Patient-Driven Analgesic Protocol Selection for Post-Cesarean Pain Management

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Title
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PI and other key investigators
Dr. Carvalho is an anesthesiologist, with an emphasis in obstetrical anesthesia and research. ████ ████ is an anesthesiologist, with an emphasis in obstetrical anesthesia and statistical analysis. ████████ is an experienced clinical research coordinator. ████████ is an experienced clinical research manager. The OB anesthesia fellows will help conduct the study.

Objectives/Purpose
Our ability to predict pain and then apply modified treatment protocols has been limited. Current practice is for physicians to select standard post-operative pain treatment protocols without patient consultation. This study hopes to determine if patient's involvement in analgesic drug/dosage protocol selection can optimize pain relief and minimize related side effects. Specifically, we will learn whether patient choice of analgesic protocols influences post-operative pain, analgesic use, side effects and maternal satisfaction in the first 48 hours following Cesarean delivery. This could result in a more patient-centered care model and individualized perioperative analgesic treatment protocols based on patient's preferences, needs and expectations.

Background Information
Acute pain after surgery is a major and largely unrecognized problem. Studies highlight the need for improving the management and prevention of postsurgical pain with aggressive early therapy, since the intensity of acute postoperative pain correlates with the risk of developing a chronic pain state, (Kehlet et al. 2006). Severe acute pain is associated with persistent pain and post-partum depression after cesarean (Eisenach et al. 2008; Lavand'homme 2006). We have recently demonstrated that post-cesarean pain can be improved and opioid use reduced when patients are able to select their intrathecal morphine dose. (SOAP Best Paper Finalist 2015). This study explores this concept further to see if patient choice in the postoperative pain protocol will improve the post-cesarean pain experience, as well as improve side effects and maternal satisfaction.

Preliminary unpublished data
Carvalho B, Mirza F, Flood P. *Women Randomized to Choice of Intrathecal Morphine Dose Before Surgery Anticipates Post-Cesarean Delivery Pain and Opioid Requirement Independent of Dose Received* (abstract presented at SOAP and submitted for publication consideration)
We are also relying on previously published work on the role of patient choice in the management of post-operative analgesia.

Study design
Qualified subjects will be identified and contacted by the obstetric anesthesia team prior to their clinical evaluation for anesthesia for their cesarean delivery. The subjects will be women scheduled to have elective cesarean deliveries for uncomplicated, singleton pregnancies. Potential subjects will be informed of the study, and if they choose to participate, all questions

will be answered and an informed consent form will be signed prior to any study related activities. We will record number of patients approached, number of people refusing to participate in the study, and number of patients withdrawing from the study.

This randomized, controlled study will include a simple, preoperative questionnaire to obtain baseline demographic and obstetric data; and complete questions (that have previously been shown to be predictive of postoperative pain) from which we will determine their expected and target postoperative pain scores. These questionnaires should take less than 3-4 minutes to complete.

The subject will then be randomized into "choice" and "no choice" groups. The randomization for choice vs. no choice will be at a 1:3 ratio i.e. 1 woman will get no choice and 3 will get a choice for their analgesic protocol. Breakdown will occur based on patient preference for the study protocols.

Treatment of Subjects

The no choice group will receive the current standard analgesic protocol: 150 mcg intrathecal morphine, and around the clock acetaminophen 625 mg po q6h and ibuprofen 600 mg po q6h. The group with the choice will be offered 3 different protocols:

1. 50 mcg intrathecal morphine, and around the clock acetaminophen 625 mg po q6h and ibuprofen 600 mg po q6h.

2 150 mcg intrathecal morphine, and around the clock acetaminophen 625 mg po q6h and ibuprofen 600 mg po q6h.

3. 300 mcg intrathecal morphine, and around the clock acetaminophen 625 mg po q6h and ibuprofen 600 mg po q6h, as well as gabapentin 600 mg po one time within 1 hr of delivery.

Women will decide on which protocol after being given a standard script explaining advantages and disadvantages of each protocol. Pain will be managed adequately no matter what group patients are assigned to or whatever protocol they choose.

Drugs and doses utilized in the study are safe for postpartum women and within dose range routinely used at our and other institutions.

All breakthrough pain will be managed the same for all patients, and adequate analgesia will be available to treat post-operative pain. Primary breakthrough rescue analgesic will be our standard oral opioid oxycodone managed using our current treatment algorithm. If pain 1-4 out of 10, 1 tablet (5 mg) will be offered, if pain >4 out of 10, 2 tablets (10 mg) will be offered PRN. Pain not responding to oral opioids will be offered IV morphine boluses or PCA as per standard treatment protocols. Additional analgesic options (e.g. TAP blocks) will also be available as per standard care. Following standard Cesarean delivery, postoperative data will be collected (directly from patients and from the electronic medical record) by study investigators blinded to group assignment.

Assessment of Efficacy

Outcome measures:

1) Pain scores at rest and on to sitting (VPS 0-10) collected at 3, 6, 12, 24, 36, 48 hours post-cesarean
2) Overall daily pain score and its deviation from target and expected pain score will be determined at 0-24 and >24-48 hours study periods.
3) Opioid use (oral and IV morphine) in the 0-24 and >24-48 hour study periods.
4) Time to first analgesic for breakthrough pain (minutes from spinal)
5) Side effect: Pruritus score (0-100), nausea score (0-100) and number of episodes of vomiting for the 0-24 and >24-48hr postoperative periods
6) Any treatment of pruritus and/or nausea/vomiting
7) Satisfaction with postoperative analgesia score (0-100)
8) Discharge time (hours/minutes from surgery end)

Discontinuation of the Study
Telephone follow-up for pain score, opioid use, and functional recovery will be performed at 1 week, 1 month, 3 months and 6 months post-Cesarean. Participants for which deception was used will be debriefed at their 6 month follow-up phone call. After the final 6 month post-Cesarean phone call, the study will be discontinued.

Selection and Exclusion of Subjects
Inclusion criteria:
- Women age 18-50 with singleton, gestation fetuses >37 weeks, not in active labor and scheduled for their 1st, 2nd, or 3rd elective CS.
- All scheduled Cesarean deliveries under spinal or CSE (with no additional epidural doses administered) anesthesia.

Exclusion criteria:
- History of chronic pain, anxiety or depression
- Women unable to understand the concept of Verbal Numerical Pain Scale at the time of informed consent
- Chronic consumption of opiates, antidepressants, or anticonvulsants
- Intake of opioids, acetaminophen, or NSAIDs 48hrs prior to the psychophysical test
- Preeclampsia (with any severe features) or diabetes (not controlled with diet and needing drugs)
- Preterm delivery (<37 weeks gestation)
- Patient refusal

Assessment of Safety and Adverse Events and Reporting
Patient care will follow standard of clinical care. Any adverse events will be reported to the PI and necessary adjustments to the protocol will be immediately instituted.

Statistics, including power calculations justifying the number of subject and details of data analysis plan
A priori power analysis predicts that we will require 160 study subjects (40/group) to detect a clinically meaningful 33% reduction in mg-morphine equivalents of opioid analgesic

consumption (Power 0.8, alpha=0.05, variance=20 mg). The expected effect size and variance was based on previous data collected at our institution and estimates from the literature.[6,8]

Potential associations between patient choice and demographic variables will be evaluated using Student's t test for normally-distributed variables and Mann-Whitney test for non-parametric comparisons. Associations among discrete variables will be investigated using Chi square and Fisher's exact test where appropriate. Time series analysis of pain and opioid rescue will be performed with mixed-effects models to allow separation of fixed effects (e.g., patient choice, morphine dose) from random effects. Final parameter estimates will be considered significant at $P < 0.05$ with a 2-sided alpha after adjustment for multiple comparisons.

Significance
Showing that patient choice can influence postoperative pain can dramatically change our practice within the specialty. In addition we have previously found that simple questions about patients' pain and opioid needs may help predict pain after cesarean delivery. We wish to explore this concept further applying these simple questions to validate its efficacy. A reliable bedside tool such as a simple questionnaire that predicts severe post-operative pain will allow us to alter intra- and postoperative analgesic regimens accordingly to improve analgesia.

Quality Control and Assurance
All investigators will be fully trained and familiar with our protocol. Consent for the study will only be obtained by these providers. Assignment to groups will be done by a separate provider who will not do outcome assessments in order to ensure appropriate blinding.

Ethics
Informed Consent:
Adequate informed consent, including a discussion of the risks, benefits, and alternatives of participation in the study will be thoroughly discussed with each potential subject. Investigators will ensure that patients are aware of their ability to be unenrolled at any time for any reason.

Beneficence/Nonmaleficence:
The above procedures provide minimal risk to the subjects because the questionnaires should not cause any psychological harm (and would absolutely not cause physical harm). The intrathecal morphine doses and all the drugs in the protocols have previously and are currently used safely as standard of care. All these drugs, doses, and protocols are utilized in our or other peer institutions and are considered safe for post-Cesarean pain management.

Data handling and Recordkeeping
Information including, age, general health and gestational age and information regarding previous experiences with pain. Results of participants questionnaires, demographic information (e.g. age and race), and the dates of enrollment in the study will be obtained. Only study research personnel will have access to all the data during the study and study analysis.

All data will be kept on Stanford encrypted and password protected computers.
Coded data in the database will be used for statistical analysis (statistician to be identified) to see if there is a way to use our data to predict the incidence of acute severe pain and long-term chronic pain after surgery. Electronic Data will be stored on a password protected and secure computer that will be kept in a locked office. Hard data (paper records/collection forms) will be stored in a locked file cabinet in a locked office.

All persons involved in this study will receive appropriate training and abide by confidentiality guidelines to protect the subject's privacy. Data will only be labeled with codes assigned to each patient. Only the research team will have access to data. The PD will maintain the key to the code on a Stanford encrypted and password-protected computer.

References to current literature
Carvalho B, Mirza F, Flood P. Women Randomized to Choice of Intrathecal Morphine Dose Before Surgery Anticipates Post-Cesarean Delivery Pain and Opioid Requirement Independent of Dose Received. SOAP Best Paper Finalist 2015. Publication status: submitted.

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