Study Protocol

OFFICIAL TITLE OF THE STUDY: HYSTEROSCOPY ANESTHESIA FOR RELIEF OF PAIN (HARP)

NCT NUMBER: NOT YET ASSIGNED

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CONTENT

HARP Assay: Hysteroscopy Anesthesia for Relief of Pain

Introduction

Ambulatory hysteroscopy is a diagnostic technique commonly used in gynecology for the evaluation of the female reproductive tract, especially for the detection and treatment of intrauterine pathology. Although generally well tolerated, the management of pain associated with this procedure remains a relevant concern for many patients. Proper pain control is critical to improving the patient experience, reducing anxiety, and avoiding complications related to discomfort during the procedure. Pain, among other factors, is precisely one of the main reasons for failure of the procedure (Pascual Pedreño et al., 2021).

Justification of the relevance of the study.

In recent years, several studies have addressed pain control in hysteroscopy, many of which have explored the use of local anesthesia to relieve pain during the intervention (Nowak et al., 2024). However, despite systematic reviews and meta-analyses on the effectiveness of these interventions, evidence in this field remains limited and scattered, especially with regard to well-designed, controlled clinical trials (Ahmad et al., 2017). For example, although some studies have shown that intracervical anesthesia significantly reduces pain during hysteroscopy, heterogeneity in pain assessment methods, the type of anesthesia used, and patient characteristics make it difficult to generalize the results (Cooper et al., 2010; De Silva et al., 2020).

In addition, Cochrane reviews show that there is a lack of sufficient evidence to show that different anaesthesia modalities have significantly different effects or whether anaesthesia is actually beneficial in all cases (Cochrane, 2020). The 2021 clinical practice guideline of the Spanish Society of Gynecology and Obstetrics (SEGO) recommends the use of anesthesia only when hysteroscopes larger than 5 mm are used, with a low quality of evidence. In this same document, it is highlighted that, although the differences found in other studies are statistically significant, they do not seem to be clinically relevant for the reduction of pain during the procedure or at 30 minutes post-procedure, since the differences are small and do not reduce the number of vagal symptoms (Pascual Pedreño et al., 2021). These differences are more significant in postmenopausal women, highlighting the need for a higher-quality randomized clinical trial that provides strong evidence on the benefits of pain management during hysteroscopy.
Some national surveys, such as the one conducted by Huang et al. (2023), reveal that only slightly more than half of hysteroscopies are performed under anesthesia, underscoring the disparity in clinical practice globally. In neighbouring countries, several authors have already pointed out this variability in the application of anaesthesia and suggest the need to establish clear recommendations through national and international guidelines (De Silva et al., 2020).

Although some previous studies have identified a moderate reduction in pain with local anaesthesia, the biases inherent in many of these studies, such as lack of masking, non-randomised design, or variability in anaesthesia techniques, limit the validity of their conclusions. These biases can lead to an overestimation of treatment effects, highlighting the importance of a well-designed, blinded clinical trial for more reliable results. In addition, pain is a subjective phenomenon influenced by psychological factors, such as anxiety, previous experience of pain, or the patient's expectations, which increases the complexity of its assessment. Without proper control for these factors, studies can be affected by expectation bias or measurement bias.

Ambulatory hysteroscopy is proposed as a cost-effective technique compared to that performed in the operating room, however, the discomfort and poor tolerability of the test affects a non-negligible number of patients, who, due to pain, require it to be performed under sedation in the operating room (Smith et al., 2021). This fact highlights the urgent need to improve the experience of patients in outpatient procedures through more effective pain management techniques.

Importance of a well-designed clinical trial.

A well-designed randomized clinical trial has the ability to reduce biases and provide more robust evidence on the efficacy of interventions, such as anesthesia, in reducing pain during hysteroscopy. In this sense, the study design should include a representative sample of patients, a standardized method of pain assessment (such as the VAS scale), and strict control of confounding variables that may influence pain perception, such as the professional's experience, previous anxiety, and the type of intervention.

Through a more rigorous design, the study will also be able to identify predictors of pain and contribute to the development of evidence-based recommendations for pain management in hysteroscopy. This evidence is critical, as it not only improves the quality of the procedure, but also has the potential to optimize the patient experience, improving treatment adherence and reducing the need for general anesthesia.

In addition, variables that will give rise to new hypotheses will be included, such as the "indication of surgical hysteroscopy for pain". Knowledge of this data will allow later, according to the results obtained in the trial and after analysing the costs per procedure, to carry out new cost-effectiveness studies and assess whether anaesthesia can really be an efficient strategy in the face of non-application of anaesthesia.

For all these reasons, this study is of great relevance for the field of gynecology and ambulatory surgery, since it will specifically address the gaps in the existing literature on pain management during hysteroscopy, strengthening the quality of the evidence in this field. This is essential to improve clinical practice, offering a solid basis for decision-making in pain management in outpatient gynecological procedures.

Objectives of the study

The aim of the study is to demonstrate whether locoregional anaesthesia has an impact on the pain perception of patients who undergo ambulatory hysteroscopy, i.e. to demonstrate whether there are significant differences in pain perception in patients who undergo such anaesthesia and those who do not.

H0: Half pain (VAS) analgesia = half pain (VAS) without analgesia

As secondary objectives, if differences are demonstrated, we will try to show which variables interfere with the patient's pain through a logistic regression analysis.

Possible limitations

The anesthesia used in this study involves the administration of injections into the uterosacral ligaments, which makes masking difficult for the patient, as she is likely to be aware of such an intervention. A double-blind design is not possible, as the doctor administering the anaesthesia knows whether or not he is administering it. In addition, in a single-blind placebo design (such as saline), there may be difficulties in masking the procedure, as the simple sensation of the injection could influence the patient's perception of pain. Therefore, irrigation of the vagina and cervix with saline solution of saline solution will be proposed, simulating the application of local anesthesia, without injecting it.

The fact that the study does not employ a blinded design, either for the patient or for the physician, introduces certain limitations and potential biases. However, some of these biases are controllable and can be minimized with specific measures. For all these reasons, biases associated with the lack of masking can be incurred. These biases that need to be addressed are the ones mentioned below

Expectation Bias (Placebo/Nocebo Effect):

If the patient knows that she has received anesthesia, she may underestimate her pain, believing that the medication will relieve the symptoms.

- If the patient knows that she has not received anesthesia, she may overestimate her pain due to anticipation.

Observer Bias:

If the doctor in charge of assessing pain knows the group to which the patient belongs (anesthesia or non-anesthesia), he could subtly influence how he collects the data (for example, by showing greater empathy or being less rigorous in control).

Selection Bias:

If randomization is not performed strictly, inhomogeneous patient selection may occur, which would affect the validity of the results.

Other Limitations:

Variability in pain perception

Pain is a subjective experience, influenced by psychological, emotional, and physical factors. Individual variability in pain perception can introduce difficulties in standardizing results. Factors such as anxiety, pain history, patient expectations, and personal tolerance can significantly influence the perception of pain during the procedure.

Clinical and technical factors:

The experience and skill of the practitioner performing the hysteroscopy can influence the pain levels experienced by the patient. The technique used, the selection of equipment (e.g., the type of hysteroscope used), and the duration of the procedure may also be factors affecting the experience of pain, making it difficult to generalize the results.

Limitations in the control of external variables:

Although attempts will be made to control for factors that may influence pain (such as anxiety and the practitioner's level of experience), it is not possible to guarantee that all external variables will remain constant throughout the study. This could lead to variability in the results.

Limited sample size:

Depending on the number of patients available to participate in the study, the sample size may not be large enough to detect significant differences between groups, which may limit the statistical validity of the results.

Protocol compliance:

Although participants and practitioners will be instructed on the study protocol, there may be variability in adherence to the study, especially in data collection or implementation of interventions, which could introduce additional biases.

Given the above, it has been decided to carry out the clinical trial without blinding. However, strict variables that may influence the perception of pain should be established and should be carefully collected and controlled during the study to minimize biases as much as possible.

Selected variables

The following variables are proposed to control for those factors that could influence pain perception during the procedure or that could be useful for further subgroup analysis. In addition, some variables are included to ensure the security of the procedure and the confidentiality of the data.

Patient variables

- **ID:** Identification number of the patient in the study (Type of variable: Nominal qualitative) - Allows the pseudonymization of the data.
- **Age** (Variable Type: Continuous Quantitative) - The age of the patient, as it can influence the perception of pain.
- **Allergies** (Variable Type: Nominal Qualitative) - All allergies relevant to the procedure will be recorded.
- **Position of the uterus** (Type of variable: Nominal qualitative) - Anteversion / Retroversion / Indifferent.
- **BMI** (Variable Type: Continuous Quantitative) **–** May have some relevance to the overall pain associated with the procedure, e.g. when placing the speculum.
- **Parity** (Variable Type: Discrete Quantitative) - Number of previous vaginal deliveries, as it can influence cervical dilation and pain during the procedure.
- **Previous interventions on the uterus** (Type of variable: Nominal qualitative) - Includes cesarean sections, curettages, myomectomies, among others.
- **Previous interventions on the cervix** (Type of variable: Nominal qualitative) - Includes conization, curettage, biopsy with diathermy loop, among others.
- **Age of menopause** (Variable type: Continuous quantitative) - Menopause could influence pain tolerance due to hormonal changes.
  Taking oral contraceptives (OCC) (Type of variable: Qualitative dichotomous) - Yes/No. The use of hormonal contraceptives can affect endometrial thickness and uterine sensitivity.
- **Time of the cycle** (Type of variable: Nominal qualitative) - First phase / Second phase / Menstrual.

- **Body Mass Index (BMI)** (Variable Type: Continuous Quantitative) - Obesity is associated with increased systemic inflammation, which may increase the perception of pain.
- **Previous dysmenorrhea** (Type of variable: Qualitative dichotomous) - Yes/No. Patients with a history of painful periods may experience increased pain during hysteroscopy.
- **Polycystic ovary syndrome (PCOS)** (Variable type: Qualitative dichotomous) - Yes/No. Associated with increased cervical resistance, which could make the procedure more difficult and increase pain.
- **Anxiety or fear of the procedure** (Variable type: Ordinal qualitative) - Will be assessed using the STAI Anxiety Scale (State-Trait Anxiety Inventory) before the procedure.
- **Taking chronic pain mediation may** influence outcomes

Procedure variables

- **Physician who performs the test** (Type of variable: Nominal qualitative) - The professional who carries out the procedure.
- **Degree of experience of the physician** (Type of variable: Ordinal qualitative):
    - Low: 5-20 procedures performed.
    - Normal: 20-50 procedures performed.
    - Discharge: >50 procedures performed.
- **Test Duration** (Variable Type: Continuous Quantitative) – The total time of the procedure, which could correlate with the pain experienced.
- **Use of the outer sheath (return)** (Dichotomous qualitative: Yes/No)
- **Bipolar energy use** (Variable type: Qualitative dichotomous) - Yes/No. The use of bipolar energy could influence pain due to the impact on the tissues.
- **Number of polyps removed** (Variable Type: Discrete Quantitative) - 1, 2 or >2. The number of polyps could affect the level of pain due to time and additional manipulation.
- **Number of biopsies taken** (Variable Type: Discrete Quantitative) - 1, 2 or >2. More biopsies may increase discomfort during and after the procedure.
- **Type of endometrial pattern** (Type of variable: Nominal qualitative) - Atrophy, proliferative, menstrual or secretory. Different endometrial patterns can influence pain perception.
- **Number of Cavity Entries** (Variable Type: Discrete Quantitative) - The number of times the hysteroscope needs to be inserted into the uterine cavity may be influence in the pain.
- **Insertion technique** (Variable type: Nominal qualitative) - Direct entry vs. with speculum and forceps. Insertion techniques could have different implications on perceived pain.

Variables of post-procedure pain

- **VAS** Scale (Visual Analog Scale) (Type of variable: Continuous quantitative) - Range 0-10. To measure the intensity of the pain experienced by the patient.
- **Need for post-procedure analgesia** (Type of variable: Qualitative dichotomous) - Yes/No. And **type of pain reliever used**.
- **Size of the speculum Used** (Type of variable: qualitative) (Small/medium/large). May influence the overall pain of the procedure
- **Complications** (Type of variable: Qualitative dichotomous) - Yes/No. Complications that occur during or after the procedure will be recorded.
- **Complication Type** (Variable Type: Open-Label Qualitative) - Details about the nature of the complication (if any).
- **Indication for surgical hysteroscopy due to pain** (Type of variable: Qualitative dichotomous) - Yes/No. If additional surgical intervention is required after hysteroscopy.

In addition, the patient's medical and personal history, as well as allergies, will be collected in the Medical Record to determine if there are contraindications to the procedure. All previously established inclusion and exclusion criteria will also be explored.

Sample size calculation

Variables used in the calculation.

Primary study endpoint: Pain measured using the VAS scale (0-10).

Since we compared two groups (with anesthesia vs. without anesthesia) on a continuous quantitative variable (VAS), we will use a Student's t-test for independent samples (or Mann-Whitney U if the distribution is not normal).

Clinically Relevant Difference:

- In previous studies, a reduction of at least 1.3 - 1.5 points in VAS has been considered to be clinically meaningful in gynecological procedures. Proposal: Establish an expected difference of 1.5 points in the VAS.

Standard deviation of pain in hysteroscopy without anesthesia:

- According to previous studies, the standard deviation of pain ranges from 1.8 to 2.5 points in VAS.
  Proposal: Use a standard deviation (σ) of 2.0 for the calculation.

Level of significance:

It is set at 5% (0.05), which implies a probability of type I error of 5% (rejecting the null hypothesis when it is true).

Statistical power:

The statistical power is set at 80% (0.8), which implies a 20% probability of type II error (not detecting a real difference).

Final Estimate

To calculate the sample size in a clinical trial comparing pain in two groups (with and without anesthesia), we used the formula to compare two independent means. The effect size (Cohen's d) is obtained by dividing the clinically relevant difference by the standard deviation, obtaining a moderate-high effect size according to Cohen's classification.

Using a t-test for two independent samples, the sample size that provides the desired power is sought. When the information is entered into sample size calculation software, the result is a sample size of 29 patients per group. This means that the study will need a total of **58 patients**.

If follow-up losses are anticipated, it is recommended to increase the sample size by 10-20%. Therefore, it would be advisable to include between **64 and 70 patients** in total to ensure adequate statistical power.

Selection criteria

A series of criteria are established to select or reject patients.

Inclusion Criteria:

- **Age ≥ 18**: To ensure that participants are adults and consent in an informed manner.
- **Indication for diagnostic hysteroscopy** in the office: The patient must be scheduled for a diagnostic hysteroscopy procedure, either for evaluation of the uterine cavity or diagnosis of pathologies.
- Simple procedures `or` **polypectomies of 1, 2 or more than 3 polyps.** Patients requiring uterine polypectomies of different sizes (1, 2 or more than 3 polyps) will be included, which will allow the response to pain to be compared depending on the extent of the intervention.

`or` Realization of **biopsy**: Patients who need an endometrial biopsy during the Hysteroscopy also Be Including.

These two variables account for the vast majority of procedures performed in the clinic.

- **Not having performed previous hysteroscopies**: To minimize the bias derived from familiarity with the procedure and its sensations, patients who have had a previous hysteroscopy will be excluded. This will help to assess pain in a more *naïve population* with respect to technique.

Exclusion Criteria:

- **Age < 18 years:** Underage patients will not be included, as valid and adequate informed consent cannot be obtained.
- **Known allergy to some type of local anesthetic**: Patients with a history of allergies or serious adverse reactions to local anesthetics will be excluded to avoid risks related to drug administration.
- **General contraindications to hysteroscopy:** Pregnancy (the status of 'non-pregnancy' is established in a surrogate manner by the interview with the patient and according to her FUR, menstrual frequency or sexual intercourse in the last month or objectively by prescribing ACHO from the indication of the test or performing a pregnancy test before it), active infection (pyometra or history of recent pelvic inflammatory disease or suggestive symptoms), recent uterine perforation, etc.
- **Complex procedures**:
    - Morcellator myomectomies: More complex surgical procedures, such as morcellator myomectomy, are excluded because of their level of invasion and difficulty, which could interfere with the isolated assessment of anesthesia-associated pain.
    - Failure to access the uterine cavity: If adequate access to the uterine cavity is not achieved, the procedure is considered incomplete and the patient will be excluded from the study.
- **Situations that prevent access to the cavity**: Patients in whom hysteroscopy is failed, with cervical stenosis or other anatomical defects that completely prevent adequate access to the uterine cavity will be excluded.
- **Long interventions with a large fluid passage or water balance above 1000 cc:** In these cases the patient may experience additional pain due to other circumstances unrelated to the routine procedure.
- **Known uterine malformations**: Patients with uterine malformations (such as septate, unicornuate, or bicornuate uterus) will be excluded, as this could complicate access and interpretation of results, as well as affect pain tolerance during hysteroscopy.
- **Waiting times longer than 60 minutes**: It has been associated with an increase in pain according to the SEGO guideline for ambulatory hysteroscopy.
  Taking analgesic medication before the test: Taking medication before the test may alter the results.
- **Major complication associated with the intervention**: Uterine perforation, creation of false pathway or false endocervical pathway or intense bleeding (expressed as hemorrhage that requires additional maneuvers than usual for resolution).
- **Failure to provide adequate informed consent in consultation** or the anxiety assessment scale prior to the procedure.

Justification of the Criteria

1. **Age and informed consent:** Ensures that all participants are adults and capable of providing informed consent in a conscious and voluntary manner.
2. **Indications for hysteroscopy**: By selecting patients with relatively common diagnostic and therapeutic indications, it is ensured that the study is representative of the general population undergoing this procedure.
3. **Absence of prior hysteroscopies**: Excluding patients with previous experience minimizes biases related to advance knowledge of the test and its possible painful sensations.
4. **Complex procedures and uterine malformations**: Excluding cases of high complexity or anatomical complications allows the study to focus on routine diagnostic procedures with less variability in terms of technique and pain tolerance.
5. **Taking medication before the test or taking chronic pain medication**: Taking medication can alter the results.

With these well-established inclusion and exclusion criteria, it is ensured that the study focuses on a homogeneous population, with a controlled level of risk and without factors that may excessively interfere with pain measurement and the effectiveness of local anesthesia. These criteria also help to improve the internal validity of the study, minimising potential biases that could affect the results.

Explanation of Proof and Delivery of Informed Consent

Informed consent is a crucial component of ensuring that participants understand the procedures, risks, and benefits of participating in the study. The detailed procedure for the delivery and explanation of informed consent in the context of this study is described below.

Delivery of Informed Consent:

Aspects Legal and Ethical

In accordance with current legal regulations, informed consent must be provided in writing, guaranteeing that the patient has understood all the implications of the study and has voluntarily given her consent to participate.

It is important for the patient to know that she will be able to withdraw at any time during the study without affecting her medical care or future treatment.

Summary of the Consent Delivery Procedure:

1. Delivery and signature of the informed consent at the time of indication of the hysteroscopy.
2. Explanation of the study and requirement of your signature for inclusion in the study, if the patient agrees to participate.
3. Simple 1:1 randomization of patients using the random system proposed in the protocol. The patient's CH should be noted for the group to which she belongs.
4. Explanation of the procedure again on the day of the intervention, ensuring that it is not mentioned if anesthesia will be used to avoid bias in the evaluation of pain.
5. Collection of the signed consent in consultation, before the intervention, to confirm participation

This procedure ensures that all ethical and legal regulations are complied with, and that the study is conducted in a controlled manner, with minimal risk of bias, ensuring data integrity and the well-being of participating patients.

Time of delivery:

The informed consent will be given to the patient at the time when the diagnostic hysteroscopy is indicated, that is, when it is decided that the patient will undergo this procedure in consultation.

The patient will receive written consent and will be given the necessary time to read it carefully, resolve any doubts with the medical staff and reflect on her participation in the study.

It will also be explained that the signing of consent is a prerequisite for the procedure and that participation in the study is voluntary, and can be withdrawn at any time without affecting your medical treatment.

Content of informed consent:

Informed consent should detail all relevant aspects of the study, including:

- The standard procedure for diagnostic hysteroscopy.
  Possible risks and benefits of the intervention.
- Description of the local anaesthesia to be administered in the relevant group, and the option of no anaesthesia in the control group and **a placebo instead**. It is important to mention this because the patient who does not receive anesthesia must wait for an intervention, otherwise, she could know that nothing is being administered.
- Confidentiality of the data and the conditions under which they will be used.
- Information about randomization in the study (whether or not anesthesia will be used), and that this decision will be made randomly.
- Delivery of the **STAI (State-Trait Anxiety Inventory) questionnaire,** which the patient must complete before the procedure.

As an important note: **The professional in charge of delivering the information should try to influence the patient's expectations as little as possible, transmitting the information clearly, but avoiding both minimizing her possible fears and inducing them unnecessarily.** That is, when explaining the procedure and the objective of the trial, it should be emphasized that there is no solid evidence that anesthesia is useful in this procedure and that, in fact, its use is not routinely standardized and that in many patients it is not administered. In addition, it will be emphasized that the objective is to demonstrate whether this practice, which can also be uncomfortable for the patient, could be avoided. They should be reassured, resolve their doubts and explain that most patients tolerate this procedure without anesthesia, however, they should not dwell too much on this aspect to minimize knowledge bias, since many patients forget irrelevant information when the day of the intervention arrives. In this way, the inherent fear that any patient has of a procedure that is painful before it is partially counteracted.

Consent collection in hysteroscopy consultation:

On the day of the intervention, the patient will deliver the signed informed consent, which was previously provided and explained.

The explanation of the procedure will be reiterated, including details about what will occur during the diagnostic hysteroscopy, but **without mentioning whether or not anesthesia will be used**. This is essential to avoid biases in the perception of pain, which could be influenced by prior knowledge of the intervention.

It will be ensured that the patient understands that consent has already been provided and that this is an additional step in the information process. The patient will be able to ask questions or express any concerns at this time.

If the patient asks if she will be given anesthesia, as it is a blinded trial, it is included in the document of the patient's participation in the trial, that the doctor may refrain from communicating to her which treatment group she is in, therefore, it is especially important that this group is hidden. However, again, an attempt will be made to reassure the patient, explaining that the procedure is usually well tolerated with and without anesthesia and that, in addition, routinely, the use of anesthesia may or may not be applied equally according to the criteria of the doctor performing the test, as there is no firm recommendation on its use. To further minimize bias, all patients will be fitted with the speculum to perform a correct vaginal and cervical examination and will be irrigated with saline solution in the control group as explained in the protocol.

Minimization of Biases by Prior Knowledge of the Intervention:

The process described also helps to minimize biases that could arise due to the expectation or advance knowledge about the application of anesthesia. Even if the patient has previously signed the informed consent, it is important to consider that a high percentage of patients do not read the entire content of the consent in detail or do not remember all the aspects mentioned, especially the part referring to anesthesia. This simulates a masking in the study, in which the patient does not know if she will be given anesthesia, which allows the perception of pain to be more objectively assessed without the expectation of treatment influencing her experience.

Even if the test has been verbally explained in the consultation, the patient may not remember all the details related to anesthesia on the day of the intervention. This approach ensures that the perception of pain in each group (with or without anesthesia) is not affected by the patient's mental or emotional predisposition to know the treatment in advance. Therefore, biases related to expectation are reduced, which improves the quality of the data obtained.

Patient Randomization

Randomization Method

For the assignment of the patient to the groups (with anesthesia or without anesthesia), a simple 1:1 randomization method will be used, which means that each patient has a 50% chance of being assigned to each group.

A completely random and reliable system will be used for patient allocation. https://www.random.org/ , which allows you to generate assignments without bias.

A random number (between 1 and 100) will be assigned to each patient, and it will be established that the odd numbers correspond to the group with anesthesia (**Group A**) and the even numbers to the group without anesthesia (**Group B**). **It will be noted in the Clinical Judgment**.

Alternatively, a system of opaque bags with numbered papers can be used to perform randomization directly in the office, in case you prefer not to use software. (But preferably you should use the software if you can)

Randomization process

Randomization will be carried out at the time the patient presents for the intervention (in consultation, when the indication is made), after she has read and signed the informed consent. At this time, you will be randomly assigned to one of two groups (under or without anesthesia) using the system previously described.

The inclusion of the patient's procedure in the trial will be recorded by writing the name in the Clinical Judgment along with the group to which she belongs according to the randomization process. The patient will also be given the specific document of inclusion in the trial to sign after explaining what it consists of

and give him consent for the test. The documents will be sent for consultation according to the usual channels after filling in the surgical demand register appropriately as it is standardized in the unit.

Patients excluded from the study:

If a patient, after being included, is subsequently rejected from participating, any data related to her will be removed from the clinical trial.

The reason for exclusion will be recorded for further analysis.

Standardization of the Procedure

To ensure the homogeneity and reproducibility of the procedures performed in the study, a detailed protocol has been established for the performance of diagnostic hysteroscopies. This protocol ensures that each intervention is performed under the same conditions, minimizing variations that may influence the results and the evaluation of the pain perceived by the patients.

1. Equipment Used

- Ultrasound with transvaginal probe: To evaluate the patient's anatomy before the test and detect possible post-procedure complications.
- Hysteroscope: A 5 mm 30º Betochi diagnostic hysteroscope will be used. **If the return pod applies, it must be specified**.
- Distension medium: 0.9% saline solution will be used to ensure adequate visualization during the intervention.
- Irrigation pressure: It will be maintained between 100-120 mmHg to ensure correct distension of the uterine cavity without compromising patient safety.

2. Hysteroscopy

The procedure will be carried out following a series of standardized steps to ensure its effectiveness and safety.

As a previous step, **in the control group**, the speculum will be placed to assess the vagina and cervix and **the vagina and cervix will be irrigated with a syringe, using 0.9% saline solution, up to 4 times, in the same way as if we applied the local anaesthetic**.

Step 1: Application of Local Anesthesia (if applicable)

Objective**: This protocol aims to ensure the correct and standardized administration of** 3% Mepivacaine for local anesthesia of the uterosacral ligaments in patients undergoing outpatient hysteroscopy, with the aim of evaluating its effect on pain management during the procedure.

1. Drug to be used: 3% mepivacaine (4 vials of 3 ml each).

2. Equipment Needed

- 4 vials of 1.7 ml 3% Mepivacaine.

- Carpule needle (length: 25 mm, gauge: 27).
- Toiletries (sterile gloves, antiseptic, sterile gauze).
- Basic monitoring (pulse oximeter for vital signs control if necessary).

3. Application technique

3.1. Patient Preparation

- Gynecological position: The patient should be placed in a gynecological position **(dorsal lithotomy)** on the examination table.
- Vaginal and perineal hygiene: **Antisepsis is not required due to the minimal risk of infection at the site of the anesthetic puncture**
- Clinical evaluation: A rapid review of the patient's general condition will be carried out to confirm the suitability of local anesthesia.

3.2. Anesthesia Injection

- The uterosacral ligaments **are** identified through **the posterior region of the** cervix**, on both sides**. 2 vials (3.4 ml) of 3% Mepivacaine will be injected into each uterosacral ligament, using a 25 mm Carpule needle.
- The needle should be inserted approximately 2-3 mm deep at each injection site.
- Infiltration should be carried out slowly, to avoid rapid dispersion of the anesthetic and to ensure its appropriate local action.

3.3. Post-Injection Monitoring

- At least 1 minute after injection should be allowed before starting hysteroscopy to ensure the effect of the anaesthetic.
- In case of persistent severe pain, additional measures may be considered, such as a new administration of anesthetic or complementary sedation, if indicated and approved.

Step 2: Entry by Vaginoscopy

The procedure will be initiated by vaginoscopy, ensuring clear visual access to the intervention area.

The insertion of the hysteroscope into the cervical canal will be performed at least 1 minute after the application of the local anesthesia.

Step 3: Insertion into the Endocervical Canal

The hysteroscope will be carefully inserted into the endocervical canal, using the minimum of maneuvers necessary to reduce the patient's discomfort.

Step 4: Uterine Cavity Access

Once the endocervical canal has been passed, the uterine cavity will be entered.

Adequate distension of the uterine cavity and a clear visualization for examination should be ensured, and the two tubal ostiums may be correctly described.

Step 5: Inspection of the Uterine Cavity and Tubal Ostium

A thorough inspection of the uterine cavity will be carried out, observing possible signs of pathology.

The tubal ostia will be examined for possible blockages or abnormalities in the fallopian tubes.

Step 6: Resolution of Benign Pathology (if applicable)

If polyps or other benign lesions are identified, the following shall be done:

- Polypectomy: Versapoint forceps (bipolar system) or flexible scissors will be used for polyp removal.
- Biopsies: Endometrial samples will be obtained with the most appropriate technique to minimize discomfort.

Step 7: Hysteroscope Removal

Once the examination or intervention is finished, the hysteroscope will be removed.

The procedure must be performed within a standard time range, avoiding unnecessary prolongation.

The duration of the test will be recorded as a variable within the study.

3. Postoperative

After the hysteroscope is removed, the patient will be informed of possible side effects and provided with post-operative instructions.

If the patient experiences unusual pain or symptoms, pain medication will be administered as needed and followed up prior to discharge.

4. Data Monitoring and Logging

During and after the procedure, vital signs and any discomfort expressed by the patient will be recorded.

During this time, a pain assessment will be performed **using a VAS scale (0-10).** The scale will be explained to the patient beforehand.

All data will be collected at the time of the consultation, after the test has been carried out. **Failure to collect the data at this time will result in a null value in bliss category**

This standardized protocol ensures that all hysteroscopies are performed under the same conditions, controlling for factors that could influence pain perception, such as the type

of equipment, technique used, and manipulation of the uterus. In addition, it allows the results to be comparable and reproducible, maximizing the validity and reliability of the study.

Data collection and analysis in the study

1. Data Collection

Data collection will be carried out on the same day of the intervention in the hysteroscopy consultation, using a predefined Excel sheet.

Data collection personnel should have carefully read the study protocol before performing any study-related tasks.

The professionals responsible for prescribing the test should be fully familiar with the study protocol and conditions before referring patients for participation.

3. Data Analysis

The data collected will be analysed using SPSS software or handed over to an external team specialised in biostatistics.

The analysis will be carried out according to the following criteria:

3.1. Analysis by Protocol

Only those patients who complete the study after having reached the necessary sample size will be included.

Incomplete or non-compliant data will be excluded from the analysis.

3.2. Analysis by Subgroups

Additional factors that may influence the variability of the pain experienced will be evaluated, such as:

Age

Parity

Type of pathology treated

Other relevant factors

This analysis will allow us to identify possible subgroups with significant differences in the results.

3.3. Descriptive Analysis

A descriptive analysis of the groups will be carried out to assess their homogeneity and ensure that the baseline characteristics of the participants do not introduce significant biases into the results.

3.4. Masking of the Principal Investigator and the Statistician

The principal investigator and the person in charge of the statistical analysis will not have access to the identification data or the assignment of the groups until after the analysis is completed.

This ensures that the analysis is conducted in an unbiased and unbiased manner, minimizing the risk of prior knowledge of the groups influencing the results.

Important annexes are detailed below, such as the protocol for action in the event of adverse effects, the conditions of study detention, the formal request to the ethics committee, the document of participation and confidentiality of the investigators and the informed consent and document of participation of the patients.

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ANNEXES

Ethical Aspects

Regulatory Framework and Ethical Approval

This study is in line with the international ethical principles established in:

- The **Declaration of Helsinki** (most recent version) of the World Medical Association (WMA).
- The **Oviedo Convention** on Human Rights and Biomedicine.
- Law **14/2007, of 3 July, on Biomedical Research**, which regulates the ethical and legal requirements for research with human beings in Spain, guaranteeing the protection of the rights and safety of participants.
- **Regulation (EU) 2016/679 (GDPR)** and **Organic Law 3/2018 on the Protection of Personal Data**, ensuring confidentiality and secure processing of data.

The protocol has been evaluated and approved by the **corresponding Research Ethics Committee (CEIm),** complying with the standards required by Spanish and European regulations.

Informed Consent

- All participants will sign an **informed consent document** before their inclusion, which will detail:
    - Objectives, procedures, risks and benefits of the study. ○ Right to withdraw at any time without penalty. ○ Randomization and partial masking process (to minimize expectation biases).
    - Data protection measures and anonymization.
- It is guaranteed that the information will be provided in clear and accessible language, with an opportunity to resolve doubts.

Data Protection and Confidentiality

- Personal data will be collected under **pseudonymization**, assigning a unique code to each participant.
- The information will be stored on secure servers at the **Reina Sofía University Hospital**, with restricted access to the research team.
- The data will be retained as required by law and will be destroyed after the study is completed.

Risk Minimization

- **Risk assessment**: Possible discomfort has been identified during hysteroscopy, but the procedure is considered low risk. Local anesthesia (3% mepivacaine) follows standardized protocols for safety.
- **Protocol for action in the event of adverse effects**: Any adverse event will be recorded and managed according to clinical guidelines, with the option of withdrawing the patient from the study if necessary.

Specific Considerations

- **Non-complete blinding**: Since the design does not allow for a double-blind (due to the nature of the intervention), measures will be implemented to reduce bias (e.g., vaginal irrigation with saline solution in the control group).
- **Inclusion of vulnerable population**: Only women over 18 years of age will be included, excluding minors and people without the capacity to consent.

Conflicts of Interest and Transparency

- The researchers declare that they have no financial or professional conflicts of interest that affect the objectivity of the study.
- The results will be published independently of their findings, ensuring transparency.

Request for approval from the ethics committee

For the attention of the Ethics Committee,

We are writing to you to present the study protocol entitled: **"HARP Trial: Hysteroscopy Anesthesia for Relief of Pain".** Below, we detail the ethical commitments assumed by the researchers and the research team to ensure compliance with current ethical and legal regulations.

Conflicts of Interest

We would like to state that there are no conflicts of interest related to this study, both on the part of the principal investigator and the investigators involved. No member of the research team has any financial, commercial, or personal interests that could influence the design, development, or interpretation of the results of this study. In addition, it is ensured that any eventuality that may arise in this regard will be transparently reported to the Ethics Committee, in compliance with ethical and legal regulations.

Pseudonymization and Data Confidentiality

In order to protect the privacy and rights of the participants, it is guaranteed that all data collected during the study will be treated confidentially and anonymously. For this purpose, the participants' data will be pseudonymized using only the medical record number and an ID assigned specifically for the study. In this way, it will be ensured that patients cannot be identified directly, guaranteeing their anonymity throughout the process.

Data Processing and Security

The processing of the data will be carried out in strict compliance with current legislation on the protection of personal data (Regulation (EU) 2016/679 of the European Parliament and of the Council on the protection of natural persons with regard to the processing of personal data). The data will be stored on secure servers, which only the authorized research team will have access to. In addition, all data will be securely deleted at the end of the study, once it is no longer needed for research purposes.

Commitment to Ethics

We assure you that this study will be carried out in accordance with the fundamental ethical principles of biomedical research, in particular the principles of respect for the autonomy of the patient, beneficence, non-maleficence, and justice. Informed consent will be obtained from all participants prior to their inclusion in the study, and they will be guaranteed the possibility of withdrawing at any time without this affecting their medical care.

We remain at the disposal of the Ethics Committee to provide any additional information that may be required and we thank you in advance for your time and consideration in reviewing this protocol.

Sincerely,

Date: 02/19/2025

Signed,

JORGE GARCÍA FERNÁNDEZ
CNP: 00026955084
License No.: 141409696
Principal Investigator
Hospital Reina Sofía
Email: jorgegarcia@gmail.com
Phone: 622 595 644

Document of Contingencies and Conditions of Detention of the Study

Introduction

This document aims to establish the conditions under which the study entitled: "**HARP Trial: Hysteroscopy Anesthesia for Relief of Pain**" may be stopped. The safety and well-being of the patients are the priority at all times, as well as compliance with the ethical and scientific protocol of the study.

Conditions for the Detention of the I am a student

The study may be stopped in any of the following situations, which must be evaluated by the principal investigator and, if necessary, by the Ethics Committee:

- **Detention for Ethical or Safety Considerations**
  The study may be stopped if at any time the principal investigator, in consultation with the Ethics Committee, believes that there are ethical or safety reasons justifying the suspension of the research. This would include situations where significant risks are identified for participants, either from serious adverse effects related to the procedure or anaesthesia, or from the occurrence of unforeseen effects that endanger their health.
- **Stopping for Outcomes Justifying Changes in Clinical Practice If** demonstrable clinical differences significant enough to suggest that local anesthesia is a determining factor for pain reduction are achieved during the course of the study, the study may be stopped for the benefit of patients, implementing anesthesia in all cases as indicated by the preliminary results.
- **Detention by Noncompliance of the Protocol**
  If it is detected that the study protocol is not being followed, either by the researchers, the support team or the participants, the study may be stopped. This includes altering procedures, inadequate data collection, or not respecting established inclusion and exclusion criteria.
- **Detention by Conflict of Interests**
  If at any time a member of the research team manifests a conflict of interest that has not been previously stated or is considered to affect their objectivity and performance in the study, that researcher will be excluded from the study. In addition, any breach of protocol by any researcher, including ethical or scientific misconduct, will lead to their immediate exclusion.
- **Detention by Risks of Confidentiality**
  The study will also be stopped if any serious breach of the confidentiality of patient data is detected, either due to unauthorized access to information or improper treatment of personal data. Information security is a primary aspect in research.

- **Termination due to Resource Exhaustion**
  The study may be terminated if the available resources necessary to continue the research are depleted or if adequate material to carry out the procedures according to the previously established protocol is not available. In this case, the principal investigator and the Ethics Committee will assess the feasibility of continuing the study under the new circumstances.
- **Funding Conditions and Notification**
  The funding for this study will be provided within the Andalusian Health System, at Hospital Reina Sofía, Clinical Management Unit of Gynecology and Obstetrics. It will be ensured that both the Head of the Department and the members of the unit are informed about the conduct of the clinical trial within this unit.
- **Commitment of the Investigators**
  All investigators who wish to participate in the study must sign this document, committing themselves to comply with the study protocol, respect the ethical and legal regulations, and guarantee the confidentiality of patient data. Any breach of these commitments will result in the exclusion of the investigator from the study.

Signature of the Investigators
Below are the signatures of the investigators participating in the study, who hereby express their agreement with the terms established in this document:

Signature of the Principal Investigator:
Name: Jorge García Fernández
ID (CNP): 00026955084
License No.: 141409596
Date: 19/02/2025

Signature of the Secondary Investigators:
Name: Balbino Povedano Cañizares
License No.: CNP/CO0489/A7
Date: 19/02/2025

Signature of the Secondary Investigators:

Name: **Susana López Villegas**
License No.: 141407330
ID (CNP): 00014820913
Date: 19/02/2025

Signature of the Secondary Investigators:

Name: **Laura Nieto Pascual**
ID (CNP): 00079197903
Date: 24/02/2025

Signature of the Secondary Investigators:

Name: **Paula Caballero Reyes**
ID (CNP): 00030547522

Date: 25/02/2025

Signature of the Secondary Investigators:

Name: **Ana Ortiz Minuesa**
Head of the Department of Obstetrics and Gynecology
Hospital Universitario Reina Sofía
Date: 25/02/2025

Signature of the Secondary Investigators:

Name: **Marta Gutiérrez Grua**
ID (CNP): 00015487208
Date: 25/02/2025

Commitment to Compliance with the Study Protocol

We, the investigators responsible for the present study entitled **"HARP Trial: Hysteroscopy Anesthesia for Relief of Pain".** We undertake to carry out the research in accordance with the ethical and methodological principles established in the approved protocol.

Specific Commitments:

1. **Compliance with the Protocol:**
    - We will ensure that we strictly follow all phases of the study, including patient selection, administration of anesthesia, data collection and analysis, as well as management of adverse effects.
    - We will not make modifications to the protocol without due justification and prior authorization from the corresponding ethics committee.
2. **Data Collection and Management:**
    - We will guarantee the correct collection of the data in the predefined Excel sheet, ensuring its integrity, veracity and confidentiality.
    - We are committed to excluding patients who do not meet the study criteria from the analysis and to properly documenting the reasons for exclusion.
3. **Respect for Ethical Principles:**
    - We will ensure that all participants sign a valid informed consent, explaining in detail the objectives, benefits, and potential risks of the study. ○ We are committed to safeguarding the privacy and confidentiality of patient information, complying with current data protection regulations.
4. **Patient Safety:**
    - We will strictly follow the safety measures set out in the protocol, especially with regard to the anesthesia injection technique and the management of adverse effects. ○ We will act immediately in the event of any adverse event, guaranteeing the well-being of patients at all times.
5. **Data Analysis and Transparency:**
    - We are committed to rigorous, unbiased analysis and data collection, and in accordance with the principles of transparency and objectivity. ○ In case of delegating the analysis to an external team, we will guarantee the delivery of data anonymously and in accordance with biostatistics standards.
6. **Completion of the Study and Dissemination of Results:**
    - We are committed to completing the study within the established deadlines and to reporting the results clearly and honestly.

The findings will be disseminated in accordance with scientific standards and through appropriate means, always respecting the confidentiality of the participants.

Signed (seal, CNP, and signature):

Signature of the Principal Investigator:
Name: **Jorge García Fernández**
CNP: 00026955084
License No.: 141409696
Date: 19/02/2025

Signature of the Secondary Investigators:
Name: **Balbino Povedano Cañizares**
CNP: CO/C0489/A7
Date: 19/02/2025

Signature of the Secondary Investigators:
Name: **Marta Gutiérrez Grua**
CNP: 00015487201
Date: 25/02/2025

Signature of the Secondary Investigators:
Name: **Susana López Villegas**
License No.: 141407638
CNP: 00014820913
Date: 19/02/2025

Signature of the Secondary Investigators:
Name: **Laura Nieto Pascual**
CNP: 00079197903
Date: 24/02/2025

Signature of the Secondary Investigators:
Name: **Paula Caballero Reyes**

CNP: 00030547522
Date: 24/02/2025

Signature of the Secondary Investigators:
Name: **Ana Ortiz Minuesa**
Head of the Department of Obstetrics and Gynecology
Hospital Universitario Reina Sofía
Date: 25/02/2025

Study Inclusion and Informed Consent Document

HARP Assay: Hysteroscopy Anesthesia for Relief of Pain

Dear Patient,

We invite you to participate in a research study that aims to evaluate the effect of local anesthesia on pain during diagnostic hysteroscopy. This study is carried out in order to improve pain management in this procedure and provide scientific evidence on its effectiveness.

Your participation is completely voluntary. You can choose not to participate or withdraw at any time without affecting the quality of your health care. Below, we explain what the study consists of and the conditions of its participation.

STUDY DESCRIPTION

A diagnostic hysteroscopy will be performed in the office, a procedure that allows the uterine cavity to be examined with an instrument called a hysteroscope. In this study, some patients will receive local anesthesia and others will not, in order to compare the effectiveness of anesthesia in pain control.

The assignment to one of these two groups will be done randomly, that is, through a random selection process. It is important that you **do not know** which group you belong to, as this lack of knowledge is essential to ensure the validity of the study. Knowing whether or not you have received anesthesia could influence your perception of pain and affect the results of the study.

For this reason, if you were to know your allocation group, you should be excluded from the study, as this could alter the quality of the data obtained.

RISKS AND BENEFITS

- **Risks:** Diagnostic hysteroscopy is a safe procedure. In some cases, it can cause mild to moderate discomfort or pain. If you are in the group receiving anesthesia, you may experience partial pain relief. However, there is currently no solid evidence on the effectiveness of this anaesthesia in this procedure, so this study is essential to clarify its usefulness.

- **Benefits:** Your participation will contribute to the advancement of scientific knowledge and may help improve the care of future patients undergoing this procedure.

CONFIDENTIALITY AND DATA PROTECTION

Your personal data will be treated as strictly confidential. The information obtained will be stored in secure databases and used for research purposes only. Her identity will not be disclosed in any reports or publications derived from this study.

In accordance with Regulation (EU) 2016/679 of the European Parliament and Organic Law 3/2018 on the Protection of Personal Data and Guarantee of Digital Rights, we inform you that your personal data will be treated confidentially, pseudonymised and used exclusively for the purposes of this study. Only the authorized research team will have access to this information. You may exercise your rights of access, rectification, deletion, opposition, limitation of processing and portability of your data at any time by contacting the person in charge of the study or the data protection unit of the centre

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RIGHTS OF THE PARTICIPANT

- Your participation is voluntary and you may withdraw at any time without affecting your treatment or relationship with the medical team.
- You can request additional information about the study at any time. You can communicate any questions or concerns with the research team.

DECLARATION OF CONSENT

I have read and understood the information contained in this document. I have had the opportunity to ask questions and my doubts have been satisfactorily resolved. I understand that my participation is voluntary and that I can withdraw at any time without affecting my medical care.

I have been informed about the technique properly verbally and I have been given adequate informed consent by the professionals.

I understand that I should not know which treatment group I belong to, as this information could affect the results of the study. In case I become aware of this information, I understand that I may be excluded from the study.

I sign this document freely and voluntarily, agreeing to participate in this study.

Patient's Name: _____

Date: _____

Signature: _____

Name of the researcher responsible for inclusion:

_____

Researcher's signature: _____

REVOCATION OF CONSENT

I understand that I can revoke my consent at any time, without the need to justify my decision, and that this will not cause any harm to my medical care or my relationship with the healthcare team.

I therefore wish to withdraw my consent to participate in the study, as well as to delete the data concerning me. And for the record, I leave for the record:

Patient's Name: _____

Date: _____

Signature: _____

Name of the researcher responsible for inclusion:

_____

Researcher's signature: _____