COVER PAGE

Statistical Analysis Plan

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. Introduction

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. Data Source

2.1 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.

3. Analysis Objectives

3.1 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.

3.2 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
- 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
- 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
- Postoperative return to work time. Measurement unit: days. Time Frame: Postoperative period up to 1 month
- 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. Time Frame: Preoperatively, 1 month postoperatively and 1 year postoperatively.

4. Analysis Set

4.1 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.

4.2 Diseases

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

4.3 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.

4.4 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.

4.5 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. Ten minutes before the operation, the patient will receive 1-2.5mg midazolam and 0.1-0.2 mg fentanyl.

4.6 Covariates

The following data will be considered as covariates

- Demographics (Gender, Age, Weight, Height, ASA)
- Symptoms (Proptosis, Bleeding, Pruritus, Pain)
- Hemorrhoid Grade

5. Statistical Methodology

5.1 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%. 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. Totally, the required number of patients is 60.

5.2 Handling of Missing Values

Missing values will be addressed using the multiple imputation method. Acceptable levels of missing values will be <10%.

5.3 Statistical Procedures

The statistical estimations of this study will be based on a per protocol analysis. Prior to any computation, all data will be submitted to a Shapiro-Wilk normality test.

Continuous variables will be compared on the basis of an independent samples t-test, whereas for categorical variables, the Pearson chi-square test will be applied.

The effect of the various patient characteristics on the primary and secondary endpoint will be evaluated by a regression analysis. More specifically, a multiple linear and a logistic regression will be used for continuous and categorical variables, respectively.

Regression analysis will be applied to all distinct endpoints. The validity of the linear regression model will be confirmed by the assessment of the following assumptions:

- Independence of observations, assessed by the Durbin-Watson test
- Linear relationship between the dependent variable and each of the independent variables and between the dependent variable and all the independent variables, collectively.
- Homoscedasticity of the data
- Multicollinearity of the data
- Absence of significant outliers, high leverage points or highly influential points
- Normal distribution of the residuals

A Forward model will be introduced in our multiple linear regression analysis. The proportion of variance explained by our model will be represented by R square. The statistical significance of our model will be evaluated by the F-test. The effect of each independent variable on the dependent outcome will be provided by the respective coefficient and the 95%CI.

Similarly, a Forward model will be applied in our logistic regression analysis. The following assumption will be tested:

- Independence of observations and mutual exclusive and exhaustive categories
- Linear relationship between any continuous independent variable and the logit transformation of the dependent variable

The explained variance will be presented by the Cox & Snell R square and Nagelkerke R square test. The percentage of the correctly classified observations will be also estimated. The statistical significance of each variable will be calculated by the Wald test. The odds ratios of each variable will be also estimated, alongside the respective 95%CI.

The variations between the different time endpoints SF-36 measurements will be evaluated on the basis of a repeated measures ANOVA model. Violation of the sphericity assumption will be determined by the Mauchly's test of Sphericity. In case of significant results, a Greenhouse-Geisser correction will be applied. Post-hoc comparisons will be performed with the introduction of Bonferroni corrections. The effect of the allocation group on the measured group will be quantified by the use of the F-test.

Continuous data will be reported as Mean (Standard Deviation), while categorical data will be reported as N (Percentage). Statistical significance will be considered at the level of p value < 0.05. All analyses will be performed in the IBM SPSS Statistics v23 software

4.LITERATURE

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