STUDY TITLE:

"VALUE OF TEMPORARY OCCLUSION OF THE UTERINE ARTERIES IN LAPAROSCOPY MYOMECTOMY"

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SUMMARY:

1. Objectives:

- Main objective: To analyze the patients who underwent a laparoscopic myomectomy, to assess whether there are significant differences in terms of a decrease in intraoperative blood loss between patients with temporary clamping of the uterine arteries and utero-ovarian ligaments and patients without temporary occlusion during the surgical technique.

- Secondary objectives: To determine the surgical time of each technique, the improvement of the symptoms for which the patient is operated, the length of hospital stay and the possible complications of each technique.

2. Methods:

- Study design : This is a randomized prospective longitudinal clinical trial in patients with fibroids who require surgery, from the Gynecology service of the Ramón y Cajal Hospital.

- Study population and total number of subjects :

A total of 37 patients who underwent laparoscopic myomectomy with temporary occlusion of the uterine arteries and utero-ovarian ligaments using clips will be analyzed with a control group of 37 patients who underwent laparoscopic myomectomy with the traditional technique (surgery without temporary occlusion of uterine arteries).

The sample size has been calculated based on data published in the literature, where there is a difference in hemoglobin levels of 0.7 g/dl between the two groups, with a statistical power of 80% and an alpha error of 5%.

1. INTRODUCTION.

Uterine fibroids are the most frequent benign tumors originating in smooth muscles of the female genital tract.

Fibroids appear in 70% of middle-aged women. They are often the cause of abnormal uterine bleeding, pelvic pain and pressure, urinary and intestinal symptoms, and/or pregnancy complications. However, many fibroids are small and asymptomatic. About 25% of white women and 50% of black women will develop symptomatic fibroids. Fibroids are more common among women who are overweight or obese. Potentially protective factors for the appearance of fibroids are pregnancy and smoking, in women who consume more than 10 cigarettes per day, except in black women, and although the mechanism by which the incidence decreases is not clear, a causal relationship does seem to exist.

Treatment of women with uterine leiomyomas should be individualized based on symptomatology, size and location of the leiomyoma , age, patient need and desire to preserve fertility or the uterus, availability of therapy, and surgeon experience.

Although hysterectomy is the definitive surgical treatment of symptomatic fibroids in women who do not wish to preserve fertility or their uterus, myomectomy is the treatment of choice in patients with an unfulfilled reproductive desire or express desire to maintain their uterus and who are not candidates for medical treatment.

Surgical planning for myomectomy should be based on the location, size, and number of fibroids with the aid of appropriate imaging tests, such as high-resolution ultrasonography or magnetic resonance imaging (MRI).

Intraoperative bleeding is one of the most frequent complications of laparoscopic myomectomy and may even require the need for transfusion on many occasions. For this reason, methods have been proposed that could reduce bleeding during surgery, such as temporary occlusion of the uterine arteries and utero-ovarian ligaments. The efficacy and safety of this technique for its application during laparoscopic myomectomy has not yet been clearly investigated.

2. GOALS

Main objective :

- To identify the efficacy of temporary occlusion of the uterine arteries during laparoscopic myomectomy by comparing blood loss (by assessing pre- and postoperative hemoglobin in g/dL and intraoperative blood aspirate in milliliters), in 2 groups of patients with symptomatic fibroids undergoing laparoscopic surgery, one with temporary occlusion of uterine arteries and uteroovarian ligaments and one without such occlusion.

Secondary objectives:

- Compare the surgical time of each technique.
- Compare the need for transfusion between both groups.
- Compare the improvement of the symptoms for which the patient is operated.
- Compare the length of hospital stay in each group
- Compare possible complications of each technique.

3. METHODOLOGY

3.1. DESIGN : Longitudinal prospective randomized clinical trial.

3.2. SUBJECTS OF STUDY : Patients with symptomatic fibroids who require surgery to treat them, from the Gynecology Service of the Ramón y Cajal Hospital. Patients will be randomized into 2 groups: exposed (patients with temporary occlusion of the uterine arteries by clips during surgery) and non-exposed (patients without temporary occlusion of the uterine arteries during surgery).

A patient will be recruited in the pre-surgical consultation when laparoscopic myomectomy is indicated, randomizing both groups by simple random sampling. An informed consent will be delivered to the patients, who have to accept and sign in order to participate in the study. The diagnosis of the presence of fibroids will be made by abdominal and/or transvaginal gynecological ultrasound and/or nuclear magnetic resonance. Fibroids will be quantified, measured and their location described.

3.3. INCLUSION CRITERIA : The inclusion criteria to participate in the study are the existence of uterine fibroids with an indication for laparoscopic surgery and the patient's desire to preserve the uterus.

3.4. EXCLUSION CRITERIA : Patients who do not meet the inclusion criteria, women with symptomatic fibroids who are not candidates for laparoscopic surgery and/or do not

wish to preserve the uterus, those patients who, despite having indications for randomization, do not have the technical possibility of clipping during the intervention.

3.5. VARIABLES TO STUDY : The patients included in the study will have their pre-surgical hemoglobin determined by preoperative analysis and another post-surgical hemoglobin sample will be determined the day after surgery. The need for transfusion, blood loss during surgery (aspirate the blood content), surgical time, hospital stay, symptom improvement and complications will be assessed.

In addition, clinical data on the patients will be collected: age, height, weight, race, concomitant diseases and treatment, family history, age at menarche, tobacco and alcohol consumption, main clinic where the surgery is performed.

3.6. INFORMATION SOURCES :

To obtain the necessary information from the study, the HCIS medical records will be used.

3.7. STATISTICAL ANALYSIS OF THE DATA

The data collected from the medical records will be tabulated in a main database with the SPSS version 23.0 program (IBM Corp. Released 2008. IBM SPSS Statistics for Windows, version 23.0 Armonk , NY: IBM Corp) For the statistical analysis, the same program will be used. The time for patient recruitment and data collection can be estimated at one year.

The absolute and relative frequency distributions of the qualitative variables will be presented.

The differences in the values of the quantitative variables will be studied using the most appropriate test in each case, Student 's t test to compare two groups and the corresponding non-parametric ones.

In the analysis of the contingency tables for qualitative variables and their possible association between them, Pearson's chi-square test will be used.

In all the analyzes the level of statistical significance is considered with a minimum probability of 95% ($p<0.05$).

4 . ETHICAL AND LEGAL ASPECTS

The study will be governed by the basic ethical principles contained in the Declaration of Helsinki (*WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI. Ethical principles For Medical Research Involving Human Subjects . Adopted by the 18th WMA General Assembly Helsinki, Finland , June 1964 and amended by the 29th WMA General Assembly , Tokyo , Japan , October 1975; 35th WMA General Assembly , Venice , Italy , October 1983; 41st WMA General Assembly , Hong Kong, September 1989; 48th WMA General Assembly , Somerset West, Republic of South Africa , October 1996 and; the 52nd WMA General Assembly , Edinburgh, Scotland, October 2000 and note of clarification on paragraph 29 added by the WMA General Assembly , Washington 2002* and its amendments of 2004, 2008 and 2013), in the Guide to Good Clinical Practices in Human Health Research, in LAW 14/2007, of July 3, on Biomedical Research, published in BOE No. 159 of Wednesday, July 4, 2007, in the Agreement for the Protection of Human Rights and the D dignity of the Human Being with respect to the Applications of Biology and Medicine, drawn up in Oviedo on April 4, 1997 and signed on July 23, 1999, and accepted by the Biomedical Research Law 14/2007. In accordance with said agreement, the data obtained will never be used for profit (article 21) and may not be used for a purpose other than that for which it is reported in this document (article 22).

4.1. CONFIDENTIALITY OF THE DATA.

The highest levels of professional conduct and confidentiality will always be maintained and the current national legislation on data protection of 2018 will be complied with (General Data Protection Regulation -RGPD- and Organic Law Organic Law on Data Protection and Guarantee of Digital Rights - LO 3/2018 PD and GDD-). Only those data from the clinical history that are related to the study will be subject to verification. The patients' right to confidentiality will be respected. For this, the information of the study subjects will be dissociated using codes. Access to your personal information will be restricted to the study doctor and his collaborators, health authorities and Research Ethics Committee, who will be subject to the duty of secrecy inherent to their profession, when necessary, to verify the study data and procedures, but always maintaining their confidentiality in accordance with current legislation . The identity of the patients will be coded in the documents used for the study data collection by means of a number that will be used (obviously omitting the name and/or other affiliation data that could identify the patient) and only duly authorized personnel will have access to the identifiable personal data when the data verification procedures require inspection of that information . Personal details that could identify the patient will always be kept confidential.

In compliance with current regulations, approval will be obtained from the Hospital's Clinical Research Ethics Committee, so that your rights and level of care are always guaranteed.

4.2. INFORMED CONSENT.

All patients who are going to undergo a laparoscopic myomectomy will be offered the possibility of participating in the study and if they accept, the relevant consent to the surgery will be delivered, approved by the SEGO Ethics Committee, which refers to the myomectomy procedure; an information sheet and a specific consent that has been designed exclusively for this study and which is attached in annex I.

5. WORK PLAN:

5.1. **Study schedule:** from the approval of the study by the CEIC to completion of the recruitment of the established sample size. Approximately one year of time is estimated.

5.2. **Patient recruitment:** Patients will be recruited in the pre-surgical consultation, when laparoscopic myomectomy is indicated, randomizing both groups by simple random sampling. An informed consent will be delivered to the patients, who have to accept and sign in order to participate in the study. Fibroids will be quantified, measured and their location described.

5.3. **Performing the surgical act:** during the laparoscopic myomectomy, temporary occlusion of the uterine arteries will be carried out using clips in those patients who are assigned to the exposed group.

5.4. **Data collection: the pre-surgical hemoglobin determination** will be collected through the preoperative analysis and another post-surgical hemoglobin sample will be determined the day after surgery. The need for transfusion, blood loss during surgery (aspirate the blood content), surgical time, hospital stay, symptom improvement and complications will be assessed ; in addition to clinical data of the patients.

5.5. **Statistical analysis of the collected data.**

6. BIBLIOGRAPHICAL REFERENCES:

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Laparoscopic-Assisted Myomectomy with Bilateral Uterine Artery Occlusion/Ligation. J Minim Invasive Gynecol. 2018 Aug 29. pii : S1553-4650(18)30435-7. doi : 10.1016/j.jmig.2018.08.016. [Epub ahead of print] PubMed PMID: 30170179.

8: Ji L, Jin L, Hu M. Laparoscopic Myomectomy with Temporary Bilateral Uterine Artery Occlusion Compared with Traditional Surgery for Uterine Myomas: Blood Loss and Recurrence. J Minim Invasive Gynecol. 2018 Mar-Apr;25(3):434-439. doi : 10.1016/j.jmig.2017.06.032. Epub 2017 Sep 21. PubMed PMID: 28943191.

ANNEX I. INFORMED CONSENT FOR PARTICIPATION IN THE STUDY.

PATIENT INFORMATION SHEET

TITLE OF THE STUDY: "VALUE OF TEMPORARY OCCLUSION OF THE UTERINE ARTERIES IN LAPAROSCOPY MYOMECTOMY"

RESEARCHERS: Dr. Enrique Moratalla Bartolomé

CENTER: RAMÓN Y CAJAL UNIVERSITY HOSPITAL

1. INTRODUCTION

The Obstetrics and Gynecology Department of the Ramón y Cajal University Hospital is conducting a study to assess whether performing temporary occlusion of the uterine arteries and utero -ovarian ligaments during laparoscopic myomectomy reduces intraoperative bleeding from this technique and postoperative anemia.

The participant are being asked to participate in this study because The participant will be undergoing a laparoscopic myomectomy at our center. The study has been approved by the Clinical Research Ethics Committee of the Ramón y Cajal University Hospital.

Our intention is that the participant receive correct and sufficient information so that the participant can evaluate and judge whether or not the participant want to participate in this study. To do this, read this information sheet carefully and the investigators will clarify any doubts that may arise after the explanation . In addition, the participant can consult with the people you consider appropriate.

When the participant have read this information and if the participant wish to participate in the study, the participant must sign the informed consent form attached to this document in duplicate.

2.- VOLUNTARY PARTICIPATION

The participant should know that your participation in this study is voluntary and that The participant can decide not to participate or change your decision and withdraw your consent at any time, without altering your relationship with your doctor or affecting your treatment.

3.- OBJECTIVE

The aim of this study is to determine whether patients who underwent laparoscopic fibroid removal and temporary placement of a metallic mechanism (called a “clip”, which acts as a clamp on the uterine arteries and utero-ovarian ligaments, have decreased bleeding during surgery, compared to patients who underwent laparoscopic myomectomy without said clips .

4.- GENERAL DESCRIPTION OF THE STUDY

This is a study in which patients who underwent laparoscopic myomectomy with temporary placement of "clips" in the uterine arteries and utero-ovarian ligaments, which are removed at the end of the intervention, are compared with another control group of patients who underwent laparoscopic myomectomy with the traditional technique (without "clips usually performed in other centers.

5.- STUDY ACTIVITIES

If you participate in the study, the investigators will give the participant this disclosure document to keep and ask you to sign an informed consent form, a copy of which will be given to you.

6.- BENEFITS AND RISKS DERIVED FROM YOUR PARTICIPATION IN THE STUDY

The participant are not expected to benefit directly from the results of this research, although others may benefit in the future. The participant will not receive any type of compensation for your participation in this study or derived from its results.

laparoscopic myomectomy surgeries .

The risks of the intervention are those inherent to those of a myomectomy that are detailed in the informed consent for the surgery.

The information obtained from this study may be useful to the scientific community, and the results may be published and contribute to improving the possibilities of treatment.

7.- PROTECTION OF PERSONAL DATA

The treatment, communication and transfer of personal data of all participating subjects will comply with the provisions of the General Data Protection Regulation (RGPD and the Organic Law Organic Law on Data Protection and Guarantee of Digital Rights (LO 3/2018 PD and GDD) . In accordance with the provisions of the aforementioned legislation The participants can exercise the rights of access, modification, opposition and cancellation of data, limit the treatment of data that is incorrect, request a copy or that the data that the participants have provided for the study be transferred to a third party (portability). To exercise your rights, contact the principal investigator of the study ".

The data collected for the study will be identified by a code and only your study doctor/collaborators will be able to associate said data with the participants and your medical history.

Since May 25, 2018, the new legislation in the European Union on personal data is fully applicable, specifically Regulation 2016/679 of the European Parliament and of the Council of April 27, 2016 on data protection .

Both the Center and the Researcher are responsible for the processing of your data and undertake to comply with current data protection regulations.

April 27, General Data Protection and will be used only for the aforementioned research purposes .

Only the data collected for the study will be transmitted to third parties, which in no case will contain information that can directly identify the participants, such as name and surname, initials, address, social security number, etc.

their confidentiality in accordance with current legislation .

8.-ECONOMIC COMPENSATION

The investigators inform the participants that no fees are expected to be paid to the participants for participation in the study or to the researchers.

9.- CONTACT IN CASE OF DOUBTS

If during your participation the participants have any questions or need more information , please contact:

Dr. Enrique Moratalla Bartolomé, telephone 913368105. Gynecology Service Ramón y Cajal University Hospital.

10.- OBTAINING AND USE OF BIOLOGICAL SAMPLES

The study samples (fibroids will be identified and sent to the Pathological Anatomy Service for diagnosis, being informed of the result at the post-surgery medical visit , but they will not be used for the purposes of the biomedical research of this study. The confidentiality of the treatment of your samples and associated data will be maintained at the level of protection indicated by the laws in force in our country (Organic Law 3/2018, of December 5, Protection of Personal Data and guarantee of digital rights and Regulation (EU 2016/679, of April 27, General Data Protection and the terms set forth in Law 14/2007 of Biomedical Research will be complied with .

OTHER RELEVANT INFORMATION

If the participants decide to withdraw consent to participate in this study, no new data will be added to the database.

By signing the attached consent form, the participants agree to abide by the study procedures that have been disclosed to the participants.

INFORMED CONSENT

TITLE OF THE STUDY: "VALUE OF TEMPORARY OCCLUSION OF THE UTERINE ARTERIES IN LAPAROSCOPY MYOMECTOMY"

I, Mrs ,… ……, with address at ..... and ID number..... I declare that

I have read the information sheet that was given to me.

I have been able to ask questions about the study.

I have received enough information about the study.

I have been informed by:

....

Dr. Enrique Moratalla Bartolomé

I hereby consent to participate in the aforementioned study.

I understand that my participation is voluntary.

I understand that I can withdraw from the study:

1º Voluntarily whenever I want.

2º Without having to give explanations.

3º Without this affecting my medical care.

I freely give my consent to participate in the study and give my consent for the access and use of my data under the conditions detailed in the information sheet.

Patient Signature :

Investigator Signature :

Name :

Name : Enrique Moratalla Bartolomé.

Date :

Date :

This document is signed in duplicate, keeping one copy for the researcher and the other for the patient.