Protocol

Treatment Of Chronic Anal fissure (TOCA): a Randomized Clinical trial on Levorag® Emulgel versus Diltiazem gel 2%

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Background

Anal fissure is an ulcer-like, longitudinal tear in the anal canal, most commonly located in the dorsal or ventral midline, and distal to the dentate line. Anal fissures constitute a common medical problem that affects sexes equally. The initiation of the fissure is most likely caused by the passage of hard stools that traumatizes the anal canal. Patients suffer from anal pain lasting up to several hours after defecation and rectal bleeding. Most acute anal fissures heal spontaneously, but a proportion progress into chronic fissures with symptoms beyond 8-12 weeks. There is no strict definition of a chronic anal fissure, but previously the presence of two of the following three symptoms has been used: 1) Pain after defecation lasting for more than three months; 2) presence of a sentinel anal tag; and 3) Exposure of the horizontal fibres of the internal anal sphincter. The severe pain may be caused by a hypertonic contraction of the internal anal sphincter leading to ischemia. Treatment strategies have therefore aimed to relieve this hypertonia by surgical and non-operative approaches. Primary therapy is initiated with ointments such as Diltiazem and glycercyltrinitrat gels.

A novel approach is the Levorag® Emulgel, an ointment classified as Medical Device class 1. According to the manufacturer (THD SpA, Italy) the effect of Levorag® Emulgel is
mediated through the effects of myoxinol, a plant extract from the Hibiscus plant with a botox-like effects on the anal sphincter and carboxymethyl glucan, a natural yeast polysaccharide with immune stimulating properties. The effect of the widely used Diltiazem gel is mediated through diltiazem hydrochloride, a calcium channel blocker that decreases the anal sphincter pressure.

**Aim of study and endpoints**

The aim of this study is to compare the standard first-line treatment-of-choice for chronic anal fissures Diltiazem 2% with Levorag® Emulgel. The primary endpoint is the rate of complete healing after 12 weeks. Secondary endpoints are complete healing after 8 weeks, incidence of adverse effects and efficacy on pain relief.

**Methods**

This is an interventional, randomized clinical trial including adult patients with chronic anal fissures referred directly to the Digestive Disease Center, Bispebjerg Hospital, University of Copenhagen, Department of Surgery, Aarhus University Hospital or referred to a private surgical practice in Copenhagen or Aarhus.

**Inclusion criteria:**

1. Danish citizens, age \( \geq 18 \) years
2. Presence of a midline anal fissure, dorsal or ventral.
3. Pain during and after defecation lasting for more than 8 weeks
4a. Presence of a sentinel anal tag or hypertrophic papilla and/or
4b. Exposure of the horizontal fibres of the internal anal sphincter.

1-3 has to be fulfilled for inclusion. Additionally 4a AND/OR 4b has to be present.
Exclusion criteria:

1. Inflammatory bowel disease, known venereal disease, immunodeficiency disease
2. Anal/perianal abscess
3. Anal or rectal surgery within 12 weeks
4. Pregnancy or breastfeeding females
5. History of migraine or chronic headache requiring treatment with analgetics
6. Any cardiovascular or cerebrovascular disease
7. Current use of calcium channel blockers in general or history of use of calcium channel blockers in the treatment of the fissure
8. Signs of other rectal diseases, fistula, infection including severe perianal eczema and tumours.

Intervention

Patients are randomized to treatment with either:

1) Diltiazem gel 2%, one application twice daily for 8 weeks, or
2) Levorag® Emulgel, one application twice daily for 8 weeks

In addition to the allocated treatment, all patients will be kept on standard care for anal fissure, including high-fibre diet proper hydration and laxatives.

Patients, who do not respond to the treatment, will be offered a Botox injection or a lateral internal sphincterotomy at the end of the study period.

Clinical examination and follow-up
All patients will be thoroughly investigated at the initial examination (week 0) including complete medical history. Included patients will be evaluated by telephone interviews at day 3 and 7 focusing on pain intensity and by clinical examinations 8 and 12 weeks after initiation of treatment. The clinical evaluation at inclusion and each follow-up visit includes a specification of fissure location, presence of a sentinel tag or hypertrophied papilla, epithelialization, registration of Wexner incontinence score, Bristol Stool Chart, assessment of pain during and after defecation score (100 mm on a visual analog scale), anal manometry and registration of adverse effects. A case report form has been constructed for this purpose (supplementary material 1)

**Randomization and blinding**

A single-blinded randomized design with variable block sizes stratified according to gender is used. Eligible patients are randomized after initial examination. The randomization key is generated online (Sealed Envelope™) and allocation letters are stored in sealed envelopes with a corresponding box containing the treatment gel for the whole study period. The evaluating physician or specialist nurse will be blinded to the allocated treatment as will the researcher analysing the data. A manuscript is then prepared and the randomization key is only revealed when the study group agrees on the results.

**Sample size calculation**

A non-inferiority design based on the primary outcome of complete healing within 12 weeks was chosen. Based on preliminary results the expected success rate of Levorag® Emulgel and Diltiazem gel 2% was 70% and 50%, respectively. Using a non-inferiority limit of 10% and an expected 15% loss to follow-up, 50 patients in each treatment group are required to provide a statistical power of 0.90 and a two sided $\alpha$ of 0.05.
Study layout

Statistics

The treatment groups are analysed on an intention-to-treat basis using chi-square and Mann-Whitney tests for categorical and continuous variables, respectively. Differences between the groups are analysed at all time points (0, 8 and 12 weeks). Differences over time are investigated using repeated measurement analysis. Data are presented as odds ratios with 95% Confidence Intervals and median with range for categorical and continuous variables, respectively. A two-sided $P$-value $< 0.05$ are considered significant.
Risks, adverse effects and disadvantages

There are no known risks or adverse effects associated with treatment with Levorag® Emulgel. Up till 10 per cent of patients treated with Diltiazem can experience a mild headache that typically lasts for a week. Patients in treatment for cerebrovascular and/or cardiovascular disease should use Diltiazem with caution and are therefore not eligible for inclusion in this study.

Patient consent

All patients must give informed written consent before inclusion. Patients will receive written information about the study at least 24 hours prior to the screening visit. All eligible patients will be thoroughly informed at the screening visit in a separate, undisturbed examination room by a dedicated specialist nurse or a project physician, who will provide the patients with oral and written information about the study including the ethical criteria concerning this study. All patients will be offered a period of at least 24 hours before signing the patient consent form. The patients are also informed regarding their rights to be joined by an assessor during the information about the study.

Respect of patients’ physical and mental integrity and right to privacy

Patients will be informed that participating in this study is without any payment or personal gain. Withdrawal of consent will be accepted at all times without further questions by the study investigators. Those patients who will not participate will receive the current standard treatment with diltiazem.

The study is to be registered and approved by the local Ethical Committee and the Data Registration Authorities whereas registration at the National Board of Health authorities is not required, because the test product has received its CE mark approval for the same indication as stated in the present
protocol. The study is registered at www.clinicaltrials.gov

The conductance of the study will comply with the Danish law regarding handling personal data.
The patients must provide informed consent to permit the study personnel to record data from the patients’ medical files according to the Danish law on health §43, part 1. These data include health related information regarding the anal fissure as well as a full medical history, and will serve to describe whether the two randomized allocation groups are comparable, which is a crucial issue for the scientific interpretation of the study results.

**Ethical considerations**

There exist no previous published studies (PubMed search) comparing the success rate of Levorag® Emulgel with other treatment regimes for anal fissures. Preliminary non-comparative and non-published data suggest that the rate of pain relief is higher and fissure healing is faster than expected for diltiazem gel 2%. If this is correct a new agent Levorag® Emulgel may be included in the standard care of chronic anal fissures. Furthermore, an additional benefit may be a lower rate of adverse events compared with diltiazem. It is therefore justified to study the efficacy of Levorag® Emulgel in a direct comparison with the standard treatment.

**Budget**

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Schedule

Recruitment of patients will commence in June 2014 and is planned to terminate in December 2018. Data analyses will be completed within 3 months and a manuscript will be prepared by March 2019 at the latest.

Publication

We will publish the results – positive, negative or inconclusive - of the study in medical journals and at surgical congresses as lectures or posters. Depending on the final results of the study and similar studies published in the coming 2 years, the final paper will be offered to the following clinical journals: Annals of Surgery, British Journal of Surgery, Diseases of the Colon and Rectum, Colorectal Disease or Surgery.

The first author will be the coordinator of the study who commits himself to write a paper within 6 months after completion of the study. Senior author will be Peter-Martin Krarup.

Any oral or written publication will have to be approved in writing by all participating physicians. If it is not possible to publish the results in a scientific journal, the authors will communicate the results in an alternative way, e.g. on the official homepage of Bispebjerg Hospital and Aarhus University Hospital.

Disclosures

This study was initiated by Peter-Martin Krarup, MD, Digestive Disease Center, Bispebjerg Hospital, University of Copenhagen. The execution of this study is supported and financed by Sacomed ApS, represented by Søren Agerbo. All financials received for this study will be directly transferred to a research account administered by Digestive Disease Center. No financial support is received from the manufacturers of the treatment products besides from the costs for the gels and
the randomization, which is received from Sacomed ApS. Support from private funds may be sought but has not yet been received. The Danish Ethical Committee will be notified if such support is obtained. None of the investigators or the study personnel has any financial association with Sacomed ApS. Only the authors will have full and uninhibited access to the data and the final publication right.
References


