Implementation of an enhanced recovery after surgery pathway for patients undergoing cesarean section: impact on clinical outcomes

Study Protocol & Statistical Analysis Plan

NCT03552822

April 24, 2020

Mark Powell, M.D., Principal Investigator
University of Alabama at Birmingham
Birmingham, AL 35294

STUDY SUMMARY

INTRODUCTION

Cesarean section (CS) is one of the most common surgeries performed worldwide. It is the most common major surgery performed in the United States, with over 1.25 million patients undergoing CS annually.[1] As enhanced recovery programs have been shown to accelerate postoperative recovery and decrease dependence on postoperative opioids in other surgical specialties,[2] they have begun to gain popularity for CS.[3,4] Such a program for CS presents an opportunity to affect outcomes for patients who could benefit from a multidisciplinary, multimodal, and opioid-sparing approach to improving their recovery. The Society for Obstetric Anesthesia and Perinatology (SOAP) strongly supports this effort and recently released a consensus statement on an enhanced recovery protocol for CS.[5]

An important aspect of many enhanced recovery protocols is a multimodal approach to opioid-sparing pain control.[2] Potential benefits of opioid-sparing pain control for women undergoing CS include decreased amounts of opioids transferred in breastmilk,[6] as well as reduced risk of maternal opioid abuse after delivery.[7] Opioid-naïve patients who undergo surgery are at particular risk for developing opioid dependence after surgery.[7-8] Approximately 1 in 300 opioid-naïve women become persistent prescription opioid users following CS.[9]

As enhanced recovery programs in obstetrics begin to gain popularity, more studies evaluating their impact are needed.[3] We therefore sought to evaluate the impact of instituting an enhanced recovery program for CS.

STUDY OBJECTIVES

The purpose of this study was to determine if there are significantly improved patient outcomes after implementing an enhanced recovery protocol for CS. Initially, we had planned to study hospital length of stay as our primary outcome; however, because of Rose's Law, we determined that length of stay would not be an appropriate primary outcome at our institution. Rose's Law is a state law that prohibits early discharge (<96 hours) of a patient after cesarean delivery unless a waiver is signed by the patient to allow for discharge before 96 hours after delivery.

The primary outcome of this study was to determine if implementation of an enhanced recovery program could reduce postoperative opioid consumption in patients undergoing CS. Secondary outcomes included determining the impact of an enhanced recovery program for CS on postoperative pain scores, length of stay, and 30-day complication rates. We hypothesized that implementing an enhanced recovery program for CS would decrease postoperative opioid consumption.

STUDY DESIGN

We compared a retrospective pre-enhanced recovery cohort (pre-ERC) of women delivered by CS to a prospective enhanced recovery cohort (ERC) exposed to the enhanced recovery program. The pre-ERC included patients from January 1, 2017 to June 30, 2018. The Enhanced Recovery for Cesarean Delivery Program was implemented July 1, 2018. The ERC included patients from July 1, 2018 to December 31, 2018.

SUBJECT SELECTION

Analysis was restricted to women undergoing scheduled, elective CS at the Women and Infants' Center who were admitted to the hospital on the day of surgery. Patients excluded from analysis included those: (1) less than 18 years of age; (2) who had an urgent or emergent CS; (3) who had a diagnosis of preeclampsia, eclampsia, insulin dependent diabetes, abnormal placentation, or opioid use disorder. The pre-ERC group included patients from January 1, 2017 to June 30, 2018. The ERC group included patients from July 1, 2018 to December 31, 2018.

STUDY PROCEDURES

Pre-Enhanced Recovery Cohort

The pre-ERC was identified through a query of our electronic medical records database. Only surgeries scheduled at least 24 hours prior to documented delivery time were considered as to exclude urgent or emergent surgeries. Also, patients were excluded if they had a documented International Classification of Diseases (ICD) diagnosis of preeclampsia, eclampsia, placenta accreta, placenta increta, placenta percreta, Type 1 diabetes, Type 2 insulin dependent diabetes, opioid dependence, or had outpatient prescriptions for insulin, methadone, buprenorphine, or buprenorphine-naloxone. Eligible charts were reviewed, and patients were further excluded if they were admitted for inpatient management prior to the day of surgery or if they had an exclusion diagnosis that was in a physician note but not captured as an ICD code.

Enhanced Recovery Program Implementation

The Enhanced Recovery after Cesarean Delivery Program was implemented on July 1, 2018. The program included the enhanced recovery protocol and a quality improvement initiative with monthly reports. The program was designed by a multidisciplinary committee with leadership from obstetric anesthesia and stakeholders including obstetricians, pediatricians, nursing leadership, pharmacy, and information technology.

Patients received a written educational handout on enhanced recovery after CS in the preoperative obstetric clinic. Instead of the previous "nil per os (NPO) after midnight" preoperative instructions, these patients were instructed to consume a 20-ounce carbohydrate sports drink up to 2 hours before arrival to the hospital. Upon admission, the ERC had an icon placed on the electronic tracking board signifying that they were in the enhanced recovery protocol. In preoperative holding, patients received the standard gastrointestinal and antibiotic prophylaxis with the addition of 1000 mg of oral acetaminophen. The acetaminophen would continue throughout hospitalization as a scheduled dose of 650 mg every six hours. A forced-air warming device was placed on the patient, and patients were warmed for 30 minutes prior to surgery.

No major changes occurred in the intraoperative setting. Patients undergoing spinal or combined spinal-epidural anesthesia received our standard spinal dose of 12 mg hyperbaric bupivacaine combined with 15 μg fentanyl and 150 μg preservative-free morphine. Patients undergoing epidural anesthesia received our standard dose of 3 mg preservative-free morphine in combination with local anesthetic. A bilateral transversus abdominis plane block was performed in the post-anesthesia care unit (PACU) with 20 ml 0.5% ropivacaine on each side for patients who underwent general anesthesia and were unable to receive neuraxial preservative-free morphine. Unless contraindicated, all patients received 30 mg of intravenous (IV) ketorolac in the PACU. The ketorolac was given as a scheduled medication every 6 hours for the first 24 hours. Patients then were transitioned to scheduled ibuprofen 600 mg every 6 hours.

Postpartum changes included earlier postoperative oral intake, earlier urinary catheter removal, increased ambulation goals, and changes in standard analgesic medication orders. Patients were now offered a clear liquid diet immediately upon arrival to the postpartum floor and advance to solid foods as soon as tolerated. Prior to July 1, 2018, the urinary catheter was removed on postoperative day (POD) 1. This meant that the catheter might have remained in place for up to 23 hours or more after delivery. The enhanced recovery protocol specified to remove the catheter eight hours after delivery while awake. Prior to the ERC, there were no clearly defined postoperative ambulation goals. In the ERC, specific activity goals included out of bed and to a chair three times a day and ambulating in the hallway once on POD 0. From POD 1 until discharge, patients were expected to ambulate in the hallway four times a day. Changes to the analgesic regimen included scheduled oral acetaminophen and ibuprofen throughout hospitalization as well as non-opioid management (heat/cold packs, distraction therapy) for mild pain. Pain scores were defined as: mild (1-3), moderate (4-6), and severe (7-10) and were recorded by nursing as part of the routine vital signs. There were as needed orders for oral oxycodone 5mg every 4 hours for moderate pain, and oral oxycodone 10mg every 4 hours for severe pain. At the time of discharge, patients were written for a maximum number of 20 tablets of oxycodone 5 mg, which was a reduction from the 30 tablets prior to enacting the enhanced recovery protocol.

After implementation of the protocol in July 2018, data were pulled monthly and summary statistics were provided to the committee. Regular feedback was solicited from providers involved in the enhanced recovery protocol. Adherence to the protocol was assessed by actions recorded in the electronic medical record including medication administration and catheter removal time, as well as times recorded for oral intake and first ambulation.

Enhanced Recovery Cohort

The ERC for data analysis was identified through a monthly query of the electronic medical record after July 1, 2018. Charts were identified based on the presence of an order for the Enhanced Recovery for Cesarean Delivery Protocol and were reviewed to confirm adherence to study inclusion and exclusion criteria, with chart abstraction as needed for missing data.

STATISTICAL PLAN

Statistical Analysis

Data were summarized using either means and standard errors (SE) for continuous outcomes or counts and percentages for categorical outcomes. Two-sample t-tests and chi-square tests were used to compare the two cohorts. Normality for continuous outcomes was assessed using probability plots and the Shapiro-Wilk test for normality; for any outcomes where normality could not be reasonably assumed, the Wilcoxon rank sum test was used in place of two-sample t-tests. For categorical outcomes, Fisher's exact test was used when assumptions for the chi-square test were not met.

Any missing observations were assumed to be missing at random. Pairwise deletion was used to handle missing data. That is, subjects with missing data were not excluded from all analyses, but only those analyses where the outcome of interest was missing. For the primary and secondary outcomes, a Bonferroni adjustment was used to correct for multiple comparisons. For these outcomes, a two-sided p-value < 0.002 ($= .05/22$) was considered statistically significant. For all other measures, p-value < 0.05 was considered statistically significant. SAS version 9.4 (SAS Institute Inc., Cary, NC) was used to conduct all statistical analyses.

Sample Size Estimate

We assessed baseline values of our primary clinical outcome to determine appropriate sample size. After initial retrieval of patient charts for the pre-ERC, and prior to chart abstraction, the baseline total oral morphine equivalents (OME) used postoperatively from July 1, 2017 to April 30, 2018 was an average of 126 (5.93) mg. Based on these values, a sample size of 138 patients would give us 80% power at the 0.05 significance level to detect a 15% decrease in morphine equivalents from baseline using a two-sample t-test. We analyzed patients in the ERC from July 1, 2018 through December 31, 2018. This was based on the monthly review of data that were part of the enhanced recovery program. Given the pattern of opioid decrease seen in these monthly reviews, we decided to finalize analysis at the end of 2018.

SAFETY AND ADVERSE EVENTS

For the study, breach of confidentiality is a rare but potential adverse event. Any adverse event will be documented and immediately reported to the departmental human studies research committee and institutional review board.

DATA HANDLING AND RECORD KEEPING

All data collected are stored electronically in the HIPAA-compliant, password-protected research drive maintained by our department. Only study personnel on the study protocol have access to the data stored in this system.

STUDY MONITORING, AUDITING, AND INSPECTING

The PI of the study is responsible for oversight of the study and all co-investigators. The research division within the department tracks and ensures all investigators of the study maintain appropriate credentialing to participate in research. The research division within the department also reviews and approves all protocols. The IRB requires a yearly progress report be submitted and includes all patients screened and enrolled, study update, and any adverse events. The study is also subject to audit by the IRB at any point during the time it is open.

STUDY FINANCES

No external funding was received for this study. All resources for this study were provided by the department.

PUBLICATION PLAN

The completed manuscript was submitted for publication and accepted in the *International Journal of Obstetric Anesthesia.* Citation for this article:

- Lester SA, Kim B, Tubinis MD, Morgan CJ, Powell MF. Impact of an enhanced recovery program for cesarean delivery on postoperative opioid use. *Int J Obstet Anesth* 2020; 43:47-55.

REFERENCES

1. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK, Drake P. Births: final data for 2016. *Natl Vital Stat Rep* 2018;**67**:1-55.
2. Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery: a review. *JAMA Surg* 2017;**152**:292-8.
3. Ituk U, Habib AS. Enhanced recovery after cesarean delivery. *F1000Res* 2018;**7**(F1000 Faculty Rev):513.
4. Corso E, Hind D, Beever D, et al. Enhanced recovery after elective caesarean: a rapid review of clinical protocols, and an umbrella review of systematic reviews. *BMC Pregnancy Childbirth* 2017;**17**:91. doi: 10.1186/s12884-017-1265-0.
5. Bollag L, Tiouririne M, Lim G, et al. Society of Obstetric Anesthesia and Perinatorlogy (SOAP) Enghanced Recover After Cesarean (ERAC) Consensus Statement. May 23, 2019. Available at: https://soap.org//SOAP-Enhanced-Recovery-After-Cesarean-Consensus-Statement.pdf. Accessed August 25, 2019.
6. ACOG Committee Opinion No. 742: Postpartum pain management. *Obstet Gynecol* 2018;**132**:e35-e43.
7. Stone AB, Wick EC, Wu CL, Grant MC. The US opioid crisis: a role for enhanced recovery after surgery. *Anesth Analg* 2017;**125**:1803-5.
8. Chen EY, Marcantonio A, Tornetta P 3rd. Correlation between 24-hour predischarge opioid use and amount of opioids prescribed at hospital discharge. *JAMA Surg* 2018;**153**:e174859.
9. Bateman BT, Franklin JM, Bykov K, et al. Persistent opioid use following cesarean delivery: patterns and predictors among opioid-naïve women. *Am J Obstet Gynecol* 2016;**215**:353.e1-353.e18.