without leaving wounds in the anal canal. In this operation a circular stapler is used to resect the rectal mucosa a few centimeters above the dentate line, thereby lifting the prolapsed hemorrhoids into the anal canal. SH has showed to cause less postoperative pain and faster recovery, but has a higher recurrence rate compared to traditional hemorrhoidectomy[11-12-13].

Hemorrhoidal Artery Ligation (HAL) and *Trans anal Hemorrhoidal Dearterialization (THD)* were introduced in 1995 and 2001 respectively. These methods are aimed at reducing the arterial blood supply to the anal venous plexus. The arteria supplying the anal venous plexus are located with a ultrasound doppler flowmeter and ligated[14 15]. During the procedure the anal prolapse is also reduced into the anal canal by a mucopexy, suturing of the mucosa. A few studies could demonstrate promising results for these operations. One non-randomized study found less postoperative pain at 1-6 months, but similar results at 1 year as regards hemorrhoidal symptoms and quality of life when compared to LigaSure™ hemorrhoidectomy[16]. A small randomized study, comparing THD to open hemorrhoidectomy, found less pain the first five days. Hemorrhoidal symptoms as pain, bleeding and the need for manual reduction of hemorrhoids were reduced one year after operation in both groups, whereas reduction of soiling was seen only in the open hemorrhoidectomy group.

LigaSure™ hemorrhoidectomy (LH) is a closed hemorrhoidectomy performed with the use of the LigaSure™ instrument instead of the traditional diathermy. The LigaSure™ technology patentented in 1998 as "Energy Delivery System for Vessel Sealing" creates vessel fusion by a combination of pressure and energy[17]. The LigaSure™ device excises the hemorrhoids and seals the wound in the same procedure delivering the energy in a controlled way between the diathermy forceps theoretically limiting thermal spray and tissue charring.

Anal continence. OH and LH are both excisional operations. Anal continence has been a concern after these operations. Anal incontinence is defined as involuntary loss of air, liquid or solid stool that is a social or hygienic problem[18]. The anal cushions contribute to the closure of the anal canal and provide 15- 20% of maximal resting pressure of the anal canal[19]. A Cochrane review found that anal incontinence was reported in 1.6% of the patients after conventional hemorrhoidectomy[20]. Another Cochrane review reported 3,6 % anal continence or hygiene problems at 1-2 years follow-up after conventional hemorrhoidectomy[12]. When patients are actually asked for symptoms of incontinence a retrospective multicenter study found that 33% of the patients reported anal incontinence after hemorrhoidectomy and 10% meant this was caused by the operation[21]. Another study found some deterioration of anal incontinence after hemorrhoidectomy in patients with preoperative impaired continence[22]. Anal continence after LigaSure™ hemorrhoidectomy is scarcely investigated.

Previous studies comparing Open Hemorrhoidectomy and LigaSure™ Hemorrhoidectomy

Open Hemorrhoidectomy and LigaSure™ are both techniques where the hemorrhoids are excised, (ablative techniques). A few studies indicates that ablative techniques have better long term results in terms of reduction of symptoms[11,23].

There are so far 18 controlled studies comparing OH to LH[24–41], all designed for and using postoperative pain as major outcome variable. There are three metanalysis the largest including 11 studies[42,43,44]. In conclusion there seems to be less post procedural pain, somewhat faster recovery, slightly less bleeding and shorter operating time after LH.

Patient' satisfaction was evaluated in a few studies with no difference between the two operations[29,40,41]. One small study on 30 patients investigated anal continence with no difference between the two operations[30].

No study has investigated hemorrhoidal symptoms with a validated instrument one year or more after the operation

Rationale

Hemorrhoidal Disease is a benign disease and should be evaluated by its effect on hemorrhoidal symptoms together with its effect on quality of life.
Hemorrhoidal symptoms should be the main outcome variable when evaluating surgery for hemorrhoidal disease. This information is largely lacking.
The use of a validated symptom score with long term follow-up could yield important information for the choice of treatment of hemorrhoidal disease.

Postoperative complications and adverse effects

Serious complications to hemorrhoidal operations occur rarely. The most commonly early complications are urinary retention, bleeding or fever/infection. Late complications are anal fissure, anal stenosis and anal incontinence. A Cochrane review reported after open hemorrhoidectomy; postoperative bleeding 2.9%, urinary retention 5.1%, anal fissure 3.1%, anal stenosis 0,9% and anal incontinence 1.6% [20].

Search Methods

A PubMed database search was conducted with following PICO query:
((("haemorrhoids"[All Fields] OR "hemorrhoids"[MeSH Terms] OR "hemorrhoids"[All Fields]) AND (((Open[All Fields] AND ("hemorrhoidectomy"[MeSH Terms] OR "hemorrhoidectomy"[All Fields] OR "haemorrhoidectomy"[All Fields])) OR Milligan-Morgan[All Fields]) OR ("diathermy"[MeSH Terms] OR "diathermy"[All Fields]))) AND (Ligasure[All Fields] OR (Ligasure[All Fields] AND ("hemorrhoidectomy"[MeSH Terms] OR "hemorrhoidectomy"[All Fields] OR "haemorrhoidectomy"[All Fields])))) AND ("complications"[Subheading] OR "complications"[All Fields])

A Cochrane was done searching for h(a)emorroidectomy and h(a)emorrhoid.

Relevant articles were chosen and by title and abstract and by reading the reference lists further texts were identified. In addition Danish and Swedish guidelines from national medical journals were included.

OBJECTIVES

Aim

To analyze and compare the long-term effects of LigaSure™ hemorrhoidectomy (LH) and Open Hemorrhoidectomy (OH) on hemorrhoidal symptoms.

Main outcome variable

Symptoms related to hemorrhoids one year postoperatively, according to a validated hemorrhoidal symptom score (HDSS)(appendix 3).

Secondary outcome variable

1) Patient satisfaction with the operation one year postoperatively, evaluated on a seven grade Lichert scale.
2) Quality of Life as evaluated by Short health Scale (SHS), Short Form 36 (SF36) and EuroQualityofLife -5 Dimensions (EQ-5D-5L) (appendix 6).
3) Anal continence as evaluated by the Wexner score[45], the Revised Fecal Incontinence Scale (RFIS) [46].

We will also analyze: anal function with anal manometry, anatomical result as evaluated by the surgeon, operation time, theatre time (time consumed in the operating room), postoperative complications, postoperative pain and need of analgesics, length of postoperative hospital stay and days before return to work or possibility of return to work.

SUBJECT CRITERIA

Subject Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Male or female aged 18 to 85 at the time of randomization
- Grade III-IV hemorrhoids and grade II hemorrhoids refractory to previous treatment with rubber band ligation or sclerotherapy.
- Hemorrhoidal symptom score of four or more
- Colonoscopy, sigmoidoscopy or rigid rectoscopy within 3 months before inclusion.
- American Society of Anesthesiologists (ASA) score of I or II. (day-care surgery)
- Provide signed and informed consent form

Subject Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Previous operation of grade III and IV hemorrhoids within the last 2 years.
- Previous operation for anal incontinence.
- Active anal fistula or anal fissure
- Incontinence for solid stool

- Active immunosuppressive therapy (increased risk of anorectal sepsis)
- Cirrhosis / portal hypertension
- Mb Crohn[47]

DESIGN AND METHOD

Trial Design

This is a single center randomized clinical trial comparing two operative techniques in the treatment of hemorrhoids.

Qualification of the surgeons

The surgeon should have experience from at least ten open hemorrhoidectomies and ten LigaSure™ hemorrhoidectomies before operating independently

Operation date and type of anesthesia

Operation time, theater time, operative bleeding, grading of complexity of the operation and type of anesthesia is recorded by the surgeon after the operation in "Protokol for operation" (appendix 8)
Study Interventions – Open Hemorrhoidectomy (OH)

Patient Material and Recruitment

According to the power calculation at least 62 subjects are needed for the analysis. Compensating for an estimated loss to follow-up of approximately 10%, 70 subjects will be included in the study. See statistical considerations in a later chapter.
Subjects for this study will be recruited consecutively from patients attending the proctologic outpatient clinic at the department of surgery at Holbæk Hospital eligible for operation.

Inclusion procedure

Subjects recruited will receive written information about the study (appendix 1). Subjects will be offered a new appointment with one of the surgeons participating in the study offering further information if needed. It will be possible to bring an assessor. Subjects will be offered 14 days to consider their participation. Before inclusion in the study a declaration of acceptance will be signed by the subject (Appendix 2). A checklist, "Protokol for inklusion" (appendix 5), will be used at the first visit in the surgical outpatient clinic to ensure correct inclusion and patient history will be obtained in "Protokol for anamnese" (appendix 4).

Randomization

Subjects fulfilling the inclusion criteria and accepting to participate in this study will be randomized to LH or OH. Randomization is stratified by gender. List for randomization will be obtained from www.random.org. Notes assigning the subject to either operation according to the randomization lists will be placed in sealed envelopes. Each envelope is assigned gender and number in the study (Male 1,2,3.. or Female 1,2,3..).
The envelope will be opened in the operating theatre after the patient has been anesthetized. Randomization lists and the sealed envelopes will be stored in a locked safe.

Anesthesia and thromboembolic prophylaxis

After consulting with surgeon and patient the anesthesiologist will decide type of anesthesia to use (general, spinal or epidural). Respecting any contraindications, patients will receive a preoperative perianal block with a total of 40ml of Ropivacaine 4,75mg/ml according to the technique described by Nyström et al[48].
All patients will receive thromboembolic prophylaxis with low molecular heparin unless contraindicated.

STUDY INTERVENTION The operation methods

Operations will be done in the outpatient day surgery setting in the surgical department of Holbæk Hospital. Irrational details will be recorded in "Protocol for operation" (Appendix 8). In the following description of the two operative techniques differences in operation is marked in *italics*.

STUDY INTERVENTION Open Hemorrhoidectomy

The procedure is according to the principles of Minimal open hemorrhoidectomy performed with the patient in lithotomy position. Initial overview is obtained using an anal speculum. The excision is done without speculum in the anus. "*The external components are grasped by clamps using gentle traction. Diathermy is used for dissection and hemostasis. The skin is incised midway to one-third of the distance from the top of the pedicle, thus, minimizing the skin excision. The subdermal fascia continuing into a submucosal fascia covering the internal anal sphincter is identified as are fibers passing between the hemorrhoid and this fascia. The hemorrhoid is dissected free from the underlying internal sphincter in this plane, leaving the sphincter unharmed. The anal mucosa is incised at the transition from anal mucosa to hemorrhoidal mucosa and only anal mucosa overlying the hemorrhoid is excised. Only the caudal part of the hemorrhoid is excised. With the hemorrhoid held with gentle traction it is divided at the anal orifice. There will thus be a residual part of the hemorrhoid intra-anally with its caudal end 1–2 cm proximal to the anal orifice. The number of excisions is individualized. The procedure is repeated for each hemorrhoid leaving adequate skin and mucosal bridges"*[49].

STUDY INTERVENTION LigaSure™ Hemorrhoidectomy

The procedure is performed with the patient in lithotomy position. Initial overview is obtained using an anal speculum, but the excision is done without speculum in the anus. *"The main hemorrhoidal masses are identified and delineated, usually in the 'classical' location corresponding to the sites of inferior hemorrhoidal vessels - left and right - posterolateral and right anterior quadrants. The hemorrhoids are prolapsed out from the anal canal with Allis clamps or similar pick up forceps. Tension should be applied to visualize the junction between the nodule and the mucosal wall (internal) or the perianal tissue (external). A small V-shaped anodermal seal is performed by applying the LigaSure™ forceps close to the edge of each pile. The seal is then transacted with scissors along the line of coagulum. Care should be taken to limit the amount of tissue removed to minimize the stricture risk. Repeated applications of the device are performed, and the excision is continued into the anal canal, lifting the pile from the internal anal sphincter to the level of the vascular pedicle that is finally sealed by LigaSure™ and divided "*[50].
The procedure is repeated for each hemorrhoid taking care of leaving adequate "skin bridges" between each excision.

Postoperative Care

All patients will be discharged on the day of the operation unless there are any immediate postoperative complications or if the patient is living alone without attendance at home the first 24 postoperative hours.

Standard postoperative pain treatment is initiated for all patients regardless of operation type and consists of:
Paracetamol tablet 1-gram x4/day for 7 days, hereafter p.n.
Ibuprofen tablet 400mg x3/day for the first 7 days, hereafter p.n. (patients ≥ 65 years old will receive supplementary Pantoprazole tablet 40mgx1/day when using ibuprofen)
Morphine tablet 10mg p.n. Max 6 tablets/day for 3 days
Magnesia tablet 1gx2/day for 7 days, hereafter p.n.
Xylocaine gel p.n.
At discharge from the hospital and in the preoperative material (appendix 1) patients are informed that there are no limitations concerning physical activity and they are encouraged to return to daily activity as soon they feel fit enough and the postoperative pain permits it. Patients are told not to drive, operate heavy machinery or performing other potentially dangerous tasks while on morphine.

Postoperative pain and return to daily activities

During the first 14 postoperative days the patient will report postoperative pain, use of analgesics and return to daily activities or work in "Patientdagbog" (appendix 10). Since weekends and holidays can influence when a patient returns to work, patients will answer a question when they feel fit enough to return to work. *It will also be noted if the patient is self-employed.*

Immediate postoperative course

Immediate postoperative complications, postoperative pain, use of analgesics and length of hospital stay will be noted in "Sygehusprotokol" (appendix 9).

Evaluation of symptoms

The questionnaire "Protokol for symptomer" (appendix 3) is used for evaluating hemorrhoidal symptoms recorded by the subject. Five questions on pain, itching, bleeding, soiling and prolapse graded from 0-4. Resulting in a score of 0-20.
The hemorrhoidal symptoms will be evaluated preoperatively at randomization, after 3 months, one-, three- and five years.

Patient's satisfaction with the operation will be evaluated on a 7-grade Lichert scale.

Evaluation quality of life

Quality of life will be evaluated by SHS, SF-36 and EQ-5D-5L, recorded by the patient preoperatively at the randomization and one, three and five years postoperatively (appendix 7).

Evaluation of anal continence

Anal continence will be evaluated using both the Wexner score and the RFIS, registered by the patient in "protokol for symptomer" (appendix 3). Five questions with a score from 0-4 resulting in a total score of 0-20 for both operations. Evaluation will be done preoperatively at randomization, after 3 months, one-, three- and five years.

Anal function will also be analyzed with anal manometry preoperatively at randomization, after 3 months, one-, three- and five years. In addition we will investigate the amount of smooth muscle in the resected specimen from the two groups indicating the amount of injury to the internal anal sphincter.

Evaluation of hemorrhoidal anatomy

Hemorrhoidal anatomy is evaluated by the surgeon using "Protokol for anatomi"(appendix 7). Late postoperative complications are also reported in "Protokol for anatomi" at follow-up.

Hemorrhoids are graded according to the Goligher classification[6]:

Grade	Grade of prolapse
I	No prolapse, just prominent blood vessels
II	Prolapse upon bearing down or by physical exercise with spontaneous reduction
III	Prolapse upon bearing down and requires manual reduction
IV	Prolapse which cannot be manually reduced

Table 1: Goligher's classification of internal hemorrhoids

The classification of hemorrhoids is based on physical examination by the surgeon and patient history. If prolapse is not present at physical examination the patient can be classified as having grade II or III based on the patient history. External skin flaps will also be recorded in "Protokol for anatomi" (Appendix 7).

Hemorrhoidal anatomy will be evaluated preoperatively at randomization, operatively and after 3 months, one-, three- and five years.

Security control

In order to detect adverse events and non-satisfactory results a security control of the study will be performed after operation of 10 patients in each arm. An open control of the immediate postoperative course, postoperative complications and postoperative hemorrhoidal symptoms three months after the operation will be performed.

STATISTICAL CONSIDERATIONS

Study Hypothesis
There is no difference in hemorrhoidal symptoms one year after an operation for hemorrhoids performed as LigaSure™ Hemorrhoidectomy or Open Hemorrhoidectomy.

Sample Size Considerations
The primary outcome variable is symptom score based on the patient questionnaire. The five questions graded from 0 to 4 results in a score from 0 to 20. Preliminary data from an ongoing study in our center comparing OH with THD and using the same questionnaire shows a symptom score after 3 months of 5 with a standard deviation (SD) of 4,2. The power calculator on www.stat.ubc.ca comparing the means for two independent samples with a two sided test has been used. We postulate that a difference of 3 points in symptom score would be clinically relevant with the standard deviation of 4,2. To demonstrate a difference in mean score of 3 points with a SD of 3.5 in both groups, an alpha error of 5% and a beta error of 20%, 31 patients in each group Is needed.

As for the secondary objectives analyzing anal incontinence by the Wexner score and the Revised Fecal Incontinence Scale, both consists of five questions graded from 0 to 4 results in a score from 0 to 20. Preliminary data from the study mentioned above shows a mean of 4 and SD of 3,9 for the Wexner score and a mean of 2,3 with an SD of 3,9 for the RFIS. To demonstrate a difference in mean score of 3 points with a SD of 3.9 in both groups, an alpha error of 5% and a beta error of 20%, 27 patients in each group Is needed.

Patient satisfaction is analyzed after year on a scale from 1 to 7. Preliminary data from the above-mentioned study shows a mean of 5,8 and a SD of 1,6. Assuming that a difference in 1,5 points would be clinically relevant 19 patients are needed in each group with an alpha error of 5% and a beta error of 20%.

Thus a sample size of 31 patients in each group should provide sufficient power in addressing analysis of primary and secondary endpoints. We estimate that there will be a loss of 9 patients for follow up. We will include 70 patients in the study.

ETHICS
The investigators will ensure that this study is conducted in full conformity with the principles set forth in the Declaration of Helsinki seventh edition[51].

The patients included in this study will have hemorrhoidal disease and satisfy the indications for surgical treatment in accordance with guidelines for treatment of hemorrhoids by The Danish Society of Surgeons. Surgery will only be performed after informed consent have been obtained following the routine in our daily clinical practice. Both operation methods are recommended in the national guidelines and are regarded safe and with low risk of serious complications[7]. Presently there are no evidence that one method is better than the other, so the operative method chosen varies between hospitals and surgeons. The participants in this study will consequently not be exposed to additional unnecessary risks. Further, a security control of the study will be

performed after inclusion of 10 patients in each group, to detect unexpected adverse effects.
This study will hopefully provide important information about the efficacy and economical aspects of hemorrhoidectomy performed with diathermy and LigaSure™ helping future decision-making in the treatment of hemorrhoids.

This trial has been approved by the Regional Committee on Health Research Ethics. (Protocol number: SJ-584)

DATA

Data handling and confidentiality

Subject confidentiality is strictly held in trust by the investigators in accordance with the Danish law of handling personal information. Data storage and analysis will be done without name and personal ID-number (CPR-number) by making a personal data transformation key, which will be stored in a locked safety box only accessible only by the study secretary.

Access to information in the patient's electronic health records (EHR) will be used for self-monitoring and to reassure the quality control required in the study. Above all, information in the EHR will be used to verify that important information regarding possible complications are not missed. This will only be done after a signed informed consent. Only the participating surgeons and the study group will have access to the patients EHR (appendix 1).

This trial will be performed after approval from the Danish Data protection Agency.

Data owners' rights

The data will be owned by the participating surgeons and the study group. The participating surgeons must not publish or present the data without permission from the study manager.

PUBLICATION

Before this clinical trial is initiated its details are to be registered in a publicly available, free to access, searchable clinical trial registry complying with WHO's international agreed standards[1].
The main findings, both positive and negative, of this clinical trial is to be submitted in a peer reviewed journal within 12 months of study completion[2]

FUNDING OF THIS STUDY

This study is to be done without funding from the medical industry. The surgical department at Holbæk Hospital provides the necessary facilities and funding. An

[1] www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

[2] See www.consort-statement.org for broadly accepted standards on presentation of results in peer reviewed manuscripts reporting clinical trials

application will be sent to Zealand region Research Fund for financial support if the study is accepted by the Regional Committee on Health Research Ethics. Neither the study manager nor the study assistant or the participating surgeons have any conflicts of interest relevant for the study.

REFERENCES

1. Ellesmore, S. & Windsor, A. Surgical History of Haemorrhoids. in *Surgical Treatment of Haemorrhoids. Charles MV, editor* 1–4 (2002).
2. Riss, S. *et al.* The prevalence of hemorrhoids in adults. *Int. J. Colorectal Dis.* **27**, 215–220 (2012).
3. Johanson, J. F. & Sonnenberg, A. The prevalence of hemorrhoids and chronic constipation. An epidemiologic study. *Gastroenterology* **98**, 380–386 (1990).
4. Schubert, M. C., Sridhar, S., Schade, R. R. & Wexner, S. D. What every gastroenterologist needs to know about common anorectal disorders. *World J. Gastroenterol.* **15**, 3201–3209 (2009).
5. Lohsiriwat, V. Hemorrhoids: From basic pathophysiology to clinical management. *World J. Gastroenterol.* **18**, 2009–2017 (2012).
6. Goligher, J., Duthie, H. & Nixon, H. Surgery of the anus, rectum and colon edn 5. *Balliere Tindall, London* (1984).
7. Buntzen S, Christensen P, Khalid A, Raahave D, Q. N. Kirurgisk behandling af hæmorider. *Danish Soc. Surg.* (2012).
8. Milligan, E., Morgan, C. & Jones, L. Surgical anatomy of the anal canal and the operative treatment of haemorrhoids. *Lancet* **2**, 1119 (1937).
9. Nyström, P.-O. & Gerjy, R. Något om konsten att skära bort hemorrojder. 2–4 (2011).
10. Longo, A. Treatment of haemorrhoids disease by reduction of mucosa and haemorrhoidal prolapse with a circular suturing device: a new procedure. in *In: 6th World Congress of Endoscopic Surgery.*
11. Nystrom, P.-O., Qvist, N., Raahave, D., Lindsey, I. & Mortensen, N. Randomized clinical trial of symptom control after stapled anopexy or diathermy excision for haemorrhoid prolapse. *Br. J. Surg.* **97**, 167–176 (2010).
12. Jayaraman, S., Colquhoun, P. H. D. & Malthaner, R. A. Stapled versus conventional surgery for hemorrhoids. *Cochrane database Syst. Rev.* CD005393 (2006). doi:10.1002/14651858.CD005393.pub2
13. Giordano, P., Gravante, G., Sorge, R., Ovens, L. & Nastro, P. Long-term outcomes of stapled hemorrhoidopexy vs conventional hemorrhoidectomy: a meta-analysis of randomized controlled trials. *Arch. Surg.* **144**, 266–272 (2009).
14. Sohn, N., Aronoff, J. S., Cohen, F. S. & Weinstein, M. A. Transanal hemorrhoidal dearterialization is an alternative to operative hemorrhoidectomy. *Am. J. Surg.* **182**, 515–519 (2001).
15. Morinaga, K., Hasuda, K. & Ikeda, T. A novel therapy for internal hemorrhoids: ligation of the hemorrhoidal artery with a newly devised instrument (Moricorn) in conjunction with a Doppler flowmeter. *Am. J. Gastroenterol.* **90**, 610–613 (1995).
16. Zampieri, N., Castellani, R., Andreoli, R. & Geccherle, A. Long-term results and quality of life in patients treated with hemorrhoidectomy using two different techniques: Ligasure versus transanal hemorrhoidal dearterialization. *Am. J. Surg.* **204**, 684–688 (2012).

17. Buysse, S. P., Kennedy, J. S. & Ryan, T. P. US Patent Number 5,827,271.
18. Norton, C., Christiansen, J., Butler, U. & Al, E. Anal Incontinence. in *Incontienence: 2 nd International Consultation on Incontinence.* 985–1043 (Plymouth, UK. Health Books, 2002).
19. Lestar, B., Penninckx, F. & Kerremans, R. The composition of anal basal pressure. An in vivo and in vitro study in man. *Int. J. Colorectal Dis.* **4**, 118–122 (1989).
20. Sw, N. & Ihjt, D. H. Conventional versus LigaSure hemorrhoidectomy for patients with symptomatic Hemorrhoids (Review) Conventional versus LigaSure hemorrhoidectomy for patients with symptomatic Hemorrhoids. *Cochrane database Syst. Rev.* (2009). doi:10.1002/14651858.CD006761.pub2.Copyright
21. Johannsson, H. O., Graf, W. & Pahlman, L. Long-term results of haemorrhoidectomy. *Eur. J. Surg.* **168**, 485–489 (2002).
22. Li, Y. D., Xu, J. H., Lin, J. J. & Zhu, W. F. Excisional hemorrhoidal surgery and its effect on anal continence. *World J. Gastroenterol.* **18**, 4059–4063 (2012).
23. Simillis, C. *et al.* Systematic review and network meta-analysis comparing clinical outcomes and effectiveness of surgical treatments for haemorrhoids. *Br. J. Surg.* **102**, 1603–1618 (2015).
24. Altomare, D. F. *et al.* Ligasure??? precise vs. conventional diathermy for Milligan-Morgan hemorrhoidectomy: A prospective, randomized, multicenter trial. *Dis. Colon Rectum* **51**, 514–519 (2008).
25. Bessa, S. S. Ligasure vs. conventional diathermy in excisional hemorrhoidectomy: a prospective, randomized study. *Dis. Colon Rectum* **51**, 940–944 (2008).
26. Milit, G., Gargiani, M. & Cortese, F. Randomised trial comparing LigaSure haemorrhoidectomy with the diathermy dissection operation. *Tech. Coloproctol.* **6**, 171–175 (2002).
27. Muzi, M. G. *et al.* Randomized clinical trial of LigaSure??? and conventional diathermy haemorrhoidectomy. *Br. J. Surg.* **94**, 937–942 (2007).
28. Onur Gulseren, M. *et al.* Randomized Controlled Trial Comparing the Effects of Vessel Sealing Device and Milligan Morgan Technique on Postoperative Pain Perception after Hemorrhoidectomy. *Dig. Surg.* **32**, 258–261 (2015).
29. Palazzo, F. F., Francis, D. L. & Clifton, M. A. Randomized clinical trial of Ligasure versus open haemorrhoidectomy. *Br. J. Surg.* **89**, 154–157 (2002).
30. Peters, C. J. *et al.* Ligasure trademark vs conventional diathermy haemorrhoidectomy: long-term follow-up of a randomised clinical trial. *Colorectal Dis.* **7**, 350–353 (2005).
31. Sakr, M. F. LigaSure versus Milligan-Morgan hemorrhoidectomy: A prospective randomized clinical trial. *Tech. Coloproctol.* **14**, 13–17 (2010).
32. Tan, K.-Y. *et al.* Randomized clinical trial comparing LigaSure haemorrhoidectomy with open diathermy haemorrhoidectomy. *Tech. Coloproctol.* **12**, 93–97 (2008).
33. Nighat, B., Foad, A., Farhat, J., Naeem, A. & Masood, J. Comparison of hemorrhoidectomy by LigaSure with conventional Milligan Morgan ' s hemorrhoidectomy. *Cochrane database Syst. Rev.* (2016). doi:10.12669/pjms.323.9976
34. Bouini, N. R. *et al.* Randomised Clinical Trial Comparing Ligasure Hemorrhoidectomy with Conventional Hemorrhoidectomy. **22**, 67–73 (2012).
35. Castellví, J. *et al.* Ligasure™ versus diathermy hemorrhoidectomy under spinal anesthesia or pudendal block with ropivacaine: A randomized prospective clinical study with 1-year follow-up. *Int. J. Colorectal Dis.* **24**, 1011–1018 (2009).
36. Fazeli, M. A prospective study comparing LigaSure and open hemorrhoidectomy. *Tehran Univ. Med. J.* **69**, 495

37. Franceschilli, L. *et al.* Radiofrequency versus conventional diathermy Milligan-Morgan hemorrhoidectomy: A prospective, randomized study. *Int. J. Colorectal Dis.* **26**, 1345–1350 (2011).
38. Franklin, E. J., Seetharam, S., Lowney, J. & Horgan, P. G. Randomized, clinical trial of Ligasure vs conventional diathermy in hemorrhoidectomy. *Dis. Colon Rectum* **46**, 1380–1383 (2003).
39. Gentile, M. *et al.* LigaSure Haemorrhoidectomy versus Conventional Diathermy for IV-Degree Haemorrhoids: Is It the Treatment of Choice? A Randomized, Clinical Trial. *ISRN Gastroenterol.* **2011**, 1–6 (2011).
40. Jayne, D. G. *et al.* Randomized clinical trial of Ligasure versus conventional diathermy for day-case haemorrhoidectomy. *Br. J. Surg.* **89**, 428–432 (2002).
41. Lawes, D. A., Palazzo, F. F., Francis, D. L. & Clifton, M. A. One year follow up of a randomized trial comparing Ligasure with open haemorrhoidectomy. *Colorectal Dis.* **6**, 233–235 (2004).
42. Nienhuijs, S. W. & de Hingh, I. H. J. T. Pain after conventional versus Ligasure haemorrhoidectomy. A meta-analysis. *Int. J. Surg.* **8**, 269–273 (2010).
43. Mastakov, M. Y., Buettner, P. G. & Ho, Y. H. Updated meta-analysis of randomized controlled trials comparing conventional excisional haemorrhoidectomy with LigaSure for haemorrhoids. *Tech. Coloproctol.* **12**, 229–239 (2008).
44. Tan, E. K., Cornish, J., Darzi, A. W., Papagrigoriadis, S. & Tekkis, P. P. Meta-analysis of short-term outcomes of randomized controlled trials of LigaSure vs conventional hemorrhoidectomy. *Arch. Surg.* **142**, 1209–18; discussion 1218 (2007).
45. Agachan, F., Chen, T., Pfeifer, J., Reissman, P. & Wexner, S. D. A constipation scoring system to simplify evaluation and management of constipated patients. *Dis. Colon Rectum* **39**, 681–685 (1996).
46. Sansoni, J., Hawthorne, G., Fleming, G. & Marosszeky, N. The revised faecal incontinence scale: a clinical validation of a new, short measure for assessment and outcomes evaluation. *Dis. Colon Rectum* **56**, 652–659 (2013).
47. Lohsiriwat, V. Treatment of hemorrhoids: A coloproctologist's view. *World J. Gastroenterol.* **21**, 9245 (2015).
48. Nyström, P. O., Derwinger, K. & Gerjy, R. Local perianal block for anal surgery. *Tech. Coloproctol.* **8**, 23–26 (2004).
49. Roervik, H. D. *et al.* Minimal open hemorrhoidectomy. *Tech. Coloproctol.* **23**, 73–77 (2019).
50. Milito, G. & Cadeddu, F. Tips and tricks: Haemorrhoidectomy with LigaSure. *Tech. Coloproctol.* **13**, 317–320 (2009).
51. The World Medical Association (WMA). WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. 1–8 (2013).