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Title: Efficacy of subcutaneous infiltration with local anesthetic during elective cesarean delivery for postoperative pain control: a randomized controlled trial

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Background/Significance

Cesarean delivery is the most common operation performed throughout the world with estimates in the United States at 30% of all deliveries being performed via cesarean section. Spinal anesthesia is the standard of care for elective cesarean births given its maternal and neonatal safety profile. Typical post-cesarean pain relief varies by institution and provider preference but typically consists of an oral narcotic with or without an oral non-steroidal anti-inflammatory inhibitor. Post-cesarean analgesia studies, especially considering the growing

opioid abuse epidemic, are of suboptimal quality. In fact, a 2015 Cochrane review noted that due to limited data available no conclusions could be drawn on the safest and most effective oral analgesics for post-cesarean pain relief.[1]

Given its success in showing improved postoperative pain in other surgical procedures, there are multiple studies showing the benefit of a Transversus Abdominis Plane (TAP) block at the time of cesarean delivery.[2–5] However, TAP blocks are long procedures requiring specialized training and an ultrasound for guidance. One study by Tawfik et al.[4] showed no difference in pain scores, opiod consumption or maternal satisfaction scores with TAP vs local infiltration. Studies have also been performed assessing placement of pain management systems into the incision to release local anesthetics or analgesics over time, however these results have also been mixed.[6]

Multiple studies have been performed in the past assessing local infiltration of multiple different kinds of anesthetic and pain medications either before cesarean delivery begins or at the end of the procedure for pain control.[7,8,17–19,9–16] These studies have had conflicting results on the utility of local anesthetics for postoperative pain control. A Cochrane review from 2009 noted that local infiltration was likely beneficial in reducing postoperative opiod consumption but not visual analog pain scales.[20] A metanalysis published in 2017 also noted that local infiltration was likely beneficial in reducing postoperative opiod consumption but its utility when used in combination with intrathecal opiods in spinal regimens (as is now the standard of care in obstetrical anesthesia) required more data.[21]

The most recently published randomized controlled trial on this topic is from Egypt in 2016 assessing postoperative pain with local infiltration of lidocaine versus lidocaine with epinephrine in women undergoing general anesthesia.[22] This study demonstrated safety of both regimens and showed improved pain relief for women receiving lidocaine with epinephrine. Our study seeks to assess pain relief with incisional infiltration of local anesthetic (with and without epinephrine) during cesareans performed under spinal anesthesia also using intrathecal opiods. Our study is more relevant given the infrequency of cesareans performed under general anesthesia in the United States. We will also be assessing women who receive no local infiltration of anesthetic, the current standard of care, as our control group.

Multiple professional societies and government agencies have recommended a decrease in the use of opioids for postoperative analgesia given the opiod misuse epidemic. Our study attempts to further assess postoperative oral opioid consumption in patients undergoing spinal anesthesia with intrathecal opiods by assessing the addition of local subcutaneous infiltration of anesthetic.

Study Design

***Objective*:** The objective of our study is to assess the addition of subcutaneous bupivacaine (Marcaine) with or without epinephrine to the standard intrathecal morphine/fentanyl combination given during spinal anesthesia during elective cesarean delivery on postoperative pain control as measured by postoperative usage of oral opioids and a postoperative pain assessment scale.

Hypothesis: The addition of subcutaneous bupivacaine with epinephrine at the cesarean incision site prior to skin closure to the standard spinal anesthesia regimen at the time of elective cesarean delivery will reduce postoperative narcotic usage in the first 24 hours postoperatively by 25%

Null Hypothesis: There will be no difference in postoperative narcotic usage in the first 24 hours after cesarean delivery with the addition of subcutaneous bupivacaine with or without epinephrine at the cesarean incision site prior to skin closure at the time of elective cesarean delivery.

Methods: Trial will be registered on ClinicalTrials.gov and follow CONSORT guidelines

- Type of study: 3 arm, blinded, randomized controlled trial involving patients who receive spinal anesthesia for elective cesarean delivery
    - *Randomization*: Subjects will be randomized using the blocking method. To achieve comparable groups, we will randomize enrollees to one of three treatment arms. Randomization will be done with block sizes of 6 to reduce the likelihood of unmasking the randomized assignment. All potential subjects will be randomized prior to study start (patient's # 001- 276) and the group that they are randomly assigned to will be written on cards placed into pre-sealed envelopes.
    - *Blinding*: The envelopes will not be opened, and the subjects' group not known, until immediately prior to the subjects' cesarean delivery to maintain the randomization process. Only the physicians drawing up and supplying the medication (the anesthesia physicians- resident and attending) will be aware of the patients group. The physicians administering the medication (i.e. the OBGYN attending and resident) will NOT be told the composition of what they are injecting. The patient will be blinded to (i.e. will not be told) their intervention group. The investigator collecting the data will be blinded to (i.e. not know) which intervention group each individual patient was assigned to while collecting the data. Therefore, the patient, the physician administering the medication, and the personnel collecting the data will all be blinded to the patient's intervention group. The anesthesia team will only record the patient's pre-assigned number into the medical record (EPIC electronic

health record) and mention that they received an injection at incision closure of "study drug- patient #001-276." The master list of what each patient received (i.e. the key to the randomization) will be kept with the anesthesia team and no one else will have access to view the key to maintain blinding.

- *Groups: Injection will consist of 5 ml of either bupivacaine 0.25%, bupivacaine 0.25% + epinephrine, or NACL 0.9% infiltrated subcutaneously in 4 approximately equidistant injections sites in the subcutaneous tissue (2 sites in the cephalad portion and 2 sites in the caudad portion) after closure of fascia and prior to subcutaneous closure (if performed) and skin closure at the cesarean section incision site. Total volume infiltrated will consist of 20 ml.*
  - **Group 1 (intervention 1):** standard intrathecal bupivacaine (Marcaine) 0.75% 1.5-1.7 ml, intrathecal morphine (Duramorph) 150mcg plus intrathecal fentanyl 10 mcg + *20 ml subcutaneous bupivacaine* (*Marcaine) 0.25%*
  - **Group 2 (intervention 2):** standard intrathecal bupivacaine (Marcaine) 0.75% 1.5-1.7 ml, intrathecal morphine (Duramorph) 150mcg plus intrathecal fentanyl 10 mcg + *20 ml subcutaneous bupivacaine (Marcaine) 0.25% with Epinephrine*
  - **Group 3 (control/standard therapy group):** standard intrathecal bupivacaine (Marcaine) 0.75% 1.5-1.7 ml, intrathecal morphine (Duramorph) 150mcg plus intrathecal fentanyl 10 mcg + *20 ml subcutaneous NACL 0.9% (placebo)*
  - **All groups:** *post-operative pain control*- as assessed per routine nursing protocol during the first 24 hours postoperatively
    - Routine post-cesarean oral analgesics:
      - Ibuprofen 600 mg PO prn mild (1-3); moderate (4-6); severe (7-10) pain
      - Percocet prn severe pain (7-10) if unrelieved by ibuprofen
    - Routine nursing protocol for postoperative pain assessment consists of patient assessment (pain scale 1-10) every hour for the first 2-4 hours postoperatively while the patient is in the PACU and every 1-4 hours for the remainder of their hospital stay while the patient is on the postpartum unit. The pain scale will be recorded in EPIC at a minimum of every 4 hours postoperatively.

- **Primary outcome:** postoperative pain medication usage
  - Documented postoperative usage of cumulative opioid pain medication (oxycodone in morphine equivalents) in the first 24 hours postoperatively

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- **Secondary outcomes**:
    - Documented postoperative usage of pain medication
        - cumulative usage of postoperative pain medication- opioid (oxycodone) (at 4 hours, 8 hours, 12 hours, 24 hours, 36 hours, 48 hours postoperatively)
    - Time to first postoperative pain medication
    - Need for additional breakthrough pain medication outside of protocol (amount and type of medication will be documented)
    - Subjective patient pain assessment
        - immediate postoperative pain scale performed in postoperative anesthesia care unit (PACU) and throughout the postoperative period according to current nursing protocol (see above)
        - Patient satisfaction with pain management
    - Time to return of bowel function
    - Time to discharge from the recovery room
    - Time to first ambulation
    - Breastfeeding during hospital stay (assessment of both initiation of and exclusive breastfeeding)
    - Maternal side effects/outcomes
        - Intraoperative: hypotension, nausea, vomiting, pruritus, respiratory depression, prolonged numbness or immobility, failed neuraxial anesthesia requiring intubation, systemic toxicity of local anesthesia
        - Postoperative: fever, postoperative wound separation, postoperative wound infection, skin site irritation, incisional hematoma/seroma formation
    - Other *variables* to be collected:
        - Demographic
            - Maternal: Age, gravidy, parity, number of prior cesarean deliveries, number of prior surgeries, maternal co-morbidities (chronic hypertension, gestational hypertension, preeclampsia, diabetes mellitus -pregestational, gestational- diet or medication controlled- autoimmune disease, known pain syndromes- i.e. fibromyalgia, etc.), reason for current cesarean delivery, history of tobacco use, history of anxiety or depression, amniotic membrane status, body mass index, ethnicity
            - Fetal: gestational age, suspected intrauterine growth restriction, estimated fetal weight, known or suspected congenital or chromosomal anomalies, placenta previa
        - Intraoperative variables

- Length of surgery, estimated blood loss, intraoperative complications, concurrent bilateral tubal ligation, any other analgesia given intraoperatively and amount of other anesthetic given

▪ Postoperative variables

- Neonatal outcomes (will be stratified based on fetal gestational age as this study includes all gestational ages and neonatal outcomes will likely be affected by gestational age; we will therefore stratify results by completed weeks of gestation: >37 weeks, 34-37 weeks, 30-34 weeks, <30 weeks)
  - APGARS, APGAR <7 at 5 min, fetal arterial blood gas pH and base deficit, neonatal intensive care unit admission, fetal weight

- **Study Population*:*** all pregnant female patients who will be undergoing an elective cesarean delivery under spinal anesthesia at any gestational age
  - Inclusion criteria:
    - Elective cesarean delivery with or without planned bilateral tubal ligation
    - Planned spinal anesthesia
    - Planned Pfannenstiel or low transverse skin incision
  - Exclusion criteria:
    - Known maternal allergy to bupivacaine or derivative
    - Known maternal allergy to oxycodone, ibuprofen, acetaminophen or derivative
    - Currently have an epidural catheter in place
    - Planned general anesthesia
    - Maternal age <18 years old
    - Emergent cesarean delivery
    - Active labor [defined as: >6cm cervical dilation and regular contractions noted on tocometer (>2 contractions in a 10 minute period for 30 consecutive minutes)]
    - Chronic antepartum opioid use
    - History of substance abuse (alcohol or drug)
    - Current tobacco use
    - Chronic steroid use or needing stress dose steroids at the time of delivery
    - Medical contraindication to neuraxial anesthesia such as thrombocytopenia (platelet count <80,000/microliter) or space occupying lesion of the brain
    - Category 3 fetal heart rate pattern

        - Maternal fever or suspected chorioamnionitis
        - Concern for morbidly adherent placenta
        - Planned cesarean hysterectomy
- **Power analysis:**
    - Sample size was determined assuming a power of 80%, p value of 0.05 to detect a 25% difference in the primary outcome of cumulative opioid usage in the first 24 hours postoperatively
        - In a previous unpublished, randomized controlled study conducted by Dr. Jeffrey Bernstein, average use of opioids in post-cesarean subjects was 47mgSD 35 morphine equivalence in the first 24 hours postoperatively
        - Therefore, in our protocol, with three groups and keeping the hypothesis as one of the groups will consume fewer opioids (SD as 25) to demonstrate a minimum 25% difference between any two groups, this will require 255 subjects total (85 subjects per group). However, to accommodate for missing data and study withdrawal we will increase the sample size by 10 % therefore there will be 276 subjects total- or 92 patients per group
- **Exclusion of any population group:**
    - Minors <18 will be excluded
        - There are regulations for protection of human subjects allow consenting adults to accept a higher level of risk than is permitted for children
    - Only subjects who have the capacity to consent will be enrolled
- **Sources of research material:**
    - Data and access to the electronic medical records (EPIC, EPF, ASOBGYN) will be obtained from individually identifiable living human subjects as part of routine clinical care.
- **Participant recruitment:** Study team members (i.e. key personnel) on labor and delivery will ask patients who present for elective cesarean delivery if they are interested in the study. The key personnel will then approach the intended patients to obtain consent for the research study. We are requesting a waiver of informed consent and HIPAA authorization to access medical records for recruitment purposes.
    - All patients will be told that the study is voluntary, they do not have to participate and whether they participate will not affect their care in any way
    - Maintenance of safety of PHI data/confidentiality
        - All records will be kept in a secure manner on a secure server. Access to the records will only be by the listed protocol key personnel and the computer records will be password protected. All patients will be

assigned a number and all information will be recorded under this number - not patient identifying information - and a separate list will be kept in a separate location under password protection listing medical records of patients identified to the code and only researcher Igel will have access to this list.

- **Informed consent**
  - The informed consent document adhering to Montefiore's template is uploaded to IRIS.
  - Informed consent will be obtained by listed key personnel when the patients present to the labor and delivery unit. These patients will be approached based on the inclusion/exclusion criteria noted above and will NOT be women in labor as outlined in the exclusion criteria. They are women for elective cesarean delivery.
  - There will be no waiver of informed consent and minors will not be included
  - There is no cost or remuneration to the participants
  - HIPPAA authorization will take place at the same time as the informed consent process
- **Risks/Benefits**
  - Anticipated risks (*e.g.* medical, social, psychological, and/or legal)
    - The anticipated medical risks involved with the addition of bupivacaine include possible allergic reaction, systemic toxicity or intravascular injection of the anesthetic. There are no social or legal risks. Psychological risks include discomfort completing questionnaires and breach of confidentiality/ loss of privacy.
    - Risks of injection process include: pain, redness, infection or allergy to medication components
    - Adverse reactions of study medications according to FDA:
      - Oxycodone: abuse, misuse, addiction; (>5%): constipation, nausea, somnolence, dizziness, vomiting, pruritus, dry mouth, sweating, asthenia; (1-5%) anorexia, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, twitching, gastritis, abnormal dreams, thought abnormalities, hiccups; (<1%): lymphadenopathy, palpitations, tinnitus, syndrome of inappropriate antidiuretic hormone secretion, abnormal vision, dysphagia, flatulence, ileus, stomatitis, increased appetite, eructation, chest pain, edema, facial edema, malaise, pain, peripheral edema, thirst, withdrawal syndrome (with and without seizures), anaphylactic or anaphylactoid reaction, pharyngitis, accidental injury,

hyponatremia, increased hepatic enzymes, ST depression, dehydration, neck pain, abnormal gait, amnesia, hyperkinesia, hypertonia (muscular), hypesthesia, hypotonia, migraine, paresthesia, seizures, speech disorder, stupor, syncope, taste perversion, tremor, vertigo, agitation, depersonalization, depression, emotional lability, hallucination, dysuria, hematuria, polyuria, urinary retention, urination impaired, amenorrhea, decreased libido, impotence, cough increased, voice alteration, dry skin, exfoliative dermatitis, urticarial, vasodilation

- Acetaminophen: (>3%) nausea, vomiting, headache, insomnia, pyrexia; (>1%): anemia, fatigue, infusion site pain, peripheral edema, aspartate aminotransferase increased, breath sounds abnormal, hypokalemia, muscle spasms, trismus, anxiety, dyspnea, hypertension, hypotension
- Ibuprofen: (>1% but <3%) Nausea, stomach pain, heartburn, vomiting, constipation, abdominal cramps, bloating, gas, dizziness, headache, nervousness, rash, itching, ringing in ears, decreased appetite, swelling, fluid retention; (<1%): ulcer, bleeding ulcer, black stools, abnormal liver function tests, inflammation of liver/ pancreas/ stomach, depression, difficulty sleeping, confusion, sleepiness, hives, thinning of hair, Stevens Johnson syndrome, hearing loss, blurred vision or changes in vision, neutropenia, aplastic anemia, thrombocytopenia, eosinophila, decrease in blood count, elevated blood pressure, bronchospasm, acute kidney failure, blood in urine, kidney injury, increase urination, inflammation of bladder, dry eyes and mouth, gum ulcer, inflammation of nose
- Bupivicaine Hydrochloride: (toxicity most commonly dose related from overdosage, rapid absorption from injection site, diminished tolerance, or from unintentional intravascular injection of local anesthetic) -excitation and/or depression, restlessness, anxiety, dizziness, tinnitus, blurred vision, tremors, convulsions, drowsiness, unconsciousness, respiratory arrest, depression of the myocardium, decreased cardiac output, heartblock, hypotension, bradycardia, ventricular arrhythmias, cardiac arrest, paralysis of legs, loss of consciousness, respiratory paralysis, urinary retention, fecal and urinary incontinence, loss of perineal sensation and sexual

function, persistent anesthesia, paresthesia, weakness, paralysis of lower extremities, loss of sphincter control, headache, backache, septic meningitis, meningismus, cranial nerve palsies; nausea, vomiting, chills, constriction of the pupils; allergic type reactions,

- Bupivicaine Hydrochloride and Epinephrine: see "Bupivicaine Hydrochloride" above; allergic-type reactions to sulfites in epinephrine-containing solutions
- Fentanyl citrate injection: respiratory depression, apnea, rigidity, bradycardia, respiratory arrest, circulatory depression or cardiac arrest, hypertension, hypotension, dizziness, blurred vision, nausea, emesis, diaphoresis, pruritus, urticarial, laryngospasm, anaphylaxis
- Morphine sulfate injection (Duramorph): pruritus, nausea, vomiting, constipation, urinary retention, headache, dizziness, euphoria, anxiety, hypotension, confusion, reduced male potency, decreased libido in men and women, menstrual irregularities including amenorrhea, depression of cough reflex, interference with thermal regulation, oliguria, urticarial, wheals, local tissue irritation, respiratory depression and/or respiratory arrest, tolerance, myoclonus, convulsions, dysphoric reactions, toxic psychoses, drug abuse and dependence; overdosage: respiratory depression with or without concomitant CNS depression, apnea, circulatory collapse, cardiac arrest

- Describe how anticipated risks will be minimized:
  - The patients will be monitored extensively during anesthesia administration and afterwards according to anesthesia protocols and will be attached to a continuous monitor and have blood pressure and pulse taken according to operating room protocol for regional anesthesia. The subjects will be monitored for local anesthetic toxicity according to routine anesthesia protocols (monitoring patients for symptoms and vital signs). During injection extreme care and caution will be used to ensure that the injection in not intravascular by aspiration prior to injection. Appropriate interventions for any perceived risk will take place. This will be performed in the operating room where all resuscitative equipment and personnel (including anesthesia physicians) are present.
- Document how potential benefits to participants or others justify potential risks

        - Benefits of potential decreased postoperative pain above current baseline postoperative pain justifies potential risks
    - Describe the plan for data storage and for maintenance of subjects' confidentiality
        - All records will be kept in a secure manner on a secure server (Box.com). Access to the records will only be by the listed protocol investigators and key personnel and the computer records will be password protected. All patients will be assigned a number and all information will be recorded under this number - not patient identifying information - and a separate list will be kept in a separate location under password protection listing medical records of patients identified to the code and only researcher Igel will have access to this list
        - Subjects will not be video or audio taped
- Data Analysis
    - Appropriate statistical methods will to be used to evaluate study objectives
        - Hypothesis: The addition of incisional subcutaneous bupivacaine with epinephrine to standard spinal anesthesia regimen at the time of elective cesarean delivery will decrease postoperative narcotic usage by at least 25% in the first 24 hours
        - A statement regarding specifically what data are to be used to test the hypothesis (or to generate the hypotheses)
            - Our hypothesis will be tested by assessing cumulative postoperative opioid usage in the first 24 hours postoperatively
        - The statistical method(s) to be used to test the hypothesis with that data
            - Depending on the distribution of the data appropriate statistical analysis including one way ANOVA or non-parametric Kruskal Wallis test will be used to analyze the data. Categorical variables such as adverse events, we will be analyzed using Chi-Square analysis. Additionally, we will be using a linear mixed effects regression analysis to model the difference in mean pain scores during the hospital stay.
        - A power analysis to determine the sample size
            - See above for sample size calculation in Methods section) for power analysis
    - Describe methods for interim analyses or early stopping, if applicable
        - Data Safety Monitoring Board (DSMB) will review interim findings at the midpoint of the study. The study will be terminated early if

evidence of effect is established, if the intervention appears futile, or if harm is established. Specifically, if the p-value of the intervention-by-time effects based on data accumulated by the midpoint of the study is smaller than 0.005 (O'Brien-Fleming boundary), we will declare the superiority of the intervention. On the other hand, if the upper bound of the 95% confidence interval for the difference between the groups is less than 5%, we will declare futility of the intervention. The DSMB will also be authorized to recommend early termination for other reasons related to patient safety. We will have a planned interim analysis halfway through patient recruitment to stop the study if there is a significant impact

- Describe how possible confounding and/or effect modification will be addressed
  - All patients will be randomized and blinded to their intervention groups. Baseline demographic variables will be collected to assess for differences among the groups. Patients with a history of chronic pain syndromes or chronic opioid use will be excluded from the study.
- Describe how loss to follow up will be addressed
  - We will increase the power calculated sample size by 10% to account for loss to follow up

Data safety monitoring plan: Patient outcomes will be monitored in real time for side effects and patient safety. In order to maintain additional patient safety, a DSMP will be in place for the study. The data will be reviewed by two clinicians familiar with spinal anesthesia, cesarean birth and perioperative and postoperative management and complications, namely Dr. Yelena Spitzer (Obstetric Anesthesia attending) and Dr. Diana Wolfe (Maternal Fetal Medicine attending). In addition, clinical researcher Dr. Singh Nair, will review the data. The Data safety monitoring committee will meet every 6 months. Minutes of the meetings including attendance, a summary of discussion and any relevant findings will be recorded. Data will be reviewed for adverse events throughout the study duration. The results of findings and recommendations of the team will be reported to the Albert Einstein College of Medicine institutional review board for review and action.

Data quality control and database management.

- Describe methods for data entry and data management
  - All data will be gathered by key personnel member Igel and entered into a password protected excel spreadsheet located on a secure Montefiore server (Box.com)
- Describe the mechanism for checking and editing the data.
  - Data will be checked monthly by randomly selecting patients to check all data input by a different key personnel member than originally entered the data
- Describe computer data security and subject confidentiality

- All records will be kept in a secure manner on a secure server (Box.com) on a secure excel spreadsheet with password protection; access to the records will only be by the listed protocol investigators and the computer records will be password protected; all patients will be assigned a number and all information will be recorded under this number - not patient identifying information - and a separate list will be kept in a separate location under password protection listing medical records of patients identified to the code and only researcher Igel will have access to this list

- Data given to researchers for future research projects:
  - The **de-identified** database *may* be used for future quality improvement and research projects. If the database is used for future research projects, it will only be available to internal researchers within the Albert Einstein institution. Researcher Igel will maintain possession of the database.

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