Title: Decreasing Postoperative Pain Following Endometrial Ablation: A Randomized Controlled Trial

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Purpose: To determine whether paracervical injection of long acting local anesthesia decreases postoperative pain following endometrial ablation under general anesthesia.

Background:

Destruction of the endometrial lining to control bothersome uterine bleeding has been implemented since 1937 (ACOG Committee on Practice Bulletins, 2007). Currently there are various different 'second generation' energy sources to avert such bleeding, five of which are now approved in the United States (ACOG Committee on Practice Bulletins, 2007). These 5 second generation devices include: Thermachoice/Cavaterm, which use high temperature fluid within a balloon; Microsulis, which applies microwaves; Novasure, which uses bipolar energy; Hydrothermablator, which uses free fluid at high temperatures; ELITT, which uses laser thermotherapy; and HerOption, which uses cryoablation. Patient selection for endometrial ablation is crucial, as it is intended for premenopausal women with normal uterine cavities and no desire for future fertility that are affected by heavy menstrual bleeding. Since the introduction of the initial 'second generation' device in 1997 these modalities have overtaken the industry mostly due to their ease of use and shorter operative times. Regardless, a Cochrane review finds insufficient evidence to prove superiority of these newer modalities over the traditional 'gold standard' resectoscopic technique (Anne Lethaby, 2013).

Endometrial ablation has been demonstrated in a variety of settings including outpatient surgical centers as well as physician's offices. Evidence suggests that microwave endometrial ablation under local anesthesia is a safe and acceptable practice (Wallage S, 2003). Very often, when endometrial ablation is performed as an outpatient procedure, patients are pre-medicated and then receive a paracervical injection of local anesthesia to control pain intraoperatively (Mark H. Glasser, 2009). When endometrial ablations are performed as an outpatient procedure through a surgical center, a variety of anesthesia techniques are employed depending on the infrastructure and human and institutional resources available. These techniques may vary from conscious sedation to general anesthesia, all of which have been proven to be acceptable methods.

In this center endometrial ablations are performed as an outpatient procedure under general anesthesia with a variety of induction techniques and intraoperative pain management practices. According to physician preference, patients may receive an

additional paracervical injection of local anesthetic before the procedure, immediately after, or not at all. To date, there are no studies evaluating the efficacy of local anesthetic in addition to general anesthesia for patients receiving endometrial ablation to guide physician practice. The purpose of this study is to evaluate the efficacy of local anesthetic, in addition to general anesthesia, in our large, community-based patient population, in meaningfully decreasing postoperative pain.

Methods:

This study will be a single center prospective single blind randomized controlled trial of premenopausal women undergoing endometrial ablation. This study will take place in the Christiana Hospital outpatient surgical center. Patients will include English speaking premenopausal women aged 30 – 55 scheduled to undergo outpatient endometrial ablation in the surgical center. These patients will be recruited either in physician's offices, by telephone based on surgical scheduling, or on the day of their procedure. All consents will be signed in person.

Study Design:

Frequently, providers will give their patients additional analgesia in the form of a local anesthetic injected as a paracervical block, either before or after the completion of the procedure with the hope of reducing postoperative pain. This practice is not standardized, as its efficacy has never been evaluated in the setting of endometrial ablation under general anesthesia.

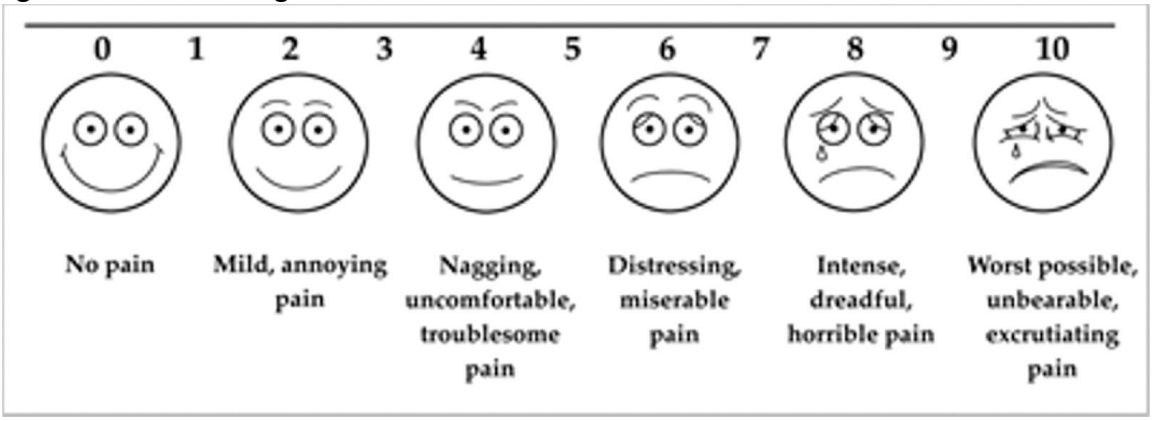
The purpose of this study is to assess the efficacy of this additional local anesthesia upon completion of endometrial ablation under general anesthesia. Patients, once consented, will be randomized in blocks of 6 to either the treatment group or control groups. Those randomized to the treatment group will receive a paracervical injection of 20 mL 0.25% Bupivacaine at the completion of the procedure (Howard W. Jones III, 2008). Patients randomized to the control group will receive an equal volume injection of normal saline with the same paracervical technique. Paracervical injection will be standardized to include a total dose of 20 mL divided into four 5 mL injections at the 2, 4, 8, and 10 o'clock positions on the cervix (Howard W. Jones III, 2008). Paracervical block will be given at the completion of the endometrial ablation.

Only the patients and PACU staff will be blinded to the injected solution. Once general anesthesia has been induced the circulating nurse will open the study patient's unique randomization sequence and the appropriate study solution will be drawn in the operating room. The endometrial ablation procedure will be performed by the surgeon in accordance with that surgeon's specific preference for technique and device. Upon completion of the procedure, and before general anesthesia is reversed, the paracervical injection of the patient's unique study solution will be administered as described above. The operating room team including the surgeon, anesthesiologist, and

ancillary staff will be aware of the injected solution's contents. The post anesthesia care unit (PACU) staff responsible for assessing immediate and delayed postoperative pain will not be aware of the contents of the injected solution, except when necessary for any unexpected complication, in which case the pharmacist maintaining the randomization coding will break the code for that particular patient. All patients will receive IV Toradol with completion of the procedure and have a standardized rescue analgesia protocol in place in the postoperative care unit setting in accordance with the current practice described above. Per the nursing protocols postoperative pain will be assessed using 10 point Visual Analog Scale (VAS) and if patient's pain is above or equal to a 5, on the 10 point scale, they may receive additional analgesia in the form of intravenous (IV) medication or by mouth tablets (PO). Pain scores, as well as rescue analgesic administered, is routinely recorded by the nursing staff and converted to a patient's electronic health record.

Due to the infrastructure set up, at CCHS outpatient endometrial ablations are performed under general anesthesia with the patients asleep for the entire procedure. Per the standard surgical center protocol postoperative patients will be assessed regularly for postoperative pain. If the patients express pain equal to or beyond a predetermined threshold of 5, on a visual analog pain scale from 0 through 10, they may receive rescue analgesia. Patients are taken directly from the operating room to the PACU where their pain is assessed on arrival by trained nursing staff. Patients are kept in Phase 1 of recovery for a minimum of 30 minutes, and a minimum of 30 minutes in Phase 2 before discharge following general anesthesia. At a minimum a postoperative patient's pain is assessed every 10 minutes in Phase 1, and every 15 minutes in Phase 2. Patients are candidates for rescue analgesic medications, generally in the form of Dilaudid or Fentanyl, if their pain score is greater than 5 out of 10. In Phase 1 pain medication is generally given in IV form whereas in Phase 2 pain medication is usually given PO.

Figure 1: Visual Analog Scale



Upon discharge all patients will be given two additional 10 point VAS forms and will be instructed to complete these two pain assessments at 4 hours and 8 hours after

their surgery. These pain scales will be labeled before discharge with the patient's study identification code, date, the times they are to be completed, and instructions to retain the forms until they have spoken with the study staff on the following day. Each patient will be discharged with an additional prescription for twelve tablets of Tylenol #3. Each patient will then be contacted on the day following their surgery by a study investigator to record the patient's home pain scores as recalled by the patient by use of the two pain scales completed at 4 hours and 8 hours postop. Each patient will also be asked to disclose how many of the twelve Tylenol #3 tablets they have remaining.

Primary Outcome:
We propose to test a 40% decrease in the mean 10 point VAS postoperative pain score at 1 hour after the operation. This percent decrease is based on a separate IRB approved retrospective chart review of the most recent patients who underwent an endometrial ablation at the Christiana Hospital surgical center. This retrospective chart review found that of the last twenty patients who underwent an endometrial ablation, without any additional local anesthesia in the form of a paracervical block, the mean postoperative pain score at 1 hour was 2.85± 2.21. The 40% hypothesized reduction in pain is equivalent to approximately 1 full point on the VAS scale and felt to be a clinically meaningful decrease at the lower end of the VAS scale that could influence policy and practice. The average standard deviation between the mean 1 hour postoperative pain scores between the reviewed charts of the 20 patients receiving a paracervical block and the 20 that do not was 1.78, approximately equal to 75% of the average mean pain scores for the 40 patients who did and did not receive a paracervical block. Using a two tailed test, a Type I error of 5% and statistical power of 80%, and an average standard deviation equal to 75% of the average VAS scores in both groups, the study requires a sample of 36 patients per study group. Assuming a 15% attrition rate this study requires 42 patients per study arm (84 total participants). Enrollment in this study will occur for 10 months, or until the number of participants needed per study group is met, whichever occurs first. This allows at least 2 months for data analysis and report composition. Enrollment will be monitored by the Principal Investigator (Klebanoff) monthly, to gauge when enrollment should stop. To ensure ongoing enrollment of similar numbers of participants in each study group, randomization in blocks of 2 will be used, so that for each 2 patients enrolled, 1 will be assigned to each study group.

Secondary outcomes: The study will also conduct descriptive analyses of the study group differences in postoperative pain scores at 4 and 8 hours following surgery, amount of rescue analgesia required postoperatively, but before discharge, time to discharge, postoperative nausea/vomiting requiring medication, blood loss, and amount of narcotic remaining at postoperative day one.

Data Points:
<u>Covariates</u>
- age
- race/ethnicity

- Insurance type

Mediating variables

- BMI (height/weight)
- Indication for surgery
- surgeon (anonymous code)
- type of ablation
- cervical dilation
- type and number of previous surgeries
- intra-operative complication incidence

Outcomes

- 1 hour postop VAS pain score (primary outcome)
- 4 and 8 hours postop VAS pain score (secondary outcomes)
- blood loss
- time to discharge
- type and amount of postop opioid given
-postop anti-emetics given
- postop complication incidence

Inclusion criteria: English speaking premenopasual women, aged 30 – 55, undergoing outpatient endometrial ablation at the CCHS SurgiCenter for menorrhagia, abnormal uterine bleeding, or thickened endometrium.

Exclusion criteria:

- Known malignancy
- Weight < 50 Kg
- Amide allergy
- History chronic pain
- Cardiac arrhythmia
- Dilaudid/codeine allergy
- History of opioid use
- Inability to take PO Opioids
- Uterine anomaly
- Previous ablation
- Concomitant laparoscopic surgery
- Primary language other than English

Data analysis: Continuous variables will be assessed using Student's t-tests and categorical variables will be assessed using the chi-square tests with Fisher's exact significance levels should there be fewer than 5 observations in any cell. Non-parametric tests may be used to compare median values of continuous variables. Linear and logistic regressions will be conducted on continuous and categorical outcomes, to adjust for any unexpected differences in covariates and to describe mediation of effect. All data will be maintained on a CCHS server accessible only to those members of the

research team. All information will be coded based on the patients unique study number.

Works Cited

ACOG Committee on Practice Bulletins. (2007, May). *www.acog.org.* Retrieved 09 21, 2015, from http://www.acog.org/Resources-And-Publications/Practice-Bulletins/Committee-on-Practice-Bulletins-Gynecology/Endometrial-Ablation

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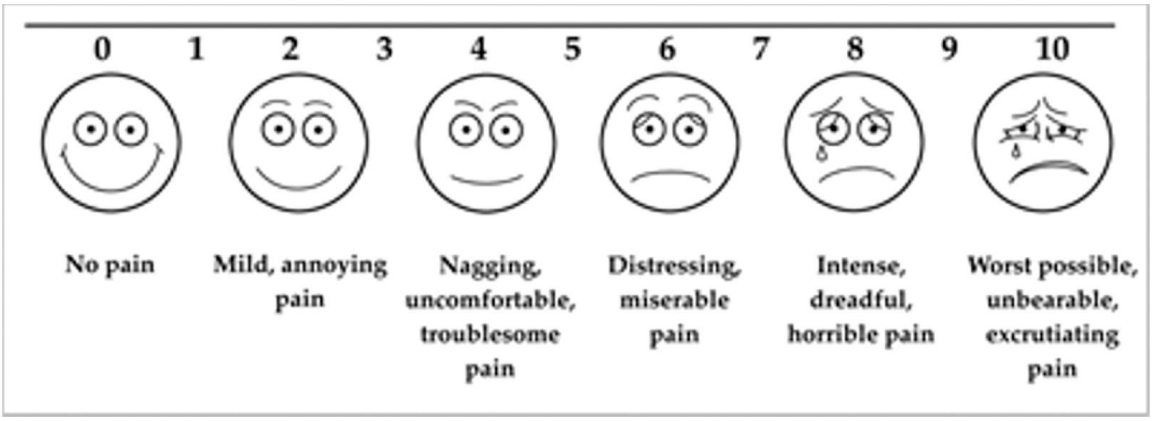
Wallage S, C. K. (2003, September). A Randomised Trial Comparing Local Versus General Anaesthesia for Microwave Endometrial Ablation. *The British Journal of Obstetrics and Gynaecology*, 799-807.

Sample Postoperative Home Pain Scores

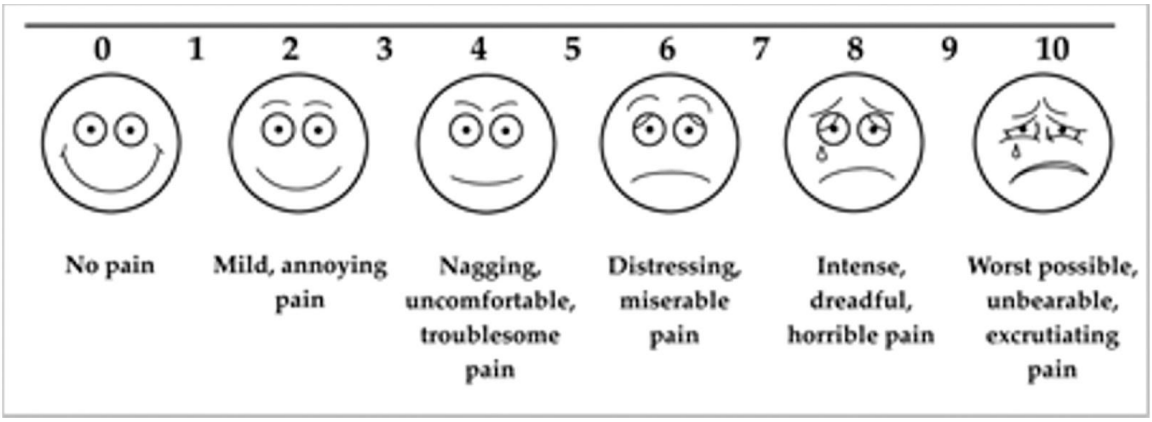
Patient Sticker
Study identification code #

Your surgery was completed at: Time and Date

Please rate your pain at: Time and Date



Please rate your pain at: Time and Date



Please retain this form until you have spoken with a member for the study team on the day following your surgery.