Study Protocol

A comparison of pain perception using topical EMLA cream versus lidocaine injection for vulvar biopsy: a randomized controlled trial

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Research Abstract

The purpose of this study is to compare pain control during vulvar biopsy following either (1) application of EMLA (a eutectic mixture of local anesthetics lidocaine 2.5% and prilocaine 2.5%) cream or (2) injection of 1% lidocaine.

Subjects recruited from the Duke Gynecology Oncology clinic and the Duke Womens Cancer Care Raleigh clinic who will be receiving a vulvar biopsy will be randomized to receive either EMLA cream or injectable lidocaine in preparation for the biopsy. Subjects will complete a baseline survey, and sociodemographic information will be collected. Pain will be assessed using a 100 mm visual analog scale: at baseline, after application of EMLA or lidocaine injection, and immediately after vulvar biopsy. Subjects will then complete an exit survey on their perception of the tolerability and acceptability of the procedures. The primary outcome is highest subjective pain score. We hypothesize that lidocaine will provide better biopsy analgesia, but the benefit will be offset by the pain of lidocaine injection compared to EMLA application, thus there will not be a significant difference in highest pain scores between the two groups. Subjects will be compensated $20 for their participation.

We chose a 16-mm difference on a standard 100-mm visual analog pain scale as value of clinical significance. In order to detect at least a 16-mm difference with 90% power and alpha of .05, we estimated a total sample size of 53. Highest mean pain scores between anesthetic methods will be compared as the primary outcome using T-test vs Wilcoxon Rank sum test. Patient perception of tolerability and acceptability of the procedure as well as the provider's satisfaction with the procedure will also be analyzed. There are no additional risks/benefits to the study participant for being part of the study as both methods of anesthesia are considered standards of care.

Primary Objectives

To compare highest subjective pain score with application of EMLA cream versus injection of lidocaine for analgesia for vulvar biopsy.

Secondary Objectives

To compare pain scores at vulvar biopsy

To investigate possible pathologic changes associated with EMLA cream administration

Purpose

We hypothesize that lidocaine will provide better biopsy analgesia, but the benefit will be offset by the pain of lidocaine injection compared to EMLA application, thus there will not be a significant difference in highest pain scores between the two groups.

Background and Significance

Performing minor procedures in-office is essential to gynecologic practices.In-office procedures allow for evaluation and diagnosis of a variety of conditions while avoiding the expense, anesthesia, and time associated with the operating room.Pain and discomfort are frequently associated with these procedures, and ensuring that the patient has the least amount of discomfort is a priority.Very painful or uncomfortable procedures could potentially discourage a patient from returning to clinic or receiving the follow up that they may need.Psychological, physiologic, and social factors influence a patient's experience of pain.Previous studies, though mostly related to first trimester abortion procedures in the office, indicate that the procedure type, anxiety, depression, and general anticipation of pain predict increased pain during in office gynecologic procedures (1-4).A review by Ireland et al., found that a multimodal approach that includes patient counseling with other techniques is most effective in achieving optimum pain control for procedures (5,6).

Vulvar biopsies are associated with significant discomfort, and some form of anesthesia is required.The current standard in our group is to inject local anesthesia prior to vulvar biopsy.However, the injection itself is associated with its own level of pain that is not insignificant, and for many, the anticipation of receiving an injection is anxiety provoking.The use of topical anesthesia in lieu of injection or as pre-injection analgesia is variable.

Several previous studies have examined the use of topical anesthetics in the place of or in addition to injected anesthesia.Drouault et al. compared EMLA cream alone to injected lidocaine alone for pain relief in vulvar biopsy and found that pain associated with administration of anesthesia was significantly less for EMLA cream, but better biopsy analgesia was obtained with injected anesthesia.The study considered combined pain scores for both groups for the overall procedure (anesthesia + biopsy), it comments that the combined scores were lower for the EMLA group but failed to reach statistical significance. The study ultimately concluded that EMLA is the less painful procedure to obtain anesthesia and that it can be used as an alternative to injection for biopsies of the genital mucosa (7). This prior study did not compare the highest pain score between groups.Consideration of the highest pain score allows us to assess whether the injection of lidocaine could result in causing more pain than the biopsy itself using EMLA cream alone for anesthesia.Further, the study did not assess the subjects' or the providers' perception of the tolerability and acceptability of performing the procedure using either method.This is an important factor in any in office procedure

EMLA cream is the most extensively studied topical anesthetic.It is FDA approved for use as a topical anesthetic on the genital mucous membranes for superficial, minor surgery.EMLA cream requires between 7-10 minutes of absorption time on the genital mucosa for analgesic effect, with variable duration of analgesia following, usually around 15-20 minutes (9).There is a highly variable absorption rate for EMLA cream depending on the characteristics of the epithelium upon which it is applied as well as the duration and surface area of cream applied.On hair-bearing non-mucosal surfaces it can require 60 minutes of application time to obtain analgesic affect (10).The vulvar area is unique in that it contains both mucosal and non-mucosal and hair-bearing surfaces; this could greatly affect the absorption of EMLA and therefore affect analgesia.For this reason, we will exclude from the study patients requiring vulvar biopsy on hair bearing portion of the vulva.

There have been case reports of EMLA induced pathologic changes in children with a variety of inflammatory skin conditions where disruptive changes on H&E were noted. Similarly in a small series of patients with vulvar dermatoses, EMLA was associated with similar disruptive changes on H&E. The extent of these changes and their ability to impact pathologic diagnoses have not been studied.

Design and Procedures

Following informed consent enrollment, subjects will be randomized to an arm of the study using the randomization tool in REDCap. eConsent will be programmed in REDcapand. Study subjects, study staff, and performing providers will not be blinded to the intervention as the interventions are different; therefore, our study design is an unblinded randomized controlled trial.Selection criteria are listed in the table below.

Selection Criteria

Participant Inclusion Criteria	Participant Exclusion Criteria
• Females above age 18 presenting to Duke Gynecology Oncology clinic for vulvar biopsy • Able to provide informed consent in English and agree to the risks of the study	a. Not able to provide informed consent b. Vulvar biopsy on a hair bearing surface

It is not standard to perform pregnancy testing prior to vulvar biopsy in Duke Gynecology Oncology clinic and Duke Womens Cancer Care Raleigh clinic as the administration of anesthesia and procedure itself present minimal risk of harming a fetus. Both EMLA cream and injected lidocaine are labeled pregnancy category B indicating that reproduction studies performed in rats have revealed no evidence of harm to

the fetus, but there are no adequate and well-controlled studies in pregnant women (10, 14). For these reasons, we will not perform pregnancy tests on possible study participants.

Because participation in the study only lasts the duration of the clinic visit during that day, and EMLA and lidocaine are pregnancy category B, there are no specific contraceptive methods required preceding or following participation in the study.

Measurement of anxiety, acceptability, and pain

Before the procedure is performed, subjects will complete the GAD-7, a validated 7 item anxiety disorder scale(15).

Subjects will report pain using a visual analog scale, a scale comprised of a 100 mm horizontal line anchored with 2 verbal descriptors, one for each symptom extreme.For pain, the scale is most often anchored by “no pain” (score of 0) and “worst imaginable pain” (score of 100 mm). The patient marks their pain with a vertical line perpendicular to the scale, and the distance from 0 is measured with a ruler (16-18).

Subjects will also be asked to rate the overall acceptability and tolerability of the procedure performed with a visual analog scale.The provider performing the biopsy will rate their overall satisfaction and perception of patient tolerability of the procedure using the same scale.The subjects will also be asked if the procedure was better or worse than they expected.

Study Procedures:

Intake information: Patients will present to their scheduled Duke Gynecology Oncology Clinic or Duke Womens Cancer Care Raleigh clinic appointment. If it is determined that a vulvar biopsy is indicated, the provider will briefly inquire about interest in the study. If interested, a study coordinator will introduce the study to the patient and perform informed consent should they decide to participate. After providing informed consent, the patient will complete a survey including sociodemographic information and a baseline anxiety survey (GAD7) (see appendices). The following information will be collected: age, race, ethnicity, level of education, baseline vulvar pain using a 100 mm visual analog scale, history of previous vulvar biopsy, daily narcotic or anxiolytic use. Information including BMI, chronic pain diagnoses, history of vulvar cancer will be collected by study coordinators from the medical record.

Participants will complete questionnaires electronically with the exception of the pain assessment by visual analog scale.The data will be collected directly into REDCap.Pain scores will be entered into REDCap by measuring from 0 millimeters the hash mark made by the patient.There will be paper forms of the questionnaires available, as a secondary option should it become necessary.

Randomization: After completing the entry intake information, the subject will be randomized to EMLA cream application or lidocaine injection using the randomization tool within REDCap

Procedure: The subject will then be placed in dorsal lithotomy position on the Gynecology Oncology pelvic exam tables in preparation for the procedure. If the patient is randomized to the EMLA cream group, the EMLA cream will be applied at the intended site of biopsy and left in place for a minimum of 10 minutes prior to biopsy. Approximately 5 g of EMLA should be applied in a thick layer to the area to be biopsied (a 1g strip is approximately 1.5 x 0.2 inches and squeezed from the tube in a narrow strip) (10). The subject will report a pain score at time of EMLA application. After 10 minutes vulvar biopsy will be performed.

For subjects receiving lidocaine injection, approximately 2 mL of 1% lidocaine will be injected superficially at the planned biopsy site using a 25- or 27-gauge needle at the discretion of the physican.The subject will report pain at time of injection on a 100 mm visual analog scale before proceeding to vulvar biopsy. The provider will then wait at least one minute after lidocaine injection before performing the biopsy.

In both arms, should the provider deem anesthesia to be inadequate prior to performance of the biopsy, an additional lidocaine injection will be allowed prior to biopsy and this will be recorded.

Vulvar biopsies will be performed using standard biopsy forceps or a punch biopsy (3-4 mm) device depending on provider preference.The subject will report pain using a 100 mm visual analog scale immediately following biopsy.

If there are multiple biopsy sites that are treated, and the pain differs between these locations, the highest pain score will be recorded.

If the procedure is interrupted secondary to pain, a pain score will be recorded prior to injecting additional lidocaine, as described above.

Exit Survey: After completion of the procedure, subjects will complete an exit survey, as described above(see appendices), answering questions about overall satisfaction/tolerability of the procedure.

The provider performing the biopsy will also complete a brief survey answering questions about their satisfaction with the procedure and their perception of the acceptability of the procedure performed.

As described above, participants will complete questionnaires electronically with the exception of the pain assessment by visual analog scale, which will be completed on paper and measured distances will be entered into REDCap.

Participants will receive a $20 check for participation in the study.All completed surveys will be collected by the study coordinator who will store the documents in a password protected file on the Duke secured server.

Post Study Pathologic Analysis: To address the concern that EMLA might induce pathologic changes that could result in altered diagnosis, pathologist independent from initial diagnostic read will re-evaluate tissue slides and look for the previously described EMLA induced pathologic changes (pallor, necrosis, spongiosis, basophilic granules, acantholysis, clefting, papillary dermal edema). Pathologist will be blinded to whether or not patient received EMLA cream for biopsy. They will provide a score for all specimens that will be used to analyse any pathologic differences between patients exposed to EMLA and those not exposed to EMLA.

Selection of Subjects

An electronic consent form will be used during the informed consent process, the signed copy of the study consent form will be emailed to the subject or printed and provided to her in clinic based on her preference. Subjects will then be assigned a unique subject number by the research coordinator. Research coordinators will maintain an enrollment log to serve as the master list for the enrolled subjects. After their information is placed into the enrollment log, the subject will only be identified by their unique number. The enrollment log as well as the study questionnaires and pain assessment forms will be collected into a REDCap data base with any exported copies saved in a password protected file on the Duke secured server.

Subject's Capacity to Give Legally Effective Consent

Subjects who do not have capacity to give legally effective consent will not be included in the study.

Risk/Benefit Assessment

There is a potential benefit for the subjects in this study in that they may receive analgesia for the procedure without the pain of an injection.However, it will be emphasized to the subject that there may be increased pain during biopsy in the EMLA arm or increased pain with injection for the lidocaine arm.

There are risks associated with vulvar biopsy including bleeding and infection.These risks are small, but they are not risks incurred as a result of participating in the study as these patients will be getting vulvar biopsies regardless of study participation.

There is a small risk of topical reaction to the EMLA cream.If irritation does occur, the area of irritation will be cleansed with water and the procedure will be postponed until the irritation is resolved.The subjects will return to clinic to assess for resolution of the area and their indicated vulvar biopsy.

Costs to the Subject

No additional costs will be incurred by the participant as a result of participating in this study

Data Analysis and Statistical Considerations

A 16-mm difference on a standard 100-mm visual analog pain scale was deemed clinically significant. In order to detect a 16-mm difference with 90% power at an alpha level of 0.05 assuming a standard deviation of 25-mm, we estimated a needed sample size of 53 participants in each treatment arm. However, due to time limitations, data collection will end on March 12, 2019. Only patients consented on or prior to March 12, 2019 will be included in the study. Data will be recorded using Research Electronic Data Capture (REDCap), and the database will be locked on March 13, 2019. Pain will be measured during the application of EMLA cream or lidocaine injection, and immediately after biopsy. The primary outcome will be the highest pain score recorded during the procedure. The primary outcome will be compared between treatment arms using linear regression adjusting for baseline pain. Secondary outcomes include pain score at vulvar biopsy, patient tolerability and acceptability, and provider's satisfaction with the procedure. All testing will be performed at a two-tailed significance level of 0.05.

If significance for the primary objective is not achieved, then patient accrual will continue based on a new sample size determined by the primary results of this analysis. This will be the number of new patients that need to be enrolled. Outcomes will be assessed again at the point when the final sample size is achieved.