Gabapentin as an adjunct to paracervical block for perioperative pain management for surgical abortion: a randomized controlled trial

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Gabapentin as an adjunct to paracervical block for perioperative pain management for surgical abortion: a randomized controlled trial

Tiffany Hailstorks MD

Mentors:
Lisa Haddad MD MPH
Carrie Cwiak MD MPH
Emory University

Date of Submission: 2/8/16
Email: tiffany.p.hailstorks@emory.edu

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Project Summary

Justification for the project

One half of all pregnancies among American women are unintended, with nearly 4 in 10 ending in pregnancy termination by abortion [22]. Elective abortions are among the most common outpatient surgical procedure, with an estimated 46 million performed worldwide annually. The management of pain is critical to patient care throughout the abortion experience since the vast majority of women will experience pain with the procedure [23]. Patients are most affected by pain during paracervical block, cervical dilation, suction aspiration, and post operatively with uterine cramping [24]. Innovation in pain control and reduction of anxiety, nausea and vomiting using a low cost, well-tolerated intervention could impact thousands of women each year.

Proposed research

We plan a randomized controlled trial of gabapentin 600 mg compared to placebo given 1-2 hours pre-operatively in conjunction with perioperative paracervical block for surgical abortion. We hypothesize that adding gabapentin to local anesthesia will reduce perioperative and post-operative pain associated with surgical abortion. Additionally, we hypothesize that gabapentin will reduce nausea, vomiting, anxiety, and consumption of pain medication.

New features

The use of gabapentin in the setting of abortion has never been evaluated. Its use in similar surgical settings as an adjunct to pain management regiments has proven to be beneficial. It is generally well tolerated, inexpensive, has minimal side effects, and few contraindications.

Problems anticipated

The high volume at our clinic will benefit our recruitment efforts. However the coordination of this study may potentially disrupt clinic flow. We will limit our daily recruitment to reduce clinic impact. Post-operative follow-up may be challenging, thus to reduce the impact of loss to follow-up, most of our outcomes are measured on the same day as the procedure. Further, multiple contact approaches will be employed and a second incentive offered after completion of the post-operative assessment.

1. Description of the Project

1.1 Rational and objectives of the study

1.1.1 Rationale

Surgical abortions in North America are typically performed using local anesthesia, oral analgesics, moderate sedation, or a combination of approaches. A 2009 Cochrane review of pain control during abortion concluded that evidence on paracervical block (PCB) alone in reducing abortion related pain was limited, while the addition of ibuprofen and naproxen can slightly reduce intraoperative and post-operative pain [1] . Evidence supports the benefit of IV sedation (moderate or deep) at reducing intraoperative and post-operative pain with abortion.[2] However, IV sedation may not be an option for all women or in all clinical settings. Other recently examined adjuncts to pain control have not proven to be beneficial at reducing abortion-related pain [3-5].

Gabapentin is widely used to treat neuropathic and chronic pain. The mechanism of action may include calcium channel blockade or modulation of nociceptive neurotransmitters. Clinical trials support the use of perioperative pregabalin and gabapentin to reduce perioperative and post-operative pain in a variety of clinical settings, for both major and minor surgical procedures [6, 7]. While pregabalin has a faster peak plasma concentration, gabapentin is a less expensive option with peak concentration reached by 2 hours, with substantial evidence to support routine use and safety in reducing perioperative pain.

Innovation in pain control and reduction of anxiety, nausea and vomiting using a low cost, well-tolerated intervention could impact thousands of women each year who undergo common outpatient gynecologic procedures. We propose a novel use of oral gabapentin administered in conjunction with local anesthesia via PCB for surgical abortion. The use of gabapentin in the setting of abortion has never been evaluated; however it is used routinely and successfully in several similar surgical settings as an adjunct to pain management regimens. It is generally well tolerated and inexpensive, with minimal side effects and few contraindications [8]. When used in other gynecologic settings, gabapentin

has been shown to improve pain scores, and reduce nausea and vomiting [14,15]. If effective, this simple adjunct to current pain regimens could expand options for the management of women undergoing surgical abortion. We believe that the addition of gabapentin given prior to the procedure will reduce intraoperative and post-operative pain. Other secondary outcomes such as nausea, vomiting, and anxiety influence a woman's ability to return to her normal baseline level activity and her experience of abortion in general. The addition of gabapentin to current analgesia may provide an option to improve a woman's experience during a surgical abortion. Gabapentin 600mg was selected as a well-tolerated intermediate dosage with benefit proven in prior preoperative studies. Multiple post-operative doses in addition to the pre-operative dose had no significant effect on VAS scores at 24 hours, thus favoring single dosage [9].

1.1.2 Objectives and hypotheses

Pain control during and after abortion is a family planning research priority, as identified by the Society for Family Planning [10]. Pain management regimens for surgical abortion may include: local anesthetic, oral analgesics, moderate sedation, deep sedation, or a combination of approaches. While several recent studies have evaluated supplemental medications or therapies intended to reduce abortion-related pain, such as non-steroidal anti-inflammatory drugs (NSAIDs), narcotics, anxiolytics, misoprostol, nitrous oxide, or music, most have failed to note improved pain scores. Optimal pain management has yet to be established as many women continue to report moderate to severe pain during and after an abortion procedure [11].

We hypothesize that adding gabapentin pre-operatively to local anesthesia will reduce perioperative pain associated with surgical abortion. Additionally, we hypothesize that pre-operative gabapentin will reduce perioperative nausea, vomiting, and anxiety, as well as reduce post-operative pain and consumption of pain medication with few adverse effects.

Primary Aim: To evaluate the impact of adjunctive pre-operative gabapentin on intraoperative pain scores (at time of evacuation with the start of suction) during surgical abortion.

Secondary Aims:

- To evaluate the impact of pre-operative gabapentin on pain scores post operatively (removal of speculum, 10 and 30 minutes after procedure, at time of discharge and 24 hours after procedure)
- To evaluate the impact of pre-operative gabapentin on:
    - Perioperative nausea and vomiting
    - Perioperative anxiety
- To evaluate the impact of pre-operative gabapentin on perioperative medication consumption, and pain medication consumption up to 24 hours after the procedure
- To evaluate safety of gabapentin in this setting (monitor side effects or adverse events of gabapentin in this setting)

1.2 Previous similar studies

There have been multiple studies evaluating pain control during first trimester abortion under local anesthesia. Paracervical block (PCB) alone does not provide optimal pain control for all women. Further, studies evaluating different concentrations of lidocaine or different methods of injection did not significantly reduce pain. Pain with aspiration does not differ when comparing 0.5% lidocaine with 1% lidocaine [1]. Aspiration-related or post-operative pain does not differ when comparing a four site paracervical block (3,5,7,9 o'clock positions) to a two site block (4 and 8 o'clock positions) [12]. Non-steroidal anti-inflammatory drugs (NSAIDS) may be helpful in reducing pain for women receiving an abortion with PCB. Ibuprofen 600 mg given 30 minutes prior to dilation and curettage slightly improved intraoperative pain scores with a mean pain difference of 7.8 mm (on 100-mm scale)between the ibuprofen and placebo groups, but showed a more significant improvement (mean pain difference of 9.3 mm) in pain scores post-operatively [13]. The clinically meaningful significance of this difference is questionable. Naproxen given 1-2 hours prior to surgery has also been shown to improve pain scores [1]. Although NSAIDs

may improve pain with PCB, pain control is still often inadequate and some women may not be able to tolerate NSAIDs as they may develop gastrointestinal distress when given. Intravenous (IV) moderate sedation has been shown to offer superior perioperative and post-operative pain control [1, 14] compared to local anesthesia with PCB; however, patients may not be able to receive IV sedation due to the clinical setting, inability to find a means of transportation post-operatively, or may find IV sedation unacceptable.

We propose a novel regimen of oral gabapentin administered in conjunction with local anesthesia via PCB for surgical abortion. Gabapentin is used to treat neuropathic pain. Clinical trials support the use of perioperative gabapentin to reduce perioperative and post-surgical pain in a variety of clinical settings [6]. Gabapentin is well-tolerated and inexpensive, with mild, if any, side effects [8]. In a systematic review of 22 randomized controlled trials (RCT) of multiple surgical procedures including ambulatory nasal surgery, orthopedic procedures and laparotomy, a single pre-operative dose of gabapentin significantly reduced 24-hour opioid consumption [8]. Of the studies evaluating gabapentin use, 13 included a single dose of gabapentin, with doses ranging from 300-1200mg administered 1-2 hours prior to surgery with results noting a 20-62% reduction in opioid consumption within 24 hours after the procedure [8]. In the setting of obstetrics and gynecology, evidence supports perioperative gabapentin before hysterectomy to reduce pain scores, nausea, and vomiting [9, 15]. Following hysterectomy, the pain intensity difference between the control and gabapentin group was greatest in the early postoperative period, and decreased after 12 hours. The dosages ranged from 400mg - 1200mg, and the timing of dosing varied (preoperative dose, followed my multiple dosing at interval times identified)[8]. In addition, VAS scores at 24 hours decreased from 9-42.7 to 2-25.3 mm [9]. This study additionally found the significant reduction in VAS score was only noted with pre-operative administration while additional dosing was not associated with significant changes when compared to placebo. Further, postoperative nausea and vomiting was also decreased by pre-operative administration of gabapentin. However this may be due to decreased opioid consumption [9].

Preoperative gabapentin prior to cesarean delivery improved pain scores at 24 hours with less need for post-operative analgesia compared to placebo [15]. A randomized

trial in the setting of cesarean delivery showed improved pain scores and decreased pain medication requirements with a 600 mg dose of pre-operative gabapentin [15]. In this study, patients presenting for scheduled cesarean delivery were randomized to gabapentin or lactose placebo given 1 hour preoperatively. Pain scores with movement were evaluated at 24 hours, with the gabapentin group reporting pain scores of 21 mm (95 % CI 13-28) and the placebo group reporting scores of 41 mm (95% CI 31-50). Further, the gabapentin arm had higher maternal satisfaction scores [15].

In an outpatient setting similar to surgical abortion, perioperative gabapentin has been shown to decrease post-operative opioid consumption and anxiety for minor orthopedic procedures and hemorrhoidectomy [16, 17]. One randomized trial evaluated gabapentin 600 mg at 2 hour(s) prior to arthroscopic anterior cruciate ligament (ACL) reconstruction [16]. Average pain scores evaluated at 6 and 24 hours following reconstructive surgery confirmed that the gabapentin arm experienced significantly lower mean pain scores (4.8 at 6 hours on a 10cm scale) in comparison to the placebo group (6.9 at 6 hours on a 10cm scale) [16].

We propose a novel use of oral gabapentin administered in conjunction with paracervical block for surgical abortion, and believe that its use in this setting will reduce intraoperative and post-operative pain. Gabapentin 600mg was selected as a well-tolerated intermediate dosage with benefit proven in prior preoperative studies. Multiple post-operative doses in addition to the pre-operative dose had no significant effect on VAS scores at 24 hours, thus favoring single dosage [9]. Gabapentin will be given 1-2 hours preoperatively. A 100-mm pain visual analog scale has been shown to be useful for the evaluation of pain in prior pain abortion research [7, 18], with a 30% difference on a 100 mm-VAS scale, or 13-mm to 22-mm difference, as clinically meaningful [19, 20] [25].

1.3 Design and Methodology

1.3.1 Research design and General Methodology Approach

This is a randomized double-blind placebo-controlled trial evaluating the impact of gabapentin given preoperatively on perioperative pain scores for women receiving a surgical abortion. Randomization will be done using computer generated random

numbers. Allocation concealment will be maintained by identically labeled sealed sequentially numbered pill containers. Gabapentin and placebo will be packaged in identical gelatin capsules and sealed by an independent pharmacy. Gabapentin and placebo gelatin capsules will be indistinguishable by appearance, thus maintaining double blinding.

Primary study outcomes: Our primary outcome measure will be pain score using a 100-mm visual analog scale (VAS) measured intraoperatively at time of evacuation.

Secondary outcomes: We will also be measuring pain on the 100-mm VAS preoperatively immediately prior to the procedure, at completion of the procedure (removal of the speculum), 10 minutes and 30 minutes following the procedure, and at discharge. Nausea and vomiting will be assessed during the same time intervals using a 100-mm VAS scale. Anxiety prior to the procedure will be measured using the preoperative state trait anxiety inventory. Side effects will be assessed using a checklist prior to discharge. We will also be contacting participants on post-operative day 1 to assess pain, nausea, vomiting, side effects and general satisfaction with the procedure (on a 5-point scale). The quantity and type of medications used perioperatively and post-operatively, including medications used at home in the 24 hours post-operatively, will be abstracted from the clinical record and assessed on the phone. Outcome measures will be collected on a tablet using a web-based password-protected relational database (REDCap). All VAS scale scoring and questionnaires will be completed using this database on a research-designated tablet.

Baseline Characteristics and Covariates:

We will collect baseline demographics, medical history (gravidity, parity, prior abortions (medical and surgical), gestational age, drug and alcohol use, psychiatric or sexual assault history, medications used at home and given at the clinic preoperatively, and indication for procedure (personal/social, fetal, or maternal health). This information will also be obtained using a research-designated tablet.

Outcome measures and baseline variables are described in table 1.

Table 1: Outcome measures and covariates
Primary outcome • Pain score validated on a 100mm VAS scale measured at time of start of uterine evacuation
Secondary outcomes: • Pain on VAS scale: preoperatively, completion of procedure (removal of speculum), 10 and 30 min following procedure in the recovery room, at time of discharge • Medication use: pain and nausea medication used during and after procedure • Nausea/vomiting: pre op and post op nausea per VAS and episodes of vomiting • Anxiety: preoperative state anxiety inventory • Side effects • Postop assessment via phone on POD#1: pain, nausea, vomiting, and overall clinic experience
Covariates of interest: • Age • Gravidity, parity, prior abortions • BMI • Gestational age • Preoperative meds • Current or history of drug abuse • Current or history of psychiatric disorder • Indication for procedure • Expectation of pain • Pain experience with prior abortion • Smoking

1.3.2 Criteria for the selection of subjects

Location:

This study will take place at Atlanta Women's Center (AWC), a free-standing abortion clinic in metro-Atlanta that offers abortion services to women up to 23 weeks 6 days gestation. This clinic operates 4 days per week (Wednesday through Sunday) with a clinical volume of 15 to 45 abortions per day. As abortion services are limited in the southeastern region of the United States, women often travel from other states, including Tennessee, Alabama, Florida, Mississippi, North Carolina and South Carolina to receive care at this clinic. Approximately 4800 women are seen annually at AWC, with 720 women having abortions under local anesthesia and 3740 women receiving deep sedation anesthesia. Approximately 3320 women are 6-12 weeks GA, 800 women are 13-18 weeks and 340 women are over 18 weeks. Based on the patient volume, we do not anticipate any difficulty in recruiting patients to complete this study within the timeline presented. Misoprostol for cervical preparation is given prior to cases at 10 to 14 weeks per provider preference. Local anesthesia is offered as an option up to 16 weeks, however most cases performed with local anesthesia are less than 14 weeks, with the later gestational ages performed with deep sedation.

AWC, where Dr. Haddad is the medical director and the study will be conducted, has documented success in participating in and recruiting for several industry sponsored and investigator initiated research studies: a randomized trial of levonorgestrel compared to

ulipristal for emergency contraception (LIFE) study through Washington University in St. Louis, and a prospective cohort study of medical abortion through 11 weeks conducted with Gynuity. This study will benefit from the existing research infrastructure and will resource share for recruitment and enrollment with another study at this site evaluating post-abortion contraception.

Participation selection:

Women who attend the AWC for an abortion will be approached during their preoperative evaluation to determine interest in participating in the study and if so, will be consented for the study and then screened for eligibility. We will enroll a total of 133 women. A baseline survey given after enrollment will collect covariates of interest that may impact a woman's abortion pain experience.

The enrollment of participants is as follows:

Group A: This is the placebo group. This group will receive local anesthesia per clinic protocol PLUS placebo 1-2 hours preoperatively.
Group B: This is the gabapentin group. This group will receive local anesthesia per clinic protocol PLUS Gabapentin 600mg 1-2 hours preoperatively.

Gabapentin 600mg was selected as a well-tolerated intermediate dosage with benefit proven in prior preoperative studies. Multiple post-operative doses in addition to the pre-operative dose had no significant effect on VAS scores at 24 hours, thus favoring single dosage [9].

Power Calculation:

A 100-mm pain visual analog scale has been shown to be useful for the evaluation of pain in prior pain abortion research [7, 18], with a 30% difference on a 100 mm-VAS scale, or 13-mm to 22-mm difference, as clinically meaningful [19, 20] [25]. Assuming a standard deviation of 26 mm on the 100-mm VAS scale [7], enrolling 96 women will provide us with

an 80% power, using a p-value of 0.05, to detect a 15-mm difference on a 100-mm VAS among women presenting for abortion. The enrollment of 96 women is estimated based on a sample size for a t-test. This sample size is adjusted based on the ARE (asymptotic relative efficiency) of the Mann–Whitney U test statistic. The ARE is based on distribution, which is unknown here. Since the ARE for the Mann-Whitney is never less than 0.864, the sample size from the t-test above will be divided by this value. This creates a sample size of 111 women. To account for a potential 20% loss to follow up, the target enrollment goal will be increased to 133 total women for participation in this study.

Inclusion and Exclusion Criteria:

Inclusion criteria include:

- Women >=18 years-old
- Presenting for a surgical abortion
- Fluency in English and able to provide informed consent
- Has a driver to take them home

Exclusion criteria include:

- Allergy, sensitivity or contraindication to gabapentin
- Severe renal disease
- Currently using gabapentin or pregalabin
- Contraindication to outpatient abortion under local anesthesia

Although patients on any chronic pain medications or with pre-existing pain conditions or history of alcohol or drug use may have a different metabolism or effect of the drugs, these women will not be excluded. Rather, data will be collected on these factors to evaluate the impact of these factors on study outcomes.

1.3.3 Subject recruitment and allocation

All recruitment, consenting, screening, and enrollment questions will be asked by trained study staff in a private room.

Recruitment:

We will be recruiting until a total of 133 women are randomized. The proposed research will take place at Atlanta Women's Center (AWC). Women who attend the AWC for an abortion will be approached during their preoperative evaluation. The flow of steps to assess women presenting for abortion occur in the following order: ultrasound for gestational age, blood draw to assess hemoglobin and Rh factor, options counseling to determine whether surgical abortion is chosen, financial payment, and nurse preoperative review. Trained research staff will approach these women to determine interest in participating in the study, consent those interested in participating, and then participants will be screened for eligibility. A standard recruitment script will be employed (Appendix A). We will enroll participants after financial counseling and before nurse preoperative review. Consent will be obtained at time of enrollment.

Screening and consent:

Individuals who are interested in participating will review the informed consent and eligibility screening. We will screen for eligibility using an eligibility checklist (Appendix A). Patient contact information will be collected at this time. Enrollment will occur after financial counseling, and consent will be obtained at time of enrollment. Following enrollment, the patient's medical history will be reviewed by a clinician to ensure study eligibility. Randomization will occur and intervention will be received after enrollment. The study drug (intervention or placebo) will be dispensed by the PI, Clinic Director, or Clinic Staff Nurse. Both the Clinic Director and Clinic Staff Nurse are registered nurses with required CITI training.

Potential subjects will typically do their 24hr consent over the phone prior to presenting to the clinic. Thus, the preoperative evaluation and procedure both occur on the same day. We are not approaching any potential subjects for interest in the study until after they have selected local anesthesia and paid for their procedure.

The abortion providers are not involved in the discussion with the patient regarding "timing, method, or procedures used to terminate a pregnancy". This is a discussion that the clinic staff has with the patient after ultrasound evaluation (to confirm gestational age) and financial counseling. The patient also goes through options counseling with clinic staff (not the abortion provider) during which the different types of procedures are discussed (medical vs surgical procedure based on gestational age). The study team will only begin interaction with the potential subject/patient once they've selected local anesthesia and paid for their procedure. The Investigators will only be involved after this point. Investigator involvement may include consenting the subject, administering the study drug, performing the procedure, and other study related activities such as administering the questionnaire. There is one abortion provider per day at Atlanta Women's Clinic and if an investigator is the provider for that day, she will not participate in any other study-related activities.

The person obtaining the consent will be a member of the study team. This person will have no prior contact with the study patient. This person will not be scheduling the appointment, discussing options counseling, advising about the procedural options, or performing ultrasound or other laboratory work-up for the participant prior to the procedure. There is a clear separation between study staff and clinic staff prior to the enrollment of participants into the study,

Randomization, Allocation Method and Blinding:

Women who enroll and meet study inclusion criteria will be eligible for participation. *Randomization* will be done using computer-generated random numbers (randomization.com) in variable blocks of 4 and 6. *Allocation* concealment will be maintained by identically labeled sealed sequentially numbered opaque pill containers. Gabapentin and placebo tablets will be indistinguishable by appearance (both gelatin capsules), thus maintaining blinding for participants and assessors. To maintain double *blinding* for both investigators and participants, an individual not associated with study conduct will create the randomization sequence and allocation containers. The study drug

and placebo will be obtained through the Duke Investigational Drug Service that will vacuum seal the containers prior to shipping to the clinic. The randomization assignments will only be revealed at the point of data analysis or if an interim assessment is needed.

1.3.4 Description of the drugs and devices to be studied

Gabapentin was originally approved by the U.S. Food and Drug Administration (FDA) in December 1993, for use as an adjuvant (effective when added to other antiseizure drugs) medication to control partial seizures in adults; that indication was extended to children in 2000 [21], and later approved for treating postherpetic neuralgia. In December 2004, the FDA granted final approval to a generic equivalent to Neurontin made by the Israeli firm Teva. It was originally synthesized to mimic the chemical structure of the neurotransmitter GABA. The mode of action of gabapentin is believed to be through its binding to the alpha 2 delta subunit of the DRN voltage-dependent calcium channels. This causes decreased entry of calcium into the nerve endings, resulting in decreased release of nociceptive neurotransmitter (glutamate, substance p, noradrenaline). Other proposed mechanisms of action include the binding to NMDA receptors, sodium channel receptors, monoaminergic receptors, and opioid receptors.

Overall, gabapentin is a safe drug. The most common side effects of its use include: dizziness, somnolence, fatigue, ataxia, peripheral edema, nystagmus, nausea and vomiting, asthenia, headache, weight gain, and amblyopia. Most of the side effects are associated with chronic usage. Other extremely rare side effects include: DRESS (drug reaction with eosinophilia and systemic symptoms), multi-organ hypersensitivity, withdrawal seizures (if given for epilepsy), suicidal behavior and ideation, neuropsychiatric reactions in pediatric patients (3-12 years of age), and sudden death.

Drug Interactions are rare and mild. Maalox or other aluminum or magnesium hydroxides decreases bioavailability of gabapentin by 20% if given at same time. Additionally, when used with hydrocodone or morphine, gabapentin may decrease the AUC. Abuse and withdrawal potential is low. The drug is almost entirely metabolized through renal metabolism, where it is eliminated unchanged in the urine, thus dosage adjustments are needed for patients with renal impairment. The half-life for the medication is 5-7 hours with a 2 hour time to peak plasma concentration.

1.3.5 Admission procedure

After financial clearance, all participants who have opted for a surgical abortion with local anesthesia will be approached for interest in the study. A study interest card will be placed on their medical chart, and the participant will be accompanied by the financial counselor and taken to the designated research room. This designated research room is a private room located in AWC. The study team will then review the recruitment script with the patient. If the patient is interested in the study, then a member of the study team will consent the participant. Following consent and enrollment into the study, the participant will be taken to the clinical nurse. The nurse will review the participant's chart to ensure eligibility for surgical abortion and gabapentin administration. The participant will then receive the study drug or placebo. Following administration of the drug, the participant will return to the designated research room. The study staff will review the baseline questionnaire that includes demographic questions. Following completion of the questionnaire, the participant will continue to wait in the designated research room or preoperative area. One hour after the administration of the drug or placebo, the participant's chart will be placed back into rotation for surgical procedures. The study team will accompany the participant to the clinical lounge where they will gown and prepare for the procedure. The participant will then undergo the procedure in order of chart placement. Prior to initiating the abortion procedure, study staff will administer the preoperative questions. Staff will administer the intraoperative questions at the time of evacuation during the uterine aspiration, and at time of removal of the speculum at the end of the procedure. Immediately following the procedure, the study staff will follow the participant to the recovery room to complete the remaining questions assessed at 10 minutes, 30 minutes and at discharge. Per clinic protocol, patients remain in the recovery room for approximately 30-60 minutes after surgical abortion with local anesthesia. When the discharge questions are complete, the participant will receive a $30 gift card and be reminded to expect a follow-up call the following day (post operative day #1).

1.3.6 Follow-up procedure

On the day following the procedure (approximately 24 hours after the abortion), study staff will contact the participant to complete the follow-up questions. The participant will be contacted via email, text communication and telephone. Upon completion of the questions, an additional $20 will be added to the original gift card.

Withdrawals, losses, and deviations:

Randomization to the study method will occur after completion of all intake forms and consent, immediately before the pill is to be taken, thus reducing the possibility of withdrawal after randomization. Any significant medical history will be reviewed prior to enrollment with a clinician at the clinic to ensure study eligibility. Primary outcome measures and most secondary outcome measures will be assessed immediately before, during or after the abortion procedure, thus any loss to follow-up will be limited to those who consent to, but change their mind while waiting for their procedure. Based on current clinical practice at this clinic, withdrawal after consent is extremely rare. Our secondary outcomes assessed post-operatively after discharge will be collected via telephone. We will maximize completion of these assessments through the following steps: participants will be told beforehand about the telephone contact following the procedure, a cellular telephone number will be collected and tested at the clinic, a secondary phone number and email will be collected as a backup, participants will be given a contact number for the study coordinator should they have any challenges with receiving phone calls, and participants will receive an additional $20 sent to their gift-card following the completion of their phone assessment. Subjects will be considered lost-to-follow-up if they have not responded to the follow up survey within 48 hours after their procedure. As we anticipate some loss to follow-up for our secondary outcome on post-operative day 1, we have adjusted our study enrollment to provide some accommodation for 20% loss to follow-up.

1.3.7 Criteria for discontinuation

An adverse event (AE) is defined as any health-related reaction, effect, toxicity or abnormal laboratory result that a study participant experiences during the course of the study, irrespective of relationship to the study intervention. This includes changes in a participant's condition that have or could have a deleterious effect on a participant's health

or well-being. A serious adverse event (SAE) is defined as any experience that is fatal or life threatening, requires in-patient hospitalization or prolongation of an existing hospitalization, or results in a persistent or significant disability or incapacity.

This study uses an additional medication for pain control in the setting of outpatient abortion. These activities are not anticipated to be associated with any deleterious impact on participants' health or well-being beyond the risks associated with the abortion procedure. AEs will be managed according to good clinical practice and the judgment of the on-site physician. All clinical and laboratory AEs will be followed-up closely by study staff. Any SAEs will be expeditiously reported to the principal investigators, via a designated SAE form. Notification and submission of SAE forms should occur within 48 hours of the site awareness of the SAE. The PI will then make the final independent judgment as to the severity, relatedness, and anticipated or unanticipated nature of the SAE and finalize the Human Subjects Adverse Event Report Form. If the event is determined to be serious, unanticipated, and the relationship is anything other than probably or definitely not related, then the PI will report the event within 48 hours and submit the required forms to the IRB at Emory. Thus, all anticipated SAEs that are at least possibly related to study intervention and all deaths that are at least possibly related to study intervention will be submitted to Emory IRB.

The study may be discontinued at any time by IRB at a participating institution or the Office for Human Research Protection. One of the co-investigators (TH) will review any adverse event and periodically review side effects to see if there are an increased number of events than anticipated by routine clinical care. If any suspicion for increased risk exists, study allocation may be revealed for a preliminary analysis and if related to the study intervention, the study could be prematurely ended.

Data Monitoring Committee/Study Termination:

A Data Monitoring Committee (DMC) will be created to perform regular and timely review of data in order to identify early, significant benefit or harm for patients while the trial is in progress. On a regular basis (frequency as to be determined by the DMC based on the enrollment rate and potential risk to subjects), non-identified safety data will be

communicated to the DMC who will then meet to review the data. The DMC will be composed of three faculty members within the Emory University Department of Gynecology and Obstetrics. Individuals who are investigators or co-investigators cannot be members. No member of the research study team will be on the committee. Members must have no financial, scientific, or other conflicts of interest with the study. All investigators understand that the DMC serves as additional human subject's protection, but does not supplant reporting of significant adverse events to the Emory IRB. The DMC may devise its own stopping rules, and if there are significant numbers of adverse events, the DMC will recommend continuation, modification, or termination of the study after each meeting. This recommendation will be communicated to the principal investigator who is responsible for reviewing the recommendation and forwarding it to the IRB. .

1.3.8 Laboratory and other investigations

Examinations will be performed prior to the surgical abortion that are in accordance with the standard of care. No additional laboratory studies will be performed for the clinical trial.

1.3.9 Data management

Prior to study initiation, a database will be developed using a web-based password-protected relational database (REDCap). All data will be collected electronically into the database on tablets. All consent documents will be filed in a locked cabinet and stored for future reference. Data will be collected on research-designated tablets.

1.3.10 Data analysis

We will compare groups on the primary continuous outcome measure (pain score on 100-mm point VAS) using T-tests and Mann-Whitney U test. Chi-square and T-tests will be used to evaluate secondary outcomes for categorical and continuous variables, respectively. Baseline characteristics will be evaluated for potential interaction or confounding with primary and secondary outcomes.

All available data from completed questions will be used for analysis, including partially completed surveys. Participants may request that their data not be used for analysis if a request is received prior to analysis as mentioned in the consent form. A statistician will be consulted to assist with the analysis as needed.

1.3.11 Number of subjects and statistical power

We will enroll a total of 133 women. This number was determined to give us sufficient power to detect a **15-mm difference on the 100-mm VAS**. A 100-mm pain visual analog scale has been shown to be useful for the evaluation of pain in prior pain abortion research [7, 18], with a 30% difference on a 100 mm-VAS scale, or 13-mm to 22-mm difference, as clinically meaningful [19, 20] [25]. Assuming a standard deviation of 26 mm on the 100-mm VAS scale [7] based on the literature, a total of 96 participants will provide us with an 80% power, using a p-value of 0.05, to detect a 15-mm difference among women presenting for abortion. The enrollment of 96 women is estimated based on a sample size for a t-test. This sample size is adjusted based on the ARE (asymptotic relative efficiency) of the Mann–Whitney U test statistic. The ARE is based on distribution, which is unknown here. Since the ARE for the Mann-Whitney is never less than 0.864, the sample size from the t-test above will be divided by this value. This creates a sample size of 111 women. To account for a potential 20% loss to follow up, the target enrollment goal will be increased to 133 total women for participation in this study. Therefore we determined that 133 women would need to be enrolled.

1.3.12 Study limitations

Strengths of this study include the location site and its ability to recruit the sample population, as well as the previous research being done at AWC. Pain perception is complex and composed of a multitude of elements. This study will also attempt to allow for the comprehensive evaluation of pain and identify behavioral factors that influence one's perception of pain throughout the abortion.

Limitations of the study include gestational age limits. Local anesthesia is only offered to patients up to 14-15 weeks so this will not allow for the evaluation of later gestational ages in which patient's may benefit from this adjunct medication.

Gabapentin is low-cost and effective in perioperative settings, and may be an effective adjunctive therapy for surgical abortion. Future direction may involve a prospective multi-site analysis (PMA). PMA methodology will evaluate the potential effect of adding gabapentin to different pain control regimens and among different patient populations, maximizing external validity. Further, we aim to leverage the developed PMA infrastructure to apply for future large research studies in abortion care, providing an innovative and feasible approach for developing generalizable research and to target low prevalent groups.

1.3.13 Duration of the project

We plan on obtaining Emory IRB approval, hiring staff and completing clinic and study staff training by Spring 2016. We are in contact with a compounding drug lab and will obtain the study drug by Spring 2016. Study recruitment and data collection is projected to begin in early 2016. The expected length of data collection is 9-12 months. We will complete data analysis and drafting of the manuscript during the last 6 months of the study period. Refer to table 2 for additional details.

Table 2: Project timeline

	2016						2017			
Study Activity	September	October	November	December	January	February	March	April	May	June
Hire and train staff										
Compounding study drug, randomization and allocation packaging, distribution										
Database development										
Study recruitment and data collection										
Site data analysis and manuscript preparation										

1.4 Project management

At Emory, the principal investigator is Dr. Tiffany Hailstorks with Dr. Lisa Haddad. Dr. Carrie Cwiak, as faculty mentor. Drs. Hailstorks and Haddad will be the primary contacts and responsible parties for the study.

1.5 Links in other projects

This project is not linked with any existing project.

1.6 Main problems anticipated

This study aims to recruit 133 women into a randomized controlled trial in an outpatient abortion setting. Given the patient volume at this clinic, coordination of the study may be challenging, however we anticipate that the patient volume is a factor that will increase the success in reaching recruitment targets quickly. To ensure that patient flow is not interrupted, we will have study staff dedicated to the study activities including consent and data collection, thus eliminating any dependence upon current clinical staff for study operation. We also anticipate that follow-up on post-operative day one may be challenging. To reduce the impact of loss to follow-up, our primary impact measure and most of our secondary measures are measured on the same day as the procedure. Further, to maximize retention, we will test a phone number at the time of enrollment, collect secondary contact information, give the patient a contact number for the study coordinator should they have difficulty receiving a call, and provide reimbursement for completion via transferring funds to a gift-card following completion of the follow-up questionnaire.

1.7 Expected outcomes of the study and dissemination of findings

The benefits of this research directly extend to potential improvements in the pain management procedures provided at the facility. Moreover, the results could potentially impact individuals globally as we aim to better address pain management in the setting of outpatient abortion. Continued efforts are needed to optimize pain control during surgical abortion. Gabapentin is a safe and inexpensive medication that has been employed as an adjunct to anesthesia with significant reductions in perioperative pain and nausea. We aim

to explore this novel medication as an adjunct to local anesthesia where other interventions have been less successful in improving pain scores.

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2. Ethical Considerations

The study will not commence until the study protocol has been reviewed and approved by the Emory University Institutional Review Board (IRB).

Risk of medication: Gabapentin has been used in several other clinical settings and is associated with few side effects, thus the risks associated with its use as an adjunct to abortion perioperative pain regimens are minimal. As this is a low-cost intervention that has promise for improving pain, the potential for risk is balanced by the potential benefit. Side effects and adverse effects will be carefully tracked and monitored during the study. Documented side effects of gabapentin include: dizziness, somnolence, fatigue, ataxia, peripheral edema, nystagmus, nausea and vomiting, asthenia, headache, weight gain, and amblyopia. Most side effects are associated with chronic usage. Other rare side effects include: DRESS (drug reaction with eosinophilia and systemic symptoms), multi-organ hypersensitivity, withdrawal seizures (if given for epilepsy), suicidal behavior and ideation, neuropsychiatric reactions in pediatric patients (3-12 years of age), and sudden death.

Sensitive information: The risks involved in study participation are those related to providing personal information about sensitive topics. Participants' privacy and the confidentiality of data will be protected through training of study staff, conducting all interviews and procedures in private, storing study materials in a locked room, and securing computer files that include identifiers. Only the study identification number will identify participant research records. Linkages between the ID number and participants' identifying information will be maintained in a computer database that is password protected and only accessible to study staff. These linkages will be destroyed 7 years after completion of study activities. We will ensure that study staff is thoroughly trained to not disclose any information about the study or the participant's attendance at the clinic to any individual other than the study participant. Breaches of confidentiality are possible, though safeguards are in place to protect the confidentiality of participants. Thus, the potential for experiencing an adverse event is minimal.

Gabapentin:

Gabapentin is indicated for the management of postherpetic neuralgia in adults, as adjunctive therapy in the treatment of seizure disorder, and for chronic pain management. Gabapentin is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients. When gabapentin is taken for chronic use, side effects are noted. Drug reaction with eosinophilia and systemic symptoms, also know at multiorgan hypersensitivity, has occurred with gabapentin. These reactions can be fatal or life threatening. Typical symptoms include but are not limited to fever, rash, lymphadenopathy, hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. In the presence of signs or symptoms, prompt evaluation and discontinuation of gabapentin is warranted. Although rare, gabapentin can cause anaphylaxis and angioedema after the first dose or any time during treatment. The patient should be instructed to discontinue the medication and seek immediate medical attention.

During the controlled epilepsy trials in patients older than 12 years of age, the patients who received gabapentin (up to 1800mg daily) reported greater rates of somnolence (19%), dizziness (7%) and ataxia (6%) when compared to the placebo group. During the controlled trials in patients with postherpetic neuralgia taking doses of gabapentin up to 3600mg, patients reported increased somnolence (21% of the gabapentin arm vs. 5% of the placebo arm), and dizziness (28% of the gabapentin arm vs. 8% of the placebo arm). Patients should be carefully observed for signs of central nervous system depression, especially when gabapentin is used with other drugs with sedative properties.

Antiepileptic drugs (AEDs), including gabapentin, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients should be monitored for the emergence or worsening depression, suicidal thoughts or behavior, and/or unusual changes in mood or behavior. Pooled analysis showed that patient randomized to one of the AEDs had approximately twice the risk of suicidal thinking or behavior compared to patients randomized to placebo. It should be noted that these trials had a median treatment duration of 12 weeks.

During the premarketing developing of gabapentin, there were 8 sudden or unexplained deaths that were recorded among a cohort of 2203 epilepsy patients treated

with gabapentin. This rate exceeds that expected in a healthy population that is matched for age and sex. This rate falls within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving gabapentin.

Below is a table that outlines adverse reactions that occurred in at least 1% of gabapentin treated patients with postherpatic neuralgia participating in placebo-controlled trials.

Adverse reactions in Pooled Placebo-Controlled Trials in Postherpetic Neuralgia

	Gabapentin (N=336, %)	Placebo (N=227, %)
Body as a whole		
Asthenia	6	5
Infection	5	4
Accidental injury	3	1
Digestive system		
Diarrhea	6	3
Dry mouth	5	1
Constipation	4	2
Nausea	4	3
Vomiting	3	2
Metabolic and nutritional disorders		
Peripheral edema	8	2
Weight gain	2	0
Hyperglycemia	1	0
Nervous system		
Dizziness	28	8
Somnolence	21	5
Ataxia	3	0
Abnormal thinking	3	0
Abnormal gait	2	0
Incoordination	2	0
Respiratory		
Pharyngitis	1	0
Special senses		
Amblyopia	3	1
Conjunctivitis	1	0
Diplopia	1	0

Otitis media	1	0

Below is a table that outlines adverse reactions that occurred in at least 1% of gabapentin-treated patients over the age of 12 who participated in placebo-controlled trials on epilepsy.

Adverse reactions in Pooled Placebo-Controlled Trials in Epilepsy patients over age 12

	Gabapentin (N=543, %)	Placebo (N=378, %)
<u>Body as a whole</u>		
Fatigue	11	5
Increased weight	3	2
Back pain	2	1
Peripheral edema	2	1
<u>Cardiovascular</u>		
Vasodilation	1	0
<u>Digestive system</u>		
Dyspepsia	2	1
Dry mouth and throat	2	1
Constipation	2	1
Dental abnormalities	2	0
<u>Nervous system</u>		
Dizziness	17	7
Somnolence	19	9
Nystagmus	8	4
Ataxia	13	6
Tremor	7	3
Dysarthria	2	1
Amnesia	2	0
Depression	2	1
Abnormal thinking	2	1
Abnormal coordination	1	0
<u>Respiratory</u>		
Pharyngitis	1	0
Coughing	2	1
<u>Skin and appendages</u>		
Abrasions	1	0
<u>Urogenital system</u>		
Impotence	2	1

Special senses		
Amblyopia	4	1
Diplopia	6	2

Data presented here is directly from FDA prescribing information. The gabapentin drug information in this section is from the FDA website. Our study will only administer a one-time dose of gabapentin, and therefore we do not anticipate the side effects listed that are more likely associated with chronic use.

Reference:

http://www.drugs.com/pro/gabapentin.html#S5.4