Official Title: Lidocaine Patch for Adjunct Analgesia for Postoperative Cesarean Birth Patients

Principal Investigator: Catherine Leclair, MD

Professor, Department of Obstetrics and Gynecology, Oregon Health & Science University

NCT No. 03500211

Protocol Version Date: 28 September 2018

IRB proposal

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PI: Catherine Leclair, MD, Obstetrics and Gynecology

IRB # 16657

1) Objectives

Purpose: Determine if lidocaine patch is effective for adjunctive analgesia in postoperative pain for cesarean birth patients.

Hypothesis: Lidocaine patches are an effective adjunct for postoperative pain for patients in the acute postoperative state from cesarean birth and result in decreased pain scores on a visual analogue score and decreased narcotic use.

Objective: Determine if a lidocaine patch is superior to placebo in achieving analgesia in acute postoperative cesarean birth patients.

Primary endpoint

1. To determine if lidocaine patch is superior to placebo as an adjunctive therapy for acute postoperative pain. This will be determined by comparing patient scores on an 11 point (0-10) visual analogue scale.

Secondary endpoints

2. To determine if narcotic use changes when patients use lidocaine patches by counting amount and frequency of narcotic use over admission.
3. Use a 2 question survey asking patient and provider about satisfaction with patch in managing postoperative pain
4. To determine if number of previous cesarean births contribute to the experience of postoperative pain.
5. To determine if length of time in the operating room is associated with increased postoperative pain (incision to dressing).
6. To evaluate if length of stay is associated with lidocaine patch use.

2) Background

Using non-opiate adjunctive medications to enhance or improve post-operative pain is a recent area of focus in anesthesia. Topical lidocaine patches have been FDA approved for postherpectic neuralgia and are thought to provide effective analgesia to nerve receptors in the skin. The ability of the lidocaine patch to directly mediate cutaneous nerves makes it a desirable choice to treat acute post-operative incisional pain. As such these patches have been used in the acute postoperative setting for treating incisional pain after laparoscopic

and open abdominal procedures (Gilhooly *et al* 2011, Saber et al 2009[1]). The efficacy of a lidocaine patch in treating acute postoperative pain as an adjunct to opioids is not well studied and specifically has not been studied in obstetric surgery. Despite the lack of evidence there is a theoretical benefit that these patches may be useful for pain control and use should be considered to decrease use of systemic narcotics.

Patients who undergo cesarean birth have two types of pain: visceral and somatic. Somatic pain arises from direct tissue trauma from the surgical incision, whereas visceral pain is thought to be[i] secondary to the inflammatory proteins released in response of healing and is associated with visceral organs. After a cesarean birth a patient perceives pain through distinct neurological pathways. Somatic pain is transmitted via the anterior division of spinal segmental nerves, whereas visceral uterine nociceptive stimuli return to the central nervous system via afferent nerve fibers that ascend through the inferior hypogastric plexus and enter the spinal cord via the T10-L1 spinal nerves (Lavand'homme 2006). It is thought that both of these pathways need to be treated for appropriate pain control in a post cesarean birth patient. Appropriate pain control is crucial. Data shows that optimal postoperative pain control is important for long term health as there are some studies that have shown that poor pain control in the acute setting post cesarean is a risk factor for pelvic pain or chronic pain (Lavand'homme 2006) (Lavoie and Toledo 2014) (Andreae and Andreae 2012). Traditionally, narcotic medications have been used for this and though effective have a concerning side effect profile particularly for postpartum patients. This has led clinical advocacy groups to call for strategies to minimize use.

Narcotic pain medications are effective in treating both somatic and visceral pain in the acute setting but have a side effect profile of sedation, dizziness, passage through breast milk and constipation (Reviewed in Verstraete and Van de Velde 2012). This is particularly challenging in the postpartum patient for several reasons: Post-delivery, breastfeeding is recommended every 2-3 hours, thus a medication that is sedating can lead to difficulty breastfeeding and could actually be dangerous if a mother falls asleep with a baby in her arms. Additionally, in the acute postoperative setting both pelvic surgery and the acute postpartum state contribute to DVT risk and early ambulation is highly encouraged. Opioid medication that leads to dizziness and sedation makes early ambulation and thus DVT prophylaxis more difficult for patients. Moreover, although there is data that the amount of opioids that get into breastmilk is low, there have been case reports of infant deaths secondary to narcotic absorption and hypermetabolism of routine post op narcotic pain medications. Most postpartum mothers wish to limit the amount of narcotic that there baby is exposed to. In addition to specific risks associated with infant care and breastfeeding, there are other specific issues with narcotic use in the postpartum setting. In the acute postpartum period both high progesterone levels and breastfeeding can contribute to constipation which can be severe; all narcotic medications cause additional constipation in these patients already pre-disposed to this problem. Because of all of the aforementioned reasons, there are many groups like the Center for Disease Control and the American Pain Society that advocate for minimizing narcotic use particularly in obstetric populations. Thus, post-operative pain from cesarean birth deserves a multimodal analgesia to optimize pain management and minimize narcotics. The use of adjuncts to narcotic pain medications would "minimize (narcotic)-related side effects to the mother and her infant therefore

allowing for early return to baseline function and preventing a prolonged hospital length of stay" (Lavoie and Toledo 2014).

A recent Cochrane review concluded that "Local analgesia infiltration and abdominal nerve blocks as adjuncts to regional analgesia and general anesthesia are of benefit in caesarean birth by reducing opioid consumption" (Bamigboye A and Hofmeyr G 2009). In particular, the local analgesic effect of a lidocaine patch is particularly an attractive feature for breast feeding patients who are interested in minimizing narcotic use. In one report, a patient who was unable to use any narcotic pain medications used 5% lidocaine patches as primary analgesia post cesarean birth with good success (Gilhooly *et al* 2011) indicating that a lidocaine patch may specifically have a role in post cesarean multimodal analgesia. Additionally, a lidocaine patch is currently being used in approximately 50% of patients who undergo cesarean birth at OHSU (unpublished) and is part of the standard post-operative order set but has never been studied in this patient population. Therefore, a study examining whether the lidocaine (Lidoderm®) patch is effective as a component of multimodal analgesia post cesarean birth is justified.

Lidocaine patches are likely safe to use in the post cesarean patient with little systemic absorption and negligible amounts being excreted into breast milk. No studies currently exist evaluating this population. However, pharmokinetics (Micromedex, Gammaitoni 2003[2]) show that systemic absorption is low at peak half-life and well below the level of concern for cardiac effects. Serum levels are directly related to the duration of use and the surface area of application. In one study where THREE patches (2100mg) were placed simultaneously, the area of distribution was 420$cm^{2.}$ Blood levels during patch use and 12 hours following patch removal showed only 64mg ± 32mg was absorbed and serum levels were 0.13 ± 0.06 micrograms/mL. The mean serum peak of 0.13 micrograms/mL is approximately 1/10 the amount needed to treat a cardiac arrhythmia. Approximately 5% of the total amount of lidocaine is absorbed from the patch with the majority of medication remaining in the used patch. Additionally, repeated dosing over three days did not show

increased serum levels. In our proposed study, we intend to use ONE patch over a distribution of 14x2 cm^2 on the lower abdomen, much below the stated level.

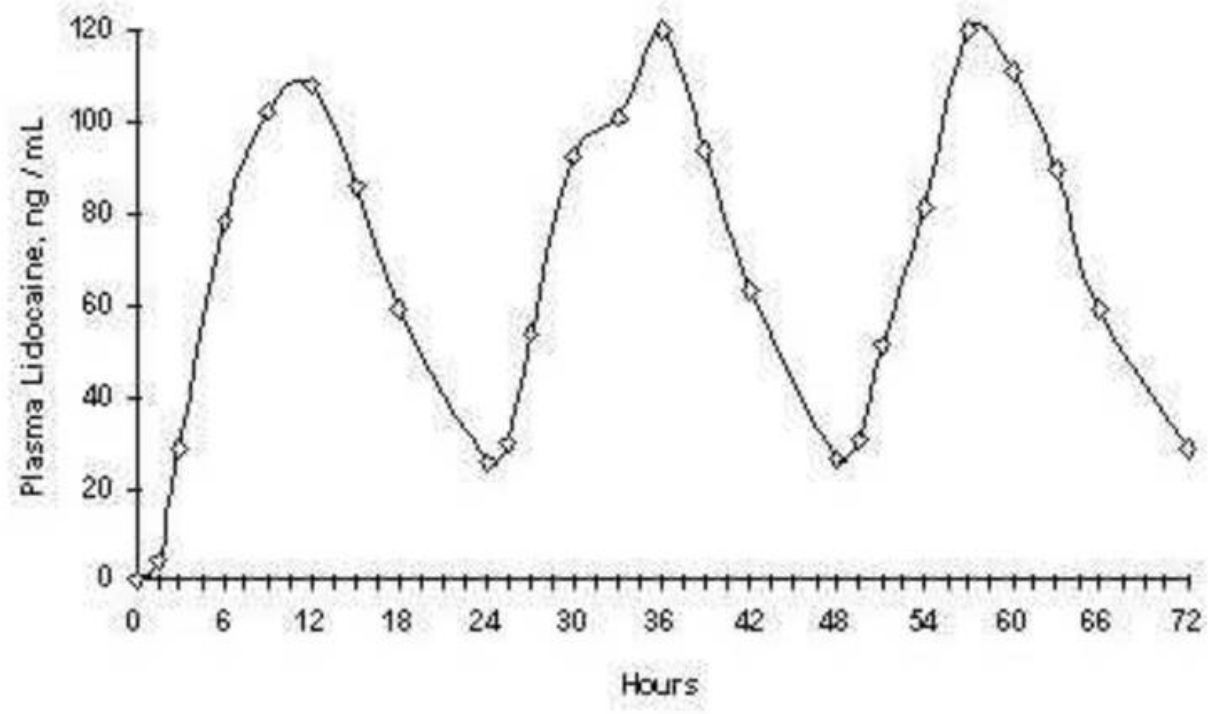


Figure 1
Mean lidocaine blood concentrations after three consecutive daily applications of three LIDODERM patches simultaneously for 12 hours per day in healthy volunteers (n = 15).

The following study tests the hypothesis that topical lidocaine patches (Lidoderm® patch) are an effective adjunct to traditional medications after cesarean birth by decreasing pain scores, decreasing opiate use and improving patient satisfaction. Specifically, we are proposing a randomized control trial of patients undergoing scheduled or non-urgent cesarean birth to 5% lidocaine patch (Lidoderm® patch) versus placebo-patch in addition to standard post op pain regimens for patients undergoing scheduled or non-urgent cesarean births.

3) Study Design – Randomized control trial with a treatment group receiving a topical lidocaine patch and a control group receiving a placebo patch

4) Study Population

a. **Number of Subjects:** 50 total, 25 for each group, will be randomized in this study. Additional participants (up to 75 total) will be consented to participate but may not be

randomized due to changes in their eligibility status between consenting and randomization. Accurate numbers will be reported annually with continuing review.

b. Inclusion and Exclusion Criteria:

Patients will be screened at the time of consent for cesarean birth. Patients will be given a written form explaining the study in addition to the verbal description. The patient must be able to give verbal and written consent.

Inclusion criteria

1. Pregnant patients > 18yo who require a scheduled or non-urgent cesarean birth
2. Patient able to receive neuraxial analgesia
3. Verbal and written consent were able to be obtained for both cesarean birth and study

Exclusion criteria

1. Patients requiring emergent cesarean birth
2. Women allergic to lidocaine
3. Patients who have already received an epidural during this admission
4. Women using chronic oral neuromodulators such as oral gabapentin, oral pre-gabalin, oral trycyclic antidepressants, oral serotonin-norepi reuptake inhibitor, or other oral neurmodulators.
5. Patients with cardiac disease
6. Patients using anti-arrhythmic agents
7. Patients with allergy to adhesive
8. Patients requiring general anesthesia for cesarean birth
9. Patients with fibromyalgia or chronic pain syndromes such as rheumatoid arthritis, osteoarthritis, or lupus.
10. Daily narcotic or opiate use for greater than the 2 months prior to enrollment in the study.

c. Vulnerable Populations: Women less than18yo or unable to give consent will be excluded from the study. This study involves consenting women while they are pregnant but involves women who are postpartum.

d. Setting: This study will occur in the labor and delivery unit at OHSU. Recruitment and consent will be done by study staff, residents and faculty in the OHSU clinics or on labor and delivery. Data analysis will be done by study staff in the OB-GYN and Anesthesia department with support from the Women's Health Research Unit.

e. Recruitment and Consent

Eligible subjects will be identified with pre-review of the OHSU L&D schedule as well as at time of presentation to Labor and Delivery. Whenever possible the subjects will be approached by study staff regarding the study and consented in the clinic prior to their scheduled procedure. If the patient is not enrolled prior to their procedure, then a verbal discussion will occur on the labor floor. Written information will be provided to patients through the IRB approved consent form. The consenting study staff or physician will enroll and consent interested patients. Eligible non-English speaking patients may participate in this study. An interpreter will be utilized in the consent process for non-English speaking patients. No compensation will be given for participation.

This proposal involves minimal risk and employs a patch that is already FDA approved for pain management. It has not been approved specifically for post-operative pain management and cesarean birth. Information will be provided by both the trained consenting physician and information provided in the consent document. As described above, patients unable to consent will be excluded from the study.

f. Blinding: In order to minimize potential for bias with regard to the subjective study outcome (perception of pain on VAS), all efforts will be made to keep the participants blinded at the time of patch placement. In addition, all efforts will be made to keep the study staff conducting the follow-up questions, symptoms and clinical findings, unaware of outcome measures until at the least the end of the first scheduled follow up. The clinical staff placing the study patch will be trained in the procedures of placement and will be prepared to shield the participant from view of the patch type. This may be accompanied by asking the participant to hold a physical barrier (i.e. magazine) in front of her closed eyes.

g. Investigational New Drug (IND): The study team determined that the use of lidocaine patch should be exempt from an IND based on the criteria below. Lidocaine patch is an FDA-approved drug for an unapproved use, but should be exempt because the following criteria are true about our investigation:

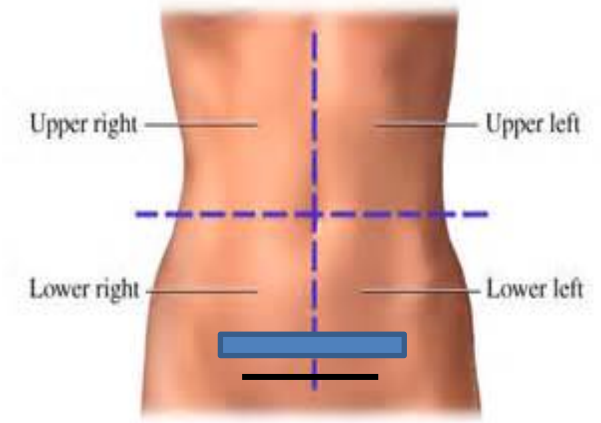
- The investigation is not intended to be reported to the FDA in support of a new indication for use nor intended to be used to support any other significant change in the labeling for this drug. While it is FDA-approved for post herpetic neuralgia, it is commonly used for postoperative pain management as supported in these studies (Kwon et al 2012[3], White et al 2010[4], Gan et al 2014[5]).
- The investigation is not intended to support a significant change in the advertising for the product
- The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risk associated with the product.

h. Cost: The study drug and supplies for the placebo patch will be billed to a study account and there will be no additional costs to the patient or the patient's insurance for participating in the study.

Procedures

1. The research team will assemble packets prior to the start of the study. The packet will include 4 copies of the 11-point visual analog scale (see attached). Each packet will be numbered 1-50. The packets will be randomized to either the lidocaine patch or the placebo patch arm using www.randomization.com. The envelope will also include a role of Elastikon© tape and a piece of white Tegaderm© in the dimensions of the patch used to place over the study medication.
2. Patient presents to L&D for either a scheduled cesarean delivery or a non-urgent cesarean birth.
3. While in the preoperative state, the patient will be approached by a consenting resident or study staff as to their interest in the study. Risks, including contact dermatitis in the area of patch placement, and benefits, including improved pain control and potentially less narcotic use, will be discussed with the patient. Enrollment in the study and consents will be signed at that time. Information will be collected about patients' use of drugs/opiates.
4. When placing admission orders for all study patients, a lidocaine study order set will be placed on their MAR as a PRN to be started 12 hours post operatively. The study drug and placebo packets will be stored in the Pixis to be retrieved by the patients nurse and handed to the resident at the time of administration. Medication use will follow the manufacturer's instructions. The patch will be placed q 24 hours, with patches removed 12 hours after placement. Lidocaine patch is used no greater than 12 hours within a 24-hour period.
5. The consenting physician will then draw a pre-randomized envelope from a binder in the staff work area on labor and delivery and place it on the patients L&D clip board. The envelope will assign a consented patient to either the treatment arm or the control arm. The treatment arm will be blinded from the patient.
6. Patient undergoes cesarean with a standardized anesthesia regimen including: 15 mcg intrathecal (IT) fentanyl, 150 mcg IT morphine, 12.75 mg IT bupivacaine. 30mg of IV ketorolac will be given at the completion of the procedure unless contraindicated. A 1,000mg acetaminophen rectal suppository will be placed after the sterile drapes are removed and prior to transfer to the PACU. Patients will not routinely be given IV NSAIDs (Toradol®) at the end of the case.
7. 12 hours will elapse before the first study patch is placed. This is to allow the neuroaxial anesthesia to wear off so that full effect of the patch medication can be appreciated. At 12 hours postoperative, the patient has secured placement on the postpartum floor, 13C, Mother Baby Unit (MBU).
8. 12 hours post cesarean an OHSU OBGYN resident will go to the patient's room after obtaining the study patch from the pixis (lidocaine is on the MAR for PRN postoperative medication use) or placebo patch from the study envelope. The patch will be cut in half, down the long axis of the patch. Each half will be placed, 2cm above

and 2cm below the patient's incision (as seen below). Since the Lidocaine patch must be placed over intact skin, it will not be placed over the incision directly.



Umbilicus middle arrow, blue box=patch placed 2 cm above and below the incision, black line=Pfannestiel incision line

9. 12 hours post operatively, study staff, will also obtain pain VAS (visual analogue scale) at the time of patch placement. Steps include:
    a. Ask patient to grade their current pain on a printed visual analog scale (see attached copy of VAS scale) before the patch is applied
    b. Staff place the patch (according to procedures in step 8)
    c. Staff will then place Elastikon© tape over the patients patch (in study packet), covering the patch completely.
    d. 24-hour post operatively the patch with accompanying tape will be removed by the staff.
    e. The patient will fill out a second VAS rating their current pain
    f. 36 hours post operatively staff will place second patch (same as the patients first) in the area surrounding their incision. Repeating steps a-f.
    48-hour post operatively the patch and surrounding tape will be removed by the staff and the patient will fill out visual analog scale rating their current pain.
    g. Prior to discharge the total IV and PO narcotic medication that the patient took during their hospitalization will be recorded.

10. Post operative day 5, a secure email message through RedCap or phone call to patient to determine how many oxycodone they have used since discharge. The exact message will be:
    " Hi, this is the study staff from OHSU Women's Health Research Unit. We hope you are feeling well after your surgery. Please respond to this message with how often you are taking your narcotic prescription (ie: Oxycodone, Norco, Percocet, Vicoden) and how many pills you have left in your bottle. Thank you and congratulations! – OHSU Women's Health Research Unit"

Time Postop	12 hours	24hours	36 hours	48 hours	5 days Post-partum

Patch	placed	removed	placed	removed	
Pain questionnaire VAS	x	x	x	x	
Chart review		x		x	
Epic MyChart Message					x

5) Data and Specimens

a) Sharing of Results with Subjects

Research related results will not be shared with the subject**s.**

b) Data and Specimen Banking

Data from chart analysis and review will be stored in RedCap. The research subjects will be given a unique study ID number, and all materials will be labeled with that coded identifier. All study documents will be stored in locked offices at either the Center for Women's Health or the Women's Health Research Unit. Data will be put into the Woman's Health Research Unit repository for future analysis. Those in the obstetrics and gynecology and anesthesia department who have gone through training on human subject research may access the electronic data in the future for additional analysis.

6) Data Analysis

The main comparison is a 11-point (0-10) Visual Analog Scale at 24-hour post-op between two group with the hypothesis that lidocaine patch will decrease the pain at 24hr significantly (more than 15mm). Sample size of 25 per each group achieve 82.3% power to detect a difference of 15mm between two group assuming controls will have mean (SD) of 36mm (18mm)[6] and lidocaine group will have mean (SD) of 21mm (18mm) with a significance level of 0.05 using two-sided two sample t-test.

7) Privacy, Confidentiality and Data Security

Upon enrollment subjects will be assigned a unique study ID number that will be used instead of their name, medical record number or other personally identifying information. Electronic files for data analysis will be labeled with that coded identifier. Codes will not contain any part of the 18 HIPAA identifiers. The key associating the codes and the subjects personally identifying information will be restricted to the PI and the study staff and will be password protected. The key will be kept secure on a restricted OHSU network drive in a limited access folder. All hard copied of study documents will be stored in locked offices at either the Center for Women's Health or the Women's Health Research Unit.

The investigators and study staff will report any AEs or UPs to the monitoring entity within 24 hours of their occurrence via paging, e-mail, or phone call. The details of the events will be appropriately documented and filed in the subject's chart.

If the event is deemed a UP by the monitoring entity, she will prepare a UP for submission to the IRB. The report will be submitted as per the OHSU UP policy: within 7 calendar days of the

monitoring entity's knowledge for deaths and life-threatening events considered to be UPs or within 15 calendar days of the monitoring entity's knowledge for all other events that are considered UPs.

The PI or co-investigators will review of study charts upon completion of 25 subjects (halfway) and again at the study's conclusion. Anytime that an AE, SAE, UP, medication toxicity, or protocol deviation is reported by an investigator or study staff, the monitoring entity will review and assess study chart and patient information, and proceed as per OHSU reporting policy. All adverse events will be assessed and reportable UPs will be submitted to the IRB, if judged related to the study protocol.

8) Risks and Benefits

a) Risks to Subjects

Patients who are randomized to the placebo arm may have higher pain scores and experience more postoperative pain.

The medication in the lidocaine patches is absorbed locally but there is a theoretical risk that this could be systemically absorbed. The current use and lack of reported side effects suggests that this is a theoretical risk only.

b) Potential Benefits to Subjects

There is no direct benefit for participating in this study other than improved pain control.

References:

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