Research Study Protocol

Title: Vapocoolant Application for Pain Reduction during Office-based Gynecologic Procedures: a Randomized Controlled Trial (VAPOR)

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3. Roles of Personnel (See Below)
4. Patient Consent Form (Separately Attached)
5. Patient Demographic Intake Form (Separately Attached)
6. Num Information - Six PDF Documents (Separately Attached)
7. Data Collection Form- Visual Analog Scale (Separately Attached)
8. Letter of Agreement (LOA) (Separately Attached)
9. Grant Application Submission to Society of Family Planning (Separately Attached)

Summary/Abstract

Study Title: Vapocoolant Application for Pain Reduction during Office-based Gynecologic Procedures: a Randomized Controlled Trial (VAPOR)

Background: Gynecologic office procedures are common and painful. For office-based procedures, providers routinely use a lidocaine injection into the cervix, known as a paracervical block, to decrease pain. However, the paracervical block itself is painful. Vapocoolant spray has been found in other specialties to decrease pain with injections, but it has not yet been investigated in gynecologic procedures. Vapocoolant spray is easy to use, rapidly acting, inexpensive (approximately 5 dollars for a single use vial) and readily available.

Objective: To determine if vapocoolant spray reduces pain associated with paracervical block.

Methods/Design: We propose a randomized, placebo-controlled, single-blinded trial among patients receiving a paracervical block. All patients will receive ibuprofen prior to the procedure per current standard of care in our clinic. Vapocoolant or placebo (sterile water) will be sprayed on the cervix prior to administering a paracervical block. Exclusion criteria includes previous use of a vapocoolant prior to an injection, use of an anxiolytic, narcotic or sedation prior to the procedure, or contraindication to receiving ibuprofen. Our primary outcome is pain at the time of the paracervical block using a 100-mm visual analog scale (VAS). Secondary outcomes include pain at tenaculum placement, pain the remainder of the procedure, patient satisfaction, provider rating of ease of vapocoolant use.

Outcomes: We hypothesize that the vapocoolant spray will decrease patients' pain at the time of the paracervical block and tenaculum placement. We hypothesize that the vapocoolant spray will have no effect on pain for the remainder of the procedure. Patients who receive the vapocoolant will have high satisfaction and providers will find it easy to use.

Sample size and population: A difference of 30% or 13-20 mm on a 100 mm pain VAS is considered clinically significant[1-3]. Based on existing research, we estimate mean pain with paracervical block to be between 54-60mm on the VAS, with a standard deviation of 25mm [1, 4, 5]. To detect a 30% difference in pain scores between the two groups with an alpha of 0.05 and 80% power and accounting for 10% participant drop-out, we will recruit 98 total participants, with 49 participants in each group.

Section 1: Background and Objections

1.1 Background and Rationale

Gynecologic office procedures like IUD insertion, endometrial biopsy and first-trimester procedural abortion are commonly done in the United States under local anesthetic. Local anesthetic is safer and less expensive than moderate sedation, particularly for these very brief procedures; however, local anesthetic may not adequately manage pain for some patients. The majority (78-97%) of patients report at least moderate pain with first trimester procedural abortion [6].

Many providers routinely use a lidocaine injection known as a paracervical block (PCB) to decrease pain with first trimester procedural abortion, and occasionally with other gynecologic procedures such as IUD insertions and endometrial biopsies [1, 5, 6]. However, the PCB itself is painful. Renner et al noted PCB administration was more painful than a sham (mean 55 mm compared with sham 30 mm, P<.001 using a 100 mg Visual Analogue Scale (VAS) 5. Chin et al evaluated pain at the time of PCB with buffered and plain lidocaine and noted median VAS scores for the PCB injection to be 30 (interquartile range (IQR) 15.3-64.5) for buffered lidocaine and and 44.5 (IQR 18.3-65) for plain lidocaine (p=0.32) 4.

Before the PCB can be placed, the clinician applies a tenaculum, which is a single-toothed instrument that punctures the cervix so that it can be moved and stabilized during the procedure. Placement of the tenaculum is painful. Providers routinely place 2 ml of anesthetic via intracervical injection at the anterior lip of the cervix to reduce pain as the tenaculum punctures the cervix, which has been shown to reduce pain associated with the tenaculum, however the injection itself is also painful [7]. An intervention to reduce pain prior to tenaculum and PCB placement could reduce the pain experienced during the procedure and improve the overall patient experience.

Vapocoolant spray consists of pentafluoropropane and tetrafluoroethane which causes the skin or mucosa to become cold and thereby provides analgesia [8]. Cold decreases pain through multiple channels, including stimulation of peripheral neural receptors, alteration of neural transmission velocity, deceleration of transmission of pain signal to central nervous system and distraction from pain [9, 10]. Vapocoolant spray is currently being used across other fields of medicine to decrease pain during injections, IV starts, blood draws, and nerve blocks [7, 8, 10-16]. Vapocoolant spray has been used in dental procedures, demonstrating safety when used on mucosal areas [17, 18].

Vapocoolant spray is easy to use, acts rapidly and is readily available and inexpensive. A single use vial costs approximately $5.00 [19]. Vapocoolant spray represents a novel intervention for the management of pain during gynecologic procedures of any kind. We were unable to identify any previous studies evaluating the use of vapocoolant spray in the vagina or on the cervix to reduce pain with gynecologic procedures, however existing research using vapocoolant in dental procedures has confirmed the safety of their use in mucosal areas [17, 18]. Therefore, we plan to evaluate if vapocoolant decreases pain with paracervical block insertion. The vapocoolant spray has a lasting effect of one minute, therefore, we hypothesize that it will reduce pain with the

paracervical block insertion and tenaculum placement, but we do not expect it to reduce pain with the abortion procedure (dilation and aspiration).

Our primary outcome is to determine if vapocoolant spray reduces pain at the time of paracervical block placement. Our secondary outcomes are to evaluate if vapocoolant spray reduces pain with tenaculum placement, pain with the remainder of the procedure, patient satisfaction, side effects and provider's perception of ease of use of the vapocoolant spray.

The study will be conducted in compliance with the protocol approved by the Research and Institutional Review Committee, and according to Good Clinical Practice standards, applicable federal regulations, and Queen's Medical Center (QMC) institutional policies and procedures.

1.2 Objectives and Hypothesis

Our study objective is to determine if vapocoolant spray reduces pain at the time of paracervical block placement.

Our secondary outcomes are to evaluate if vapocoolant spray reduces pain with tenaculum placement, pain with dilation, pain with aspiration. We will also evaluate patient satisfaction, side effects and provider's perception of ease of use of the vapocoolant spray.

Before the procedure, we will collect demographic information from the patient and have the patients complete a baseline anxiety measure on a visual analog scale (VAS) (all data collection forms can be found in Appendix 5). Before, during and immediately after the procedure, we will use the VAS to evaluate patients' pain. We will also use the VAS immediately after the procedure to determine the patient's satisfaction and the provider's perception of ease of use of the vapocoolant spray (all data collection forms can be found in Appendix 5).

Section 2: Criteria for Subject Selection

2.1 Sample Size and Duration

A difference of 30% or 13-20 mm on a 100 mm pain VAS is considered clinically significant [1-3]. Based on existing research, we estimate mean pain with paracervical block to be between 54-60mm on the VAS, with a standard deviation of 25mm [1, 4, 5]. To detect a 30% difference in pain scores between the two groups with an alpha of 0.05 and 80% power and accounting for 10% participant drop-out, we will recruit 98 total participants, with 49 participants in each group.

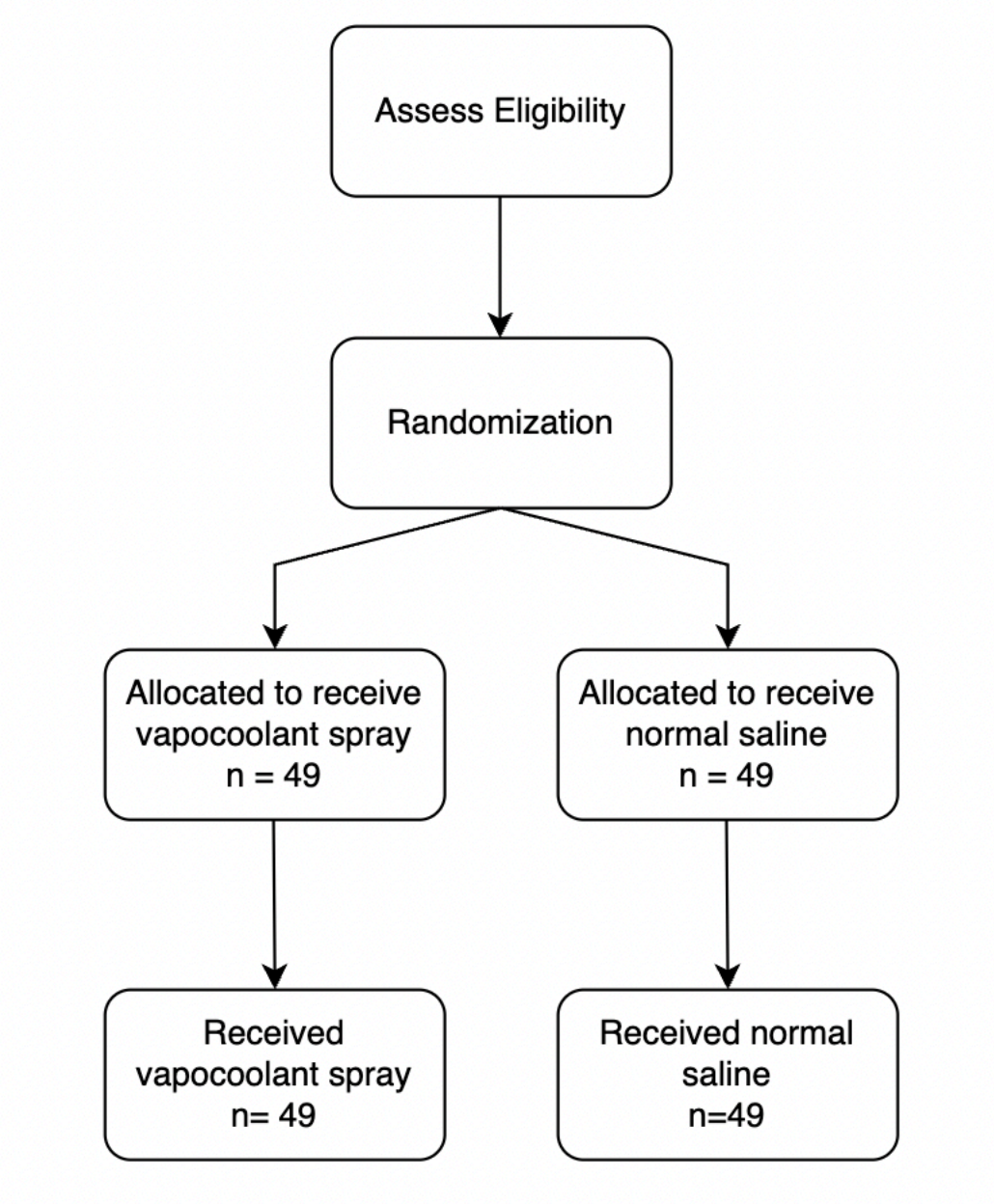
For a sample size of 98, we estimate participant enrollment to take 6 - 15 months. Chin 2020 evaluated lidocaine v buffered lidocaine for paracervical block for patients undergoing outpatient uterine aspiration of a first-trimester pregnancy or an early pregnancy loss. Chin 2020 study was performed with this same physician group in their prior practice location, which had nearly identical set-up and patient flow as the Queen's POB1 office. That study took 15 months for participant enrollment. Currently, at our clinic, we do about eight procedures requiring paracervical block per week. Assuming a 50% enrollment rate, enrollment would take about 6 months. Based on these two data points, we estimate between 6-15 months for enrollment.

2.2 Study Population

The study population will consist of patients who are having a procedure requiring a paracervical block. This study will be conducted at The Queen's Medical Center POB1 Clinic 1004.

2.3 Eligibility Criteria

- Inclusion Criteria
    - Age 18 years of age or older
    - Undergoing a procedure requiring paracervical block in the Queens's POB1 Suite 1004 office (e.g. abortion <13weeks 6days, IUD insertion, laminaria placement)
    - English-speaking
    - Able and willing to sign the informed consent form and agree to terms of the study
- Exclusion Criteria
    - Required or requested narcotics, anxiolytics, IV sedation, or general anesthesia for the procedure
    - Declines or has a contraindication/allergy to ibuprofen
    - Previously received vapocoolant spray in a medical setting
    - Contraindications or allergies to lidocaine for paracervical block or vapocoolant spray components (1,1,3,3-pentafluoropropaine or 1,1,1,2-tetrafluroethane)
- Of note, the manufacturer does state not for use in diabetic patients or patients with poor circulation. This is due to cooling/freezing effects on areas with poor vascularization like fingers. As the cervix is well perfused, we believe it is safe to use the vapocoolant spray on diabetics.



Section 3: Methods and Procedures

3.1 Overall Study Design

- Prospective, Single Blind, Randomized, Placebo Controlled Trial study of patients receiving paracervical block for a gynecologic procedure
- This prospective randomized control trial will consist of two study arms. As participants are enrolled they will randomly be assigned to Arm 1, vapocoolant spray, or to Arm 2, normal saline placebo spray.
- Allocation 1:1

- Participants will be randomized to receive Num Vapocoolant Spray versus Nature's Tears Spray Placebo (Sterile water).
- Settings and locations
    - Queen's Medical Center POB1 Suite 1004

3.2 Subject recruitment, admission and allocation

Potential participants will be patients having a gynecologic procedure requiring a paracervical block at POB1 Suite 1004. If a patient in the clinic decides to undergo a procedure which requires a paracervical block, the patient will first receive standard counseling for that procedure and complete informed consent for that procedure. All these steps will be completed prior to the patient being informed of their potential eligibility for the research study.

- The doctor will then evaluate if the patient meets inclusion/exclusion criteria for this study. If patient is a candidate for the study, the OBGYN resident/CFP Fellow/Attending will approach the patient about being in the study and consent the patient if they desire to participate in the study,
- The patient receive their pre-procedure medications (ibuprofen 600 mg and whatever other medications are required for the specific procedure the patient is having). After the ibuprofen 600 mg is given, the patient waits 10 minutes to 4 hours before the procedure to ensure the medications are working for the procedure.
- During this 10 minute-4 hour wait period, the research coordinator will introduce themselves to the patient to complete the Data Collection sheet.

The research coordinator will be present to the room for the procedure.

Allocation: if a patient opts to participate in the study, they will be randomly assigned to either vapocoolant spray or placebo spray. They will be assigned by the doctor picking the next concealed envelope.

3.3 Screening/Preoperative Evaluation

Potential participants will be identified at their office visits at POB1 Suite 1004 at The Queen's Medical Center. If a patient in the clinic decides to undergo a procedure which requires a paracervical block, the patient will be first consented for their procedure. Then OBGYN resident/CFP fellow/attending will evaluate if the patient meets inclusion/exclusion criteria for this study. The doctor will directly ask the patient is she has taken anxiolytic that day, desires an anxiolytic for the procedure, taken a narcotic or other sedative that day, if the patient has any medical condition that forbids them from taking ibuprofen, if the patient does not desire ibuprofen, if the patient has used vapocoolant spray previously.

Based on the answers to these above questions, the patient's eligibility for our study will be determined. Provider will inform the patient they are eligible for a research study and ask if they are interested in learning more about the study. If they opt to hear more, study physician will meet with the patient and complete the consent process.

It will be made clear to all patients that their decision to enroll or not enroll in the study will not affect their access to requested abortion care , their post-procedural care, and their relationship with their physician or QMC. Consent for the study will be obtained by study investigators and/or physicians following the informed consent standard operating procedure. After enrollment, a copy of the study consent will be given to the subject (see Consent Form attachment). At this time, participants will also receive $50 remuneration for their participation in the study via a gift card.

3.4 Procedure Setting and Providers

At The Queen's Medical Center POB1 Suite 1004 office, one of four complex family planning trained providers (all listed as study co-investigators) will perform all procedures. Fellows and residents may participate in the procedure under direct supervision. In study documents, we will record the name of the attending and if residents or fellows participated in the procedure.

All patients will received standard of care for the procedure they have consented to that requires a paracervical block. In terms of the research, the patient will receive standard of care + a spray after speculum placement. The spray being either the vapocoolant spray or placebo Nature's Tears. All other aspects of the procedure will remain the same.

Study team will collect pertinent demographic and medical history information (as indicated in the data collection form) directly from the patient prior to the procedure during the 10 min-4hour wait after taking ibuprofen. Physician-investigators
will be asked their opinion on ease-of-use of the vapocoolant after each procedure.

3.5 Randomization and Allocation Concealment

Prior to the start of the study, an individual not involved with the conduct of the study will determine allocation of subjects by computer-generated random numbers in block sizes to be determined by that individual. This individual will then place allocation assignment cards in sequentially numbered, sealed, opaque envelopes containing study group assignments which will be opened on the day of the procedure by the doctor performing the procedure.

The envelopes will be kept in the clinic. After a patient has chosen to participate in the study, the doctor performing the procedure, will pick the next numerical, sealed, opaque envelope. The doctor will open the envelop and see if the patient will be receiving the vapocoolant spray or the placebo spray. The doctor will then get the correct spray from the cabinet, which will be stored in the clinic. The doctor will wrap the spray in a blue towel and place on the tray for the procedure under the blue sterility drap of the instruments. Once in the room, the doctor will place the spray still wrapped in the blue towl in the drawer between the patients legs. This prohibits anyone from seeing the spray besides the doctors.

The patient will be blinded to what spray they receive.

Investigators will assign each subject a study identification number in sequential order.

3.7 Implementation

A research assistant, unaware of the study allocation, will stand at the head of the bed to collect data from the patient during the procedure. The provider will ensure that the spray used is not visible to the participant or the research assistant throughout the data collection period. The spray will be placed in the drawer between the patient's legs, only visible to the doctor performing the procedure.

3.8 Blinding

The participants and the research assistants collecting data from the participant during the procedure will be blinded to study allocation.

The providers performing the procedure will not be blinded. In prior research conducted with vapocoolant, the studies were designed to be double blinded, however through personal communication with those studies', Dr. Mace, we learned that to provide blinding was almost impossible. Even with identical packaging, the providers could determine which product was being applied because the vapocoolant is cold on the provider's hand when they spray and turns the skin white, while the normal saline drips on contact with the skin [11, 12]. Based on this, we determined we would not be able to blind providers to study group allocation and have used other techniques (described below) to reduce the potential bias this lack of blinding may introduce.

3.9 Criteria for Discontinuation

Participants may end study participation upon request at any point in the study. After study consent and randomization but prior to the procedure, patients may be discontinued from study participation if the provider deems it necessary, the patient chooses to discontinue, or if exclusion criteria are newly identified.

We will follow intention-to-treat principles and analyze all data based on its allocation regardless of whether or not the intervention was received.

3.10 Standardization of Procedure

Preprocedural counseling and evaluation are consistent with clinic protocols. All participants will receive premedication of 600 mg oral ibuprofen before (10 minutes to 4 hours) the procedure.

All patients who consent to the study will receive standard counseling prior to their procedure. The provider will wear a face mask during the procedure as is standard of care. The procedure will start with a bimanual exam by the provider. Next, the provider will place a speculum. At this

point, participants assigned to Arm 1 will receive vapocoolant spray (treatment), while participants assigned to Arm 2 will receive normal saline spray (placebo).

The vapocoolant spray is a single-use spray bottle containing (8.5 grams) vapocoolant spray. Providers will follow the manufacturer's brochure for the vapocoolant application (Appendix 6.1). To use the spray, the provider will twist to break the tamper evident label, pull off the base cap, and then pull off the sterile barrier tab on the nozzle. From 3-6 inches away, the provider will spray the cervix for 4-6 seconds until the cervix turns white. The Num vapocoolant spray has a cooling effect of 1 minute ([19], Appendix 6.1)

We will plan to use Nature's Tears for placebo in the same method, spraying from 3-6 inches away from the cervix for 4-6 seconds.

Clinicians will all be trained to use both the Num vapocoolant spray and Nature's Tear prior to first study patient encounter. Additional supplies will be purchased to allow for all doctors involved in the study to practice consistent use of the device following the Num Vapocoolant Application Guide (Appendix 6). Natures Tears is a standard spray can. The provider simply needs to hold down the nozzle. To ensure standardization between the two groups, the provider will also spray the cervix with Natures Tear from 3-6 inches away and for 4-6 seconds.

Both sprays are to be aimed at the cervix, however, some of the spray may come in contact with the vaginal sidewall. The bivalve speculum will protect the anterior and posterior vagina, but the side walls could have collateral effects of feeling the spray.

There is potential for the doctor performing the procedure to inhale the spray. To decrease this risk, the providers will be wearing a face mask and be gloved as is standard of care.

After the treatment or placebo spray is administered, the provider will then immediately follow a standardized protocol for administering the paracervical block based on existing research on tenaculum placement and paracervical block best practices [1, 4, 20]

Paracervical Block Standard Administration: The providers will inject two ml at the tenaculum site, 12 o'clock superficially into the cervix. The provider will then place the tenaculum, using a standardized "slow" placement of the tenaculum (e.g. counting to 10 while placing the tenaculum).

Prior to the procedure, as is standard office protocol, the MA will prepare a syringe loaded with 20 ml of 0.5% lidocaine, 20 gauge spinal needle. The providers will inject the remaining 18 mL slowly over 60 seconds into the cervicovaginal junction in two equal aliquots at 4 and 8 o'clock 1. We will perform a continuous injection from superficial to deep (3cm) to superficial (injection with insertion and withdrawal)

The providers will standardize language during the PCB application to reduce bias or priming of the patient. Each provider will use the following language: "You may or may not feel a sharp pinch as I am injecting numbing medicine". This will be repeated as necessary throughout injection of the paracervical at 4 and 8 o'clock 1.

During the procedure, the research assistant will ask the patient to verbally report their level of pain based on the 100 mm visual analog scale (VAS) at the following points of the procedure:

1. Prior to the start of the procedure (baseline)
2. After tenaculum placement
3. After paracervical block
4. After gynecologic procedure complete
5. Five minutes post-procedure
6. Post procedure: Physician Ease of Use

Post Procedure evaluation
After the procedure, which is usually about 10 minutes, the provider will immediately evaluate the vagina and cervix as is standard of care. Besides evaluating for bleeding, the provider will also evaluate for any side effects from the vapocoolant/placebo, including second and third degrees burns, cryogenic injury, failure of the cannister, bruising, blistering, bleeding, pain, blister, cryogenic burn, infection, discharge.

Physician Ease of Use
We will submit waiver of consent for provider physician investigators to collect their evaluation of ease of use for each subject. We anticipate ease of use will be uniform, but perhaps the ease of use will vary based on patient characteristics, which is why we want to ask the question for each subject. Collection of such data is considered standard in our field whenever a new pain management technique is evaluated.

3.11 Follow up

One to two days after the procedure, one of the study investigators will text and/or call the patient to see if they have any concerns or concerning symptoms. If the patient does report concerning symptoms and need for evaluation, the patient will be scheduled for an appointment as soon as possible back in the clinic for a physical exam (pelvic exam to evaluate the vagina/cervix, if necessary).

3.11 Description of the intervention to be studied

Num is a sterile vapocoolant topical anesthetic spray used to numb the skin prior to needle procedures. It is made by 623 Medical in Morrisville, NC.

3.12 Vapocoolant Supply, Packaging, Labeling and Storage

Num (Vapocoolant Spray) is not currently stocked by the QMC Pharmacy. We will order it as part of the research study and have it stocked in our clinic. Num can be ordered in cases of 50 units. We plan to order 1-2 cases over the course of the study – as our planned project is a sample size of 49 participants in the treatment group. The Num product is temperature sensitive

and needs to be stored in an environment <140 Degree Fahrenheit. Our clinic has central air conditioning and is usually between 65-85 Degrees Fahrenheit. Num has a shelf life of 3 years.

The placebo (Nature's Tears) is not currently stocked by the QMC Pharmacy. Will will also order this medication and have it stocked in our clinic. We plan to order about 50 units and keep them in our clinic with the Num product. Nature's Tears has a shelf life of 5 years.

3.13 Data Analysis and Statistical Methods

We will assess the primary objective by comparing the mean pain score after paracervical block injection from participants receiving vapocoolant spray versus normal saline. If VAS scores are normally distributed, we will report means as primary outcomes and use student's t-test to compare groups. If VAS scores are non-normally distributed, we will report median scores as primary outcome and use nonparametric testing (i.e. Mann Whitney U test) to compare the two groups.

Secondary Outcomes:

- Patient pre procedure anxiety – VAS
- Patient pre procedure pain score – VAS
- Pain with tenaculum placement – VAS
- Pain with procedure- VAS –
- Pain 5 minutes after procedure – VAS
- Satisfaction with pain control during procedure – VAS
- Satisfaction with procedure – VAS
- Provider ease of use of product – VAS

We will also use the Student T-test or Mann Whitney U test to assess our secondary objectives by comparing mean/median difference in pain during other time points in the procedure and overall satisfaction with pain.

No interim analysis is planned. Dr. Rault and Dr. Raidoo will be responsible for protecting and monitoring the rights, safety and welfare of the subjects and can perform an interim analysis if it is deemed necessary for determining the safety of continuing the trial. If more than 5 participants note side effects at the 1-2 day text/phone call follow up, we will perform an interim analysis. Statistical analysis will be performed with either Excel or SPSS . Data will be analyzed using intention to treat principles.

3.14 Data Handling and Record Keeping

Only the primary investigators and research assistants will have access to study records, which will be kept in locked file cabinets in the study investigator's office. Each participant will be assigned a unique study ID. We will create a coded database using these study IDs but containing no PHI for analysis, which will be stored on an encrypted and password protected computer in the research office. The codebook linking participant identifiers to StudyID will be stored in a password protected, secure database accessible only to the study team. Any publications or presentations will be reported without reporting any personal health identifiers. Any deviations from the planned statistical analysis will be documented.

3.15 Confidentiality and Data Security

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period."

Hard copies of clinical information and data will always be kept in a secured place in our research offices, and only study team members will be able to access them on an as-needed basis. Key personnel may not alter the data in any database without specific cause and approval of the Investigator. For de-identification, all subjects will be assigned a unique study ID number when they enter the study. Data will be recorded on the paper data collection form and converted into an electronic file database, such as REDCap or Excel. Study databases will be password protected, and all portable devices will be fully encrypted. No data will be sent over the Internet unless it is de-identified. Data will be de-identified prior to any analysis. We will keep codes linking the study identification number with the name of the subject confidential, secured by password-protected data file within the locked research unit of the Principal Investigators. Further measures to ensure data security will adhere to security standards set by the Queen's Medical Center and the RIRC.

3.16 Record Retention

Study documents will be retained for at least three years after the formal discontinuation of this project. They will be stored in locked, secured cabinets in the PI's office. All data will be de-identified. Any electronic files will be password protected and encrypted. If the Primary Investigator leaves Hawaii, she will make arrangements to destroy the data at the designated time.

3.17 Direct Access to Source Data/Documentation

The investigators will permit study-related monitoring, audits, RIRC review, and regulatory inspections/audits by providing direct access to all study related data/documents. This will be indicated in the consent process with the potential subjects.

Section 4 Risks/Benefit Assessment

4.1 Risks

This study presents with risks from the use of vapocoolant spray. Vapocoolant spray has adverse side effects, such as irritation, thermal burn, cryogenic injury, bruising, blistering, bleeding, pain, thawing process may be painful, infection, discharge and delayed healing.

All patients will receive the standard of care for their paracervical block procedure, with the addition of either a numbing vapocoolant agent or placebo. Previous studies evaluating vapocoolant spray have shown that patients tolerate it well on skin or on mucosa in dental procedures [17, 18].

4.2 Potential Benefits

Our hypothesis is that subjects who participate in this study will likely benefit from the vapocoolant spray by having decreased pain with the paracervical block. There is a possibility they will experience no benefit. This study could help patients having in office first trimester abortions in the future have less pain..

4.3 Alternatives to participation

If a participant decides to withdraw from the study, the patient will receive our standard of care for the procedure, without either vapocoolant spray or normal saline spray.

4.4 Financial Obligations/Cost:

Participants will not be billed for the vapocoolant or placebo. All standard of care labs, medications and procedures for the gynecologic procedure will be billed through the subject's insurance, if they plan to use insurance, or at patient’s own expense. There will be no compensation offered for injury or adverse events of this study.

4.5 Safety and Adverse Events

The principal investigators, Dr. Rault and Dr. Raidoo, will be primarily responsible for protecting and monitoring the rights, safety and welfare of the subjects. They will meet regularly

(i.e. weekly or bimonthly depending on subject enrollment) with the research coordinators to monitor data quality.

We will monitor if there are adverse side effects from the vapocoolant spray noted by the physician during the immediate post procedural evaluation of the vagina or cervix or by the patient at the follow up text/phone call encounter 1-2 days post procedure. If patients encounter concerning symptoms/side effects 1-2 days post procedure, we will schedule the patient for an in person visit as soon as possible to evaluate concerns with a physical exam (pelvic exam if necessary).

5. Ethical Considerations

This study will be conducted according to US and international standards of Good Clinical Practice, applicable government regulations and institutional research policies and procedures.

This protocol and any amendments will be submitted to The Queen's Medical Center Research and Institutional Review Committee (RIRC) for formal approval to conduct the study. The decision of the RIRC concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

All subjects for this study will be provided an informed consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the RIRC for the study. The formal consent of a subject, using the RIRC-approved consent form, must be obtained before the subject enters the study. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining consent.

6. Study Finances

Study funds from this project are through a grant from the Society of Family Planning (application pending). These funds will go towards salaries of staff and paying for the vapocoolant/placebo. (see Appendix 2 – Budget for more information).

7. Publication and Presentation Plans

Findings from this study will be disseminated by multiple means. Results will be presented at the Annual Society of Family Planning Meeting in 2025. We plan to present at a national meeting such as the American College of Obstetricians and Gynecologists or the Annual National Abortion Federation Meeting. This study will be submitted for publication to a nationally recognized peer-reviewed journal such as Obstetrics & Gynecology, Contraception, or the American Journal of Obstetrics & Gynecology.

8. Timeline

After IRB approval is granted, we anticipate completing recruitment and enrollment in about 18 months with data analysis to occur within a month after completion of enrollment. Please see attached study timeline.

Appendix and Attachments:

1. Study Calendar: Proposed Project Timeline (See Below)
2. Budget (See Below)
3. Roles of Personnel (See Below)
4. VAPOR Patient Consent Form (Separately Attached)
5. Data Collection Form - Patient Demographic Form and Visual Analog Scale (Separately Attached)
6. Num Information - Seven PDF Documents (Separately Attached)
7. Letter of Agreement (LOA) (Separately Attached)
8. Email Correspondence with Written Financial Support through Lakshmi Devi and Devraj Sharma Endowment

Appendix 1.
Study Calendar (Proposed Project Timeline)

Year 1	**Oct-23**	**Nov-23**	**Dec-23**	**Jan-24**	**Feb-24**	**Mar-24**	**Apr-24**	**May-24**	**Jun-24**	**Jul-24**	**Aug-24**	**Sep-24**
Study Development	x	x	x	x								
Consent material development	x	x	x	x								
Institutional human subjects review	x	x	x	x								
Study Activities												
Staff training			x	x	x							
Database development			x	x	x							
Subject recruitment				x	x							
Data Collection				x	x	x	x	x	x	x	x	x
Data entry					x	x	x	x	x	x	x	x
Year 2	**Oct-24**	**Nov-24**	**Dec-24**	**Jan-25**	**Feb-25**	**Mar-25**	**Apr-25**	**May-25**	**Jun-25**			
Data Collection	x	x	x	x	x	x	x					
Data entry	x	x	x	x	x	x	x	x				
Data Analysis												
Data cleaning							x	x	x			
Data analysis							x	x	x			
Final report and manuscript writing							x	x	x			

Appendix 2. Budget

DETAILED BUDGET AND BUDGET JUSTIFICATION			
Study Title: VAPOR: Vapocoolant Application for Pain Reduction during Office-based First-trimester Abortions: a Randomized Controlled Trial			
PI Name: Catherine Rault			
Institution: The Queen's Medical Center			
Project Start and End Dates: 10/31/2023 to 6/1/2025			
A. MATERIALS, SUPPLIES, AND OTHER EXPENSES			
	Quantity	Cost/Unit	Total Cost
Num Vapocoolant (individual use)	49	$5.00	$245
Placebo (Nature's Tears Sterile Water, individual use)	49	$4.31	$212
Participant remuneration	98	$50	$4,900
	Total Materials, Supplies, and Other Expenses		$5,357
	TOTAL BUDGETED AMOUNT		**$5,357**

Part A. Personnel Costs

Note: Dr. Rault's study will be supported by the following contributions from the Family Planning Research Center and the University of Hawaii, Division of Family Planning:

- Drs. Reni Soon, Bliss Kaneshiro, Shandhini Raidoo, and Mary Tschann will provide ongoing guidance and consultation in the implementation, analysis, and dissemination of Dr. Rault's study.
- The Family Planning Research Center of Hawaii will contribute the support of its full-time research coordinators throughout the implementation of the study, including assistance with participant recruitment, data collection, IRB and regulatory compliance, and data cleaning.

Part B. Materials, Supplies, and Other Expenses

- The Vapocoolant product (Num @ $5 per unit) for the 49 participants in the treatment arm

- The placebo product (Nature's Tears sterile water spray @ $4.31 per unit) for the 49 participants in the treatment arm
- $50 remuneration per participant for study participation

Appendix 3. Roles of Personnel

Lule Rault, MD, MPH (Principal Investigator): is an obstetrician-gynecologist who is currently completing a fellowship in Family Planning. She will be involved in all facets of the study including abortion care to the participants enrolled.

Shandhini Raidoo, MD, MPH (Mentor, Principle Investigator) is a board-certified obstetrician-gynecologist who specializes in Family Planning and has completed a fellowship in Family Planning. She is an Assistant Professor in the UH Department of Obstetrics and Gynecology and will provide abortion care to subjects in this study.

Bliss Kaneshiro, MD, MPH: is a board-certified obstetrician-gynecologist who specializes in Family Planning and has completed a fellowship in Family Planning. She is a Professor in the UH Department of Obstetrics, Gynecology and Women's Health and Program Director for the Family Planning Fellowship. Dr. Kaneshiro has extensive research experience and has conducted several randomized controlled trials. As Program Director, she is involved in all aspects of Dr. Rault's training including her research training. Dr. Kaneshiro will be involved in all facets of the study including abortion care to the participants enrolled.

Reni Soon, MD, MPH (Fellowship Program Director): is a board-certified obstetrician gynecologist who specializes in Family Planning and has completed a fellowship in Family Planning. She is a Professor in the UH Department of Obstetrics, Gynecology and Women's Health and Program Director for the Family Planning Fellowship. As Program Director, she is involved in all aspects of Dr. Rault's training including her research training. Dr. Soon will be involved in all facets of the study including abortion care to the participants enrolled.

Melissa Faith Natavio, MD, MPH is a board-certified obstetrician-gynecologist who specializes in Family Planning and has completed a fellowship in Family Planning. She is an Associate Clinical Professor in the UH Department of Obstetrics and Gynecology and will provide abortion care to subjects in this study.

Tracy Chen, MD is an obstetrician-gynecologist who is currently completing a fellowship in Family Planning. She will provide abortion care to subjects in this study.

Olivia Manayan, MD is a physician completing a residency in obstetrics and gynecology. She will provide abortion care to subjects in this study.

Eileen Chen, MD, OBGYN resident intern rotating through Complex Family Planning rotation.

Jen Hayashi, MD OBGYN resident intern rotating through Complex Family Planning rotation.

Sarah Maruyama, MD. OBGYN resident intern rotating through Complex Family Planning rotation.

Mary Tschann, PhD, MPH is a scientist at the Queen's Medical Center department of Women's Health. She will provide assistance in planning and implementation of this study, data analysis and manuscript development.

Taylor Ronquillo, MPH is a research associate with the Family Planning Division of the UH Department of Obstetrics and Gynecology. She will assist with enrollment, consenting, managing study documents and data entry. She will be present at surgical procedures to assist with recording variables, as well as measuring blood loss. She will provide assistance in planning and implementation of this study as well as protocol and manuscript development.

Zarina Wong is a research associate with the Family Planning Division of the UH Department of Obstetrics and Gynecology. She will assist with enrollment, consenting, managing study documents and data entry. She will be present at surgical procedures to assist with recording variables, as well as measuring blood loss. She will provide assistance in planning and implementation of this study as well as protocol and manuscript development.

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