Hamlet TRIAL

PROTOCOL

Full title: **Multicenter randomized controlled trial of Doppler guided Hemorrhoid Artery Ligation (DGHAL) and mucopexy versus mucopexy alone in the treatment of grade III Hemorrhoids .**

S

hort title: **Hamlet (Hemorrhoids Artery Mucosal Ligation prospEctive Trial) trial**.

Alternative title: Doppler-guided or non doppler-guided arterial ligation and mucopexy for third degree hemorrhoids? That is the question. The Hamlet (Hemorrhoids Artery Mucosal Ligation prospEctive Trial) trial.

Developed by Department of Emergency and Organ Transplantation (DETO), University of Bari, Italy

Hamlet Trial Management Group

Surgery

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Randomization

Simple randomization will be centralized and carried out by assigning the 3 treatment options to consecutive computer generated random number obtained through the website http://www.randomizer.at

The randomization code will be obtained by contacting the number or the Tel number +39 3492185104/ +39 3397593066 or by the e-mail address arcangelopicciariello@gmail.com or donatofrancesco.altomare@uniba.it .

Clinical queries during office hours should be directed to one of the clinical coordinators or to an appropriate member of the Hamlet Management Group

Data Monitoring and Ethics Committee

Clinical data monitoring will be carried out by Ms Angela Accettura: Dept of Emergency and Organ transplantation, University of Bari e-mail: angela.accettura@uniba.it Tel +39.0805592235

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Protocol approval n. 4555/2014

Trial Sponsor: University of Bari, Department of Emergency and Organ Transplantation, DETO, Section of Surgery, Bari, Italy, Tel: +39 5592107 – +390805478764

Clinicaltrial.gov ID number: **Protocol version: 14/3/18**

Hamlet Study Office

For general queries, supply of trial materials, and collection of data:

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CONTENTS

1. INTRODUCTION

1.1 Background

Hemorrhoidal disease is one of the most common proctological disease affecting the general population from the mid-teens onward with considerable implications for the National Health Service (NHS) both from an economic point of view and from surgeon's workload[1]. Even if hemorrhoids are a benign condition, they severely impact patients' quality of life. In fact, symptoms include bleeding, pain, prolapse, soiling and itch. The treatment of hemorrhoidal disease is directed at relieving its related symptoms.

1.2 Management of disease

While Goligher's grade I-II hemorrhoids can be readily treated with conservative measures and grade IV hemorrhoids find the gold standard treatment in the hemorrhoidectomy, several minimally invasive treatment options, including Doppler-guided hemorrhoidal artery ligation and mucopexy have been introduced for the management of grade III hemorrhoids with the aim of minimizing postoperative pain and sparing the sensitive anoderm

1.3 Doppler guided hemorrhoidal artery ligation

Improved understanding of the pathogenesis of haemorrhoids and of the complications associated with excisional haemorrhoidectomy led to the invention of newer surgical procedures, including Doppler guided haemorrhoidal artery ligation (DGHAL).

This technique was introduced in 1995 by Morinaga et al. and consists in the use of a proctoscope with a Doppler transducer that detect the arterial structures[1].

Since DGHAL does not involve tissue excision, it is expected to be associated with reduced postoperative pain if compared with hemorrhoidectomy[2].

In the last decade several devices (THD and AMI/ HAL-RAR – Hemorrhoidal Artery Ligation and Recto Anal Repair) have been developed in order to improve and facilitate the execution of the technique, making easier the procedure [3, 4].

1.4 Mucopexy

The addition of suture mucopexy to DGHAL has extended the indication of this technique to III degree hemorrhoids with encouraging results in terms of postoperative pain and complication and long term recurrences.

About 6 mucopexy with resorbable sutures are usually performed with this procedure starting from 2 o'clock in clockwise direction.

A RCT and some case series have cast doubts on the usefulness of making DGHAL, claiming that mucopexy alone can yield similar results and with less time (Aigner et al). However, these studies have some weak points including small sample size and use of different devices.

2. STUDY HYPOTHESIS

The hypothesis of the study is that a simple mucopexy procedure by suture-fixation of anal cushion without the aim of a Doppler device, could be as effective as DGHAL and mucopexy to manage prolapsing grade III hemorrhoids.

3. STUDY DESIGN

3.1 General Design

Prospective, multi-centre, parallel-arm randomized controlled equivalence trial. Eligible patients will be randomized to either mucopexy without Doppler guided artery ligation or mucopexy with doppler guided hemorroidal artery ligation.

3.2 Endpoints

3.2.1 Primary

Primary aim of the Hamlet trial is to demonstrate that mucopexy without DGHAL for grade III haemorrhoids have equivalent recurrence rate at 1 year follow up of DGHAL with mucopexy procedure

3.2.2 Secondary

- **SAFETY**: Demonstration that the new treatment will not add related morbidity
- **Comparison of the outcome among the two devices** (THD and AMI/ HAL-RAR) for DGHAL
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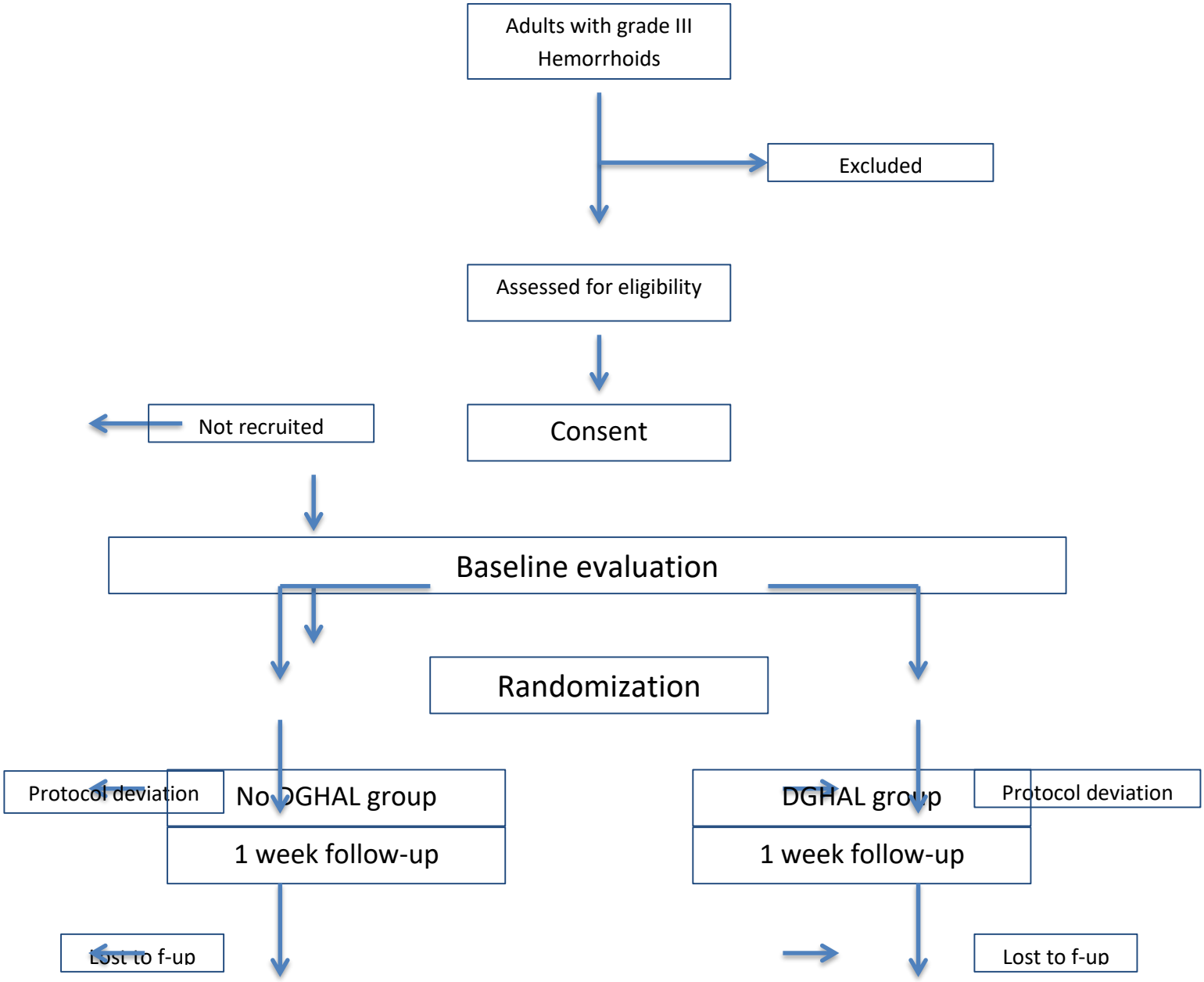

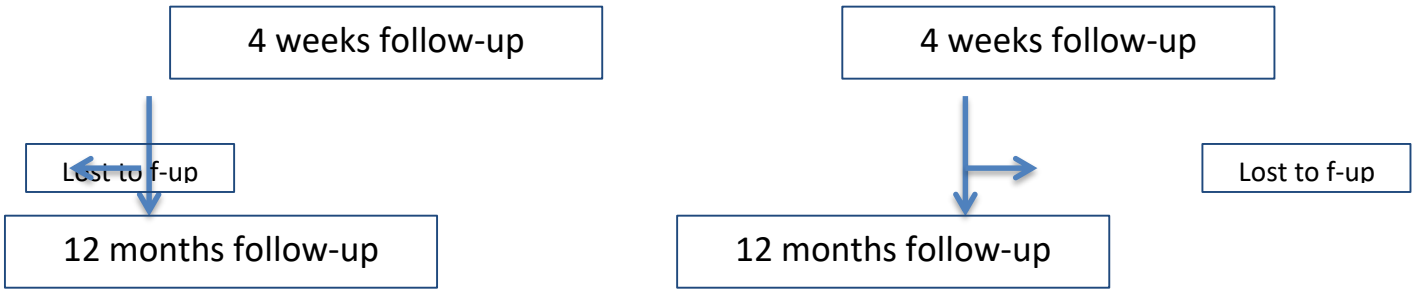

3.2.3 SWOT analysis

STRENGHTS	**WEAKNESS**
- Possibility to improve patient's outcome and reduce hospital costs - Low cost of the new treatment	- High number of patients to be recruited - Variability of the techniques
OPPORTUNITIES	**THREATS**
- Applicable to a relevant proportion of patients affected by grade III hemorrhoids. - Reduce time of the operation - Reduce hospital costs - Improvement of the patients QoL	- Common risks of all surgical procedures used for hemorrhoids

3.3 Randomization

Written informed consent will be obtained prior to surgery by the operating surgeon. Computer-generated randomization will be used to create an allocation sequence to assign patients to the

different study arms. Randomization will be computer generated and centrally controlled by an operator not involved in the study.

3.4. Subject Recruitment and Screening

Each patient with grade III hemorrhoids eligible for the inclusion and exclusion criteria will be randomized after obtaining written informed consent about the study. Patients will be given information about the risks, discomforts, and potential benefits of both treatments. The randomization protocol will be explained to the patient before consent is obtained.

3.5 Participating Institution and Surgeons

This multicenter trial is opened to the contribution of surgeons across Europe in order to achieve the required number of patient recruitment in the shortest period.

- All surgeons must have prior experience in the treatment of hemorrhoids with DGHAL and mucopexy.
- All participating institutions must have IRB (Institutional Review Board)/Ethics Committee approval in order to enroll patients in the trial.
- Recruitment of Centers will be by direct invitation or spontaneous proposal of Coloproctology Units interested in the study.
- Surgeons involved MUST have no potential conflict of interests in the procedure

3.6 Definition of Outcome Measures

Please use the following definitions:

- duration of the hospital stays (defined as from beginning of surgery to time of discharge, measured in hours)
- questionnaires administered to patients at 1 week, 4 weeks and 1 year follow-up
- Recurrence is defined as persistent or recurrent hemorrhoid symptoms including prolapse, proctorragia, hemorrhoidal thrombosis
- Hemorrhoidal prolapse is defined as III degree if the prolapse needs to be repositioned into the anal canal manually and of II degree if it returns spontaneously into the anal canal.

- Hemorrhoid engorgement visible only at control anoscopy but without symptoms will not be considered as Hemorrhoidal prolapse
- Proctorrhagia will be defined as minor if traces of blood can be detected at defecation, moderate if there is occasional bleeding at defecation, severe if bleeding occur after any defecation

3.6.1 Definition of Adverse Events

- Urinary retention will be defined as the condition of urinary dysfunction that occurs following surgery and requires intervention, including placement of urinary catheter.
- Pyrexia will be defined as any documented patient temperatures >38.0 C that require any treatment intervention such as antipyretics or that result in an increase in hospital stay.
- Surgical site infection purulent discharge from the wound with positive culture
- Post operative bleeding requiring reintervention, or balloon tamponade of the anal mucosa or transfusion within 1 month from the operation

3.7 ELIGIBILITY CRITERIA

3.7.1 Inclusion Criteria

- Patients over 18 years old
- Symptomatic grade III hemorrhoids according to Goligher
- No other source of anal bleeding than hemorrhoids
- Written informed consent

3.7.2 Exclusion Criteria

- Any previous hemorrhoid surgery
- Participants expressing clear preference for one of the interventions
- Pregnancy
- Inability to understand the informed consent
- Oral anticoagulants of congenital defects of the coagulation
- Patients with immunodepression (i.e. HIV)
- Other proctological diseases (fissures, fistulas, condyloma, etc)
- IBD involving the anus ore the rectum

3.8 Withdrawal Criteria

Study participants will be informed of their ability to withdraw from the study or refuse initial enrollment at any time. Patients may withdraw without explanation.

4 STUDY INTERVENTION

4.1 Preoperative work-up

All the patients will have full proctological examination including anoscopy. Those with familiarity for colorectal cancer and those over 50 will be invited to have screening colonoscopy to exclude other sources of bleeding

4.2 Operative protocol

Patients with symptomatic grade III haemorrhoids will enter the study if they fulfil the entry and exclusion criteria and after written informed consent. They will be randomized in 2 groups: DGHAL with mucopexy (group A) and DGHAL without mucopexy (group B).

A cleansing enemas will be performed early in the morning at least 2 h before the operation. Antibiotic prophylaxis was not considered.

General or epidural anaesthesia will be performed according to the patient or anaesthetist preferences.

A urinary catheter will be inserted in all patients and removed after few hours from the operation. The patients will be placed in the lithotomy position.

4.2.1 Technique

4.2.1.1 Devices:

THD device produced by THD SpA (Correggio, Italy), consists of a proctoscope equipped with a Doppler probe and a light source. The proctoscope model (THD SlideTM, THD SpA) has a sliding part comprising the operating window and Doppler probe for better proximal and distal movement without repositioning the proctoscope during mucopexy

AMI device, HAL-RAR – Haemorrhoidal Artery Ligation and Recto Anal Repair is produced by the A.M.I. – Agency for Medical Innovations, Austria. The device includes an illuminated proctoscope (RAR Flexi Probe) which is introduced into the rectum, then rotated slowly to search for arteries. This proctoscope is connected with a Doppler signal which indicates the position of the hemorrhoid arteries.

4.2.1.2 DGHAL

A lubricating gel is applied to the tip of the THD or the AMI device and, with the patient in the lithotomy position, the proctoscope is introduced into the anal canal. The terminal branches of the superior rectal artery are detected by the Doppler signal 2–3 cm above the dentate line. The tip of the instrument is gently tilted and the arteries are ligated with a figure-of-eight suture using 2／0 polyglycolic acid inserted using a special needle-holder through an aperture in the operating proctoscope.

4.2.1.3 Mucopexy

After the haemorrhoid artery ligation, the suture is continued with three to five sutures applied 5 mm apart, making sure that the last is at least 5 mm above the dentate line. The suture is then tied to create a hemorrhoidopexy. The procedure is repeated after all artery ligations (6 ligations).

In the NON doppler group the mucopexy will start at two o'clock and repeated at 4, 6 8, 10, 12, in clockwise direction.

4.3 Post-Operative Management

Postoperative care will be according to current standards as directed by the operative surgeon.

- Pain control will initially be provided using parenteral (intramuscular, intravenous or epidural) administration of narcotics or analgesics.
- bulking agents (psyllium) or osmotic laxatives will be prescribed in order to allow easy defecation

5. STATISTICAL ANALYSIS

5.1 Sample Size Determination:

A sample size calculation shows that 100 subjects per arm will suffice for accepting of the equivalent hypothesis with power of 0.8 and a type I error probability of 0.05, an equivalent limit of 15% and expected percentage of success in both control and experimental group of 90% (sample size calculated with R).

5.2 Statistical Methods:

Results will be expressed as either mean and standard deviation (SD) or frequency (percentage). Between-group comparisons will be performed using Student's t -test (normally distributed data) or Mann-Whitney$U$ test (skew data) for continuous variables or Chi-square test for categorical variables. All hypotheses will two-tails with $p < 0.05$ considered as statistically significant.

5.3 Subject Population for Analysis

Data analysis will be performed in accordance with the intention to treat principle. If a violation of randomization occurs, all patients will be analyzed according to the original allocation.

The following information will be prospectively collected and reported:

- All-randomized population: Any subject randomized into the study, regardless of whether they receive the intervention.
- Protocol-compliant population: Any subject who was randomized and received both the study intervention and received the required protocol processing.

6. ETHICS

6.1 Risks of Participation

Patients in both study arms will be informed of standard risks of hemorrhoid surgery, such as bleeding, surgical site infections, thrombotic complications, cardiac, or pulmonary complications.

6.2 Institutional Review Boards

This study will be conducted in accordance to the principles of the Declaration of Helsinki and good clinical practice guidelines. The study protocol will be approved by the Ethics committee of all

participating institutions. Prior to randomization, written informed consent will be obtained from all patients.

6.3 Data Safety Monitoring Committee

A data safety monitoring board (DSMB) will be established with experts independent of the authors. The chairman of the DSMB will receive the clinical data forms continuously from the coordinating center and will review data. The DSMB chair may at any time suggest to the Study Chair to terminate the study in case of ethical concerns such as unacceptable complication rates and others.

7. AUTHORSHIP AND PUBLICATION

The rules described herein apply to any presentation of this study. Members of the Protocol Writing Committee as well as Study Chairs qualify for authorship of this study. Vancouver Authorship Guidelines rules shall apply (for full document please see full article at http://www.icmje.org/index.html). Surgeons that include patients will attain authorship through a group authorship where names of surgeons will be mentioned. The order of the authors in the group authorship according their active contribution to the trial. The study results may only be published and/or presented as final analyses after the completion of the study and needs authorization by the study chairs. Publication and/or presentation are defined as any article, podium presentation, poster, abstract, or any other public presentation of this research. As is generally accepted, members of the DSMB should be independent and not involved in the study in any way including authorship.

8. SPONSORSHIP

The trial is not officially sponsored.

9. APPENDICES

Consent form

Form of words

10. REFERENCES

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