Impact of local anesthetic wound infiltration on postoperative pain following Cesarean delivery

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Background:

Cesarean delivery is one of the most common surgical procedures performed in the United States, accounting for over 1.4 million surgeries per year in 2007 and over 30% of all live births, and this number is increasing [1]. Pregnant women undergoing Cesarean deliveries make up a unique surgical population in that in addition to their own recovery, mothers must also begin caring for their newborns after delivery. After Cesarean delivery, postpartum women also have a higher risk of thromboembolic complications [2], so optimal analgesia is important to facilitate early mobilization. Furthermore, the rate of chronic post-operative pain in this population has been reported to be over 12% [3]. The most significant predictive factor for chronic pain is the severity of acute postoperative pain [4]. In fact, women experiencing severe acute postoperative pain following Cesarean delivery have a 2.5 times greater risk of developing chronic pain and a 3 times greater risk of developing postpartum depression (PPD) [5]. This link to PPD is important because, in addition to its deleterious effects on mothers, PPD has also been shown to negatively affect the cognitive development of newborns [6]. Therefore, achieving adequate postoperative analgesia after Cesarean delivery is critical for optimizing short and long-term outcomes for both the mother and neonate.

Currently the gold standard regimen for postoperative analgesia in women undergoing Cesarean delivery involves a multimodal approach with neuraxial opioids, regular non-steroidal anti-inflammatory drugs (NSAIDs), and regular acetaminophen [11]. However, despite this multimodal analgesic regimen, postoperative pain remains inadequately controlled in this patient population [2]. In the United States, the Joint Commission established standards for pain assessment and treatment in healthcare facilities, with the goal of generating postoperative pain scores of no more than 3 out of 10 at rest and with movement. Similarly, The Royal College of Anaesthetists of the United Kingdom established a goal of having more than 90 % of women report a pain score of no more than 3 on a scale of 0-10 after Cesarean delivery [12]. However, using the current gold standard analgesic regimen, these goals are achieved in only 38 % of patients [13]. This highlights the need for incorporating other analgesic modalities in our postoperative analgesic regimen following Cesarean delivery. The choice of additional modalities must take into account the need to minimize sedation and analgesic transfer into breast milk. Therefore, adjunct local anesthetic modalities would be highly desired. While epidural infusion of local anesthetics can provide excellent postoperative analgesia, its use can interfere with ambulation and the care of newborns; consequently this technique has little place in the management of post-operative pain in women undergoing Cesarean delivery [14]. Transversus abdominis plane blocks have been shown to be beneficial in women who do not receive intrathecal morphine, but the success of the technique might be operator dependent and could be technically challenging in morbidly obese patients [15], who constitute an increasing proportion of the obstetric patient population. Furthermore, this technique did not improve postoperative analgesia in women receiving neuraxial morphine [11], which is the current standard of care following cesarean delivery.

A promising technique in this patient population is local anesthetic wound infiltration using an elastometric pum. In the general surgical population, a systematic review reported that local anesthetic wound infiltration catheters were effective in reducing pain scores and opioid use after a broad range of surgeries, and were associated with reduced opiate-related side effects and improved patient satisfaction [16]. However data regarding the use of this technique in women undergoing Cesarean delivery are limited. A previous Cochrane review suggested that local anesthetic wound infiltration and nerve blocks are helpful in reducing postoperative opioid consumption in women undergoing cesarean delivery [17]. However the review included only

four studies. Since the publication of the Cochrane review, a number of other studies investigating this technique were published. The findings of those studies suggest a number of directions that could be investigated to optimize this technique. For instance, limited data suggest that local infusion of NSAIDs using a pump might significantly enhance postoperative analgesia. Lavand' homme reported that local infusion of diclofenac was a more effective analgesic than systemic administration of the same agent and as effective as local infusion of ropivacaine [18]. Subsequently, two studies reported that the addition of NSAIDs to local anesthetics resulted in improved analgesia compared to local anesthetic infusions alone [19] [20]. The location of the catheter used for wound infiltration is also important, with one study suggesting significantly improved analgesia when the infusion catheter is placed below rather than above the fascia layer [21]. A significant limitation of most of the published studies, however, is that they do not incorporate the administration of neuraxial morphine, which is the current standard of care in this patient population. In fact, a meta-analysis investigating the efficacy of transversus abdominis plane block in this patient population suggests that such a block was helpful in patients who did not receive intrathecal morphine, but did not confer additional benefit in patients receiving neuraxial morphine [11]. Therefore studies are needed that specifically investigate the use of local infusion techniques in women receiving neuraxial morphine. Furthermore, a multimodal regimen incorporating the scheduled administration of NSAIDs and acetaminophen has seldom been used in those studies. Therefore, studies are needed that investigate the efficacy of local pump infusion techniques in women who receive a multimodal analgesic regimen in addition to neuraxial morphine.

Our group has recently performed a systematic review and meta-analysis of studies evaluating the analgesic efficacy of local anesthetic wound infiltration in women undergoing Cesarean delivery [presented at the 2015 meeting of the Society for Obstetric Anesthesia and Perinatology (Adesope OA, Ituk U, Habib AS: Local anesthetic wound infiltration for post-cesarean analgesia: a systematic review and meta-analysis, revision of the manuscript is currently being peer reviewed)]. The meta-analysis involved 11 studies using an infusion technique and suggested that this modality might be helpful in improving postoperative analgesia in this patient population. Subgroup analysis also suggested that catheter placement below the fascia was significantly more effective in improving analgesia compared to placement above the fascia, and that continuous infusion was more effective in reducing pain scores compared to intermittent administration of local anesthetic. The review identified limitations in current literature and highlighted future lines of research within this area. There were very limited data on the efficacy of this technique in patients receiving neuraxial morphine. Furthermore, most studies did not include a multimodal analgesic regimen, and only three studies investigated the local administration of NSAIDs with promising results. We have used the technique of wound infusion on 10 subjects in our practice to assess study feasibility. Those 10 subjects were satisfied with pain management, and reported low pain scores and no complications associated with the technique.

Experimental design and methods:

We will test the hypothesis that wound infiltration with local anesthetic plus a NSAID will result in significantly improved analgesia after Cesarean delivery. The primary endpoint of the study will be pain scores on movement (sitting in bed from a supine position) at 24 hours after surgery. Secondary endpoints will include pain scores at rest, opioid consumption, time to first rescue analgesic, opioid-rerated side effects, length of hospital stay, patient satisfaction with postoperative analgesia, and development of chronic pain and postpartum depression.

We will recruit the study population from the Duke University Birthing Center. This will be a randomized, placebo-controlled, double-blind trial.

Inclusion criteria:
American Society of Anesthesiology (ASA) class 1,2, and 3, English speaking women at a gestational age > 37 weeks scheduled for cesarean delivery under spinal or combined spinal epidural anesthesia who are 18 years or older.

Exclusion criteria:
BMI > 50 kg/m^2, history of intravenous drug or opioid abuse, previous history of chronic pain syndrome, history of opioid use in the past week, allergy or contraindication to any of the study medications, non-English speaking, emergency cesarean section.

Study methods:
Women scheduled to undergo a cesarean delivery under spinal or combined spinal epidural anesthesia will be approached to participate in the study. After obtaining informed consent, mechanical temporal summation (MTS) assessment using a 180 gram von Frey filament applied to the patient's arm, as demonstrated by Weissman-Fogel, et al. [22], will be done prior to surgery and results recorded. Patients will then be stratified based on the presence or absence of MTS and randomized to one of two groups: ropivacaine plus placebo group (R) or placebo (P) (normal saline) group, using a computer generated randomization in blocks of 20. The patients' study allocation assignment will be placed in sealed opaque envelopes. Blinded study drugs will be prepared by the investigational drug service at Duke University Medical Center. The anesthetic technique will be standardized. All women will receive antacid prophylaxis with 30 ml sodium citrate. The spinal anesthesia administered to the patients in both groups will be standardized doses of intrathecal hyperbaric bupivacaine (10.5-12 mg), fentanyl (15 mcg), and preservative-free morphine (150 mcg). Before placing the spinal anesthetic, the skin at the site will be infiltrated with 3 ml 1.5% lidocaine as per standard practice. Patients will be asked to rate the pain of skin infiltration on an 11 point scale with 0= no pain, 10= worst possible pain. Surgery will be performed according to standard practice. The catheter for wound infiltration will be placed by the surgeon below the fascia before its closure, along the full length of the wound. When the wound is closed, a 10-mL bolus of study drug will be administered through the catheter. The catheter will then be connected to an elastomeric pump (OnQ pump) set to deliver 5 mL per hour for 48 hours containing either 540 mg ropivacaine and 30 mg ketorolac in 271 mL volume or saline placebo. IDS at Duke conducted pH readings and physical observations on single strength study IP (440 mg Ropivacaine and 30 mg Ketorolac in 270 mL total volume and on double strength (880 mg Ropivacaine and 60 mg Ketorolac in 270 ml total volume). Each preparation was observed for 72 hours for precipitation, gas formation and discoloration. Each preparation was clear with no gas formation and no discoloration at the end of the 72 hour observation period. Each preparation was tested for pH and there were no abnormalities for either preparation at the end of the 72 hour observation period.

Intraoperative and postoperative management will be according to standard practice. Acute pain in the postoperative care unit (PACU) will be treated with IV boluses of fentanyl as needed based on a numerical pain scale (25 mcg for NRS 3-6, and 50 mcg for NRS 7-10). The postoperative regime will also be standardized with patients receiving scheduled doses of ketorolac 15 mg every 6 h for 24 h followed by ibuprofen 600 mg every 6 hours for 48 hrs, and acetaminophen 975 mg every 6 h for the first 72 h as per standard practice. The total amount of ketorolac administered systemically and by infusion is lower than the maximum allowed amount of ketorolac to be administered over a 24 h period. Rescue narcotics will be administered as oral oxycodone. The dose of oxycodone will be administered based on numerical rating scale

(NRS 0-10) for postoperative pain (oxycodone 5 mg for NRS 3-6, and 10 mg for NRS 7-10) every 4 h as needed. Promethazine 6.25 mg IV will be administered for treatment of postoperative nausea and vomiting in the recovery room. Nalbuphine 2.5 mg IV will be administered for the treatment of pruritus. The wounds will be assessed for signs of infection or other wound complications by the managing obstetric team as a part of normal clinical practice. At 48 h, patients will be asked to rate their satisfaction with pain control on a 0-10 scale. As per standard of care, subjects stay in the hospital for 3 nights after cesarean delivery, so they will be in the hospital for the entire duration of the study, and the ONQ pump will be discontinued and the catheter removed by treating team prior to subject's discharge.

Data will be collected at 2 h, 24 h and 48 h after surgery. Patients will be contacted by phone at 8 weeks and 6 months postpartum to assess for the presence of persistent postpartum pain (including intensity, frequency, location, treatment and impact on daily activities), as well as postpartum depression using the Edinburgh Postnatal Depression Scale. Patients with scores on the depression scale consistent with postpartum depression will be referred to their obstetrician or primary care physician for further assessment and management. Subjects who do not have a primary care provider will be referred to psychiatry or social work

Training of OB providers: The study team will discuss the insertion method with every provider before the case, and have a sample catheter to demonstrate to them. The study team is also available during the surgery to guide the OB providers through the process of placing the catheters as needed.

Statistical Analysis:

Pilot data from 18 patients from our institution show that with our current standard of care postoperative analgesic regimen, mean (SD) pain scores on movement are 5.1 (1.0). A sample size of 29 patients per group will have 80 % power at α=0.05 to show a 30 % reduction in pain scores on movement with local anesthetic wound infiltration. To allow for dropouts, we will target to enroll 35 patients per group. We will request approval for up to 100 consented subjects, to allow for screen failures, but the aim will be to have 70 total subjects receive the wound infiltration. We will describe the patient cohort with summary statistics and assess the balance of patient characteristics between the two treatment groups. The primary hypothesis about differences in 24 hour pain scores will be assessed with a Wilcoxon Rank Sum test or two-sided two-group t-test at α=0.05. The secondary numeric measures of pain, nausea, and satisfaction will be assessed for normality and t-tests or Wilcoxon Rank Sum tests will be used to test for group differences as appropriate. Differences and trends in repeated scores over time will be assessed via repeated measures analyses and least square means estimates for differences between treatment groups at each time point. Anticipating that some patients will not require rescue oxycodone, we plan to analyze the time to rescue oxycodone via Kaplan-Meier mean time to event analysis. Dichotomous variables will be assessed via chi-square tests or fisher exact tests. Given the randomized design of the study it is anticipated that all factors will be balanced between the two groups. If any potentially confounding factors are unbalanced between the two treatment groups we will perform each of the above analyses adjusted for the confounding factors.

Subject identification, recruitment, and compensation

In compliance with our submitted HIPAA waiver of authorization and consent, Maestro will be reviewed for potentially eligible participants who are scheduled for elective Cesarean delivery at

Duke Hospital. Recruitment will be equitably based on inclusion and exclusion criteria so that all demographic groups have access to study participation. About 100 pregnant women will be recruited for study participation from Duke Hospital and ObGyn offices that provide obstetric services at Duke Hospital, including Duke Perinatal, Duke Women's Health Associates, and Durham County Health Department.

A letter or email will be sent to eligible candidates on behalf of their OB/GYN provider informing them of the study with the research team's contact phone number and email address which includes an opt-out option. A research team member will follow-up about 2 weeks after letters are mailed or 1 week after emails are sent, if there has been no response from candidates. In addition, recruitment will also be facilitated by use of Duke "My Chart." The same recruitment letter will be sent to potential subjects on behalf of their OB/GYN provider informing them of the study with the research team's contact phone number and email address which includes an opt-out option. Research team members will follow up 1 week after MyChart letters/communication have been sent if there has been no response from potential candidates. Study personnel responding to individuals by phone or email will utilize the IRB approved phone script.

Additionally, patients scheduled for elective cesarean delivery who were not contacted through their ObGyn office will be screened, and those meeting the eligibility criteria will be approached on the day of their surgery to participate in the study. A caregiver known to the subject will introduce the study. The subject's physician will be asked for approval for enrollment in the study. In order to ensure patients can be contacted for their follow-up telephone interviews, participants will be asked to provide alternate telephone contact numbers, home addresses and an email address. There will be no compensation to the subjects as a result of participation in this study.

Subject competency:

Only competent subjects will be approached to participate in this study.

Costs to the subject:

There will be no additional cost to the subjects as a result of participation in this research study.

Data storage & confidentiality:

Study records will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security and authorized access. Except when required by law, patients will not be identified by name, social security number, address, telephone number, or any other direct personal identifiers in study records disclosed outside of Duke University Health System (DUHS). For records disclosed outside of DUHS, patients will be assigned a unique code number. The key to the code will be kept in a locked file in Dr. Habib's office.

Data Integrity:

The data will be housed on the Department of Anesthesia's Parnassus server and the PI, and study team members will have access to the study data.

Data monitoring:

Data will be monitored closely for the occurrence of AEs, and reported to the IRB as needed. If unanticipated AEs or if expected events appear to be occurring more frequently than expected, those AEs will be explored per treatment arm.

In accordance with federal regulations the PI will monitor for, review, and promptly report to the IRB, appropriate institutional officials, sponsor, coordinating center and the appropriate regulatory agency head all unanticipated problems involving risks to subjects or others that occur in the course of a subject's participation in a research study (45 CFR 46.103(b)(5)(i) and 21 CFR 56.108(b)(1)), all AE reports will be reported per the DUHS IRB policies.

Benefit / harm assessment:

There might be improved postoperative pain in women receiving wound infiltration with local anesthetics and NSAIDs. The main side effect noticed in previous studies using wound infiltration is the potential of fluid leakage from the wound.

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