Project title: A Comparison of the Post-Cesarean Section Analgesic Effects of Neuraxial Duramorph vs. Bilateral Transversus Abdominal Plane (TAP) Block With Combined Bupivacaine and Liposomal Bupivacaine (Exparel).

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A Comparison of the Post-C/S Analgesic Effects of Neuraxial Duramorph vs Bilateral TAP Block With Liposomal Bupivacaine

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Summary/Program Objective:

The primary objective is to reduce or eliminate the use of all narcotics/opiates for post Cesarean section pain management. We hypothesize that in comparison with epidural or intrathecal Duramorph, a TAP block with liposomal bupivacaine (Exparel) will provide better, longer-acting pain control and will significantly reduce the use of post-operative IV or p.o. opiates. This is a prospective, randomized clinical trial. We will compare the analgesic efficacy and duration of an ultrasound guided bilateral TAP Block (with combined bupivacaine and liposomal bupivacaine) to Duramorph (an opiate). Neuraxial duramorph provides approximately 24 hours of pain relief (analgesia), whereas a bilateral TAP block with liposomal bupivacaine is expected to provide up to 72 hours of analgesia. The patient's analgesia will be assessed by reviewing patient-reported pain intensity based on an 11-point numeric rating scale (NRS; 0= no pain, 10= worst possible pain) and post-operative opiate usage. Secondary objectives include a comparison of the opiate related post-surgical adverse events (AEs) (defined as somnolence, sedation, confusion, respiratory depression, dry mouth, nausea, vomiting, constipation, urinary retention and pruritus), and overall satisfaction with their postsurgical analgesia (patient-reported, using an 11 point scale whereby 0= not at all satisfied and 10= extremely satisfied) at hospital discharge.

Purpose of the study:

To determine if a bilateral transversus abdominal plane block with combined bupivacaine and liposomal bupivacaine can provide safe, effective, long-acting pain control that minimizes narcotic usage.

1. Specific Aims:

All patients will have neuraxial anesthesia (either a spinal or epidural) for their non-urgent or elective Cesarean section.

The control group (Group 1) will receive either intrathecal or epidural Duramorph (preservative-free morphine sulfate). Post-operatively, participants will have orders to receive, on an as-needed basis, IV/oral acetaminophen and/or IV/oral non-steroidal anti-inflammatory drugs (NSAIDS) for mild-moderate pain, and narcotics for severe pain; specifically- oxycodone or hydromorphone. All patients must receive acetaminophen and NSAIDS (unless contraindicated) before receiving narcotics. This multi-modal pain management regimen is our current standard of care.

The experimental group (Group 2) will also receive a spinal or epidural anesthetic. This group will not receive neuraxial Duramorph for post-operative pain. Instead, the patient will receive an ultrasound guided bilateral TAP block with a combination of bupivacaine and liposomal bupivacaine solution immediately after the Cesarean section. Additionally, they will receive the same post-operative analgesia orders as group 1.

Specific Aim 1) To show that participants in the TAP block group will have better and longer acting pain relief than the Duramorph group. We will record and compare patient-reported post-operative pain intensity using an analogue visual score card with an 11-point numeric rating scale at 6, 24,48 and 72 hours.

Specific Aim 2) To show that the TAP block group will use less post-operative narcotics than the Duramorph group. We will measure and analyze the times at which participants in both groups request narcotics and the amount administered. We will also record each participant's pain level prior to receiving narcotics. It is anticipated that participants in TAP Block group will need significantly less post-operative narcotics when compared to the Duramorph group (standard of care)

Specific Aim 3) The TAP block group will have a decreased incidence of opiate- related side effects such as somnolence, sedation, confusion, respiratory depression, dry mouth, nausea, vomiting, constipation, urinary retention, and pruritus (itching).

Specific Aim 4) To measure patients' overall satisfaction with their postsurgical analgesia. Using an 11 point scale where 0= not at all satisfied and 10= extremely satisfied, we will record their overall satisfaction with their postsurgical analgesia. It is anticipated that participants in the TAP block group would report their pain control as being better than participants in the Duramorph group.

Analysis of our initial data, presented below, anticipates that group 2 will have better post-operative analgesia with a longer duration and less post-operative narcotic usage and fewer opiate-related adverse effects.

2. Background / Significance:

Postsurgical pain is a significant concern for patients undergoing surgical procedures. Many patients are concerned about pain. In a recent survey, (1) nearly 80 percent of patients had some anxiety over post-operative pain, with almost 2/3 of those concerned with pain reporting moderate to severe post-operative pain. Although, narcotics play a significant role in providing post-operative pain relief, they often casue nausea, vomiting, constipation, pruritus. More worrisome is the opiate related life threatening risks of hypoventilation and respiratory failure. Additionally, there is the public health concern of unused and unmonitored prescription opiates being used for nonmedical purposes that could cause injuries or even deaths (2).

Liposomal Bupivacaine suspension is currently indicated for single-dose infiltration into the surgical site for postsurgical analgesia. This formulation combines bupivacaine with DepoFoam®, a proven product delivery technology that delivers medication over a extended time period. A single dose of Liposomal Bupivacaine is shown to provide significant reductions in cumulative pain scores with a decrease in opioid consumption.

Exparel® was FDA approved in 2011.

We have used Exparel® infiltrated bilaterally into the TAP to provide prolonged postoperative analgesia in patients undergoing umbilical hernia repairs. TAP blocks have been successfully used for post-operative pain relief for surgical procedures involving incisions of the mid and lower abdominal wall (3,4). Our experience has demonstrated that a TAP block with non-liposomal bupivacaine provides 12-18 hours of analgesia. whereas. TAP blocks utilizing the extended release liposomal bupivacaine provide up to 72 hours of pain relief (5,6).

Exparel and Cesarean sections

TAP Blocks have been used to reduce post-cesarean section opiate administration and pain scores Previous studies with wither bupivacaine or ropivicaine alonehave demonstrated a reduction in rest pain at 6, 12, and 24 hours--but not at 48 hours.

We just completed another small case series that showed the prolonged analagesic effects of liposomal bupivacaine in bilateral TAP blocks in a cohort of patients who have undergone cesarean section with neuraxial anesthesia. (6).

After IRB approval, this Center conducted a trial of Exparel. We performed a bilateral TAP block using the combination of bupivacaine and liposomal bupivacaine in twelve patients who were scheduled for elective C-Section under neuraxial anesthesia. These patients also received neuraxial preservative free morphine for postoperative analgesia. An ultrasound guided bilateral

TAP block was performed at the end of the surgery.. 20ml of liposomal bupivacaine mixture (20 ml of liposomal bupivacaine mixed with 20 mls 0.25% bupivacaine) was injected on each side (a total of 20 ml was injected into each side.) The patients were ordered acetaminophen and ketorolac for mild/moderate pain and oxycodone for severe/breakthrough pain. Patient postoperative analgesia VAS scores and administration of opiates were recorded after 6, 12, 24, 48, and 72 hours.. Patients who received bilateral TAP blocks with liposomal bupivacaine had pains scores (on a scale of 0-10) of 1.0±1.4, 1.4±2.1, 1.7±1.9, 1.9±3.3 and 1.9±2.3 (mean ± SD) at 6, 12, 24, 48 and 72 hours respectively (Table 1). At 48 hours, long after the Duramorph had worn off, patients had an average pain score 1.9 suggesting that they had excellent analgesia from the TAP block alone.

Overall, patients who received the bilateral TAP blocks used little narcotics. On postoperative day 3 (72 hour after the TAP block), only one patient requested and received 5 mg of oxycodone 3 times.. Within 24 hours, 2 patients used acetaminophen/oxycodone. One of these 2 patients received acetaminophen/oxycodone for anticipated pain in a monitored unit despite having only pain scores of 0.

On an 11 point scale, the mean patient satisfaction score was 9.3±1.1 (Table 2).

Table 1: Patients pain scores after bilateral TAP Block after cesarean section

Table 1

	6 hours	12 hours	24 hours	48 hours	72 hours	Overall	
Pain score	1.0	1.4	1.7	1.9	1.9	1.5	Mean
	1.4	2.1	1.9	3.3	2.3	2.2	SD

Patient pain scores from all 12 patients were recorded at every visit. There were asked on a scale of 0-10, where 0 was no pain and 10 was the worst pain you can imagine: how do you rate you pain?

Table 2: Patient satisfaction with their pain management

Table 2							
	6 hours	12 hours	24 hours	48 hours	72 hours	Overall	
score	9.33	9.08	9.33	9.33	9.22	9.26	Mean
	1.07	1.24	1.15	0.78	1.30	1.07	SD

Patient satisfaction were recorded from all 12 patients at either last visit or they were called at home. There were asked on a scale of 0-10, where 0 was the worst and 10 was the best, how do you rate you pain management?

The mean pain score in the TAP block group when first requesting pain medication was 1.3±2.3 on a scale of 0-10. The mean pain score at all request for pain medication was 0.8±1.8. These results demonstrate that the patients receiving the TAP blocks with liposomal bupivacaine had profound postoperative pain relief (Table 1) and used minimal postoperative narcotic.

These results were better than expected. For comparison purposes, we performed a chart review. We selected a similar cohort of the first 60 subjects for a chart review, beginning on January 1, 2012, who underwent elective Cesarean delivery with a spinal anesthetic consisting of hyperbaric 0.75% bupivacaine, fentanyl 15mcg, and 0.3mg Duramorph ™ without TAP blocks. Thirty-nine out of 60 patients in this group received Percocet postoperatively. Pain scores were recorded only at the time when the patient was requesting pain medication. The mean pain score at the first request for pain medication was 5.3±1.8. The mean pain score recorded at all requests for pain medication was 5.5±1.9. Patient in this group used an average 24±17 mg of oxycodone. Compared to the chart review (neuraxial Duramorph), the number of patients using narcotics in the liposomal bupivacaine TAP blocks group was less than the chart review group (which is our standard of care group): 3/12 vs 39/60 $p< 0.013$, respectively. Within 24 hours, the difference in the use of narcotic between the two groups was not significant (<0.629); however, after 48 hours the TAP block group used significantly less narcotic (<0.02) than the control group (2/12 for the TAP Block group vs. 32/60 Duramorph (chart review) group). On postoperative day 3, an additional patient in the TAP block group requested and received 5 mg of oxycodone 3 times. (The liposomal bupivacaine TAP block group used significantly less opioids, 1 out of 12, on day 3 compared to the Duramorph group, (22 out of 60, $p<0.05$).

The combination of these results suggest that the patients receiving TAP blocks with liposomal bupivacaine had significant postoperative pain relief (Table 1) and used little postoperative narcotic in comparison with neuraxial Duramorph.

Since our initial study of TAP blocks, (5), we have improved and refined our administration technique. We now consider liposomal bupivacaine to be like an infusion that should be initiated with a bolus (a large initial dose) in order to achieve therapeutic levels that will be maintained by liposomal bupivacaine. As per the Exparel liposomal bupivacaine package insert, bupivacaine HCl and EXPAREL may be administered simultaneously in the same syringe, and bupivacaine HCl may be injected immediately before EXPAREL as long as the ratio of the milligram dose of bupivacaine HCl solution to EXPAREL does not exceed 1:2' (7). Exparel® can be given with ½ the total dose of the bupivacaine found in the liposomes (266mg). That means we can co-administer 133 ml of 0.25% bupivacaine (=53.2 ml of 0.25% bupivacaine) with the liposomal bupivacaine. We will be adding 40 ml of the 0.25% bupivacaine, which is well below the maximal dose. From our experience and personal communications from other anesthesiologists, administering 30-35 ml on each side of the TAP block results in the 'best' block. We will explain our TAP block in the Methods section.

3. Research Design and Methods:

This is specifically for postpartum women. The purpose of this study is to test the effectiveness of Exparel (liposomal bupivacaine) administered in a bilateral TAP block to provide better analgesia after Cesarean section than neuraxial duramorph, which is the current standard of care: neuraxial Duramorph, and minimize use of post-operative narcotics and their annoying common side effects at one of the most enjoyable moments of life: having a new baby.

This is a prospective, randomized study evaluating the effectiveness of abdominal analgesia when using 266 mg EXPAREL delivered into the bilateral TAP blocks. TAP blocks are an excellent method for providing adequate analgesia following lower abdominal surgery (3-6). To be eligible for the study, the patient has to be undergoing a non-urgent Cesarean section (either elective, or for non-urgent conditions such as failure to progress) with neuraxial anesthesia via an epidural, spinal or combination epidural/spinal. When patients arrive for their Cesarean section they will be assessed if they are eligible for the study and they will be asked to participate in the study after the risks and benefits are explained. If a patient does not want to participate, they will be offered TAP blocks with regular bupivacaine. Those patients who wish to participate will be asked to sign a study consent form. Patients that decide to participate in this study will be randomized to either group 1 or group 2 (like the

flip of a coin). Both groups will receive standard neuraxial anesthesia for their Cesarean Section and post-operative standard of care breakthrough medications for post-operative pain control. They will be randomized to receive either (group 1) standard neuraxial anesthesia with neuraxial Duramorph for post-operative pain or (group 2) standard neuraxial anesthesia without neuraxial Duramorph and a transversus abdominal plane (TAP) blocks immediately after surgery, with a mixture of bupivacaine and Exparel, for post-operative analgesia.

There are only two groups in this study: Group 1 will have our present standard of care: neuraxial anesthesia, with Duramorph added to the epidural or spinal for post-operative pain. Group 2 will also have neuraxial anesthesia but will receive bilateral TAP blocks for post-operative pain control with 40 ml of 0.25% regular standard bupivacaine and with 20 ml of liposomal bupivacaine (Exparel) and 10-20 ml of normal saline (a salt solution, for a total of 70-80mls: 35-40 ml on each side). The TAP block plane will be identified with ultrasound. A 100 mm needle will be ultrasound guided into the TAP plane. 5-10 milliliters of normal saline will be used to hydro-dissect the plane. After hydro dissection 15 ml of 0.25% regular standard bupivacaine will be injected followed by 10 milliliters of liposomal bupivacaine (Exparel) diluted with 5 ml of 0.25% regular standard bupivacaine. This will be repeated on the opposite side. We will follow pain levels closely after the Cesarean section. If patients request medication for breakthrough pain, they will be given Tylenol, first. If the pain persists, they will be given Toradol 30 mgs, unless contraindicated. For persistent pain, they may receive another dose of 30 mgs of Toradol, but for severe pain they will be offered oxycodone 5-10 mg, depending on the intensity of the pain. Patients must be given both Tylenol and Toradol, unless contraindicated, before receiving narcotics for severe pain. We will ask you a set of questions to access to quality of analgesia (pain control): 1) How is your pain at that time point? 2) What was your highest pain score? And 3) Did you require narcotic pain medication, when did you receive it and what was your pain level at that time? To assist your evaluation of your pain, we will show you a card that has a visual analogue (Faces) pains scale combined with numerical (0-10) analogue scale (0 is no pain, 10 is the worst pain you can imagine). We will be recording your pain at

- 6 hours after the end of anesthesia or the TAP block
- 24 hours after the end of anesthesia or the TAP block.
- 48 hours after the end of anesthesia or the TAP block.
- And at72 hours after the end of anesthesia or the TAP block.
- Before you leave the hospital, we will ask you to rate your pain control.

At all-time points patients and/or nurses taking care of the patient will be asked about: somnolence (sedation or excessive tiredness), respiratory depression, hypoxia, dry mouth, nausea, vomiting, itching, constipation, urinary retention, sedation, and confusion.

We will also record time and date of any and all post-operative narcotics used by the patient as well as their pain scores just prior to receiving narcotics.

Additionally, patients will be asked about their overall satisfaction with postsurgical analgesia at the end of their hospital stay. If after Day 10±5, the investigator is made aware of an AE that occurred during this period of time, this will be reported to the IRB.

Eligibility Criteria:

Inclusion Criteria:

• Females, aged 18-45 years inclusive and ASA physical status 1-3.

• Undergoing non-urgent Cesarean section with neuraxial anesthesia/analgesia.

• Subjects must be physically and mentally able to participate in the study and complete all study assessments.

• Subjects must be able to give fully informed consent to participate in this study after demonstrating a good understanding of the risks and benefits of the proposed components of the TAP infiltration.

Exclusion Criteria:

• History of hypersensitivity or idiosyncratic reactions to amide-type local anesthetics

• Any subject whose anatomy, or surgical procedure, in the opinion of the Investigator, might preclude the potential successful performance of a bilateral TAP infiltration.

• Any subject who in the opinion of the Investigator, might be harmed or be a poor candidate for participation in the study.

• Any subject, who in the opinion of the Investigator, is on chronic pain medicine, including large doses of NSAIDs.

• Subjects who have received any investigational drug within 30 days prior to study drug administration, or planned administration of another investigational product or procedure during their participation in this study.