COVER PAGE

Research Protocol

OFFICIAL TITLE: Comparison between the ligation and hemorrhoidopexy technique and the conventional ligation of hemorrhoidal arteries using ultrasound: a prospective, randomized controlled study

BRIEF TITLE: Ligation and Hemorrhoidopexy Technique Versus Ligation of Hemorrhoidal Arteries Using Ultrasound for Hemorrhoids

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Comparison between the ligation and hemorrhoidopexy technique and the conventional ligation of hemorrhoidal arteries using ultrasound: a prospective, randomized controlled study

1. Research Subject

1.1 Description of the proposed project

The purpose of this study is to compare two techniques for treating hemorrhoids, the ligation and hemorrhoidopexy technique and the conventional ligation of hemorrhoidal arteries using ultrasound, in patients with non-complicated hemorrhoids.

2. INTRODUCTION

2.1 Literature

Surgical operations for the treatment of perianal diseases are a major part of all elective surgical cases. The reduction in the hospitalization time of patients undergoing surgical procedures for benign perianal diseases is to the benefit of both the patient and healthcare provider[1]. The importance of 'one day' surgical operations lies in the fact that the patient returns directly to his social and working environment, while the number of occupied hospital beds and the total hospitalization costs are reduced. A typical example is the goal set by NHS, where the 75% of the scheduled operations should consist of 'one day' operations[1]. In order to achieve this goal, several obstacles should be dealt with, including the implementation of more efficient and safe surgical techniques. Therefore, this would be associated with a decrease in the operation time, early recovery and faster hospital discharge.

Hemorrhoids is one of the most common benign perianal diseases. According to a recent prospective study[2] of 976 patients, 38.93% of them suffered from hemorrhoids, with 8.16% and 0.53% being Grade III and IV, according to Goligher classification, respectively. The percentage of the symptomatic patients was, also, significant (44.74%). Symptomatic hemorrhoids, includes bleeding, pruritus, pain, poor hygiene and the presence of palpable hemorrhoid nodules.

As far as the blood supply of the rectum and the broader anatomic region is concerned, it is provided by the superior, middle and inferior hemorrhoidal arteries. The superior hemorrhoidal artery is a branch of the inferior mesenteric artery and is carried behind the rectum, where it provides branches up to the internal sphincter muscle. The right and left middle hemorrhoidal artery originate from the respective internal iliac artery and their branches are cross-linked with the respective branches deriving from the superior hemorrhoidal artery. Finally, inferior hemorrhoidal arteries derive from the respective internal pudendal arteries. Correspondingly, hemorrhoidal venous plexus consists of the middle and inferior hemorrhoidal veins, which through the internal iliac veins drain into the inferior cava vein. Hemorrhoidal tissue constitutes a continence mechanism of the upper rectum and consists of vascular tissue, connective tissue and smooth muscle fibers, within the rectal canal. Through the approximation of the hemorrhoidal tissue, closure of the anal canal and protection of the sphincter mechanism is achieved. Since modern pathogenesis theories of hemorrhoids attribute to the increased arterial flow in the hemorrhoidal plexus the generating cause of this disease, recent anatomical studies mapped the vascular network, indicating that the arteries are not confined to the anatomical regions described in the literature[3].

According to recent guidelines [4], the modification of dietary intake, through the increase of fluid and fiber intake, consists the first line treatment of symptomatic hemorrhoids. However, in Grade III-IV hemorrhoidal disease or in Grade II, where conservative therapy failed, surgical intervention is required. Surgeon has plenty of techniques at his disposal, in order to treat hemorrhoids. Examples of these techniques are operations, such as hemorrhoidectomy (open [5], closed [5], Milligan-Morgan [6], Parks [6], using staplers [7], using energy sources, e.g. Harmonic [8], Ligasure [9], Laser [10], bipolar forceps[11]), elastic rings ligation[12], sclerotherapy [13] and hemorrhoidal arteries ligation (HAL) or Transanal Hemorrhoidal Dearterialization (THD) [14].

Ligation of hemorrhoidal arteries using a Doppler apparatus, is a minimally invasive technique that was first applied by Morinaga et al.[15] in 1995 and has as principle the elective ligation of the arteries that supply the hemorrhoidal plexus. In a recent meta-analysis the superiority of HAL in areas such as, postoperative bleeding, emergency reoperation, operative duration, length of hospital stay and postoperative pain, was shown. A major drawback of this technique, however, remains the high rate of recurrence, which ranges from 11.1% to 59.3%, for Grade IV hemorrhoids[17].

Despite the comparative advantages of this minimally invasive technique, the high cost of the necessary equipment and the respective consumables, is a barrier to its broad application. Gupta et al.[18] in a prospective randomized study, compared Doppler-Guided HAL (DG-HAL) to hemorrhoid artery ligation and hemorrhoidopexy. Ligation was performed on the hemorrhoid nodule at the 3rd, 7th and 11th hours, followed by continuous hemorrhoidal nodule ligation and hemorrhoidopexy[19]. The DG-HAL group had a significantly longer operative time (31 min vs 9 min) and post-operative pain (4.4 vs 2.2), without any differences in complication or recurrence rates. Similarly, Huang et al.[20], reported a respective ligation technique, where, through the use of the index finger, the artery was palpated, followed by repeating compression and ligation cycles, in order to fix the affected hemorrhoids above the dental line. In this group, operative time was longer when compared to the DG-HAL group (35.57 vs. 12.73). There was no difference in terms of postoperative improvement of symptoms and hospitalization duration. In the experimental group, however, the cost of hospitalization and the relapse rate was significantly lower. Finally, Aigner et al.[21], in a recent randomized study, investigated the efficacy of hemorrhoidopexy for Grade III hemorrhoids. They concluded that the techniques of hemorrhoidopexy are effective and the addition of DG-HAL does not affect the results.

Given these facts, the present trial was designed, in order to compare the two techniques for hemorrhoids treatment, the ligation and hemorrhoidopexy technique and the conventional ligation of hemorrhoid arteries using ultrasound.

2.2 Research Group Experience

In a prospective 4-year study with a total of 90 patients [22], the immediate post-operative and long-term course of patients undergoing DG-HAL hemorrhoid artery ligation was investigated. Totally, 64.4% of the included patients was discharged from the hospital, within 24 hours of the operation, 4.4% of patients needed additional analgesic treatment in the next 24 hours, while only 6.6% developed disease recurrence, one year after the operation. Additionally, a prospective randomized study of our clinic, compared pudendal nerve block and local anesthesia in 120 patients who underwent ultrasound scissors hemorrhoidectomy. A statistically significant lower rate of additional postoperative analgesic treatment was observed in the pudendal nerve block, while the level of postoperative pain, calculated on the Visual Analogue Scale (VAS scale), on the operative day was higher in the group of local anesthesia (5.1 vs. 2.2 $p<0.001$) [23].

3. RESEARCH PROTOCOL

3.1 Sample

The sample will consist of male and female patients aged 18 to 80 years, with an American Society of Anesthesiologists (ASA) score of I and II.

3.2 Diseases

Patients with Grade≤III hemorrhoids, according to Goligher's classification, will be included.

3.3 Exclusion Criteria

The exclusion criteria include:

- Acute perianal diseases, such as perianal abscesses, complicated hemorrhoids (e.g., thrombosis) and acute anal fissure
- Malignant perianal disorders
- Patient age 80 years
- ASA score III
- Presence of inflammatory bowel disease
- History of a previous rectoanal operation
- Presence of a clinically significant cardiovascular, respiratory, renal, hepatic or metabolic disorder. Furthermore, diseases, such as obesity, psychiatric disorders or gastrointestinal disorders constitute exclusion criteria.

3.4 1st Arm

The patient will be placed in the Lloyd-Davies position and having provided a sterile field, using a 10% povidone iodine solution, rectal dilatation will be performed with a 10% xylocaine gel, thus allowing the entrance of the proctoscope (THD America). The proctoscope will be combined with a Doppler sensor in order to detect the hemorrhoidal arteries and, also, a light source. Furthermore, a casing at the distal end of the apparatus that allows the proper placement and rotation of the needle-holder and a special window above the sensor and, thus, enables the placement of the ligations at the correct height and depth, through the capturing of the mucosa and the submucosa and the prevention of the perforation of the rectal wall. After the hemorrhoidal artery location, through the use of the ultrasound, Z ligations will be placed, using an absorbable polyglycolic acid suture (2-0, 5/8 inch needle). The proper artery ligation will be confirmed by the absence of the Doppler signal. In the presence of residual hemorrhoidal tissue, the upper part of the proctoscope will be removed and hemorrhoidopexy will be performed, by applying a continuous suture from the hemorrhoidal stem and peripherally. During hemorrhoidopexy, only the mucosa and the submucosa of the hemorrhoidal nodules, above the dental line, will be captured. At the end of the procedure, a hemostatic gauze will be placed in the surgical field. Prior to operation, the patients will be submitted to spinal anesthesia. Using an atraumatic 25 Gauge (G) needle, a levobupivacaine 5mg/ml and fentanyl 25mg solution, will be administered at the height of lumbar (L)2-L3 or L3-L4[24].

3.5 2nd Arm

In the experimental arm, the patient will be placed in the Lloyd-Davies position and having provided a sterile field, using a 10% povidone iodine solution, rectal dilatation will be performed with a 10% xylocaine gel, thus allowing the entrance of a conventional proctoscope, with an attached light source. After the identification of the hemorrhoidal nodules (3rd, 7th, 11th hour), their ligation, using an absorbable polyglycolic acid suture (2-0, 5/8 inch needle), will be performed. The location of the hemorrhoidal artery will be confirmed, through palpation, with the use of the index finger. Initially, a fixative suture will be placed in the hemorrhoidal nodule and then, using a continuous suture from the hemorrhoidal stem and peripherally, hemorrhoidopexy, will be performed. During hemorrhoidopexy, only the mucosa and the submucosa of the hemorrhoidal nodules, above the dental line, will be captured. At the end of the procedure, a hemostatic gauze will be placed in the surgical field. Prior to operation, the patients will be submitted to pudendal nerve block. Using an atraumatic 25 Gauge (G) needle, a 20ml lidocaine solution (diluted with saline in a 1:1 rate) will be administered bilaterally, medially to the ischial tuberosity[25]. Ten minutes before the operation, the patient will receive 1-2.5mg midazolam and 0.1-0.2 mg fentanyl.

3.6 Primary endpoint

The primary endpoint of the present study, is the identification of difference in the symptoms remission rate, within one month postoperatively, between the ligation and hemorrhoidopexy technique and the conventional ligation of hemorrhoidal arteries using ultrasound, in patients with non-complicated hemorrhoids. If the symptoms are treated then it will be defined as=1 'YES' If the symptoms are not treated then it will be defined as=0 'NO'. The time frame will be 1 month postoperatively.

3.7 Secondary endpoints

The secondary endpoints of the present study are:

- Operative time. Measurement unit: minutes. Time Frame: Intraoperative period
- Postoperative mobilization time. Measurement unit: hours. Time Frame: Postoperative period up to hospital discharge. Maximum time frame 24 hours
- Postoperative pain level at 12 hours after surgery, quantified with the use of the VAS scale. Time Frame: 12 hours postoperatively
- Onset of oral feeding. Measurement unit: hours. Time Frame: Postoperative period up to hospital discharge.Maximum time frame 24 hours
- Difference in the rates of adverse effects during hospitalization:
    - Hypotension. Occurrence of postoperative hypotension. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. Time Frame: Postoperative period up to hospital discharge. Maximum time frame 24 hours

- Nausea. Occurrence of postoperative nausea. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. Time Frame: Postoperative period up to hospital discharge. Maximum time frame 24 hours
- Vomiting. Occurrence of postoperative vomiting. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. Time Frame: Postoperative period up to hospital discharge. Maximum time frame 24 hours
- Headache. Occurrence of postoperative headache. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. Time Frame: Postoperative period up to hospital discharge. Maximum time frame 24 hours
- Urinary retention. Occurrence of postoperative urinary retention. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. Time Frame: Postoperative period up to hospital discharge. Maximum time frame 24 hours
- Bleeding at the operative site. Occurrence of postoperative bleeding at the operative site. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. Time Frame: Postoperative period up to hospital discharge. Maximum time frame 24 hours

o Postoperative time that the patient can be safely discharged. Measurement unit: hours. Time Frame: Postoperative period up to hospital discharge. Maximum time frame 48 hours

o Complications occuring at 7 days postoperatively:
- Pain on the basis of the VAS scale. Postoperative pain level at 7 days after surgery, quantified with the use of the VAS scale. Time Frame: 7 days postoperatively
- Oedema at the operative site. Occurrence of postoperative oedema at the operative site. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. Time Frame: 7 days postoperatively
- Hematoma at the operative site. Occurrence of postoperative hematoma at the operative site. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. Time Frame: 7 days postoperatively
- Infection at the operative site. Occurrence of postoperative infection at the operative site. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. Time Frame: 7 days postoperatively
- Stenosis at the operative site. Occurrence of postoperative stenosis at the operative site. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. Time Frame: 7 days postoperatively

o Postoperative return to work time. Measurement unit: days. Time Frame: Postoperative period up to 1 month

o Complications occurring at 1 year postoperatively:
- Pruritus. Occurrence of postoperative pruritus at the operative site. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. Time Frame: 1 year postoperatively
- Mucosal proptosis. Occurrence of postoperative mucosal proptosis at the operative site. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. Time Frame: 1 year postoperatively
- Perianal nodules. Occurrence of postoperative perianal nodules. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. Time Frame: 1 year postoperatively
- Constipation. Occurrence of postoperative constipation. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. Time Frame: 1 year postoperatively
- Tenesmus. Occurrence of tenesmus. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. Time Frame: 1 year postoperatively.

- Reoperation. Occurrence of reoperation. If the patient is reoperated, then it will be defined as=1 'YES' If the patient is not reoperated, then it will be defined as=0 'NO'. Time Frame: 1 year postoperatively

- Disease recurrence rate at 1 year postoperatively. Disease recurrence rate If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. Time Frame: 1 year postoperatively
- Satisfaction level at 1 year postoperatively. Satisfaction level measured at a 0-10 scale. Time Frame: 1 year postoperatively
- Difference in the quality of life of the patient, at 1 month and 1 year postoperatively, compared to the respective preoperative measurements, based on the SF-36 questionnaire, weighted for the Greek[26]. Time Frame: Preoperatively, 1 month postoperatively and 1 year postoperatively.

3.8 Sample Size calculation

The calculation of the sample size is based on the primary endpoint. According to the literature, the rate of the remission rate of symptoms, of patients who were submitted to hemorrhoidal artery ligation using ultrasound is 72.5%, while the respective rate of the ligation and hemorrhoidopexy technique is 90%[20]. Therefore for a non-inferiority trial, with alpha= 2,5%, beta= 80% and a non inferiority limit of 10% , the calculated sample for each group is 30 patients[27]. Totally, the required number of patients is 60.

3.9 Randomization

The randomization of the patients, between the two groups, will be performed using a software and a 1: 1 allocation ratio will be performed. Furthermore, an opaque envelope, which will contain the allocation group for the specific patient, will be opened preoperatively upon the entry of the patient into the surgical room, thus determining which technique will be applied.

3.10 Blinding

Blinding will exist at the level of the patient and the investigator who will record the data postoperatively, regarding the surgical technique applied. There will be no blinding at the level of the surgeon and the anesthesiologist.

3.11 Data

The following data will be recorded:

- Demographics (Gender, Age, Weight, Height, ASA)
- Hemorrhoid Grade
- Operation type
- Anesthesia type
- Operative time
- Mobilization time after the anesthesia administration
- Occurrence of adverse effects
- Level of pain based on the VAS scale (0-10) at 12 hours postoperatively.
- Time of onset of oral feeding
- Postoperative use of additional analgesia .
- Postoperative time that the patient can be safely discharged
- Complications occurring at 7 days postoperatively
- Postoperative return to work time
- Remission of symptoms, at 1 month postoperatively
- Complications occurring at 1 year postoperatively
- Disease recurrence at 1 year postoperatively
- Satisfaction level at 1 year postoperatively
- SF-36 questionnaire, preoperatively, at 1 month and 1 year postoperatively

3.12 Discharge Criteria

The patient will be discharged, when it is ensured that is medically safe to be released. In particular, as the exit time of the patient, will be regarded the time that the patient will fulfill the Clinical Discharge Criteria. More specifically, the patient should meet the following : steady vital signs, be oriented, without nausea or vomiting, mobilized with a steady gait, without a significant bleeding[28].

3.13 Follow up

One week after the operation, the patient will be summoned to reply for any postoperative complications, the return to work time, and the current pain level. One month postoperatively, the patient will be asked about the remission of the symptoms. One year after the operation, the patient will be examined for disease recurrence and will be asked about the overall satisfaction regarding the operation.

3.14 Medication

Preoperatively, the patient will not receive any kind of analgesic treatment. Additionally, 8 and 1 hour preoperatively, the patient will receive a fleet enema. Intraoperatively, besides the applied anesthetic technique, additional analgesia (paracetamol 1000mg I.V.) will be administered if deemed necessary. Perioperative antibiotic chemoprophylaxis will include the administration of a single dose of cefoxitin I.V. 2gr, and in case of allergy to cefoxitin, ciprofloxacin I.V. 400mg. With regard to the postoperative analgesic treatment, the patient will receive paracetamol 1000mg I.V every 6 hours, and if needed lornoxicam 8mg. In case of nausea or vomiting, granisetron 3mg/3ml I.V. will be administered. The patient will receive his systematic medication. Oral feeding will start upon absence of nausea and vomiting.

3.15 Research Group

Both the surgeon and the anesthesiologist who participate in the research group have years of experience in their field and have, therefore, completed the learning curve for the required operative and anesthesia techniques, respectively. The data collection and recording will be carried out by an independent, third party, researcher.

3.16 Trial

The study will be conducted in the Department of Surgery of the University Hospital of Larissa. Patient data will be recorded both in the patient charts and in an electronic database. The required laboratory examinations will be defrayed by the patient insurance funds. There will be no form of financial support for the present study.

4.LITERATURE

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